Designation: F 2129 – 03~~4~~

# Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices[1]

This standard is issued under the fixed designation F 2129; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

## 1. Scope

1.1 This test method assesses the corrosion susceptibility of small, metallic, implant medical devices, or components thereof, using cyclic (forward and reverse) potentiodynamic polarization. Examples of device types that may be evaluated by this test method include, but are not limited to, vascular stents, filters, support segments of endovascular grafts, cardiac occluders, aneurysm or ligation clips, staples, and so forth.

1.2 This test method is used to assess a device in its final form and finish, as it would be implanted. These small devices should be tested in their entirety. The upper limit on device size is dictated by the electrical current delivery capability of the test apparatus (see Section 6). It is assumed that test methods, such as Reference Test Method G 5 and Test Method G 61 have been used for material screening.

1.3 Because of the variety of configurations and sizes of implants, this test method provides a variety of specimen holder configurations.

1.4 This test method is intended for use on implantable devices made from metals with a relatively high resistance to corrosion.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

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[1] This test method is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.15 on Material Test Methods.

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## 2. Referenced Documents

2.1 *ASTM Standards:* [2]

D 1193 Specification for Reagent Water

F 1828 Specification for Ureteral Stents

G 3 Practice for Conventions Applicable to Electrochemical Measurements in Corrosion Testing

G 5 Reference Test Method for Making Potentiostatic and Potentiodynamic Anodic Polarization Measurements

G 15 Terminology Relating to Corrosion and Corrosion Testing

G 61 Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements for Localized Corrosion Susceptibility of Iron-, Nickel-, or Cobalt-Based Alloys

G 102 Practice for Calculation of Corrosion Rates and Related Information from Electrochemical Measurements

## 3. Terminology

3.1 *Definitions:*

3.1.1 *potentiostat, n*—an instrument for automatically maintaining an electrode in an electrolyte at a constant potential or controlled potentials with respect to a suitable reference electrode (see Terminology G 15).

3.1.2 *potentiodynamic cyclic polarization (forward and reverse polarization), n*—a technique in which the potential of the test specimen is controlled and the corrosion current measured by a potentiostat. The potential is scanned in the positive or noble (forward) direction as defined in Practice G 3. The potential scan is continued until a predetermined potential or current density is reached. Typically, the scan is run until the transpassive region is reached, and the specimen no longer demonstrates passivity, as defined in Practice G 3. The potential scan direction then is reversed until the specimen repassivates or the potential reaches a preset value.

3.1.3 *scan rate, n*—the rate at which the controlling voltage is changed.

3.2 *Symbols:*

3.2.1 $E_b$ = *Breakdown or Critical Pitting Potential*—the least noble potential at which pitting or crevice corrosion or both will initiate and propagate as defined in Terminology G 15. An increase in the resistance to pitting corrosion is associated with an increase in $E_b$.

3.2.2 $E_r$ = *Rest Potential*—the potential of the working electrode relative to the reference electrode measured under virtual open-circuit conditions (working electrode is not polarized).

3.2.3 $E_{zc}$ = *Zero Current Potential*—the potential at which the current reaches a minimum during the forward scan.

3.2.4 $E_f$ = *Final Potential*—a preset potential at which the scan is stopped.

3.2.5 $E_i$ = *Initial Potential*—the potential at which the potentiostat begins the controlled potentiodynamic scan.

3.2.6 $E_p$ = *Protection Potential*—the potential at which the reverse scan intersects the forward scan at a value that is less noble than $E_b$. $E_p$ cannot be determined if there is no breakdown. Whereas, pitting will occur on a pit-free surface above $E_b$, it will occur only in the range of potentials between $E_p$ and $E_b$ if the surface is already pitted. The severity of crevice corrosion susceptibility increases with increasing hysteresis of the polarization curve, the difference between $E_b$ and $E_p$.

3.2.7 $E_v$ = *Vertex Potential*—a preset potential, at which the scan direction is reversed.

3.2.8 $i_t$ = *Threshold Current Density (mA/cm$^2$)*—a preset current density, at which the scan direction is reversed. Typically, the scan is reversed when a current density two decades higher than the current density at the breakdown potential ($E_b$) is reached.

## 4. Summary of Test Method

4.1 The device is placed in an appropriate deaerated simulated physiological solution, and the rest potential ( $E_r$) is monitored for 1 h. The potentiodynamic scan is then started at an initial potential ($E_i$) 100 mV more negative than $E_r$, and scanned in the positive or noble (forward) direction. The scan is reversed after the current density has reached a value approximately two decades greater than the current density measured at the breakdown potential. The reverse scan is stopped after the current has become less than that in the forward direction or the potential is 100 mV negative to $E_r$. The data is plotted with the current density in mA/cm$^2$ on the *x* axis (logarithmic axis) versus the potential in mV on the *y* axis (linear axis).

## 5. Significance and Use

5.1 Corrosion of implantable medical devices can have deleterious effects on the device performance or may result in the release of corrosion products with harmful biological consequences; therefore, it is important to determine the general corrosion behavior as well as the susceptibility of the devices to localized corrosion.

5.2 The forming and finishing steps used to create an implantable device may have significant effects on the corrosion resistance of the material out of which the device is fabricated. During the selection process of a material for use as an implantable device, testing the corrosion resistance of the material is an essential step; however, it does not necessarily provide critical data regarding device performance.

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For Annual Book of ASTM Standards volume information, refer to the standard's Document Summary page on the ASTM website.

5.3 To accommodate the wide variety of device shapes and sizes encountered, a variety of holding devices can be used.

5.4 Note that the method is intentionally designed to reach conditions that are sufficiently severe to cause breakdown and deterioration of the medical devices and that these conditions may not be necessarily encountered *in vivo*. The results of this corrosion test conducted in artificial physiological electrolytes can provide useful data for comparison of different device materials, designs, or manufacturing processes. However, note that this test method does not take into account the effects of cells, proteins, and so forth on the corrosion behavior *in vivo*.

## 6. Apparatus

6.1 *Potentiostat*, calibrated in accordance with Reference Test Method G 5.

6.2 *Working Electrode*, to be used as the test specimen, as described in Section ~~8.~~ 9. Its configuration and holder will depend on the type of specimen being tested, as described in Section 7. In all cases, the metallurgical and surface condition of a specimen simulating a device must be in the same condition as the device.

6.3 *Reference Electrode*—A saturated calomel electrode (SCE), as described in Reference Test Method G 5, shall be used as a reference electrode.

6.4 *Salt Bridge*, such as a Luggin probe, shall be used between the working and reference electrode, such as the type shown in Reference Test Method G 5.

6.5 *Auxiliary Electrodes*:

6.5.1 Two platinum auxiliary electrodes may be prepared from high-purity rod stock. The surfaces may be platinized, as per Reference Test Method G 5.

6.5.2 Alternatively, high-purity graphite auxiliary electrodes may be used in accordance with Reference Test Method G 5. Care should be taken to ensure that they do not get contaminated during a test.

6.5.3 The auxiliary electrode surface area should be at least four times greater than the sample surface area. Use of wire-mesh platinum might be more cost-effective than platinum cylinders when testing larger specimens or whole devices.

6.6 *Suitable Polarization Cell* , with a volume of about 1000 $cm^3$, equivalent to or similar to that recommended in Reference Test Method G 5. Furthermore, the cell needs to be appropriately sealed to avoid oxygen access and include a secondary bubbler for the release of exhaust gas without the back diffusion of oxygen.

6.7 *Water Bath*, or other heating appliance capable of maintaining the test solution temperature at 37 ± 1°C (see X1.6).

6.8 *Purge Gas Delivery System*, capable of delivering nitrogen gas at 150 $cm^3$/min.

## 7. Specimen Holders

7.1 There are a variety of holders that may be used in this test method. Each is designed for a specific type or class of device.

7.2 *Short wire or coil specimens* :

7.2.1 Specimens can be held suspended from a clamping device. For example, the threaded end of a Reference Test Method G 5 holder can be used to hold two stainless steel nuts. The wire test specimen is clamped between these nuts and bent so as to enter the test solution.

7.2.2 The surface area of the test specimen shall be calculated based on the length of wire or coil immersed in the test solution.

7.2.3 This type of holder exposes the specimen to the air-liquid interface, which is subject to localized crevice corrosion. Test specimens should be examined carefully after testing to ensure that there is no localized corrosion at or just below the interface.

7.2.4 If specimens show evidence of localized corrosion at the air-liquid interface, then the portion of the specimen passing across this interface shall be sealed with an impervious coating.

7.3 *Stents or cylindrical devices* :

7.3.1 A fixture for holding stents **(1)**[3] or alternative methods can be used to create an electrical connection.

7.3.2 The fixture consists of a cylindrical mandrel of the shape shown in Fig. 1.

7.3.3 The larger diameter end of the mandrel has a recessed thread that will accommodate a standard electrode holder described in Reference Test Method G 5. The smaller diameter end of the mandrel is machined to the maximum internal diameter of the stent to be mounted on it.

7.3.4 The stent is stress fit over the smaller end of the cylindrical mandrel.

7.3.5 A conductive epoxy is then used to bind the stress fit stent to the mandrel to obtain good electrical contact. This interface is sealed by applying a nonconductive masking agent over the interface. The whole fixture then is threaded on to an electrode holder in accordance with Reference Test Method G 5.

7.3.6 The surface area of the specimen shall be calculated based on the surface area of the stent in contact with the test solution.

## 8. Reagents

8.1 Reagent grade chemicals shall be used for this test method. Such reagents shall conform to the specifications of the

[3] The boldface numbers in parentheses refer to the list of references at the end of this standard.

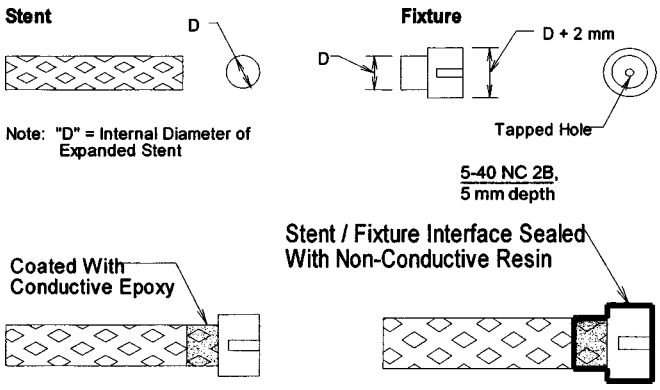


**FIG. 1 Diagram for Assembly of Stent-Holding Fixture**

Committee on Analytical Reagents of the American Chemical Society.[4]

8.1.1 The water shall be distilled or deionized conforming to the purity requirements of Specification D 1193, Type IV reagent water.

8.1.2 Unless otherwise specified, phosphate buffered saline (PBS) should be used as the standard test solution. A standard PBS formulation is given in Appendix X2, along with the formulations of two simulated bile solutions for testing implantable medical devices intended for use in the biliary system, the formulations of two artificial urine solutions for testing implantable indwelling materials intended for use in the urinary tract, and the compositions of two other commonly used physiological solutions.

8.1.3 The pH of the electrolyte should be adjusted based on the nature of the solution by the addition of NaOH or HCl. When the electrolyte is deaerated, its pH may change significantly if it is not sufficiently buffered. Several pH controlling methods are provided in Appendix X2.

~~8.1.4 High-purity nitrogen~~

8.1.4 Nitrogen gas ~~(~~ with a minimum purity of 99.999 %~~)~~ should be used for purging the test solution of oxygen.

## 9. Test Specimen

9.1 Unless otherwise justified, all samples selected for testing should be taken from finished, clinical-quality product. Cosmetic rejects or other nonclinical samples may be used if the cause for rejection does not affect the corrosion behavior of the device. Sterilization may be omitted if it can be demonstrated that prior sterilization has no effect on the corrosion behavior of the device.

9.1.1 Test specimens used for design parameter studies can be prepared as detailed in Reference Test Method G 5 for working electrodes, with the requirement that the metallurgical and surface conditions of the specimens are the same as the intended implantable medical device.

## 10. Procedure

10.1 Prepare the specimen such that the portion exposed to the test solution is in the same metallurgical and surface condition as the implantable form of the medical device being studied.

10.1.1 Calculate the total surface area of the specimen exposed to the solution in order to determine the current density (current per surface area) generated by the specimen during the test.

10.2 Prepare enough test solution to immerse the device and auxiliary electrodes and so to avoid any appreciable change in the solution corrosivity during the test through exhaustion of the corrosive constituents or by accumulation of corrosion products that may affect further corrosion. At a minimum, transfer 500 mL of electrolyte to a clean polarization cell. Measure and record the pH of the solution before and after each test.

10.3 Place the auxiliary electrodes, salt bridge probe, thermometer, and gas purge diffuser in the test chamber and bring the temperature of the test solution to 37 ± 1°C.

10.4 Purge the solution for a minimum of 30 min with nitrogen gas at a flow rate of 150 $cm^3$/min.

10.5 Gently immerse the test specimen in the test solution and connect it to a potentiostat. Continue the nitrogen purge throughout the test.

10.6 Monitor $E_r$ for 1 h.

10.7 At the end of 1 h of monitoring $E_r$, start the potentiodynamic scan in the positive or noble (forward) direction, as defined in Practice G 3. The scanning program should be set with the following parameters:

10.7.1 Starting or initial potential ( $E_i$) at 100 mV negative or active to $E_r$.

[4] *Reagent Chemicals, American Chemical Society Specifications* , American Chemical Society, Washington, DC. For suggestions on the testing of reagents not listed by the American Chemical Society, see *Analar Standards for Laboratory Chemicals*, BDH Ltd., Poole, Dorset, U.K., and the *United States Pharmacopeia and National Formulary*, U.S. Pharmacopeial Convention, Inc. (USPC), Rockville, MD.

10.7.2 A scan rate of either 0.167 mV/s or 1 mV/s should be used. Note that the scan rate may affect the breakdown potential of the device and the shape of the passive region of the polarization curve. Comparisons should not be made between test results using different scan rates, even if all other experimental parameters are held constant.

10.7.3 A current density threshold two decades greater than the current density recorded at breakdown can be used to reverse the voltage scan.

10.7.3.1 Alternatively, a reversing or vertex potential ($E_v$) of 1 V may be used to control the potentiostat (see X1.7).

10.7.4 The final potential ($E_f$) is 100 mV negative or active to $E_r$.

10.7.4.1 Alternatively, the scan may be manually stopped at potentials above $E_{rf}$ in cases in which a protection potential ($E_p$) is observed as a drop in current density below that of the passive current density or when no hysteresis loop is formed once the scan is reversed ($E_v$), indicating repassivation or oxygen evolution as shown in Fig. 2.

10.8 If control specimens are used, they shall be tested using the same method as the investigated devices.

## 11. Report

11.1 The report should contain a detailed description of the test specimen, including metallurgical and surface conditioning.

11.1.1 When specimens are not finished devices, for example, surrogates, the sample preparation should be described in detail.

11.2 A description of the test conditions should also be reported.

11.3 The following results should be presented in the report (see Fig. 2):

11.3.1 The rest potential ($E_r$);

11.3.2 The zero current potential ($E_{zc}$);

11.3.3 The breakdown potential ($E_b$);

11.3.4 The protection potential ($E_p$). In the absence of repassivation, the final potential ($E_f$) shall be reported instead of $E_p$. If no hysteresis loop is formed, the vertex potential ($E_v$) shall be reported instead of $E_b$ and $E_p$.

11.4 The pH of the solution should be reported before and after each test.

11.5 A copy of the cyclic polarization curve should be provided in the report.

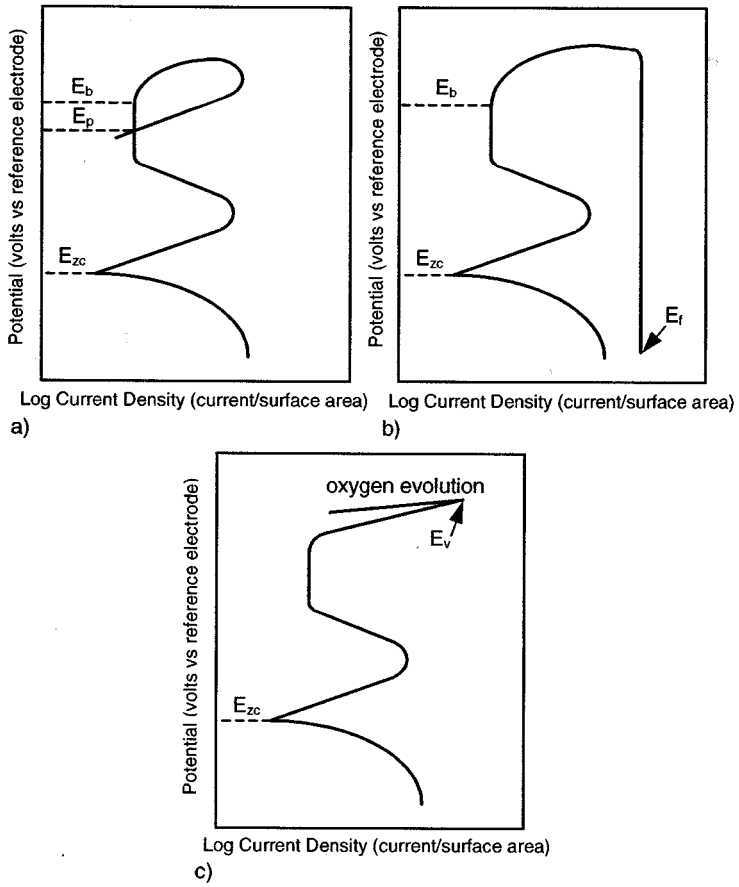


**FIG. 2 Schematic of Cyclic Potentiodynamic Curves Illustrating Corrosion Parameters: (*a*) Material That Exhibits a Protection Potential ($E_{zc}$, $E_b$, and $E_p$), (*b*) Material That Does Not Exhibit a Protection Potential ($E_{zc}$, $E_b$, and $E_f$), and (*c*) Material That Exhibits Oxygen Evolution at Its Surface ($E_{zc}$ and $E_v$).**

11.6 A generic description of the appearance of any corrosion observed on the specimen should be described. Photographic documentation may be appropriate.

## 12. Precision and Bias

12.1 The precision and bias of this method have yet to be established.

## 13. Keywords

13.1 corrosion; cyclic polarization; medical device testing; pitting potential; protection potential; rest potential

## APPENDIXES

**(Nonmandatory Information)**

### X1. RATIONALE

X1.1 This test method is a modification to Reference Test Methods G 5 and Test Method G 61, to provide information regarding the corrosion susceptibility of small, finished medical devices in physiologic solutions. It is based on the original work of Pourbaix et al. **(2)**, Wilde and Williams **(3)** and Wilde **(4)**, who showed that susceptibility to pitting was indicated by the breakdown potential ($E_b$) and susceptibility to crevice corrosion by the protection potential ($E_p$). These concepts were applied to orthopedic implant materials by Cahoon et al. **(5)**. The critical data point is the potential above which pits nucleate and grow, that is, $E_b$. The higher the $E_b$, the more resistant the metal is to pitting corrosion. Once the direction of the potential scan is reversed, and the potential begins to drop, a measure is attained of how quickly the pits will heal. If $E_p$ is high, that is, minimal hysteresis, then the metal is said to be very resistant to crevice corrosion. If there is some hysteresis, as in Fig. 2, then the metal may be susceptible to crevice corrosion; however, for materials or devices exhibiting a value of $E_b$ above the physiological range of potentials, the presence of hysteresis during the reverse scan does not necessarily indicate susceptibility to crevice corrosion under normal physiological conditions. If the metal does not repassivate until a potential below $E_r$ is reached, then it is very susceptible to crevice corrosion.

X1.2 While all currently used metallic biomaterials have well characterized corrosion properties, many device manufacturing processes may alter the cyclic polarization characteristics of finished implant devices. Furthermore, complex-shaped devices with corners, recesses, and other design irregularities may have a significant effect on localized current densities. It is of concern that finished device testing may create fluctuating current densities that cannot be normalized over the complex-shaped surface areas. In such cases, careful examination of test specimens after testing is necessary. For some devices, cyclic polarization may not provide useful information.

X1.3 Deaerating the solution with nitrogen gas before and during the test will lower the concentration of dissolved oxygen in the solution. This condition is necessary for the determination of the critical potentials $E_b$ and $E_p$, if their actual values are close to or lower than the rest potential in the presence of oxygen. Since the current measured during anodic polarization (the applied anodic current) is the difference between the anodic and cathodic currents, cathodic reduction of dissolved oxygen may cause an error in the measurement of the anodic current density (that is, a greater cathodic current will cause a smaller difference between anodic and cathodic currents). Consequently, this may result in artificially higher values of $E_b$ or $E_p$. Lowering the oxygen concentration moves the potential, at which the oxidation and reduction currents are equal, to a lower value. This allows determination of true values of $E_b$ or $E_p$ at potentials, at which the oxygen reduction current in the aerated solution would be significant.

X1.4 Since the absolute potential range that an implant should be able to withstand *in vivo* has not been established, absolute potential values such as the breakdown potential ($E_b$) and the protection potential ($E_p$) cannot ensure that a device has sufficient resistance to corrosion; thus, if possible, it is recommended that tests be performed on reference specimens, under the same conditions, for comparison. If used, the reference should consist of a device, which is similar to the investigated device and has a history of good corrosion resistance *in vivo*, is used in a similar environment or location, and is used to treat a similar disease.

X1.5 It is required to start the polarization 100 mV below the rest potential. Note that hydrogen might be introduced in the material during cathodic polarization; however, it has been shown in seawater conditions that cathodic potentials more noble than -1.0 V (SCE) at ambient temperature should not be detrimental for titanium and titanium alloys from a corrosion standpoint **(6)**.

X1.6 Corrosion cell setup and the methods of heating should be carefully chosen to avoid creating electromagnetic noise, which can create an offset bias in the system. It has been observed in laboratory experiments that this type of electrical bias can generate potential shifts in excess of 100 mV. A method of testing for this is to monitor the rest potential of a test sample with the heating system on, and then turn it off and monitor the system for any changes. Higher noise environments are suspected of reducing breakdowns.

X1.7 It is acknowledged that for the temperature and pressure conditions of the test cell in this test method that the Nernst equation predicts oxygen evolution at potentials slightly above 0.5 V (SCE). However, exceeding this potential does not equate to an immediate increase in current as a result of the generation of oxygen. In practice, even though oxygen evolution is thermodynamically favorable, the kinetics of the reaction is typically slow (the exchange current density is very low).

X1.7.1 There is a rationale for using the relatively high limit of 1 V (SCE) for potential reversal. Since the test conditions in this standard are not a perfect simulation of the conditions in the human body, polarizing the sample to this potential provides somewhat of a "safety margin." For instance, pitting initiation depends not only on the potential, but also on time. Hence, if the sample is polarized to a potential at which pits can be initiated, it may take a significant amount of time for pits to develop. At the scan rate of 1 mV/s, which is one of the scan rate options in this test method, the sample will be at the reversing potential for only a few seconds. Therefore, by scanning to 1 V (SCE) instead of 800 mV, corrosion processes are given a greater amount of time to initiate and develop.

## X2. COMPOSITION OF DIFFERENT PHYSIOLOGICAL ENVIRONMENTS

X2.1 Table X2.1 presents the composition of three different body fluids **(7)**.

X2.2 Table X2.2 presents the comparison of blood plasma composition with saliva and bile **(8)**.

X2.3 For reference purposes, the composition of different artificial physiological solutions used as electrolytes for corrosion testing is reported in Table X2.3.

X2.4 Since corrosion behavior of metals is often strongly affected by the pH of the electrolyte, it is important to ensure when using one of the solutions simulating blood or interstitial fluid, that the test is performed at the physiological pH value of 7.4. When simulated test solutions are prepared in the laboratory according to the compositions in Table X2.3, and the pH is adjusted to 7.4, deaeration causes a pH increase of about one to one and a half pH units, as a result of the displacement of carbon dioxide from the solution. To maintain pH 7.4 during a test, one of the following methods may be used: (*a*) pH adjustment after deaeration, using appropriate measures to avoid oxygen access; (*b*) use of a suitable buffer; however, for simulated physiological solutions other than the phosphate buffered saline recommended in Table X2.3 (which is adequately buffered with $Na_2HPO_4$ so that the pH does not change significantly with bubbling nitrogen over six hours) evidence must be provided or available that the buffer does not affect the corrosion behavior or parameters; (*c*) saturation of the electrolyte with a gas mixture containing $CO_2$ in conjunction with the appropriate amount of $NaHCO_3$ in the electrolyte. A $NaHCO_3$ concentration of about 1.45 g/L in Hanks solution or 1.35 g/L in Ringer's solution, together with a mixture of 5 % $CO_2$ in nitrogen provide effective buffering at pH 7.4, as well as bicarbonate and $CO_2$ concentrations close to physiological values.

X2.5 *Simulated Bile Solutions*:

X2.5.1 When testing implantable medical devices for use in the biliary system, two different simulated bile solutions are the following: (*1*) Ox bile—1000 mL distilled water and 100 g unfractionated dried bovine bile; heat at 37ºC and stir until the bile is in solution; pH of 6.5 desired; and (*2*) Human simulated bile[5]—1000 mL lactated Ringer's irrigation, 25.3 g cholic acid, 15.2 g chenodeoxycholic acid, 7.6 g deoxycholic acid, 9.5 g glycine, 2.5 g lithocholic acid, and 5.0 g sodium hydroxide pellets; heat at 37ºC and stir for at least 15 min; add small amounts of sodium hydroxide pellets (in addition to the amount listed in the primary

[5] Based on Guidant Corporation internal test solution for simulated human bile, Guidant Corporation, Vascular Intervention Group, Santa Clara, CA, 2003.

**TABLE X2.1 Composition of Selected Components of Three Body Fluids[A]**

| Component | Interstitial Fluid, mg/L | Synovial Fluid, mg/L | Serum, mg/L |
|---|---|---|---|
| Sodium | 3280 | 3 127 | 3 265 |
| Potassium | 156 | 156 | 156 |
| Calcium | 100 | 60 | 100 |
| Magnesium | 24 | - | 24 |
| Chloride | 4042 | 3 811 | 3 581 |
| Bicarbonate | 1892 | 1 880 | 1 648 |
| Phosphate | 96 | 96 | 96 |
| Sulfate | 48 | 48 | 48 |
| Organic acids | 245 | - | 210 |
| Protein | 4144 | 15 000 | 66 300 |

[A] Based on data from *Documenta Geigy Scientific Tables*, L. Diem and C. Lentner, Eds., 7th ed., Ciba-Geigy.

**TABLE X2.2 Composition of Blood Plasma, Saliva, and Bile**

| Component | Blood Plasma, mg/L | Saliva, mg/L | Bile, mg/L |
|---|---|---|---|
| pH | 7.35–7.45 | 5.8–7.1 | 7.8 |
| Sodium | 3128–3335 | 240–920 | 3082–3588 |
| Potassium | 140–220 | 560–1640 | 156–252 |
| Chloride | 3430–3710 | 525–1085 | 2905–3850 |
| Bicarbonate | 1403–1708 | 122–793 | 2318 |

**TABLE X2.3 Composition of Simulated Physiological Solutions at a pH of 7.4**

| | Phosphate Buffered Saline[A] g/L | Ringer's,[B] g/L | Hanks,[C] g/L |
|---|---|---|---|
| NaCl | 8.0 | 8.6 | 8.0 |
| $CaCl_2$ | | 0.33 | 0.14 |
| KCl | 0.2 | 0.3 | 0.4 |
| $MgCl_2$ $6H_2O$ | | | 0.10 |
| $MgSO_4$ $7H_2O$ | | | 0.10 |
| $NaHCO_3$ | | | 0.35 |
| $Na_2H_2PO_4$ | 1.15 | | |
| $Na_2HPO_4.12H_2O$ | | | 0.12 |
| $KH_2PO_4$ | 0.2 | | 0.06 |
| Phenol red | | | 0.02 |
| Glucose | | | 1.00 |

[A] Sigma-Aldrich Co., 2002
[B] The Pharmacopeia of the United States, Twenty-Sixth Revision, and the National Formulary, Twenty-First Editions.
[C] J.H. Hanks and R.E. Wallace, *Proc. Soc. Exp. Biol. Med.* 71, 196, (1949).

mix) as needed to completely dissolve the acids; add a few drops of nitric acid and let stir until the precipitate that forms completely dissolves; pH of 8.5 ± 0.2 desired (repeat adding nitric acid until the desired pH is obtained).

X2.5.2 Investigation has shown that the composition of bile is dynamic and modulated through a complex series of feedback mechanisms. An evaluation of the literature showed that no single pH could be utilized for testing. Rather, measured pH values range from 6.5 to 8.5 **(9, 10)**. The two simulated bile solutions listed in this test method encompass these values.

X2.6 *Artificial Urine Formulations*:

X2.6.1 *Formulation Number 1* **(11)**:

X2.6.1.1 Components per litre of solution:

| | |
|---|---|
| NaCl | 6.17 g |
| $NaH_2PO_4$ | 4.59 g |
| $Na_3$Citrate | 0.944 g |
| $MgSO_4$ | 0.463 g |
| $Na_2SO_4$ | 2.408 g |
| KCl | 4.75 g |
| $CaCl_2$ | 0.638 g |
| $Na_2$Oxalate | 0.043 g |
| Distilled water | bring to 1 L volumetrically |

NOTE X2.1—Add the above salts to a 1000 mL volumetric flask, then add the distilled water for a total volume of 1000 mL.
NOTE X2.2—Adjust pH to 5.5 to 6.5 range with a 1 *N* solution of $NH_4OH$ or 1 *N* $H_4Cl$.

X2.6.2 *Formulation Number 2* **(12)**:

X2.6.2.1 Components per litre of solution:

| | |
|---|---|
| Urea | 25.0 g |
| NaCl | 9.0 g |
| Disodium hydrogen orthophosphate, anhydrous | 2.5 g |
| Potassium dihydrogen orthophosphate, anhydrous | 2.5 g |
| $NH_4CL$ | 3.0 g |
| Creatinine | 2.0 g |
| Sodium sulfite, hydrated | 3.0 g |
| Distilled water | bring to 1 L volumetrically |

## REFERENCES


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