(104) J. T. Carstensen and M. N. Musa, *J. Pharm. Sci.*, **61**, 1112(1972).

(105) E. R. Garrett and T. E. Eble, *J. Amer. Pharm. Ass., Sci. Ed.*, **43**, 385(1954).

(106) E. R. Garrett, *ibid.*, **43**, 536(1954).

(107) T. E. Eble and E. R. Garrett, *ibid.*, **43**, 539(1954).

(108) K. Pfoertner and J. P. Weber, *Helv. Chim. Acta*, **55**, 921(1972).

(109) R. Hoffmann and R. B. Woodward, "The Conservation of Orbital Symmetry," Verlag Chemie, New York, N.Y., 1970, pp. 52, 80, and references cited therein.

(110) T. Kanzawa and S. Kotaku, *J. Pharm. Soc. Jap.*, **73**, 1357(1953).

(111) K. J. Keuning, *Pharm. Weekbl.*, **100**, 889(1965).

(112) C. Knobler, C. Romers, P. B. Braun, and J. Hornstra, *Acta Crystallogr.*, **28B**, 2097(1972).

(113) D. C. Hodgkin, M. S. Webster, and J. D. Dunitz, *Chem. Ind.*, **1957**, 1148.

(114) J. K. Guillory and T. Higuchi, *J. Pharm. Sci.*, **51**, 100(1962).

(115) J. G. Baxter and C. D. Robeson, *J. Amer. Chem. Soc.*, **64**, 2407(1942).

(116) R. Dobrucki, *Farm. Pol.*, **27**, 353(1971); through *Chem. Abstr.*, **75**, 80230(1971).

(117) E. I. Funkelstein, E. V. Alekseev, and E. I. Kozlov, *Zh. Org. Khim.*, **10**, 1027(1974).

(118) S. Bhattacharyen, *J. Inst. Chem. (India)*, **41**, 33(1969).

(119) B. Leszczynska, S. Halina, and H. Krowczynska, *Cesk. Farm.*, **19**, 109(1970).

(120) Y. Ogata, Y. Kosugi, and K. Tomizowa, *Tetrahedron*, **70**, 5939(1970).

(121) D. Lerner, J. C. Mani, and M. Mousseren-Canet, *Bull. Soc. Chem. Fr.*, **1970**, 1968.

(122) M. Mousseren-Canet, J. C. Mani, C. Farie, and D. Lerner, *C. R., Ser. C*, **262**, 153(1966).

(123) W. E. Oberhansli, H. P. Wagner, and O. Isler, *Acta Crystallogr.*, **B30**, 161(1974).

(124) A. I. Kitaigorodsky, "Molecular Crystals and Liquid Crystals," Academic, New York, N.Y., 1973, p. 168.

(125) R. S. Miller, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, **3**, 2784(1971).

(126) J. Dekher and P. A. Ark, *Antibiot. Chemother.*, **9**, 327(1949).

(127) J. E. Tingstad and E. R. Garrett, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 352(1960).

ACKNOWLEDGMENTS AND ADDRESSES

RESEARCH ARTICLES

Glass for Parenteral Products: A Surface View Using the Scanning Electron Microscope

T. J. ROSEMAN *ˣ, J. A. BROWN ‡, and W. W. SCOTHORN *

Abstract □ The scanning electron microscope was utilized to explore the internal surface of glass ampuls and vials used in parenteral products. The surface topography of USP Type I borosilicate glass containers was viewed after exposure to "sulfur," ammonium bifluoride, and sulfuric acid treatments. The scanning electron micrographs showed startling differences in the appearance of the surface regions. "Sulfur treatment" of ampuls was associated with a pitting of the surface and the presence of sodium sulfate crystals. The sulfur treatment of vials altered the glass surface in a characteristically different manner. The dissimilarity between the surface appearances was attributed to the method of sulfur treatment. Ampuls exposed to sulfuric acid solutions at room temperature did not show the pitting associated with the sulfur treatment. Scanning electron micrographs of ammonium bifluoride-treated ampuls showed a relief effect, suggesting that the glass was affected by the bifluoride solution but that sufficient stripping of the surface layer did not occur to remove the pits associated with the sulfur treatment. Flakes emanating from the glass were identified with the aid of the electron microprobe. Scanning electron micrographs showed that these vitreous flakes resulted from a delamination of a thin layer of the glass surface. It is concluded that the scanning electron microscope, in conjunction with other analytical techniques, is a valuable tool in assessing the quality of glass used for parenteral products. The techniques studied should be of particular importance to the pharmaceutical industry where efforts are being made to reduce the levels of particulate matter in parenteral dosage forms.

Keyphrases □ Glass—ampuls and vials, internal surface, effect of sulfur, ammonium bifluoride, and sulfuric acid treatments, scanning electron micrographs □ Scanning electron microscopy—internal surface, glass ampuls and vials, effect of sulfur, ammonium bifluoride, and sulfuric acid treatments □ Parenteral containers—glass, scanning electron micrographs, surface view □ Containers, glass—surface, effects of sulfur, ammonium bifluoride, and sulfuric acid treatments, scanning electron micrographs

Glass vials and ampuls are the primary containers for parenteral products. The general inertness of glass has been the basis for its use since it is desirable for pharmaceutical products to have acceptable physical and chemical stability for extended periods, *i.e.*, up to 5 years. This report is concerned with the quali-

Table I—Electron Microprobe Analysis of Four Flakes

Element	Sample A, %	Sample B, %	Sample C, %	Sample D, %
Silicon	25—30	35—45	30—35	25—30
Aluminum	10—12	3—5	8—10	10—11
Potassium	4—6	Not detected	3—5	3—4
Calcium	1—2	Not detected	Not detected	1—2
Boron	3—8	2—6	3—8	Present
Sodium	1—3	1—2	1—3	1—2

ty of glass as viewed with the scanning electron microscope and its relationship to the formation of vitreous flakes in sterile solutions. The presence of particulates or foreign matter is undesirable in any product; but in the case of intravenously administered dosage forms, it must be avoided. Since the drug solution is administered directly into the vascular system, the presence of particulate matter is potentially harmful to the patient (1).

History demonstrates that glass has been an acceptable container for parenteral products. However, glass is not completely inert; it is attacked by different solution media (2–5) and its performance is affected by the method of manufacture of the final container (6). Specifications are set forth in the USP (7) for a water attack and a powdered-glass test. The USP test, however, does not guarantee that glass will withstand attack when in direct contact with a product. Physical inspections of the final dosage form are necessary to assure that no foreign material is present.

Three types of glass intended for parenteral products are set forth in the USP with corresponding test limits for titratable basicity. Type I is a highly resistant borosilicate glass, while Types II and III are "sulfur-treated" and "non-sulfur-treated" soda lime glass, respectively. The powdered-glass test is used to measure the overall degree of alkalinity, while the water attack test is used to measure surface alkalinity of sulfur-treated Type II glass. Since the inside surface of Type II glass is dealkalized by the sulfur treatment, the effectiveness of the treatment cannot be determined by powdering the glass and the water attack test is used (8).

Particulate matter can be derived from intrinsic sources other than glass such as stopper components, drug–stopper interactions, and bulk drug itself and from extrinsic sources such as unclean containers having lint or other contaminants attached to them. The constraints on parenteral dosage forms were reviewed recently (9), and an official standard for particulate matter in large-volume parenteral solutions is in the British Pharmacopoeia (10). Because the product is in intimate contact with the glass container, the quality of the glass can be an important factor in the formation of particulates. Glass of poor or variable quality can contribute particles that are seen with standard inspection techniques or even smaller particles, i.e., less than 20 μm, which can be observed with more critical physical inspection systems.

The technology for quantitating (11–13) particulates and the automated detection (14–16) of them in containers appears to be advancing rapidly. It is believed that a greater understanding of the topography of the glass surface will be helpful in developing formulations to meet future standards. This paper explores the use of the scanning electron microscope to provide insight into the characteristics of the glass surface. Special emphasis is given to treatment processes such as "sulfuring" and ammonium bifluoride.

EXPERIMENTAL

All glass ampuls[1] and vials[1] employed were of Type I USP (7) borosilicate composition. The sulfur-treated containers were identical in composition, but they were exposed to the sulfuring process. Samples were obtained for scanning electron microscopic analysis by cutting approximately 1.27 × 1.27-cm sections with a circular saw. Unless otherwise specified, sections were cut approximately 0.8 cm above the bottom of the container.

Each sample was then washed several times with distilled water and analyzed. The washing procedure removed all traces of the sodium sulfate bloom present on the sulfur-treated containers. One sample was fractured and not washed so that the surface could be viewed in the presence of sodium sulfate.

A bifluoride wash of ampuls was performed with 5 and 20% aqueous ammonium bifluoride[2] solutions, prepared with distilled water. For non-sulfur-treated ampuls, the ammonium bifluoride solution was injected into inverted ampuls for 30 sec, followed by a 15–30-sec rinse with filtered deionized water. Bifluoride wash of the sulfur-treated ampuls was performed in a slightly different manner. Upright ampuls were filled completely with solution for 30 sec and then rinsed for 30 sec with distilled water. In each experiment, control ampuls were prepared by treatment with distilled water.

The samples for scanning electron microscope analysis were mounted on double-back tape[3] on the specimen stubs with the inside surface up. They were then placed in a vacuum evaporator and shadowed with gold to give surface conductivity. This procedure is necessary because the electron beam in the microscope[4] charges nonconducting materials, and the charge then repels the electron beam.

To examine the details of the surface properly, the samples were viewed at an oblique angle. The angle on all pictures was 70° unless otherwise noted. Some photographs were obtained at 45° for better detail. This angle is the angle of the specimen to the horizontal, with the electron beam impinging perpendicular to the horizontal. The net result is that the beam impinges on the specimen at 20° in the case of the angle designated 70° and at 45° in the case of the angle designated 45°. With the 70° angle, a shallow depth of field results in distorted shapes; e.g., a circle appears as an ellipse.

The vitreous flakes were isolated from solution by the following procedure. A 5-ml ampul containing an aqueous parenteral solution was selected based upon the visual observance of flakes in the solution. The ampul was opened by melting off the ampul tip with an oxypropane flame. This procedure eliminated the shower of glass fragments commonly encountered when an impul is opened in the conventional manner, i.e., breaking. The opening of the ampul, as well as the technique of isolating a single flake, was performed under U.S. Government Class 100 clean room conditions (17).

The open ampul was mounted in an upright fashion, with a strong beam of light[5] illuminating the ampul parallel to its longest axis. Under these conditions, the flakes appeared to twinkle or glitter as reflected light as they reached the observer's position, which was perpendicular to the axis of the light beam. By using a particulate-free capillary pipet, fitted with a dropper bulb, a single flake was aspirated into the pipet. The flake, with accompanying
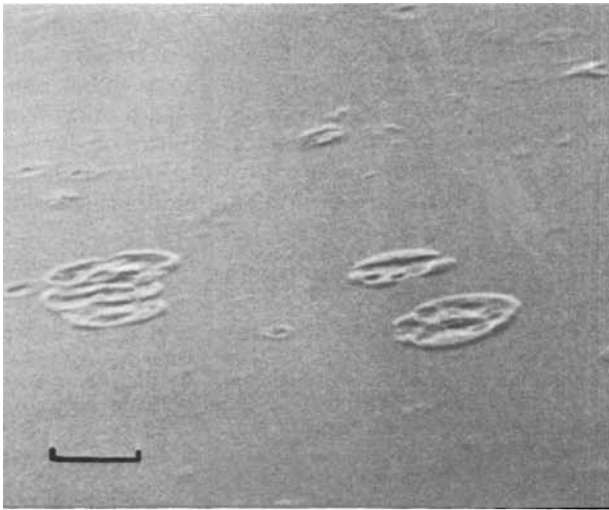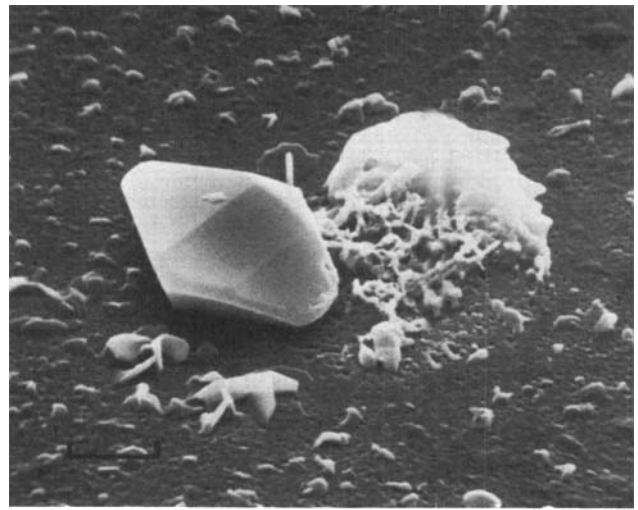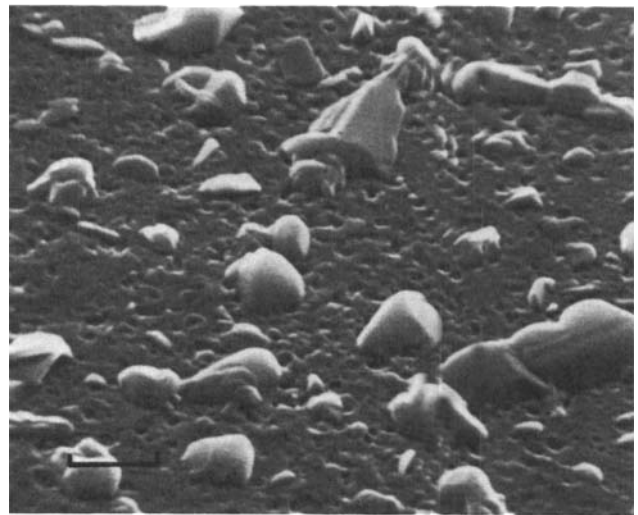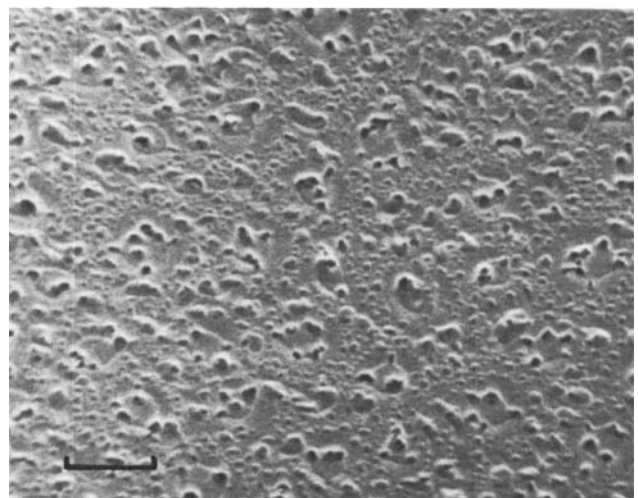
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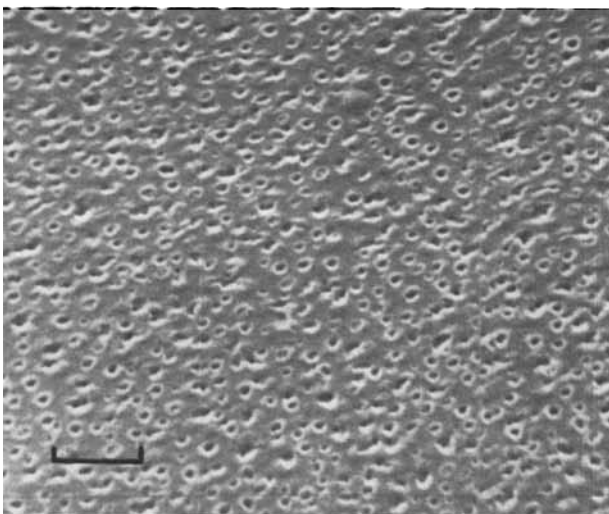
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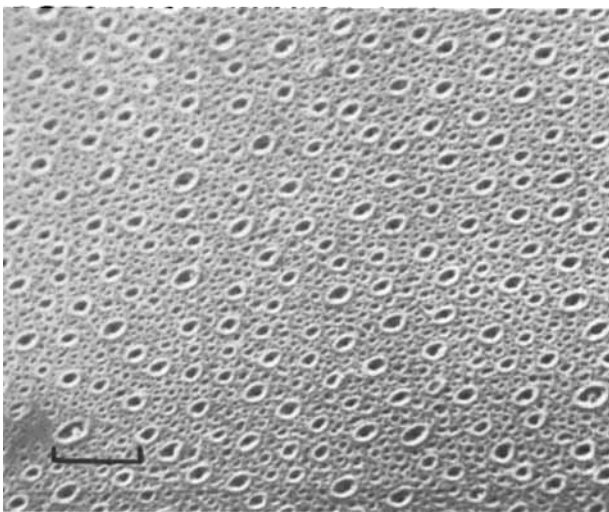
C

Figure 1—Effect of sulfur treatment on the surface of glass ampuls (10,000× magnification; scale marker = 1 µm). Key: A, non-sulfur-treated 5-ml ampul; B, sulfur-treated 5-ml ampul (45° angle); and C, sulfur-treated 8-ml ampul (45° angle).

A

B

C

Figure 2—Surface view of a sulfur-treated ampul which was not washed prior to obtaining the scanning electron micrographs. Key: A, 5000× magnification, scale marker = 2 µm; B, 10,000× magnification, scale marker = 1 µm; and C, control ampul which was washed (10,000× magnification; scale marker = 1 µm). Note the absence of sodium sulfate crystals on the surface of the control ampul.
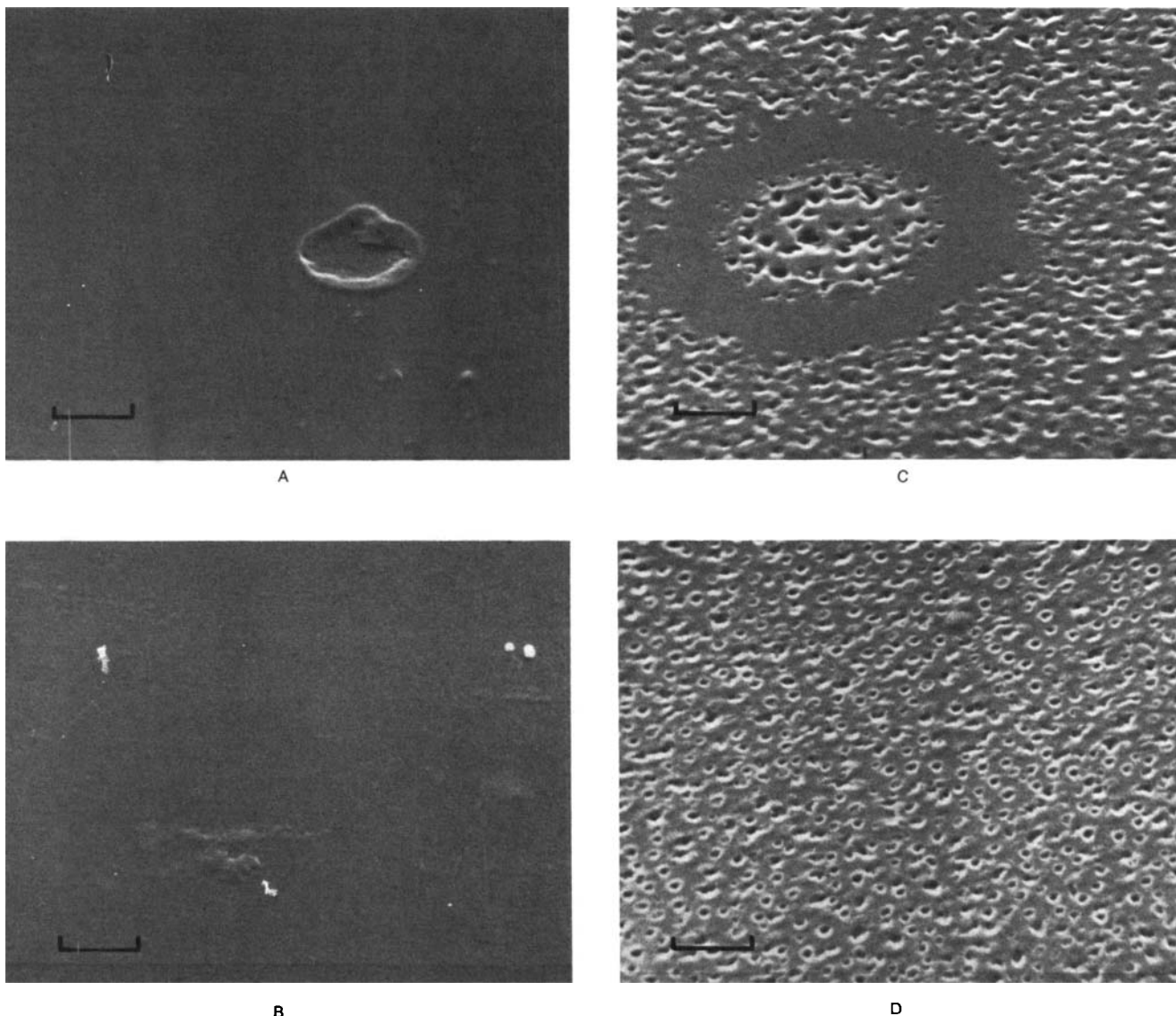
Figure 3—*Comparison of sulfuric acid soak with sulfur treatment of 5-ml ampuls (10,000× magnification; scale marker = 1 μm). Key: A, non-sulfur-treated control; B, non-sulfur treated but soaked in 50% (v/v) H_2SO_4 for 2 hr at room temperature; C, sulfur-treated control (45° angle); and D, sulfur treated and soaked in 50% (v/v) H_2SO_4 for 2 hr at room temperature.*

solution, was placed in the center of a scrupulously cleaned 2.54 × 7.62-cm glass microslide.

The preceding operations were performed with no supplemental magnification aiding the operator. The following operations were performed using a stereomicroscope[6] between 25 and 50 times magnification. By using moistened filters[7,8], the solution surrounding the flake was carefully wisked away from the flake. The procedure was repeated two times using a drop of filtered distilled water to wash the flake. After the flake was allowed to air dry in a stream of filtered air (high efficiency particulate air) (17), it was affixed to the glass microslide with a tiny drop of flexible collodion in isoamyl acetate. The collodion film provided a satisfactory bond.

The flakes for electron microprobe analysis were transferred to a beryllium plate with a tungsten needle. Since beryllium does not produce a detectable signal of its own when subjected to electron microprobe[9] analysis, the background is low. The flakes were glued to the beryllium with a thin film of collodion. Because boron is a difficult element to detect in low amounts, the accelerating voltage

was dropped to 10 kv (from the usual 25 kv) and the specimen current was boosted from 200 namp (usually 10 namp). The light element spectrometer was then *manually turned*, using a boron nitride standard, and measurements were done. Standard and sample readings were repeated many times to minimize error.

RESULTS AND DISCUSSION

Ampuls—The effect of sulfur treatment on the inside surface of a glass ampul is shown in Fig. 1. After the sulfuring process was performed, many circular pits of uniform dimensions (<0.5 μm in diameter) were noted. The untreated ampul showed no pits, but some irregular areas were noted.

The sulfuring process was performed after the ampul was formed but before it entered the lehr. The procedure involves the injection of a small volume of a dilute solution of ammonium sulfate into the ampul. Vaporization of the ammonium sulfate occurs in the lehr, which is maintained at an elevated temperature [~593° (~1100° F)]. The *in situ* formed vapor reacts with the glass to neutralize its surface alkalinity, yielding sodium sulfate crystals which appear on the surface (18).
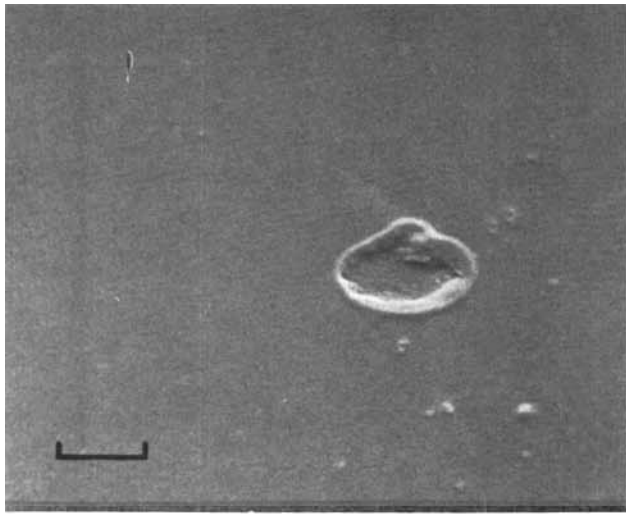
A literature survey indicates that the sulfur treatment of glass was mentioned as early as 1930 (19). In the case of soda lime glasses, this reaction has been well studied (20, 21). During the reaction, the surface composition of the glass is altered as hydrogen ions

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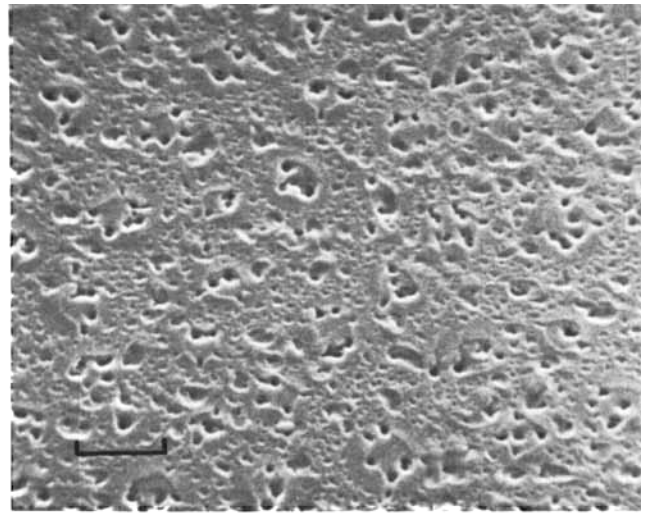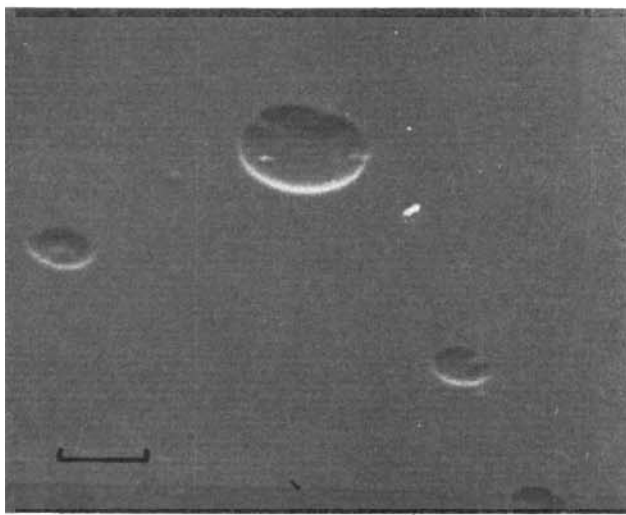
Figure 4—Effect of bifluoride treatment on non-sulfur-treated 5-ml ampuls (10,000× magnification; scale marker = 1 μm). Key: A, nontreated control; B, 5% ammonium bifluoride; and C, 20% ammonium bifluoride.
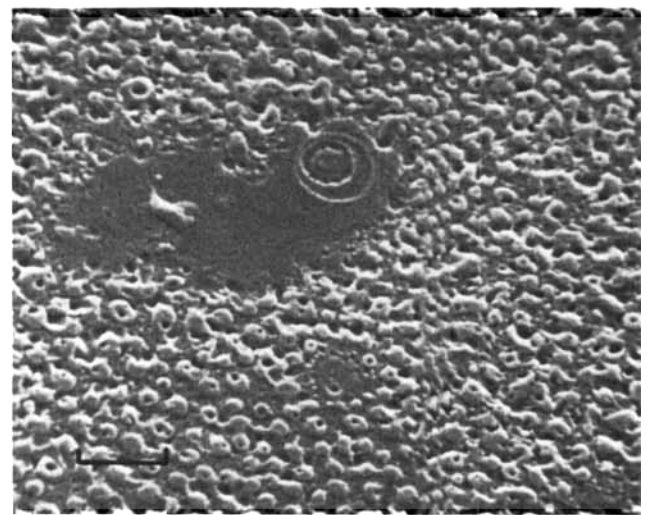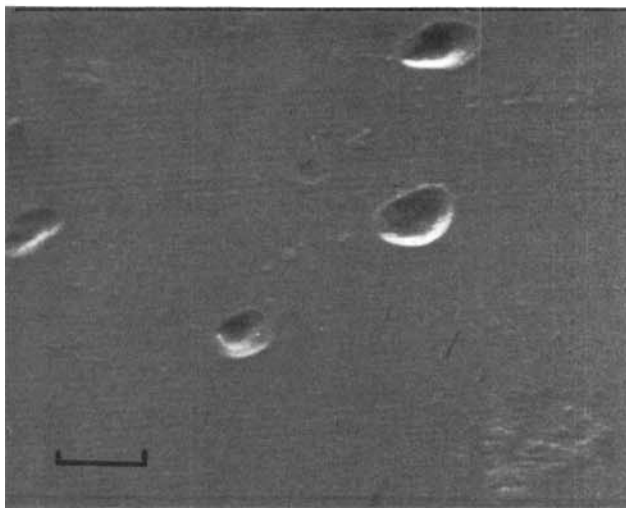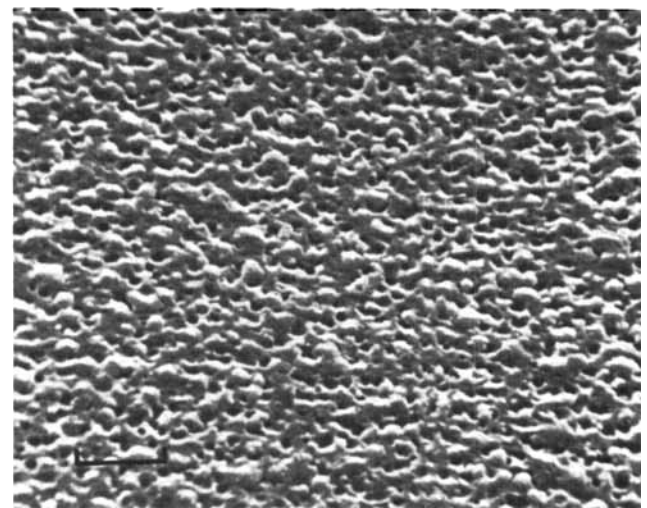
Figure 5—Effect of bifluoride treatment on sulfur-treated 5-ml ampuls (10,000× magnification; scale marker = 1 μm). Key: A, sulfur-treated control; B, 5% ammonium bifluoride; and C, 20% ammonium bifluoride.

from water exchange for the depleted sodium ion; it has been shown that this "hydrogen glass" can undergo a dehydration process (loss of water), yielding a compacted layer of glass on the surface. The rate of diffusion of sodium through this compacted layer is slower than through the parent glass, and sodium depletion rates have been analyzed according to Fick's law of diffusion (20). As a result of this process, attack by water is reduced and there is an improvement of the chemical durability of the glass toward neutral and acidic solutions and to weathering. In addition, it was reported that the mechanical strength of the glass can increase (21). Interestingly, these studies were performed with soda lime glass while sulfur-treated borosilicate glass received little attention.

In Fig. 1, the exact mechanism for the alteration of the surface topography with a sulfur treatment is not known. However, it may be a consequence of the formation of a crystalline material (e.g., sodium sulfate) at elevated temperatures during the annealing step. If this is the case, treatment with an acidic gas such as hydrogen chloride should result in the formation of a sodium chloride bloom with a similar pitting pattern.

Figure 2 shows the surface of a sulfur-treated glass ampul before rinsing with distilled water. The presence of crystalline material on the surface is noted, with pits below the crystals. A similar pattern of pitting is seen in Fig. 1. Energy-dispersive X-ray analysis of these well-defined crystals indicated that they contained a high content of sodium and sulfur and probably were sodium sulfate, as noted with soda lime glass (18).

Figures 3–5 show the effect of different room temperature treatments. For the regions under consideration, the sulfuric acid soak (Fig. 3) had no apparent effect on either sulfur-treated or non-sulfur-treated ampuls. In contrast, ammonium bifluoride treatment of the glass resulted in a noticeable change. Figure 4 indicates that the bifluoride treatment of non-sulfur-treated ampuls relieves the appearance of the surface irregularities. Figure 5, however, shows this effect more dramatically, where the sulfur-treated ampuls were bifluoride treated. Here the pits, associated with the sulfur treatment, have a sharper appearance, which is not observed with sulfur-treated glass that is not bifluoride treated.

The action of the ammonium bifluoride seems to be consistent with the concept that a thin surface layer of the glass is removed; however, the bifluoride treatment did not penetrate to a sufficient depth to remove the pits associated with the sulfur treatment. Hinson (22) reported that an ammonium bifluoride wash of ampuls is superior to conventional wash methods. Based upon the results of the USP water attack test, it was concluded that bifluoride treatment is equivalent to a good sulfur treatment of USP Type I borosilicate glass. Although the chemical resistance as measured by the water attack test compared favorably, the mechanisms of action of the two treatments are dissimilar, with corresponding differences being observed with the scanning electron microscope.

Vials—Figure 6 presents a comparison of a non-sulfur-treated vial and treated vials. The surface of the nontreated vial was essentially smooth, as previously noted with ampuls (Fig. 1). The sulfur-treated vials, however, had pitting that was characteristically different than the pitting noted with ampuls (Fig. 7), and vial-to-vial variability was noted (Fig. 6). Scanning electron micrographs of numerous samples suggest that there is indeed a greater variability in the surface appearance of vials than ampuls.

This variability with vials and the difference between ampuls and vials are believed to be a consequence of the dissimilar treatment processes for the two containers. As mentioned previously, ampuls were treated with an aqueous solution of ammonium sulfate. Vials were treated with a mixture of sulfur dioxide and sulfur trioxide gases because the higher temperature of the glass in forming the vial is not conducive to treatment with an aqueous solution. Some variability in dissolved silica or titratable alkalinity has been reported with sulfur-treated soda lime bottles (18). It is possible that more variability occurs by injection of a gas because it is more difficult to confine in the container and moisture conditions are not as well controlled. The importance of gas composition, temperature, and time with respect to the sulfur treatment has been pointed out (21), and the influence of moisture on the sulfuring process was discussed previously (23).

Flake Formation—Glass is attacked by numerous reagents other than strong alkali or hydrofluoric acid. Among these substances are sodium citrate, sodium gluconate, and other salts of β-hydroxy acids (4) along with inorganic phosphate solutions (2). Attack on glass can be quantitated by various methods as outlined in
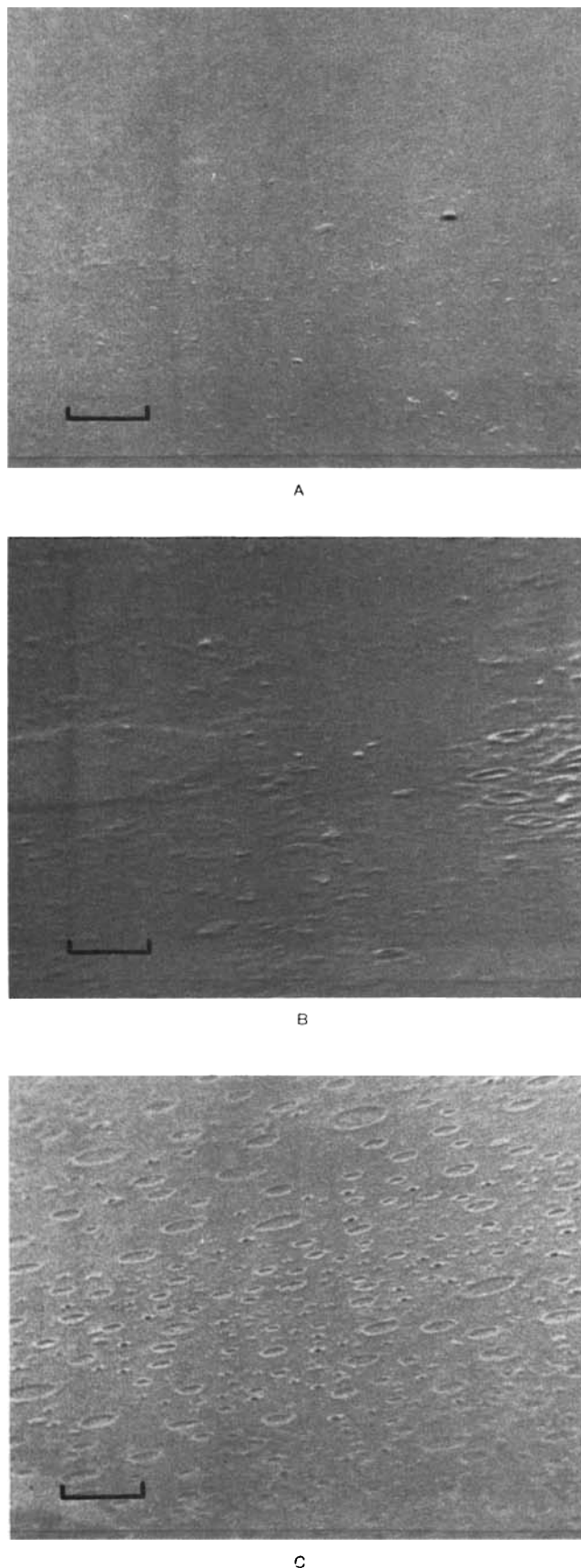

A

B

C

Figure 6—Effect of sulfur treatment on the surface of 10-ml vials and vial-to-vial variability (10,000× magnification; scale marker = 1 µm). Key: A, untreated vial; B, treated Vial 1; and C, treated Vial 2.
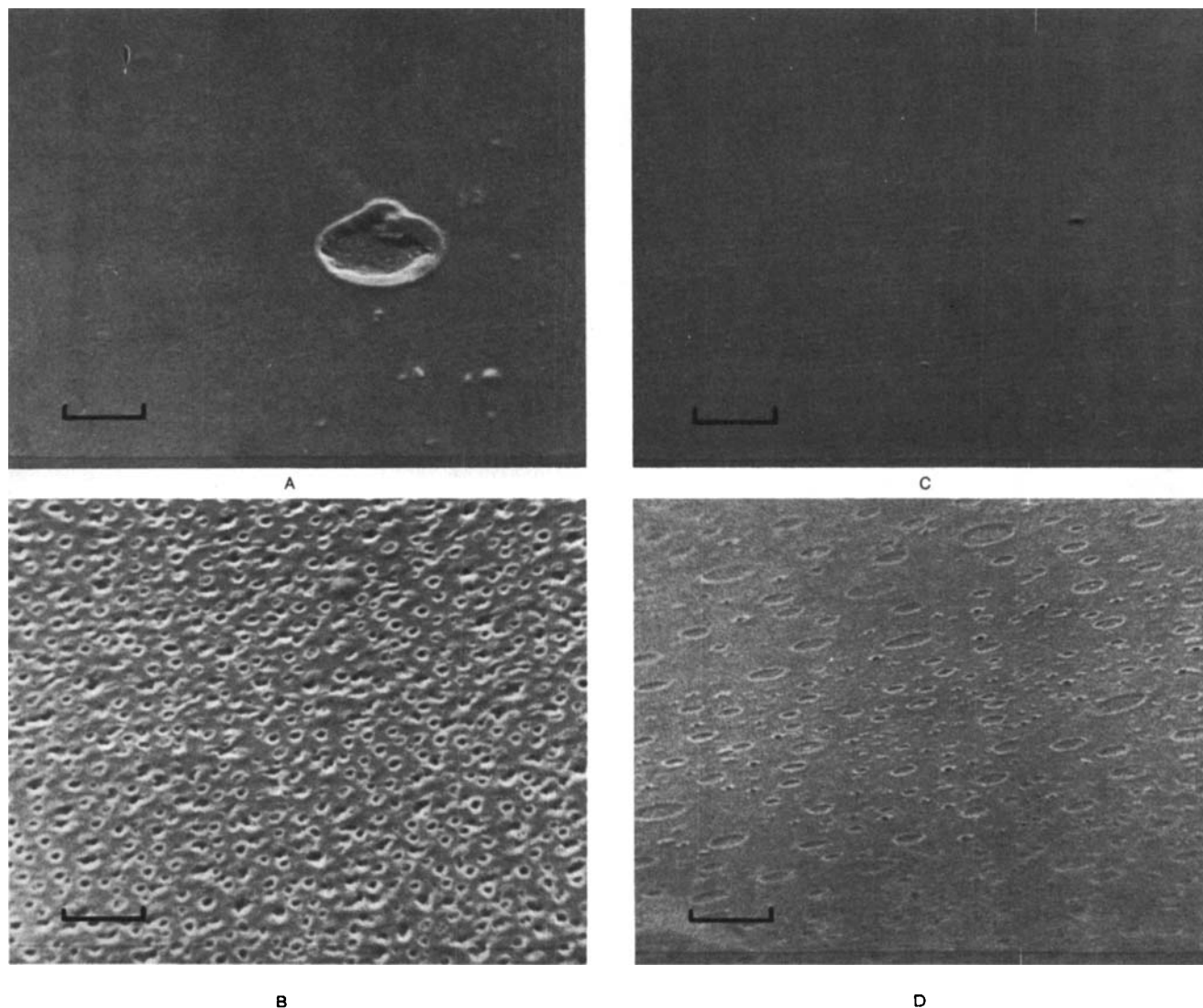
Figure 7—*Comparison of sulfur treatment on 5-ml ampuls and 10-ml vials (10,000× magnification; scale marker = 1 μm). Key: A, non-sulfur-treated ampul; B, sulfur-treated ampul (45° angle); C, non-sulfur-treated vial; and D, sulfur-treated vial.*

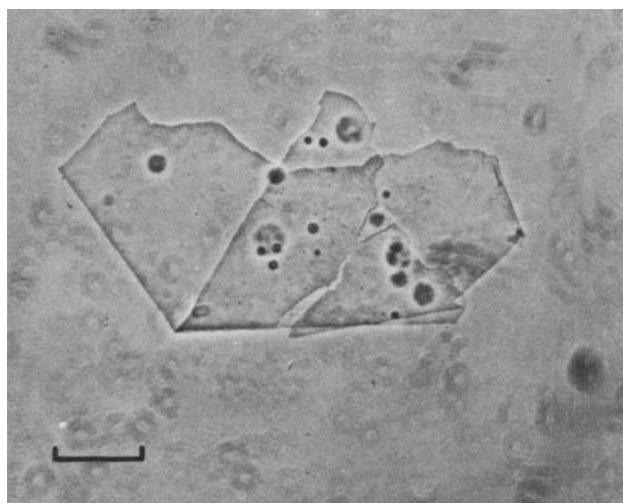**Figure 8**—*Bright-field phase contrast photomicrograph of a vitreous flake (312.5× magnification; scale marker = 45 μm).*

a review article (3), where it was pointed out that the chemical resistance of glass is dependent upon its chemical composition, the temperature of the attacking agent, the length of contact, and the previous history of the glass (i.e., method of production, annealing, special treatments, and storage).

Generally, there does not appear to be a direct correlation between the attack of glass as measured by the presence of dissolved silica and the formation of glass-related flakes in solution upon storage. The formation of these flakes after exposure to various solutions is documented (4, 24). The undesirability of foreign particulate matter in parenteral solutions was discussed earlier, but little information about the region of the glass from which these flakes emanate is available, and scanning electron microscope data are lacking. Products of disintegrated glass have been described as soft, hydrous, gel-like siliceous films (25) and have been reported to consist mainly of silicon dioxide (3). The composition of the flakes depends upon the type of glass employed and its history. Therefore, it is not possible to relate conclusively the following data with previous work, but flakes similar to the ones to be described have been noted under various conditions in this laboratory after storage of solutions in ampuls.

Figure 8 shows a photograph, taken through the optical microscope, of a flake after removal from a solution stored in an ampul. The flake is colorless and plate-like (<1 μm in thickness), does not melt below 300°, and exhibits a refractive index similar to glass. All flakes observed in the solution had similar characteristics, but their size ranged from a few micrometers to hundreds of micrometers in length. The electron microprobe analysis of four flakes is given in Table I.

Because the flake is composed of elements similar to those of the glass, an ampul was broken and a fragment was analyzed in an
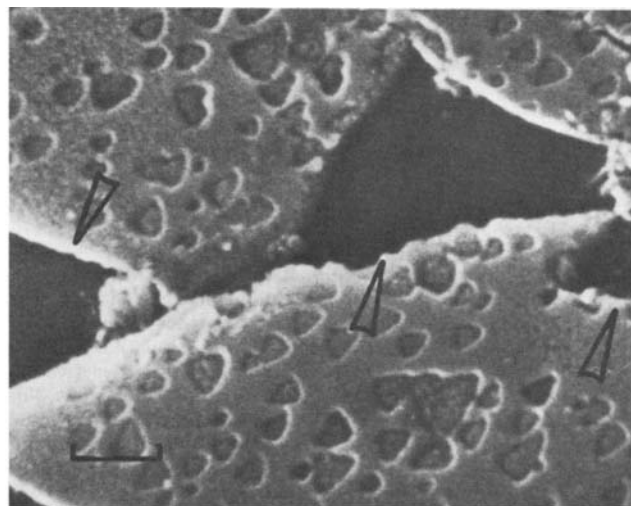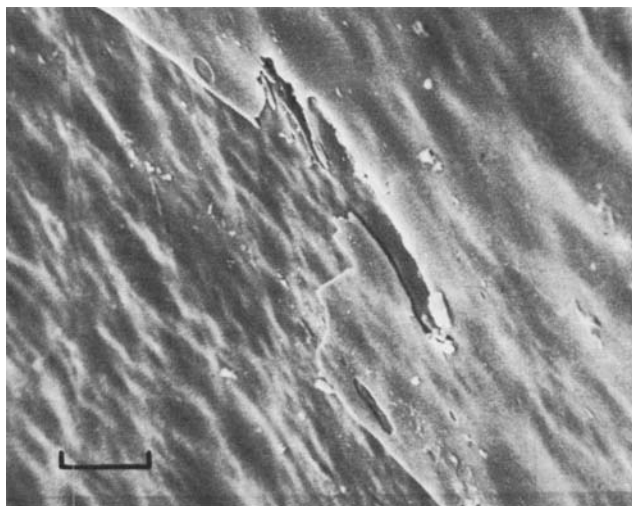
Figure 9—*Scanning electron micrographs of 5-ml ampuls which produced vitreous flakes. Left: delaminated region is on the left side of the micrograph while the intact glass surface appears on the right. Jagged edge separates the two regions (2000× magnification; scale marker = 5 μm). Right: delaminated region is at 20,000× magnification (scale marker = 0.5 μm). Arrows point to delaminated regions.*

identical manner as the flake. The following results were obtained from four replicate samples that yielded the same values: silicon, 30–40%; aluminum, 2–5%; potassium, not detected; calcium, not detected; boron, 4–10%; and sodium, 4–6%. (The elemental composition of the glass fragment agrees favorably with the values listed in Ref. 8, although the exact values differ.)

Since the composition of the flakes and glass fragments is similar, these flakes are believed to result directly from the glass ampul. The presence of boron was observed in all samples, further implicating the glass, since borosilicate glass was employed. Therefore, the scanning electron microscope was used to determine the region in the ampul from which the flakes came. Scanning electron micrographs about 0.8–2.0 cm up the side wall of the ampul did not show etched regions corresponding to the size of the flakes.

Further studies indicated that the area just above the bottom of the ampul showed distinct regions of delamination that were not noticed in control ampuls. Figure 9 shows this area quite vividly, where it appears as if a surface layer of the glass has peeled away. Careful examination of the delaminated area indicates that it extended at least halfway around the ampul. Triangular pits are also noted at high magnification in this photograph and may indicate that the glass had undergone a devitrification process during manufacture. This area of the glass represents a region where thermal stress could play an important role because intense heat is used to form the bottom of the container (6). It is not known, however, if a preferential chemical attack is a prerequisite for the removal of the flake. The sulfur treatment of the glass, however, did prevent this process from occurring.

Data in these laboratories indicate that the surface topography of ampuls can vary among manufacturers, even though the same treatment process is employed. Therefore, caution should be used when comparing sulfur treatments from different sources. In addition, the method of manufacture and thermal history of the glass can vary. In this work, a concerted effort was made to assure that the scanning electron micrographs were representative, recognizing that it was not possible to use the same ampul as its own control.

REFERENCES

(1) S. Turco and N. M. Davis, *Hosp. Pharm.*, **8**, 137(1973).

(2) J. B. Brown and A. S. Watts, *J. Amer. Ceram. Soc.*, **20**, 245(1937).

(3) V. Dimbleby, *J. Pharm. Pharmacol.*, **5**, 969(1953).

(4) F. R. Bacon and F. C. Raggon, *J. Amer. Ceram. Soc.*, **42**(4), 199(1959).

(5) F. R. Bacon, *Glass Ind.*, **49**, 438(1968).

(6) A. Peters, *Glastech. Ber.*, **46**(8), 161(1973).

(7) "The United States Pharmacopeia" 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 924.

(8) F. R. Bacon, "Specifications of Glass Containers for Pharmaceutical Use," Owens-Illinois Glass Co., Toledo, Ohio, 1970.

(9) W. E. Hamlin, "Parenteral Drug Delivery Systems," 16th Annual National Industrial Pharmaceutical Research Conference, Land O'Lakes, Wis., June 1974.

(10) "British Pharmacopoeia 1973," Her Majesty's Stationery Office, London, England, 1973, p. A123.

(11) J. Y. Masuda and J. H. Beckerman, *Amer. J. Hosp. Pharm.*, **30**, 72(1973).

(12) R. C. Hohmann, N. Conca, and K. P. Munnelly, *Bull. Parenteral Drug Ass.*, **27**, 96(1973).

(13) G. H. Hopkins and R. W. Young, *ibid.*, **28**, 15(1974).

(14) P. R. Rasanen and R. C. Louer, *ibid.*, **27**, 243(1973).

(15) A. B. McGinn, *ibid.*, **27**, 247(1973).

(16) R. J. Walsh and J. A. Monahan, *ibid.*, **27**, 250(1973).

(17) P. R. Austin, "Design and Operation of Clean Rooms," Business News Publishing, Birmingham, Mich., 1970.

(18) F. R. Bacon and S. W. Barber, "The Chemical Durability of Sulfur Treated Glass Bottles," Technical Bulletin, Owens-Illinois Glass Co., Toledo, Ohio, June 1948.

(19) K. Kamita, U.S. pat. 1,782,169.

(20) R. W. Douglas and J. O. Isard, *J. Soc. Glass Technol.*, **33**, T289(1949).

(21) E. L. Mochel, M. E. Nordberg, and T. H. Elmer, *J. Amer. Ceram. Soc.*, **49**, 585(1966).

(22) A. L. Hinson, *Bull. Parenteral Drug Ass.*, **25**, 266(1971).

(23) F. R. Bacon and G. L. Calcamuggio, *Amer. Ceram. Soc. Bull.*, **46**, 850(1967).

(24) J. P. Majeske, *Bull. Parenteral Drug Ass.*, **16**(4), 1(1962).

(25) G. A. Hudson and F. R. Bacon, *Amer. Ceram. Soc. Bull.*, **37**(4), 185(1958).

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