Calcium (Ca) – Serum, Plasma, Urine, Dialysate Solutions
Beckman UniCel DxC Systems

Technical Procedure 3115

Principle

Intended Use

ISE Electrolyte Buffer reagent and ISE Electrolyte Reference reagent, when used in conjunction with UniCel® DxC 800 System(s) and SYNCHRON® Systems AQUA CAL 1, 2 and 3, are intended for the quantitative determination of calcium concentration in human serum, plasma, urine or dialysate solutions.

Clinical Significance

Calcium measurements are used in the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany (intermittent muscular contractions or spasms). Urinary calcium measurement is used in the differential diagnosis of absorptive hypercalciuria and hypercalciuria caused by hyperparathyroidism, hyperthyroidism, Paget's disease or "renal leak" type of calciuria as seen in renal tubular acidosis.

Methodology

The SYNCHRON® System(s) determines total calcium concentration by indirect potentiometry utilizing a calcium ion selective electrode in conjunction with a sodium reference electrode.

In principle, a calcium ion selective electrode measures un-bound free calcium ions in solution. Total calcium can only be calculated from free calcium when the molar ratio between free and total calcium concentrations is constant. This constant molar ratio is achieved by the buffered solution which contains strong calcium complexing agents.

A precise volume of sample (40 microliters) is mixed with the buffered solution. The ratio used is one part sample to 33 parts buffered solution. The high molar strength buffer is used to establish a constant activity coefficient for calcium ions, calibrating the electrode to concentration values.(1,2)

Chemical Reaction Scheme

The calcium ion selective electrode consists of a calcium ionophore membrane cast on a solid support. When sample buffer mixture contacts the electrode, changes in electrode potential occur as calcium ions react with the ionophore. These changes in potential are referenced to the sodium reference electrode. The "referenced potential" follows the Nernst equation and allows the calculation of calcium concentration:

$$E = \text{Constant} + (\text{slope})\ (\log[Ca^{2+}])$$

For more accurate measurement, the reference reagent containing calcium ions is introduced into the flow cell following the sample cycle, and the same reaction scheme takes place. The differential potential (voltage) between sample and reference reagent cycles is used for the calculation.

Under ideal conditions, the electrode imparts a selectivity of 1000:1 over sodium and potassium and is insensitive to hydrogen ions in solution buffered from pH 4 to 10.

Specimen

Acceptable Sample Containers

13 x 75 PST, SST and Red Top BD tubes
PST, SST and Red Top BD microtainers

Spot urines should be aliquoted into a 13 x 75 clear cap BD tube

24 hour urine collections are received in 3000 mL plastic urine collection jugs
Dialysate solutions should be aliquoted into a 13 x 75 Clear Cap BD tube

Type of Specimen

Biological fluid samples should be collected in the same manner routinely used for any laboratory test.(3,4) Freshly drawn serum, plasma or properly collected urine (random/timed) are the preferred specimens. Whole blood is not recommended for use as a sample.

Specimen Storage and Stability

Tubes of blood are to be kept closed at all times and in a vertical position. It is recommended that the serum or plasma be physically separated from contact with cells within two hours from the time of collection.(5)

Separated serum or plasma should not remain at room temperature longer than 8 hours. If assays are not completed within 8 hours, serum or plasma should be stored at +2°C to +8°C. If assays are not completed within 48 hours, or the separated sample is to be stored beyond 48 hours, samples should be frozen at -15°C to -20°C. Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.(5)

It is recommended that random urine assays be performed within 2 hours of collection.

For timed specimens, the collection container is to be kept in the refrigerator or on ice during the collection period. No preservative is required. Upon receipt in the laboratory, the collection container must be stored refrigerated until testing is performed. Adjust pH of entire collection to 1.5-2.0 by adding a sufficient volume 6M HCl before aliquoting and testing. **Testing must be performed within 4 days (96 hours) of start of collection**.(6,7)

Sample Volume

The optimum volume, when using a 0.5 mL sample cup, is 0.3 mL of sample. For optimum primary sample tube volumes and minimum volumes, refer to the *Primary Tube Sample Template*.

Unacceptable Specimens

Urine samples aspirated by the IRIS IQ are not acceptable for urine chemistry testing.

Urine collected in a BD UA Preservative Tube is not acceptable for urine chemistry testing.

Refer to the *Procedural Notes* section of this chemistry information sheet for information on unacceptable specimens.

Reagents

Contents

Each kit contains the following items:

ISE Electrolyte Buffer Reagent **Kit Reorder # 467915**
Two Electrolyte Buffer Reagent Bottles (2 x 2 L)

ISE Electrolyte Reference Reagent **Kit Reorder # 467935**
Two Electrolyte Reference Reagent Bottles (2 x 2 L)

Volumes per Test

Sample Volume	40 µL
Reagent Volume	
ISE Electrolyte Buffer	1.27 mL
ISE Electrolyte Reference	3.23 mL (not part of sample dilution)

Reactive Ingredients

Reagent Constituents

ISE Electrolyte Buffer Reagent

Tris	230 mmol/L

ISE Electrolyte Reference Reagent

Sodium	7 mmol/L
Potassium	0.2 mmol/L
Chloride	5 mmol/L
Carbon Dioxide	1.5 mmol/L
Calcium	0.1 mmol/L

Also non-reactive chemicals necessary for optimal system performance.

CAUTION: Avoid skin contact with reagent. Use water to wash reagent from skin.

Materials Needed But Not Supplied With Reagent Kit

SYNCHRON® Systems AQUA CAL 1, 2 and 3
At least two levels of control material

Reagent Preparation

No preparation is required.
Date and initial reagent container(s) and document in reagent log before loading each new carboy.

Acceptable Reagent Performance

The acceptability of this reagent is determined by successful calibration and by ensuring that quality control results are within acceptance criteria, as defined in the Clinical Chemistry Quality Control Procedure #3000.T.

Reagent Storage and Stability

ISE Electrolyte Reference reagent stored unopened at room temperature is stable until the expiration date printed on the bottle label. Once opened, the reagent is stable at room temperature for 30 days, unless the expiration date is exceeded.

ISE Electrolyte Buffer reagent stored unopened at room temperature is stable until the expiration date printed on the bottle label. Once opened, the reagent is stable at room temperature for 30 days, unless the expiration date is exceeded.

For any electrolyte reagents frozen in transit, warm to room temperature, and mix thoroughly. Mix by gently inverting the bottle at least 20 times to redissolve salts back into solution.

Equipment

This test is performed on the Beckman UniCel DxC 800 systems; Beckman-Coulter, Brea, California. For technical assistance, call the Beckman-Coulter hotline: 1-800-854-3633.

Refer to the UniCel DxC 800 systems *Reference Manual* for detailed instructions.

Calibration

Calibrator Required

SYNCHRON® Systems AQUA CAL 1, 2 and 3 (**Kit Reorder #s 471288, 471291, 471294**)

Calibrator Preparation

No preparation is required.

Calibrator Storage and Stability

If unopened, the calibrators should be stored at 2°C to 8°C until the expiration date printed on the calibrator bottle. Once opened, the calibrators are stable at room temperature for 30 days unless the expiration date is exceeded.

Repetitive refrigeration of the aqueous calibrators may facilitate crystal formation. Once removed from refrigerated storage, these calibrators should remain at room temperature.

Calibration Information

The system must have a valid calibration in memory before controls or patient samples can be run.

Under typical operating conditions the CALC assay must be calibrated every 24 hours or with each new bottle of reagent and also with certain parts replacement or maintenance procedures, as defined in the UniCel DxC 600/ 800 System *Instructions for Use* (IFU) manual.

For detailed calibration instructions, refer to the UniCel DxC 600/800 System *Instructions For Use* (IFU) manual.

The system will automatically perform checks on the calibration and produce data at the end of calibration. In the event of a failed calibration, the data will be printed with error codes and the system will alert the operator of the failure. For information on error codes, refer to the UniCel DxC 600/800 System *Instructions For Use* (IFU) manual.

Traceability

Calcium (analyte) in this calibrator is traceable to NIST* SRM 915a.

**NIST=National Institute of Standards and Technology*

The set point values were established based upon the gravimetric addition of specific quantities of the measurand to achieve the appropriate concentration.

The values are verified using representative samples from each lot of calibrator and are specific to the assay methodologies of the SYNCHRON systems. Values determined by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Quality Control

At least two levels of control material should be analyzed each shift. In addition, these controls should be run with each new calibration, with each new reagent cartridge, and after specific maintenance or troubleshooting procedures as detailed in the UniCel DxC 800 System *Instructions For Use* manual. More frequent use of controls or the use of additional controls is left to the discretion of the user based on workload and workflow.

NOTICE
Do not use controls containing diethylamine HCl.

The following controls should be used in accordance with the package instructions for use inserts. Quality control results should be evaluated and handled with respect to the Clinical Chemistry Quality Control Procedure #3000.T. Controls are compiled statistically in the LIS and reagent lot changes are documented on DxC Reagent Log sheets.

Quality Control Material

Control	Storage
MAS ChemTrak 1	+2°C to +8°C*
MAS ChemTrak 3	+2°C to +8°C*
MAS Urine Chemistry 1	+2°C to +8°C**
MAS Urine Chemistry 2	+2°C to +8°C**

*Controls are received frozen and stored at –15°C to –25°C. Bottles of controls in use are thawed and stored at 2°C to 8°C and are good for 14 days.
**Urine controls are received and stored at 2°C to 8°C. Bottles of controls in use are stored at 2°C to 8°C and are good for 30 days.

Testing Procedure

1. If necessary, load the reagent onto the system.
2. After reagent load is completed, calibration is required.
3. Program samples and controls for analysis.
4. After loading samples and controls onto the system, follow the protocols for system operation.

For detailed testing procedures, refer to the UniCel DxC 800 System *Instructions For Use* (IFU) manual.

Calculations

UniCel DxC Systems perform all calculations internally to produce the final reported result. The system will calculate the final result for sample dilutions made by the operator when the dilution factor is entered into the system during sample programming.

If the dilution was programmed in Remisol, the final calculated result from a dilution will not be calculated by the UniCel DxC system but by Remisol.

24 hr timed urine specimens are calculated from the following equation:

$$\text{Urine Calcium } \frac{\text{mg}}{\text{dL}} \times \frac{\text{dL}}{100\text{mL}} \times \text{Total volume collected (mL)} = \text{mg/24hr}$$

Calculations are only performed on 24 hour collections (±15 minutes) and reported as mg/24hr. Do not round off total collection time.

Reporting Results

Equivalency between the SYNCHRON LX and UniCel DxC 800 Systems has been established. Chemistry results between these systems are in agreement and data from representative systems may be shown.

Dialysate results are reported in meq/L and are converted in the LIS. The conversion factor from mg/dL to meq/L is 0.4990.

Reference Intervals

The following reference intervals were taken from literature and a study performed on SYNCHRON Systems.(6)

Reference Intervals

Intervals	Sample Type	Conventional Units		S.I. Units
Literature	Serum or Plasma	8.6 – 10.0 mg/dL		2.15 – 2.50 mmol/L
	Urine (timed)	100 – 300 mg/24 hrs		2.50 – 7.50 mmol/L
SYNCHRON	Serum or Plasma	8.9 – 10.3 mg/dL		2.23 – 2.58 mmol/L
UCDMC	Serum or Plasma	< 1 yr	7.3 – 12.0 mg/dL	1.82 – 2.99 mmol/L
	Serum or Plasma	1 yr – 2 yr	8.0 – 12.0 mg/dL	2.00 – 2.99 mmol/L
	Serum or Plasma	2 yr – 16 yr	8.8 – 10.6 mg/dL	2.20 – 2.62 mmol/L
	Serum or Plasma	16 yr - adult	8.6 – 10.5 mg/dL	2.15 – 2.62 mmol/L
	Urine (timed)	50 – 400 mg/24 hrs		1.25 – 9.98 mmol/L

Refer to References (8,9,10) for guidelines on establishing laboratory-specific reference intervals.

Pediatric reference intervals are cited from literature. No in-house studies were performed. This information should serve as a general guideline.

Reference interval for a spot or random urine sample has not been established.

There are no published reference intervals for dialysate solutions. These are custom solutions for each patient and results from analysis are used to verify accuracy of dialysate solution preparations.

Critical Values

Serum and plasma alcium results **≤ 6.0** mg/dL and **≥13.0** mg/dL are considered critical values and should be called immediately to the attending physician or charge nurse.

Procedural Notes

Anticoagulant Test Results

If plasma is the sample of choice, the following anticoagulants were found to be compatible with this method based on a study of 20 healthy volunteers:

Compatible Anticoagulants

Anticoagulant	Level Tested for In Vitro Interference	Average Plasma-Serum Bias (mmol/L)
Ammonium Heparin	14 Units/mL	NSI[a]
Lithium Heparin	14 Units/mL	NSI
Sodium Heparin	14 Units/mL	NSI

[a] NSI = No Significant Interference (within ± 4.0 mmol/L or 4%).

Limitations

If urine samples are cloudy or turbid, it is recommended that they be centrifuged before transfer to a sample cup.

For each serum calcium measurement, the sodium concentration is used in the calculation. If sodium is not calibrated or the result is suppressed, a nominal value for sodium is used.

For each urine calcium measurement, the sodium and potassium concentrations are used in the calculation of the calcium concentration. If the sodium or potassium chemistries are not calibrated or the sodium or

potassium results are suppressed, the calcium value will be suppressed when a urine sample is analyzed.

Recovery of aqueous calibrators or linearity standards, may exhibit a recovery bias since the calcium algorithms have been optimized to compute recovery of patient samples.

Urine Proficiency Survey samples should not be acidified.

Interferences

The following substances were tested for interference with this methodology:

Interferences

Substance	Source	Level Tested	Observed Effect[a]
Bilirubin (unconjugated)	Bovine	30 mg/dL	NSI
Hemoglobin	RBC Hemolysate	500 mg/dL	NSI
Lipemia	Intralipid[b]	500 mg/dL	NSI
Aluminum	Aluminum Nitrate	20 mgl/dL	-0.2 mg/dL
Bromide	Lithium Bromide	1 mmol/L	+1.5 mg/dL
Methicillin	NA[d]	10,000 µg/mL	-0.2 mg/dL
Methylbenzethonium	NA	0.2 mg/dL	-0.2 mg/dL

[a] Plus (+) or minus (-) signs in this column signify positive or negative interference.
[b] NSI = No Significant Interference (within ±4.0 mmol/L or 4%).
[c] Intralipid is a registered trademark of KabiVitrum, Inc., Clayton, NC 27250.
[d] NA = Not applicable.

Serum or plasma from patients receiving EDTA therapy may yield depressed calcium values.

Flint glass containers contain calcium and should not be used to store samples.

Grossly lipemic samples should be ultracentrifuged and the analysis performed on the infranate.

Refer to References (11,12,13) for other interferences caused by drugs, disease and preanalytical variables.

Performance Characteristics

Analytical Measurement Range

The SYNCHRON® System(s) method for the determination of this analyte provides the following analytical range:

Analytical measurement Range (AMR)

Sample Type	Conventional Units	S.I. Units
Serum/Plasma/Fluid	2.0 - 20.0 mg/dL	0.5 - 5.0 mmol/L
Urine	2.0 - 30.0 mgld/L	0.5 - 7.5 mmol/L

Clinical Reportable Range:

Clinical Reportable Range (CRR)

Sample Type	Conventional Units	S.I. Units
Serum/Plasma/Fluid	2.0 - diluted result mg/dL	0.5 - diluted result mmol/L
Urine	2.0 - diluted result mg/dL	0.5 - diluted result mmol/L

Serum/plasma/fluid samples with concentrations below the AMR and CRR (< 2.0 mg/dL) are reported as "**< 2.0 mg/dL**". Serum/plasma/fluid samples with concentrations greater than the AMR (> 20.0 mg/dL) are diluted with deionized water and reanalyzed.

Urine samples with concentrations below the AMR and CRR (< 2.0 mg/dL) are reported as "**< 2 mg/dL**". Urine samples with concentrations greater than the AMR (> 30.0 mg/dL) are diluted with deionized water and reanalyzed.

If the dilution was programmed in Remisol, the final calculated result from a dilution will not be calculated by the UniCel DxC system but by Remisol.

Sensitivity

Sensitivity is defined as the lowest measurable concentration which can be distinguished from zero with 95% confidence. Sensitivity for CALC determination is 2.0 mg/dL (0.5 mmol/L).

Equivalency

Equivalency was assessed by Deming regression analysis of patient samples to accepted clinical methods.

As determined by Beckman

Serum or Plasma (in the range of 2.19 to 20.29 mg/dL):

Y (SYNCHRON LX Systems)	= 0.981X + 0.17
N	= 92
MEAN (SYNCHRON LX Systems)	= 9.50
MEAN (SYNCHRON CX Systems)	= 9.51
CORRELATION COEFFICIENT (r)	= 0.996

Urine (in the range of 1.34 to 31.00 mg/dL):

Y (SYNCHRON LX Systems)	= 0.982X + 0.60
N	= 97
MEAN (SYNCHRON LX Systems)	= 13.18
MEAN (SYNCHRON CX Systems)	= 12.80
CORRELATION COEFFICIENT (r)	= 0.998

Serum or Plasma (in the range of 2.0 to 19.3 mg/dL):

Y (UniCel DxC Systems)	= 1.007X - 0.03
N	= 184
MEAN (UniCel DxC Systems)	= 9.6
MEAN (SYNCHRON LX Systems)	= 9.6
CORRELATION COEFFICIENT (r)	= 0.999

Urine (in the range of 2.1 to 30 mg/dL):

Y (UniCel DxC Systems)	= 0.983X + 0.09
N	= 103
MEAN (UniCel DxC Systems)	= 9.9
MEAN (SYNCHRON LX Systems)	= 10.0
CORRELATION COEFFICIENT (r)	= 0.999

Refer to References (14) for guidelines on performing equivalency testing.

Equivalency assessed by Deming regression analysis of patient samples to accepted clinical methods.

As determined at UCDMC

Serum or Plasma (in the range of 2.7 to 14.8 mg/dL):

Y (UniCel DxC800-4118)	= 1.002X + 0.01
N	= 32
MEAN (UniCel DxC800-4118)	= 8.69
MEAN (UniCel DxC800-1805)	= 8.67
CORRELATION COEFFICIENT (r)	= 0.9986

Serum or Plasma (in the range of 2.7 to 14.8 mg/dL):

Y (UniCel DxC800-4427)	= 0.989X + 0.23
N	= 32
MEAN (UniCel DxC800-4427)	= 8.81
MEAN (UniCel DxC800-1805)	= 8.67
CORRELATION COEFFICIENT (r)	= 0.9992

Serum or Plasma (in the range of 2.7 to 14.8 mg/dL):

Y (UniCel DxC800-4449)	= 0.980X + 0.26
N	= 32
MEAN (UniCel DxC800-4449)	= 8.76
MEAN (UniCel DxC800-1805)	= 8.67
CORRELATION COEFFICIENT (r)	= 0.9989

Serum or Plasma (in the range of 2.7 to 14.7 mg/dL):

Y (UniCel DxC800-4427)	= 0.987 + 0.23
N	= 32
MEAN (UniCel DxC800-4427)	= 8.81
MEAN (UniCel DxC800-4118)	= 8.69
CORRELATION COEFFICIENT (r)	= 0.9990

Serum or Plasma (in the range of 2.7 to 14.7 mg/dL):

Y (UniCel DxC800-4449)	= 0.978X + 0.25
N	= 32
MEAN (UniCel DxC800-4449)	= 8.76
MEAN (UniCel DxC800-4118)	= 8.69
CORRELATION COEFFICIENT (r)	= 0.9988

Serum or Plasma (in the range of 2.9 to 14.7 mg/dL):

Y (UniCel DxC800-4449)	= 0.991X + 0.03
N	= 32
MEAN (UniCel DxC800-4449)	= 8.76
MEAN (UniCel DxC800-4427)	= 8.81
CORRELATION COEFFICIENT (r)	= 0.9928

Precision

A properly operating UniCel DxC System(s) should exhibit imprecision values less than or equal to the maximum performance limits in the table below. Maximum performance limits were derived by an examination of the imprecision of various methods, proficiency test summaries, and literature sources.

As determined by Beckman

Maximum Performance Limits

Type of Precision	Sample Type	1 SD		Changeover Value[a]		%CV
		mg/dL	mmol/L	mg/dL	mmol/L	
Within-run	Serum/Plasma	0.2	0.05	10.0	2.5	2.0
	Urine	0.3	0.08	10.0	2.5	3.0
Total	Serum/Plasma	0.3	0.08	10.0	2.5	3.0
	Urine	0.45	0.11	10.0	2.5	4.5

[a] When the mean of the test precision data is less than or equal to the changeover value, compare the test SD to the SD guideline given above to determine the acceptability of the precision testing. When the mean of the test precision data is greater than the changeover value, compare the test % CV to the guideline given above to determine acceptability. Changeover value = (SD guideline/CV guideline) x 100.

Precision established at UCDMC

Type of Precision	Sample Type	n	Mean (mg/dL)	1 SD	%CV
DxC800-4118 Within-run	SYNCHRON 1	20	7.81	0.03	0.4
	SYNCHRON 3	20	13.80	0.11	0.8
DxC800-4427 Within-run	SYNCHRON 1	20	8.13	0.07	0.9
	SYNCHRON 3	20	14.05	0.07	0.5
DxC800-4449 Within-run	SYNCHRON 1	20	7.96	0.09	1.2
	SYNCHRON 3	20	14.11	0.22	1.6

Type of Imprecision	Sample Type	n	Mean (mg/dL)	SD	%CV
DxC800-4118 Day to Day	MAS ChemTrak 1	1326	6.2	0.07	1.1
	MAS ChemTrak 3	1326	11.0	0.12	1.1
DxC800-4427 Day to Day	MAS ChemTrak 1	1318	6.2	0.07	1.1
	MAS ChemTrak 3	1306	11.0	0.12	1.1
DxC800-4449 Day to Day	MAS ChemTrak 1	1334	6.3	0.06	1.0
	MAS ChemTrak 3	1331	11.0	0.11	1.0

Comparative Performance

The data for a SYNCHRON LX System evaluated using the NCCLS Approved Guideline EP5-A appears in the table below.(15)

As determined by Beckman

NCCLS EP5-A Precision Estimate Method

Type of Imprecision	Sample Type	No. Systems	No. Data Points[a]	Test Mean Value (mg/dL)	EP5-A Calculated Point Estimates	
					SD	%CV
Within-run	Serum Control 1	1	80	7.69	0.16	2.0
	Serum Control 2	1	80	13.45	0.11	0.9
	Urine Control 1	1	80	8.59	0.18	2.1
	Urine Control 2	1	80	11.05	0.12	1.1
Total	Serum Control 1	1	80	7.69	0.17	2.2
	Serum Control 2	1	80	13.45	0.13	1.0
	Urine Control 1	1	80	8.59	0.20	2.3
	Urine Control 2	1	80	11.05	0.16	1.5

[a] The point estimate is based on the data from one system, run for twenty days, two runs per day, two observations per run on an instrument operated and maintained according to the manufacturer's instructions.

NOTICE

These degrees of precision and equivalency were obtained in typical testing procedures on a SYNCHRON LX® System and are not intended to represent the performance specifications for this reagent.

Additional Information

For more detailed information on UniCel DxC Systems, refer to the *Instructions for Use* and *Reference* manual.

References

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Prepared By	Date Adopted	Supersedes Procedure #
Michael Inn	October, 2000	Reformatted

Revision Date	Type of Revision	Revised by	Review/Annual Review Date	Reviewed By
			11/27/2000	G. Kost
			12/28/2001	G.Kost
			10/16/2002	G. Kost
			10/10/2003	S. Devaraj
			10/25/2004	S. Devaraj
			11/28/2005	G. Kost
			09/26/2006	G. Kost
			11/05/2007	G. Kost
			06/16/2008	G. Kost
			09/15/2009	G. Kost
			10/12/2010	G. Kost
12/2010	update	M. Inn	11/16/2011	G. Kost
06/22/2012	Added dialysate solutions as a sample type	M. Inn	06/22/2012	G. Kost
08/07/2013	No reference interval for spot/random urines	M. Inn	08/16/2013	G. Kost
			09/17/2013	G. Kost
04/03/2015	Updated 24-hour collection stability, controls, and pH adjustment	kdagang	04/05/2013	J. Gregg