

On the Sealing of Gas-Filled Glass Ampoules¹

DONALD GREIFF, HEWLETT MELTON, AND TERENCE W. G. ROWE

*Department of Pathology, The Medical College of Wisconsin, Milwaukee, Wisconsin
53233 and Edwards High Vacuum Limited, Manor Royal, Crawley,
Sussex, England*

To gather data concerning the thermal stabilities of preparations of interferon dried by sublimation of ice *in vacuo*, the samples, in tip-sealed glass ampoules, were placed in a water bath at 50°C for several months. Even though the ampoules which were tip-sealed in our laboratories tested negative by the methods used commonly for detecting "leakers" (1, 2), to our surprise many ampoules upon removal from the water bath contained beads of moisture on their interior surfaces.

To determine if the water within the ampoules had entered through undetected openings in the sealed ends, we used a laser imaging apparatus to examine the ends. Using this apparatus, we carried out a series of studies on handsealed and machine-sealed ampoules, to determine if true sealing had occurred. In addition, we sought for a barrier that could be interposed between the external and internal environments of ampoules, if openings were found to be present, to prevent the migration of molecules into and out of the ampoules.

Received June 14, 1974.

¹ Supported, in part, by the Office of Naval Research, Department of the Navy, Medicine and Dentistry Branch, Contract N00014-69-C-0199, and, in part, by the Infectious Disease Branch, National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Contract NIH 69-2070.

MATERIALS AND METHODS

The hand-sealed ampoules used in these studies were of borosilicate glass (Wheaton Glass Company, vitro, Type 1, cryules) and were closed by two different methods: (a) tip-sealing and (b) draw-sealing. Large machine-sealed ampoules were furnished by Parke, Davis and Company, Detroit, Mich.; small machine-sealed ampoules were obtained from the Lakeside Laboratories, Milwaukee, Wis.; and special machine-sealed ampoules were prepared by the International Laboratories for Biological Standards, London, England.

Tip-Sealing

Ampoules were tip-sealed by holding their openings in the hot portion (external shell) of an oxygen-gas flame. The open ends of the ampoules were observed to contract, with the formation of gatherings of glass at the ends. These openings appeared to close and the fine capillaries present during the sealing process disappeared or closed in regions bounded by the outer surfaces. The ampoules were withdrawn immediately from the flame when closures appeared to be complete (Fig. 1-A). By holding the ends of the ampoules in the flame for slightly longer periods, the gathers of glass expanded to form balloons; the diameters of the balloons were approximately twice the diameters of the necks of the ampoules (Fig. 1-B).

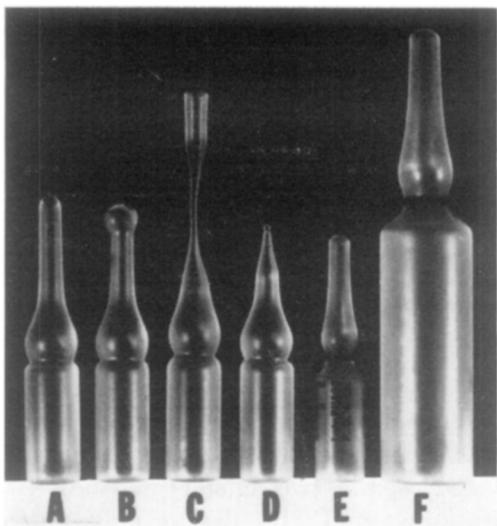


FIG. 1. Examples of sealed ampoules. A, tip-sealed; B, balloon-sealed; C, initial step, draw-sealing; D, draw-sealed; E and F, machine-sealed.

Draw-Sealing

The necks of the ampoules were heated carefully, removed from the flame, and then drawn out for approximately 1 in. This resulted in the necks being much reduced in diameter at the drawn portions (Fig. 1-C). After cooling, the ampoules were then sealed by holding the constricted portions momentarily in the oxygen-gas flame (Fig. 1-D).

Machine-Sealing

Ampoules, both small and large, were sealed in machines commercially available and used frequently by the pharmaceutical industry (Figs. 1-E, 1-F, and 12). Machine-sealing is a combination of draw-sealing, tip-sealing, and a controlled amount of

ballooning to produce ampoules in which the thickness of glass is nearly constant throughout the ends.

Laser-Imaging (3)

Ampoules could not be viewed directly due to unwanted (interfering) refraction of light by the glass of the ampoule tips. However, immersion of the ampoules in a liquid of the same index of refraction as the glass of the ampoules—the liquid being contained in a rectangular “optical gate”—allowed imaging of the ampoules with little or no distortion of the images by refracted light. Consequently, boundaries within the glass, such as small channels, bubbles, and debris trapped within the glass, were clearly visible.

The apparatus for laser imaging is shown in Fig. 2. Two modes of laser imaging were used in these studies. In the first—“dark-field” imaging—a zero stop, consisting of a spot of light-opaque material mounted on a glass slide and when positioned at the principal focus of the lens removed all undiffracted light from the system. Dark field imaging was particularly useful for matching the index of refraction of the liquid to that of the glass of the ampoules. At the point of matching only the diffracting boundaries were imaged; the homogeneous regions were viewed as relatively dark areas. A mismatch between the liquid and glass resulted in the homogeneous areas being viewed as bright areas. The match of fluid to glass was made by adjusting mixtures of benzene and methyl alcohol until dark field images composed only of boundaries were obtained. The sharpness and crispness of the images, as well as the true dark field character of the images, were dependent on the accuracies of the match, approximately one part in 1000.

The second mode of imaging—“interference imaging”—was the production of interference bands by placing a glass slide

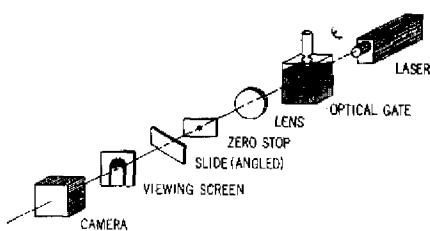


FIG. 2. Laser imaging apparatus.

at an angle between the lens and the screen with the zero stop absent. The interference patterns obtained were interrupted at boundaries and rendered small structures readily visible; this was especially useful when the openings through the tips of the ampoules were of small diameters. Interference imaging was used also to detect the flow of liquids through the openings of ampoules into the matching refractive medium. The nature of the flow, the behavior of the coherent light of the laser beam in relation to the changes in the refractive index of the matching liquid resulted in an almost total refraction of light out of the field of view; the emerging fluid appeared as a black, jet stream with its origin at the openings of the sealed ampoules.

Although our early studies were carried out with dark field imaging, the precision and visualization obtained by interference imaging led us to use this method for the majority of our studies.

RESULTS

Representative examples of dark-field imaging of tip-sealed, balloon-sealed and draw-sealed ampoules, are shown in Figs. 3-5. In tip-sealed ampoules, uniform long channels were present in the gatherings of glass at the ends of the ampoules; the lengths of the channels were approximately ten times their diameters. In balloon-sealed ampoules, pore-like openings were found; the lengths of the pores were approximately four times their diameters. In draw-sealed ampoules, channels of small diameters were observed; the lengths of the open pathways were approximately 30 times their diameters.

Based on the sizes of the images obtained with laser imaging, the magnifications used for photographic reproduction and the original measurements of the sealed ampoules, we estimated the openings in tip-sealed and balloon-sealed ampoules to range from 5 to 8 μm and the diameters of the chan-

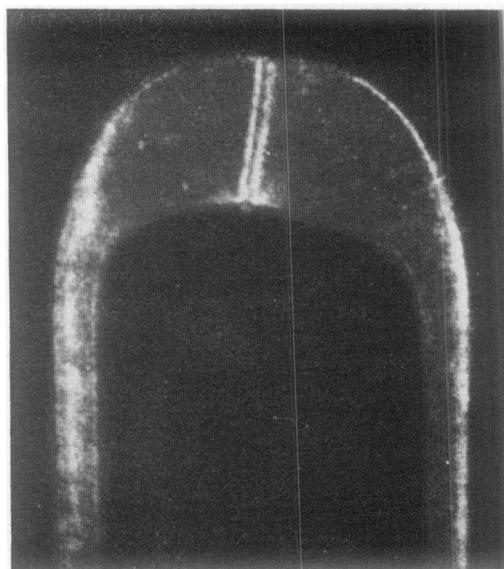


FIG. 3. Dark-field laser image of tip-sealed ampoule.

nels in draw-sealed ampoules to be less than 3 μm .

Two examples of openings in sealed ampoules observed by interference imaging, are shown in Figs. 6 and 7. The straight channel of the tip-sealed ampoules possesses an almost constant diameter throughout its length (Fig. 6). The continuation of the interference pattern across the opening indicates that this is a true opening and not the result of diffraction caused by

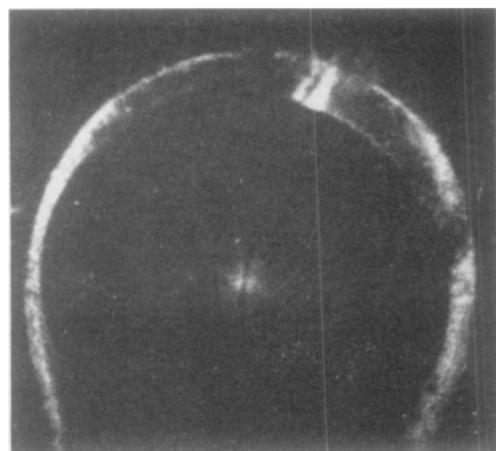


FIG. 4. Dark-field laser image of balloon-sealed ampoule.

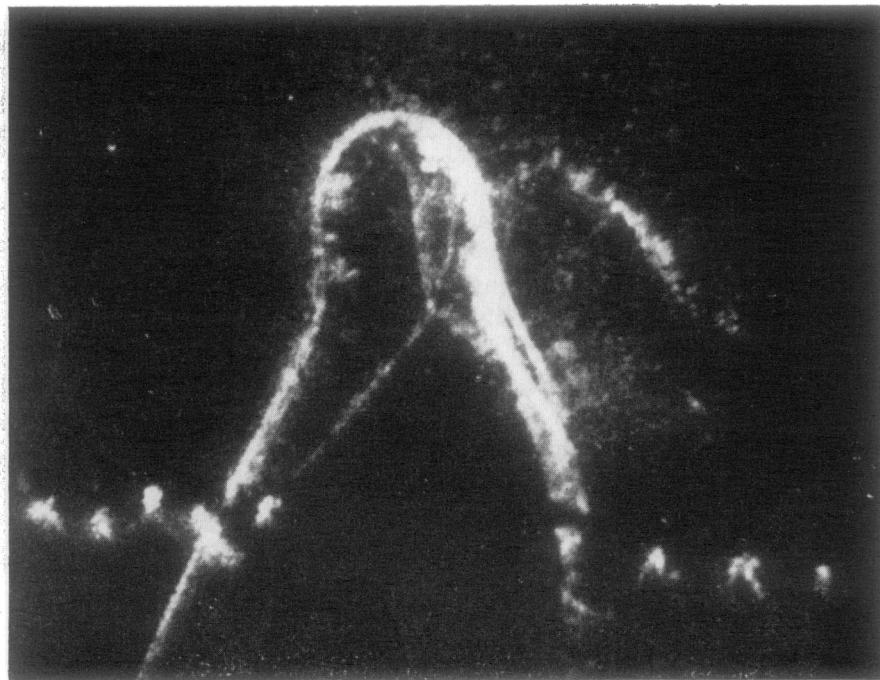


FIG. 5. Dark-field laser image of draw-sealed ampoule.

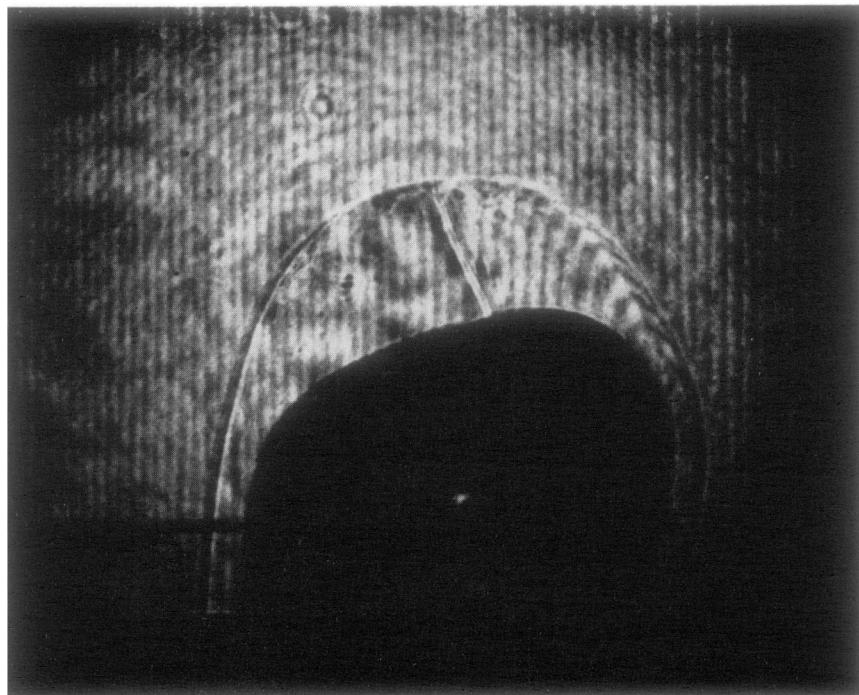


FIG. 6. Interference pattern laser image of tip-sealed ampoule.

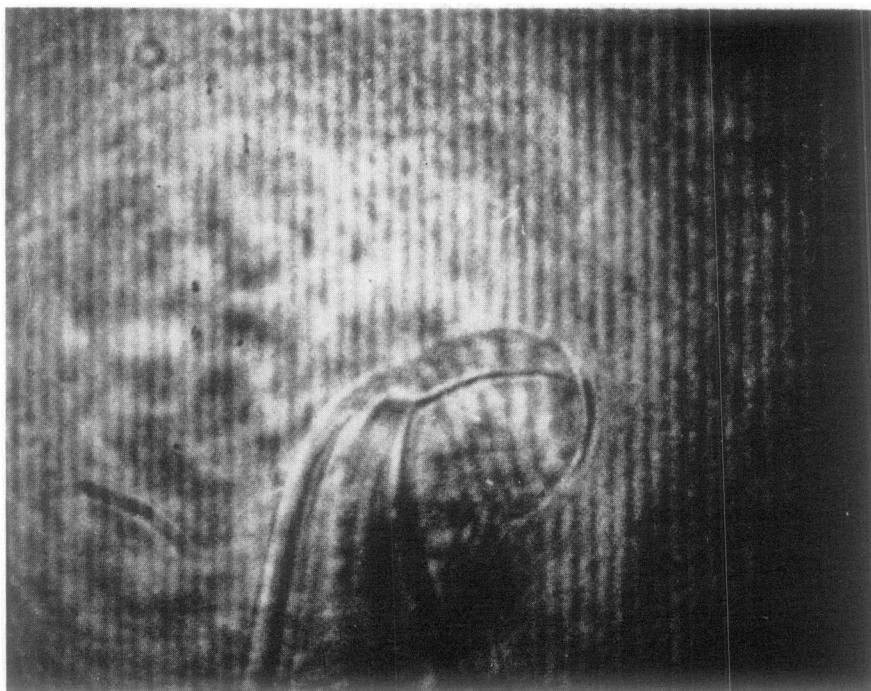


FIG. 7. Interference pattern laser image of draw-sealed ampoule.

layers of glass touching. In fact, in Fig. 6, the channel can be seen to expand as it approaches the outer surface of the tip of the ampoule, resembling a distorted umbrella. If the opening observed resulted from two layers of glass touching, we would

expect the interference pattern to exhibit sharp discontinuities at the interface of the glass boundaries and at the interface of the tip with the matching liquid.

The second example, interference imaging of a draw-sealed ampoule, shows the

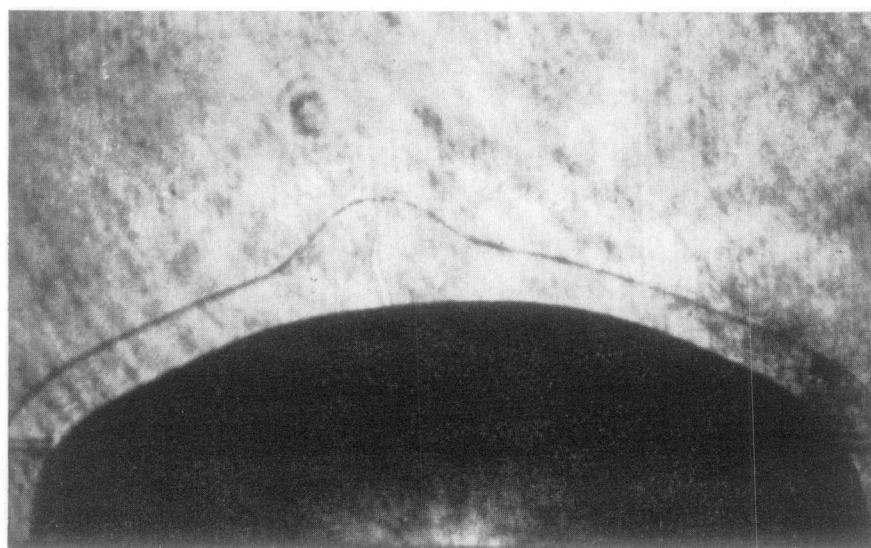


FIG. 8. Interference pattern laser image of machine-sealed, large ampoule.

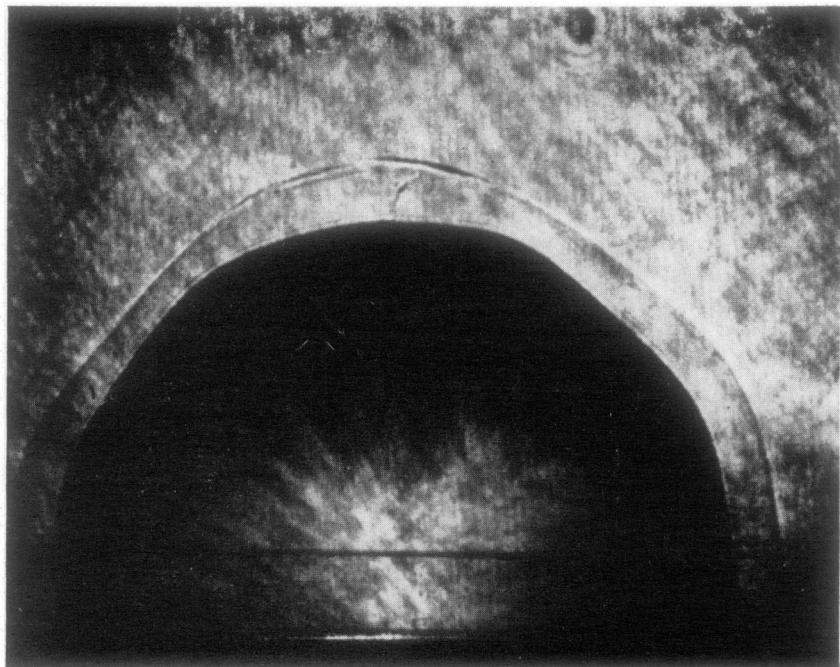


FIG. 9. Interference pattern laser image of machine-sealed, large ampoule.

unique property of this mode for visualizing very small channels (Fig. 7). It can be seen easily that the channel extends throughout the gathering of glass at the end of the ampoule; all of the channels could not be oriented within the plane of

focus, a circumstance which was an ever-present difficulty.

The observations above were based on the examination of approximately 30 ampoules for each kind of sealing and for each method of imaging.

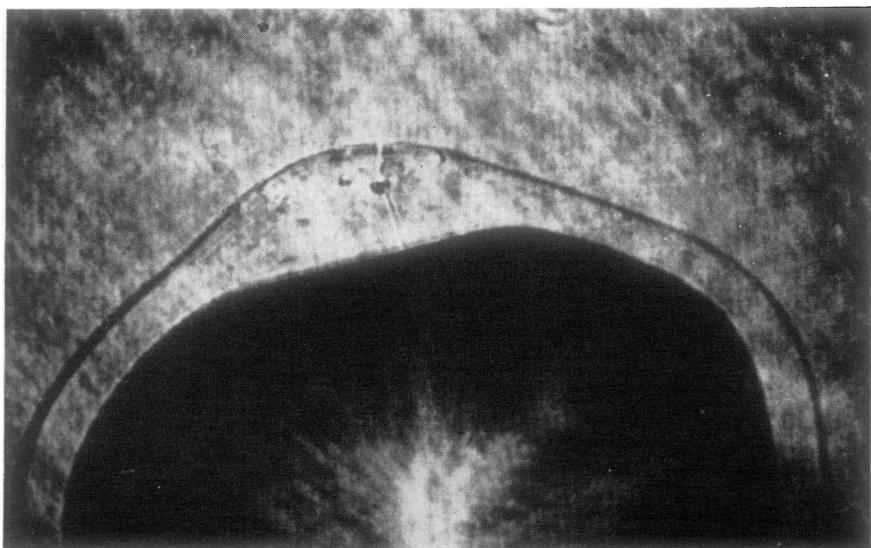


FIG. 10. Interference pattern laser image of machine-sealed, large ampoule with the channel blocked by debris.

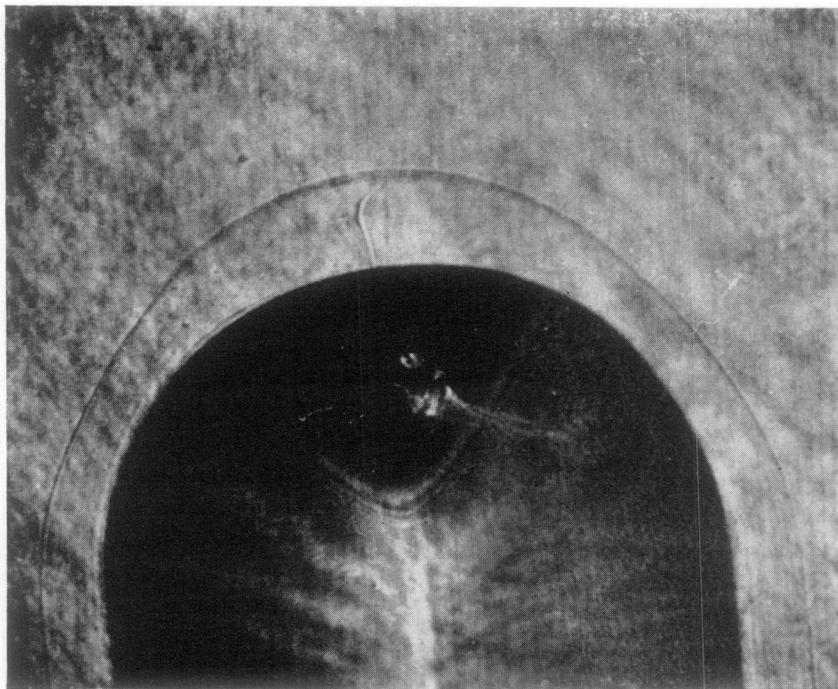


FIG. 11. Interference pattern laser image of machine-sealed, small ampoule.

Twenty-five randomly selected, machine-sealed, large ampoules were examined by laser imaging and all were found to have channels. Because of the motions used in machine-sealing, twisting and drawing simultaneously, the channels of these ampoules were helical (Figs. 8 and 9). An appreciation of the helix was achieved by rotating the ampoules while viewing the image. In some ampoules, channels were occluded by pockets of debris (Fig. 10). The diameters of the helix-like channels in machine-sealed ampoules were less than 5 μm .

Results similar to the above were observed in a number of machine-sealed, small ampoules, prepared by Lakeside Laboratories, Milwaukee, Wisc. (Fig. 11).

We obtained recently a number of sealed ampoules prepared by the International Laboratories for Biological Standards, National Institute for Medical Research, London, England (Fig. 12). These ampoules differ markedly from those used

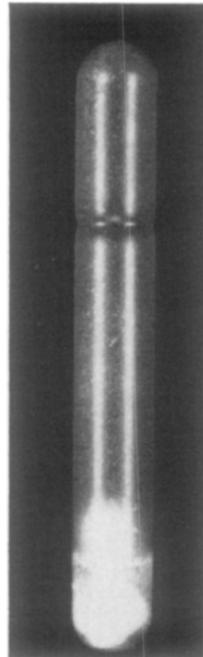


FIG. 12. Ampoule used by the International Laboratories for Biological Standards. These ampoules are machine-sealed.

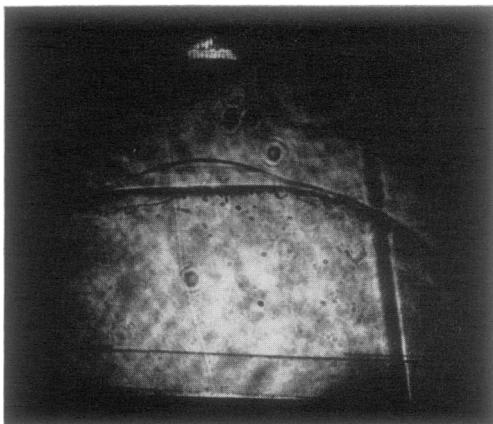


FIG. 13. Interference pattern laser image of ampoule used by the International Laboratories for Biological Standards.

commonly by the majority of laboratories. They are made of borosilicate glass and are cylindrical in shape, with a diameter 12.0–12.5 mm and a wall thickness of 0.4–0.6 mm. After the filling of the ampoules with predried materials or after a cycle of freezing and freeze-drying of liquid ma-

terials, the ampoules are back-flushed with dry nitrogen and machine-sealed.

Because the large radii of curvature of the closings resulted in long boundaries being presented to the laser beam, those portions of the channels near the center surfaces were difficult to image (Fig. 13). Even when liquid and glass were well matched, refraction was accentuated objectionably by the large angles of incidence. In addition, only portions of the channels could be observed for given positions of ampoules within the laser optics; total channels could be visualized only by rotating the ampoules. Channels were less than 3 μm in diameter.

Methyl alcohol, because of its low surface tension, low viscosity and high vapor pressure, was used for studies on the ability of fluids to flow through the channels and pores of hand-sealed ampoules. Sealed ampoules containing 1 ml of methyl alcohol were fixed in the laser imaging apparatus in their normal position, i.e., with the

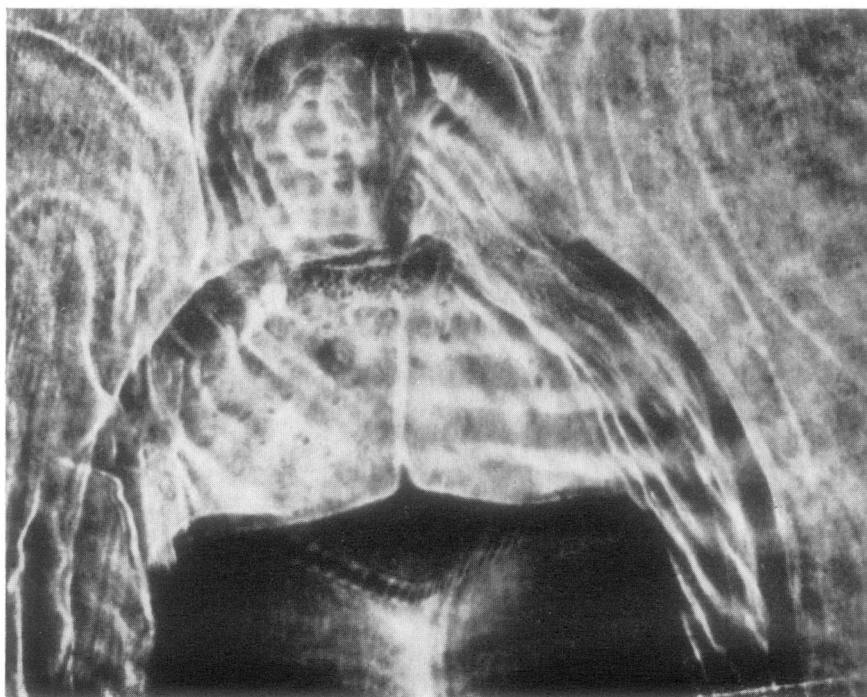


FIG. 14. Flow of methyl alcohol through the channel of a tip-sealed ampoule after the application of moderate heat. Interference pattern laser imaging was used.

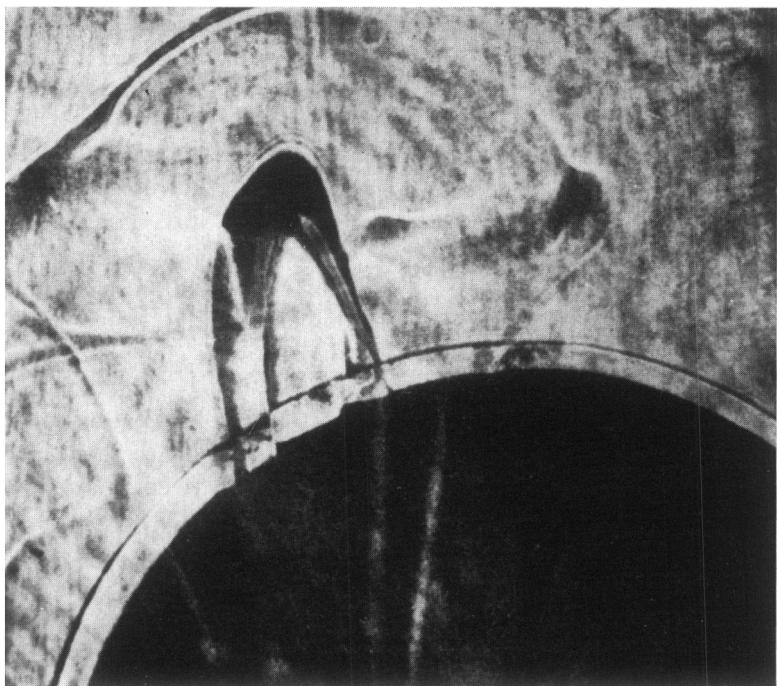


FIG. 15. Flow of methyl alcohol through the pore-like opening of a balloon-sealed ampoule after the application of light heat. Interference pattern laser imaging was used.

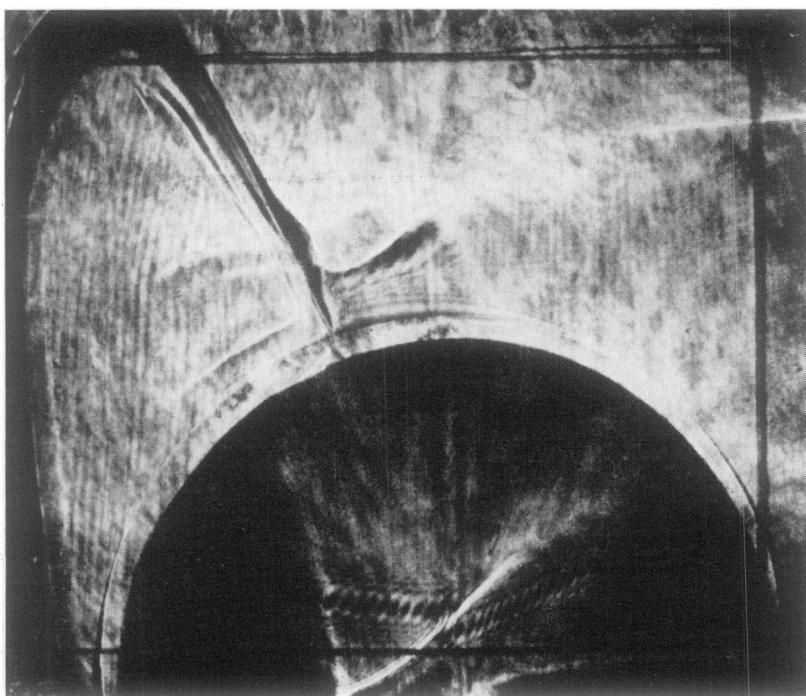


FIG. 16. Flow of methyl alcohol through the pore-like opening of a balloon-sealed ampoule after the application of moderate heat. Interference pattern laser imaging was used.



FIG. 17. Plastics holder for holding ampoules during dipping procedure to minimize the chances of "bleb" formation.

sealed ends of the ampoules immersed in the refractive fluid of the optical gate. The bottoms of the ampoules were heated to increase the pressure of gases within the ampoules; the escape of methyl alcohol through the channels of tip-sealed ampoules resulted in umbrella-like configurations (Fig. 14). The dark parts at the tops of the umbrellas and the dark stalks emerging from the opening of the channel were composed of methyl alcohol; the remainder of the umbrella-like structures resulted from the disturbance of the interference patterns by the outflow of alcohol. Because of the lowered impedance to the flow of alcohol through the pores of balloon-sealed ampoules, the flow of escaping fluid appeared as jet streams (Fig. 15); with continued heating the streams enlarged and became more intense (Fig. 16).

Neoprene Sealing

After our discovery that hand-sealed and machine-sealed ampoules contained channels or pores, we tested a number of compounds to be used as barriers between the external and internal environments of ampoules. *A priori*, we desired a compound with the following characteristics: (a) ready availability, (b) liquid at room temperature, (c) rapid-drying at ambient temperatures, (d) ready adhesion to glass, (e) ability to be stored at low temperatures (-20 to -70°C) over long periods without flaking, chipping, cracking, or fragmenting, and (f) effectiveness as a thin film barrier to oxygen, carbon dioxide and water vapor. Of the many liquid formulations of natural and man-made elastomers tested (neoprene, methacrylate, polyvinyl alcohol, acrylic paint, liquid suran, natural rubber, shellac, etc.), neoprene, dissolved in toluene in sufficient amounts to form free-flowing solutions, fulfilled best the criteria above. This compound was obtained from Adhesive Products Corporation, Bronx, N. Y. 10460, and is sold under the trade name APCO 607 adhesive. Although the brittle temperature of the compound as supplied was given as a -40°C , in our experience thin coatings of this compound on glass when stored at -70°C could be removed only with difficulty. At -196°C (liquid nitrogen) the neoprene could be flaked away with a sharp instrument, but only along the path of the instrument; the adherence of neoprene in the vicinity of the chipped area was not affected. An engineering report on the physical and chemical properties of neoprene and solutions of neoprene can be obtained from E. I. Du Pont de Nemours and Co., Inc., Elastomer Chemicals Department, Des Plaines, Ill. 60016.

A problem that arose occasionally during the dip-sealing of ampoules was the formation of blebs at the tips of ampoules. These blebs resulted from the thermal expansion of gases within the ampoules, if

hand held during the dipping procedure, and the entrapment of emerging gases by thin layers of neoprene. Because blebs were not adherent to the glass, they were vulnerable to accidental puncturing or fragmentation.

To avoid the formation of blebs, the ampoules were inserted in a plastic holder of low thermal conductivity (Fig. 17). Using this holder, the ends of the ampoules were dipped into the neoprene solution and removed from the solution with a rotating motion. Rotation was continued for 10–15 sec to allow the neoprene to develop a set when the neoprene loses its high shine and takes on a dull appearance; the ampoules were then removed from the holder and placed upon the work bench. To promote a more rapid evaporation of solvent from the neoprene solution, we found a stream of air at ambient temperature to be useful. Setting of the neoprene occurs in thirty minutes to one hour depending upon ambient temperature, relative humidity and the amount of solvent in the neoprene solution. When "watery" solutions of neoprene were used, the tips of the ampoules were doubledipped but for more viscous solutions only single dips were required.

If the neoprene caps produced by dipping are not aesthetically pleasing to the manufacturer or the consumer, the wiping away of these caps following dipping and short exposure to ambient temperatures appears to leave enough neoprene in the opening of channels or pores to act as plugs. Ampoules prepared in this way did not show the characteristic stream effects of methyl alcohol upon heating, but rather a slow emergence of alcohol which would cling to the glass surfaces of the ampoules. In order to initiate and maintain the flow of methyl alcohol it was necessary to approach its boiling temperature.

DISCUSSION

The need for effective methods for closing ampoules and vials for long term stor-

age of chemical and biological standards and reference materials is well recognized. For many years, all those concerned with this problem have insisted that all-glass systems be used. It has been accepted without question that the fusion of the open ends of glass ampoules in an oxygas flame results in the formation of glass plugs impermeable to gases, vapors and particles. Thus, the WHO Secretariat in its recommendations concerning the preparation of standard and reference reagents (2) makes the following statement

In all cases, the sealing of the ampoules should be by fusion of the glass. Sealing by rubber or plastic closures is unsatisfactory for long-term preservation of international standards, reference preparations and reference reagents.

In the light of our studies, we feel that the assumptions which have led to the preferred use of fusion-sealed ampoules over stopper-closed vials must be re-examined; the channels and pores which we have found to be present in fusion-sealed ampoules, although of small dimension, are real and cannot be ignored. The initial observations that led to the present investigations, and the ability of methyl alcohol to flow through channels and pores in fusion-sealed ampoules, in addition to the structural findings by laser imaging, provide dynamic support for the position above.

The physical properties of glass make it doubtful if ampoules containing liquid or freeze-dried preparations under gases can be sealed completely by ordinary means (10). Glass is an undercooled (super cooled) liquid whose viscosity varies continuously with temperature. At ordinary temperatures its viscosity is so high that it can be considered infinite; as the temperature increases, viscosity decreases and after a prolonged period in the viscous or plastic phase the glass gradually assumes the character of a liquid. The initiation of plastic flow in the borosilicate glasses lies between 700 and 1100°C and the temper-

atures for melting between 1400 and 1600°C. Glass ampoules during sealing by hand or by machine will be maintained in the viscous phase over an extended temperature range and the following will occur: (a) plastic flow, (b) formation of glass plugs with restricted openings, and (c) thermal expansion of gases within the ampoules. Because of the events above, the ends of the ampoules begin to balloon before the melting temperature of glass is reached and true fusion can occur. If the ampoule is not removed from the flame at the initiation of ballooning, the glass at the tip will thin out rapidly and eventually fracture.

A recent review by one of us (TWGR), discusses the pros and cons of glass-sealed ampoules versus stopper-sealed vials (13). On balance, it would appear that stoppered vials have several advantages over glass-sealed ampoules; this is true especially when mold blown vials closed with properly formulated stoppers are used. Mold blown vials closed with suitably formulated and prepared composition stoppers were used in a series of studies to determine the thermal stabilities of freeze-dried preparations of viruses (5, 7, 8) and interferon (6). These preparations were sealed in a vacuum or under gases. For isothermal inactivation, dried preparations were kept at elevated temperatures, 35–68°C, for periods of 6 mo. For nonisothermal inactivation, the dried preparations were placed in a linear programmed water bath and the temperature raised from 50 to 90°C over a span of 20 hr. The control preparations for the studies above were stored at –20 and –70°C for periods of up to approximately 1 yr. Under the conditions above, all preparations were physically stable as measured by the exclusion of water and the maintenance of vacuum. These studies showed that the integrities of stopper-sealed vials were maintained under adverse conditions.

In order to estimate mass flow of liquids from imperfectly sealed ampoules, we used an equation based on Poiseuille's law defining viscous laminar flow through cylindrical tubes (9, 14):

$$t = (m 8 \nu L) / (\pi (P_2 - P_1) a^4 D)$$

where t is time (in seconds), m is the mass of fluid that has passed through the channel (in grams), ν is the viscosity of the fluid (in dyne-seconds per square centimeter), L is the length of the channel (in centimeters), P_2 and P_1 are the upstream (interior) and downstream (exterior) pressures (in dynes per square centimeters), a is the radius of the channel (in centimeters), and D is the density of the liquid (in grams per cubic centimeter).

If one considers a "sealed ampoule" with a channel 1 mm in length and 5 μm in diameter containing 1 ml of methyl alcohol heated to approximately 65°C, the vapor pressure of the methyl alcohol will be 1 atm above the pressure outside the ampoule. Under these conditions, approximately 6 min would be required for 7.5 mg of the methyl alcohol, 1% of the amount present, to escape; reduction of the channel diameter to 2.5 μm would increase the time required to 1.6 hr and for a 1 μm channel the time would be 2.6 days.

If one forces 10 mg of water, 1% of the amount present, through channels of the same dimensions as above with a pressure difference of 1 atm, the times required would be approximately 6.6 min for a channel 5 μm in diameter, 1.7 hr for a channel of 2.5 μm and 3 days for an opening of 1 μm .

Our experience agreed with the above calculations. Openings in ampoules 5 μm or greater were detected easily by the methyl alcohol test; openings of 2 μm or less were not detectable within the time periods of our preliminary experiments. We concluded, therefore, that the usual methods used to test for "leakers" were not successful for small bore channels because

pressure differences were less than 1 atm and the time period insufficient. We plan long-term experiments to verify the calculations of the time periods required for measurable amounts of material to escape from and hence, also, to enter ampoules with channels of small bore.

All of the above calculations approximated the minimum time requirements for a given mass within the ampoule to flow through channels of the dimensions found in tip-sealed ampoules. Factors such as turbulent flow, and increased impedance to flow, resulting from the entrapment of debris within the channels or changes in the directions of the channels, were not considered. Should such considerations be made, all other conditions being the same, the time requirements would be increased.

The flame used for working glass is produced by the burning of combustible gases with oxygen supplied to the burner and with that from the atmosphere (4, 12). The flame consists of three distinct zones: the inner zone, containing a mixture of heated gases and oxygen, in which no burning takes place; the intermediate zone where the reaction (burning) occurs between combustible gases and the oxygen which flows from the burner; the outer zone containing the products of burning and the remaining unburned gas, both at a high temperature. It is in the outer zone that the remaining gases are burned, consuming oxygen from the surrounding atmosphere. The temperature in the flame increases from the inner zone towards the outer zone, reaching a temperature of approximately 1600°C.

Depending upon the position of the tips of the ampoules in relation to the outer and intermediate zones, the products of combustion (hydrogen, carbon monoxide, methyl alcohol, various hydrocarbons, nitrogen, and carbon dioxide) will surround the ends of the ampoules. Small amounts of these gases will diffuse into the ampoules during the sealing procedure

and may result in the inactivation of dried preparations or liquid suspensions of biologic materials.

The tips and necks of stored ampoules often have a rough appearance, "weathering," a surface phenomenon resulting from changes in the composition of glasses brought about by atmospheric vapors (11). The process consists of the hydrolysis of the alkali silicates with the formation of alkali hydroxides and colloidal silicic acid. The alkali hydroxide reacts with the carbon dioxide from the air, forming a film of alkali carbonates with separation of silica. In addition, packing paper or cardboard in contact with the ends of the ampoules sometimes contains materials which can attack glass. The paper may also act as a wick to convey water to glass surfaces. To minimize weathering, therefore, it is advisable to store glass ampoules, unwrapped or wrapped in plastics, in a dry place. Glass ampoules suspected of weathering should be immersed in a 1–5% hydrochloric acid solution for several seconds, followed by a warm, demineralized water rinse (40–50°C) and drying at 80–100°C.

SUMMARY

Studies in our laboratories involved the placing of argon-filled hand-sealed glass ampoules (tip-, balloon-, or draw-sealed) containing biological materials dried by sublimation of ice *in vacuo* in water baths at elevated temperatures. Although these ampoules tested negative for "leakers," many ampoules upon removal from the water bath contained beads of moisture. To determine if the water within the ampoules entered through openings in the closed ends, we used a laser imaging apparatus to examine the sealed ends. We carried out studies also on machine-sealed ampoules.

Two modes of laser imaging were used: dark-field imaging and interference imaging. In tip-sealed ampoules, uniform, long channels were found in the gatherings of

glass at the ends of the ampoules; the lengths of the channels were approximately ten times their diameters. In balloon-sealed ampoules, pore-like openings were found; the lengths of the pores were approximately four times their diameters. In draw-sealed ampoules, channels of small diameters were observed; the lengths of the open pathways were approximately 30 times their diameters. Based on the sizes of the images obtained with laser imaging, the magnifications used for photographic reproductions and the original measurements of the sealed ampoules we estimated the openings in tip-sealed and balloon-sealed ampoules to range from 5 to 8 μm and the channels in draw-sealed ampoules to be less than 3 μm in diameter. The diameters of the helix-like openings in machine-sealed ampoules were less than 5 μm .

To prevent the migration of molecules into and out of ampoules, we sought for a barrier that could be interposed between the external environments of the ampoules. Many liquid formulations of natural and man-made elastomers were tested; neoprene dissolved in toluol was found best.

REFERENCES

1. Avis, K. E. Parenteral preparations. In "Remington's Pharmaceutical Sciences," 14th ed. (J. E. Hoover, Ed), pp. 1519-1544. Mack, Easton, Pennsylvania, 1970.
2. Bangham, D. R., Evans, D. G., Hulse, E. C., Krag, P., and Outshoorn, A. S. (The WHO Secretariat). Notes on the preparation of materials to serve as international biological standards, reference preparations and reference reagents. *Expert Committee on Biological Standardization, World Health Organization. Geneva, 27 September-2 October 1965.*
3. Born, M., and Wolf, E. "Principles of Optics." Macmillan, New York, 1964.
4. Gaydon, A. G., and Wolfhard, H. G. "Flames, Their Structure, Radiation and Temperature," Third ed., revised, Chapman and Hall, London, 1970.
5. Greiff, D., and Greiff, C. Linear nonisothermal, single-step, stability studies of dried preparations of influenza virus. *Cryobiology* 9, 34-37 (1972).
6. Greiff, D., Jameson, P., and Grossberg, S. E. Unpublished observations.
7. Greiff, D., and Rightsel, W. Stability of suspensions of influenza virus dried to different contents of residual moisture by sublimation *in vacuo*. *Appl. Microbiol.* 16, 835-840 (1968).
8. Greiff, D., and Rightsel, W. A. Stabilities of dried suspensions of influenza virus sealed in a vacuum or under different gases. *Appl. Microbiol.* 17, 830-838 (1969).
9. Guthrie, A. Vacuum technique. In "Handbook of Physics" (E. U. Condon and H. Odishaw, Eds.), Chapter 6, Part 5, pp. 73-89. McGraw-Hill, New York, 1967.
10. Roth, A. Glass to glass (and quartz) seals. In "Vacuum Sealing Techniques," pp. 101-116. Pergamon, Great Britain, 1966.
11. Roth, A. Glass to glass (and quartz) seals. In "Vacuum Sealing Techniques," pp. 116-119. Pergamon, Great Britain, 1966.
12. Roth, A. Glass to glass (and quartz) seals. In "Vacuum Sealing Techniques," pp. 121-126. Pergamon, Great Britain, 1966.
13. Rowe, T. W. G. Machinery and methods in freeze-drying. *Cryobiology* 8, 153-172 (1971).
14. Seeger, R. J. Fluid mechanics. In "Handbook of Physics" (E. U. Condon and H. Odishaw, Eds.), Chapter 2, Part 3, pp. 14-39. McGraw-Hill, New York, 1967.