Freezing Unit Dose Injections prior to Freeze Drying

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Abstract □ A new method, used on an industrial scale, for freezing vials to be lyophilized was studied, by which a dried mass in the shape of an internal hollow paraboloid with very thin layers is obtained. The apparatus is also described.

Keyphrases □ Freezing of solutions, emulsions, and suspensions—improvde rotating freezer for liquids in ampuls or small containers □ Injections, unit dose—improved rotating freezer for use prior to freeze drying □ Lyophilization, injectables—improved method for freezing vial contents

Up to the present day, the most used industrial techniques for freezing vials containing pharmaceuticals to be lyophilized have been the: (A) single-cylindric tablet (bottom freezing) (Fig. 1*a*), (B) cylindric tablet composed of two or more separated strata (1, 2) (Fig. 1*b*), (C) shell form (agar slant) tablet (Fig. 1*c*), and (D) double shell (3) (double agar slant) tablet (Fig. 1*d*).

Technique A, being the cheapest and simplest, is the one most used. In this method the vials are placed vertically on suitable trays, which are then transferred to refrigerated shelves or, sometimes, immersed in freezing baths. The freezing is monodirectional and bidirectional in the two cases, respectively, and proceeds from the outer to the inner part of the liquid cylinder. An external layer of frozen liquid is set up which renders rather difficult the heat exchange; as a consequence, a long treatment at low temperature is required to freeze the liquid completely.

Technique C needs specific equipment. The liquid is distributed on part of the vial wall to obtain a larger evaporation surface. By consequence, the mass freezes in thinner layers than in both the A and B techniques while the time required for both freezing the solution and evaporating the solvent is minimized, with an obvious reduction of production costs.

Techniques B and D, much more laborious and expensive than the others, are carried out to avoid the mixing of interreacting substances (4). It is known that the best lyophilization conditions are assured by the quick cooling of large surfaces of material in thin layers (5–7).

During the last 10 years, different kinds of rotating freezers have been patented (8) to reach these conditions. Such equipment allows only the freezing of bottles similar to those containing plasma (9, 10). The liquid mass is spread over most of the internal surface of the bottle, producing a shell form either by a slow or fast rotation of the flasks. The cooling of the bottles is provided either by immersion in a freezing liquid or by spraying the flasks with a cold fluid. This kind of apparatus works with few units at a time, and an external contamination could occur due to the use of the refrigerant fluid. Another type of rotating freezer (11), suggested for flasks, works as a normal centrifugal under vacuum machine, having an inclined rotation axis. The prefreezer does not require a freezing liquid because the cooling is obtained by rapidly rotating the product under vacuum (adiabatic cooling). With this type of freezer, the evaporation may cause the precipitation of the solids even before freezing, with obvious disadvantages in the drying phase and the final product. In fact, with this freezing procedure, fractioned crystallization of some components might occur in relation to their physical properties, and the developing crystals accumulate at the boundary layers of the mass to be frozen due to the centrifugal force.

Up to now, no similar industrial procedure has been applied to liquids to be frozen in ampuls or small containers. We improved and patented (12) a rotating freezer by which frozen solutions, emulsions, and suspensions are obtained in the shape of an internal hollow rotation paraboloid (Fig. 1*e*). With such a system, larger surfaces and thinner layers than those accomplished by the static freezers are obtained and the freezing time is reduced.

EQUIPMENT

The new rotating freezer consists of (Fig. 2):

1. A turning frame (No. 25), with trays containing the ampuls to be frozen, placed in a covered (No. 18) box (No. 17). The box bottom and walls are cooled by a refrigerant group (Nos. 29 and 30), which is able to lower the air temperature of the box to −50° within 25 min.
2. A ventilation system (No. 32) generating a blast of cold air at −45° which passes over the ampuls from the higher to the lower part of the vial at 90 m./sec. and 15 mm. water pressure.
3. A box (No. 17) that can be inclined at a suitable angle, dependent both on the diameter of the ampul and the volume of the liquid to be frozen. In this way, the liquid surface sets itself like an agar slant. By rotating the turning frame at a slow speed (20–30 r.p.m.), the liquid freezes in very thin layers on the inner surface of the ampul, forming a rotating hollow paraboloid (Figs. 3 and 4).

EXPERIMENTAL

The described equipment can be used for freezing mixtures of biological products having different eutectic points. This report concerns the freezing of an aqueous solution containing 15% solids, showing an eutectic point at −12°.

The freezing of 1.2 ml. of solution in vials of 13–13.5-mm. diameter resulted in a frozen mass in which thickness was about 0.2–2 mm. on the walls and 3–3.5 mm. at the bottom (Table I, Column *b*). Under the same conditions using a static freezer, the

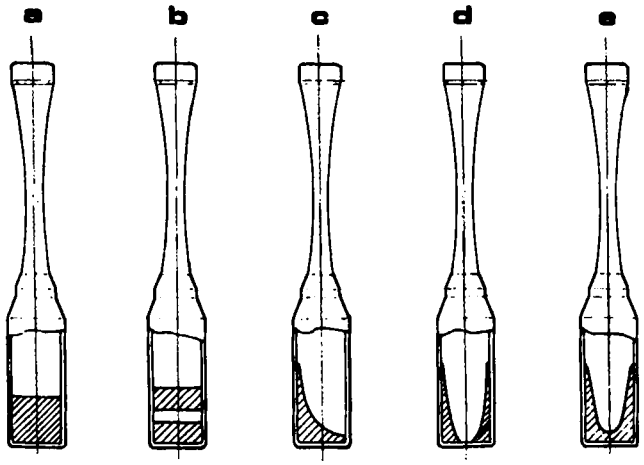

Figure 1—*Freeze-dried vials. Key: a, single-cylindric tablet (bottom freezing); b, cylindric tablet composed of two or more separated stratums; c, shell form (agar slant) tablet; d, double shell (double agar slant) tablet; and e, rotating paraboloid tablet.*

frozen mass thickness was 10–11 mm. (Table I, Column *B*). Moreover, the freezing time of 4–6 hr. (13) (Fig. 5) with static freezers was reduced to 20–25 min. with the study apparatus (Fig. 6) due both to the increased exchange surface (Table I, Column S_2) and the forced circulation of cold air which increases the total heat transfer coefficient. The drying time (Fig. 7) of the frozen vials was also reduced in comparison with that of statically frozen vials (Fig. 8). In fact, the temperature of the heating liquid being 40°, the frozen samples reached 0° within 5 hr., while 13 hr. was required for frozen samples with a cylindric shape.

As shown in Fig. 7, the maximum drying was reached within 1–3.5 hr. while for statically frozen vials the same drying was obtained within 1–10 hr. (Fig. 8). For paraboloid tablets, the maximum difference between the vapor pressure in the drying room and that in the condenser occurs within 3–4 hr. and the pressure in the drying room reaches a minimum value of 10 μ after 9 hr. For the

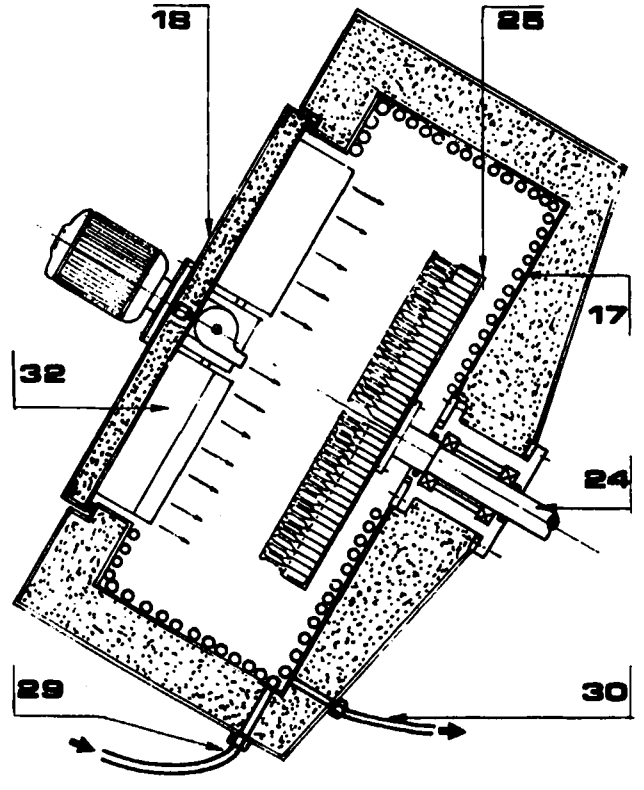

Figure 2—*Cross section of the rotating freezer. (See text for explanation of numbers.)*

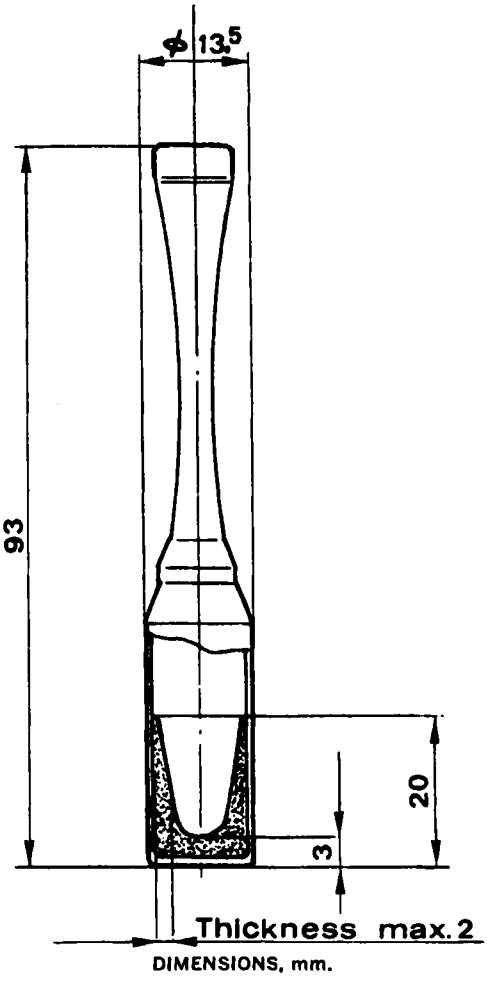

Figure 3—*Frozen vial in the shape of an internal hollow rotation paraboloid. Bottom and sides are 3 and 2 mm. thick, respectively. On the sides the frozen liquid is 20 mm. high.*

cylindric tablets, the maximum pressure difference is reached within 3–7 hr., and the pressure in the drying room reaches the minimum value of 10 μ after 19 hr. These differences are due to the major development of the evaporation surface (Table I, Column *S*), which in the first case is four times (Table I, Column *Rs*) as much as in the second case, and to the reduced resistance offered by the thin layer to the evaporation. In conclusion, the freeze drying of the above-mentioned solution, which would require 22 hr. if performed on the product frozen in a static freezer (Fig. 8), requires only 10–11 hr. in the case of the product frozen in the dynamic freezer (Fig. 7). Therefore, a saving of the required energy and an improved productivity can be obtained.

METHODS

The vials, filled by the usual filling machines, are placed in suitably drilled trays. These trays are placed on the rotating frame of the freezer, previously chilled, and the box is inclined at the suitable angle to distribute the liquid in a shell form, like an agar slant, on the inner side of the vial wall. Both the rotation of the frame and a cold air blast, flowing from the higher to the lower part of the outer surface of the vials, are started up. After 20–25 min., the liquid is completely frozen in contact with the internal wall of the vial. The stratum, having an average thickness of a few millimeters, is formed by several superimposed thin layers showing a spiral form; at the bottom of the vial, the frozen layer is about 3–3.5 mm. thick (Table I, Column *b*), depending on the diameter of the vial and the liquid volume (Table I, Column *VL*). The trays containing the frozen vials are placed into a conventional static freezer until the loading of the drying equipment is completed and are then lyophilized as usual.

Table I[a]—Cubic Paraboloid Measured and Calculated Values[b]

ϕ, mm.	VL, cm.³	V, cm.³	H, mm.	B, cm.	b, cm.	S, cm.²	Rs	S_1, cm.²	S_2, cm.²
12	1.0	1.090	20	0.96	0.28	5.104	4.52	4.77	8.69
13	1.2	1.308	20	0.98	0.32	5.405	4.07	5.33	9.50
14	1.5	1.653	20	1.06	0.42	5.542	3.60	6.20	10.34

[a] For the calculations and solutions, see text. [b] ϕ = vial diameter, VL = volume of 15% aqueous solution still at liquid state, V = VL volume at frozen state, H = height of fluid on wall of frozen paraboloid-shaped vial, B = height and thickness of statically frozen solution, b = thickness of bottom side of solution when frozen in paraboloid shape, S = evaporating surface of frozen paraboloid-shaped solution, Rs = ratio between evaporating paraboloid surface S and one of the same solution statically frozen, S_1 = surface of thermal transfer of statically frozen vial, and S_2 = surface of thermal transfer of same frozen cubic paraboloid-shaped vial as in S_1.

RESULTS

Compared with the usual static procedures, the rotational freezing procedure described here shows the following advantages:

In the Freezing Phase—1. Thinner layers: 0.2–2 mm. on the walls and about 3 mm. at the bottom (Table I, Column *b*) instead of 10–11 mm.

2. Minimized freezing periods (Fig. 6): about 25 min. instead of 4–6 hr. (Fig. 5) (13). This occurs because the heat exchange surface is almost doubled (Table I, Column S_2) and the heat transfer from a paraboloid-shaped mass is much faster than for cylindric tablets; the heat exchange decreases with the increasing frozen layer thickness.

3. Reduced chemical and physical changes: *e.g.*, oxidation reactions on the surface of the tablet, concentration of salts and possible protein (enzymes) denaturation, particle accumulation from suspensions, and emulsion cracking due to the reduced freezing time.

4. Absence of undercooled areas which might be formed in the cylindric tablets due to the rotation of the solution during the freezing time.

5. Absence of fractional crystallization of products contained in the solution to be frozen.

6. Constant thickness of the layers due to the rotation during the freezing. As a consequence, a shorter time and a regular progression in the drying process can be obtained (14).

7. Formation of tiny and compact crystals from which a compact and amorphous freeze-dried product is obtained.

8. Possibility to reduce the amount of support to be added to the solution.

9. Reduced refrigeration energy consumption to overcome the eutectic zone and to get complete freezing.

In the Drying Phase—1. High development of the evaporation surface (Table I, Column *S*), which is about four times as large (Table I, Column *Rs*) as the surface of the solution frozen in single-cylindric tablets in similar vials.

2. Rapid and deep heat penetration into the layer.

3. High drying rate (Fig. 7) due to the minimal resistance of the dried layer to the evaporation of the solvent.

4. Increased drying efficiency as a result of Points 2 and 3.

5. Absence of both visible and invisible fusion areas.

6. Compact and homogeneous aspect of the final product.

7. Higher reconstitution rate of the solution.

8. Reduced thermal energy required for ice elimination.

A comparison of the working conditions of the rotating freezer (Column A) and those of the conventional system (Column B) is shown in Table II. In Case A, a conventional freeze-drying apparatus was used, equipped with a static freezer with 24 trays, a freeze-drier with 24 trays, and a rotating freezer with two trays. In Case B, the same apparatus as in A was used except for the ab-

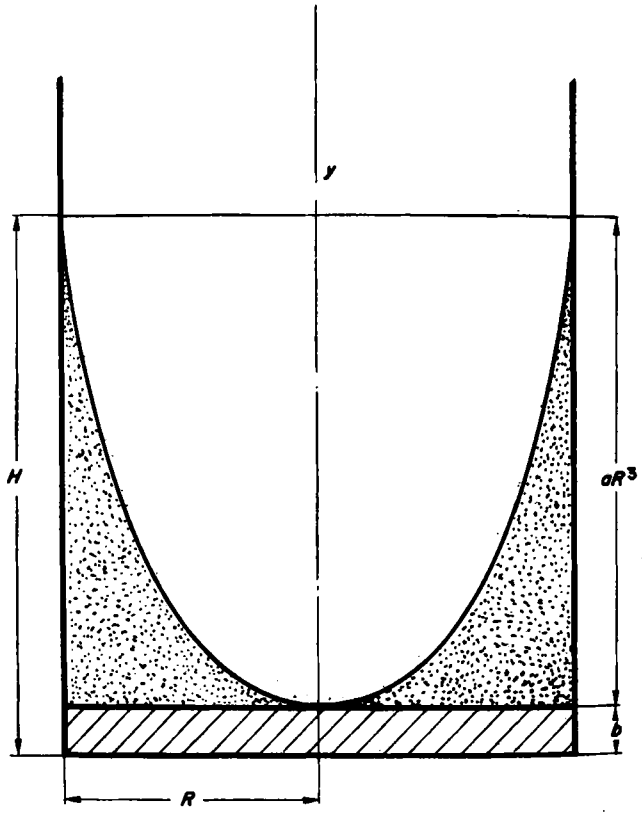

Figure 4—*Geometry of the rotating paraboloid tablet. Key:* H = *total height*, aR^2 = *paraboloid height*, b = *bottom thickness*, R = *paraboloid radius, and* y = *paraboloid axis.*

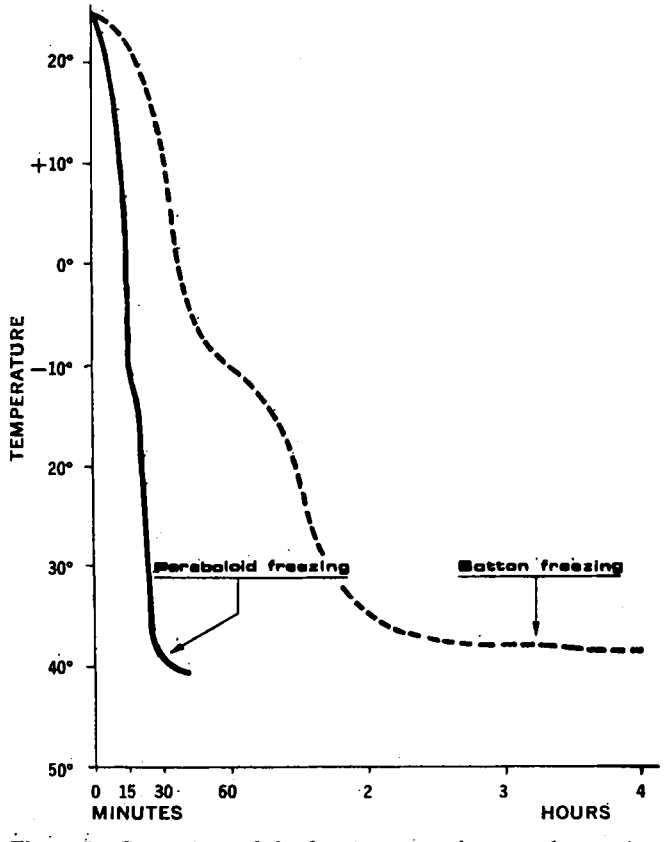

Figure 5—*Comparison of the freezing curves between the rotating paraboloid-shaped vial* (——) *and the cylindric (or bottom freezing) vial* (- - -).

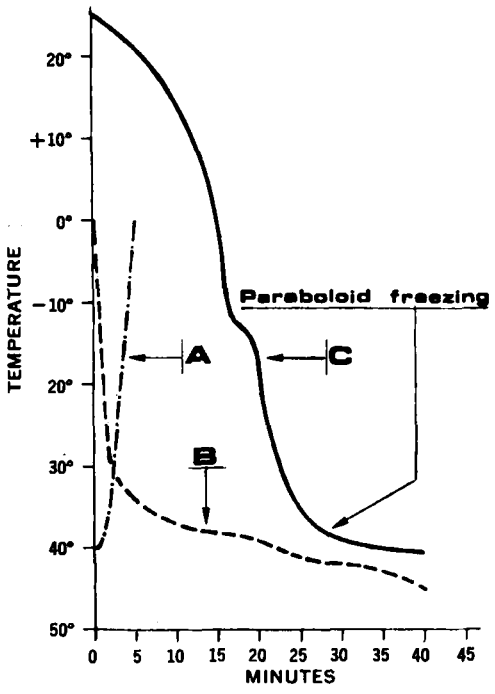

Figure 6—*Graph of the frozen curve of the rotating paraboloid-shaped vial (C). The temperature control was set at −45°. Key: A, temperature of open devia during loading process; B, temperature of closed devia during freezing process; and C, product temperature during freezing.*

sence of the rotating freezer. The minimal times shown in the table are relative to compact cycles without "dead time," while the maximum times represent the real operative time. From the data reported in Table II, it is evident that with A it is possible to reduce the time of operation to 30–50%.

CALCULATIONS

The values of ϕ, VL, and H were measured and the therms were calculated from the cubic paraboloid using the following formulas:

Calculation of V—The volume of the solution when it is at the frozen state is given by:

$$V = \frac{cVL}{0.9} + dVL \qquad \text{(Eq. 1)}$$

where:

VL = volume of solution at liquid state
V = volume of VL at frozen state
c = real percent of water in solution
d = percent of substance dissolved in solution
0.9 = ice density

Calculation of a—This constant of the cubic paraboloid has the following equation:

$$y = ar^2 \qquad \text{(Eq. 2)}$$

Table II—Comparison of Working Hours between Paraboloid (A) and Bottom Freezing (B) Methods

A		B		Remarks
0.5 hr.	6 hr.	6 hr.	15 hr.	Freezing time, 24 trays[a]
10 hr.	12 hr.	20 hr.	24 hr.	Drying time, 24 trays
10.5 hr.	18 hr.	26 hr.	39 hr.	Total hours

[a] This time course is calculated from the moment when the last tray full of dosed vials is placed into the statical freezer to the moment when the first tray with frozen vials is carried from the freezer to the drying room.

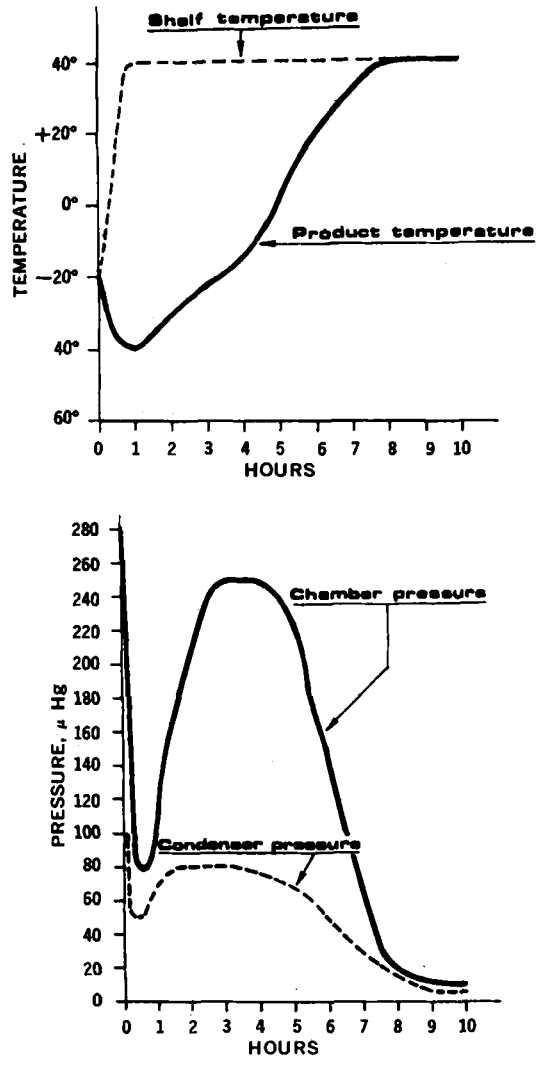

Figure 7—*Temperature–time and pressure–time curves characteristic of the drying cycle for the rotating paraboloid-shaped vials.*

after a series of control measurements. This equation reproduces satisfactorily the shape of the surface of the product frozen in an inclined vial and on a turning support.

$$V = \pi R^2 H - \frac{3}{5}\pi R^5 a \qquad \text{(Eq. 3)}$$

where:

$\pi R^2 H$ = total volume at total height H (Fig. 4)
$\frac{3}{5}\pi R^5 a$ = volume of cubic paraboloid (empty part of Fig. 4)

Equation 3 is used to find out a required to calculate b and S. Thus it becomes:

$$a = \frac{\pi R^2 H - V}{\frac{3}{5}\pi R^5} \qquad \text{(Eq. 3a)}$$

Calculation of b—The bottom thickness (Fig. 4) is given by:

$$b = H - aR^2 \qquad \text{(Eq. 4)}$$

where:

H = total height
aR^2 = paraboloid height

Calculation of S—The inside paraboloid surface is given by:

$$S = 3\pi a \left\{ \frac{R^2}{2} \cdot \left(\frac{1}{9a^2} + R^4 \right)^{1/2} + \frac{1}{18a^2} \ln \left[R^2 + \left(\frac{1}{9a^2} + R^4 \right)^{1/2} \right] - \frac{1}{18a^2} \ln \frac{1}{3a} \right\} \quad \text{(Eq. 5)}$$

Calculation of *Rs*—The ratio between paraboloid (*S*) and the upper surface of a cylindric tablet is given by:

$$Rs = \frac{S}{\pi R^2} \quad \text{(Eq. 6)}$$

Calculation of S_1—The surface of thermal exchange for a statically frozen vial is given by:

$$S_1 = Sf + Scs \quad \text{(Eq. 7)}$$

where:

Sf = base surface
Scs = cylindric lateral surface corresponding to height of statically frozen solution

Calculation of S_2—The surface of the thermal exchange of the frozen paraboloid-shaped vial is given by:

$$S_2 = Sf + Scp \quad \text{(Eq. 8)}$$

where:

Sf = base surface
Scp = cylindric lateral surface corresponding to height of paraboloidally frozen solution

CONCLUSIONS

With the above-described apparatus and technique, solutions, suspensions, and emulsions can be frozen in vials or small containers. An improvement of the freeze-dried product and a reduced cost are obtained due to the large surface and the thickness of the layer.

The increased freezing and drying rates make it possible to carry out two working cycles a day with the same lyostat. The described method is carried out with a rotating freezer, which represents only a further addition to the normally used apparatus of a freeze-drying department. Therefore, it is not necessary to make any substitution or to change the existing plants, except for the collecting vial trays with a drilled bottom. The reported calculations (Table I) are useful to obtain the necessary thickness at the vial bottom with a given height of the frozen paraboloid-shaped liquid. This height depends

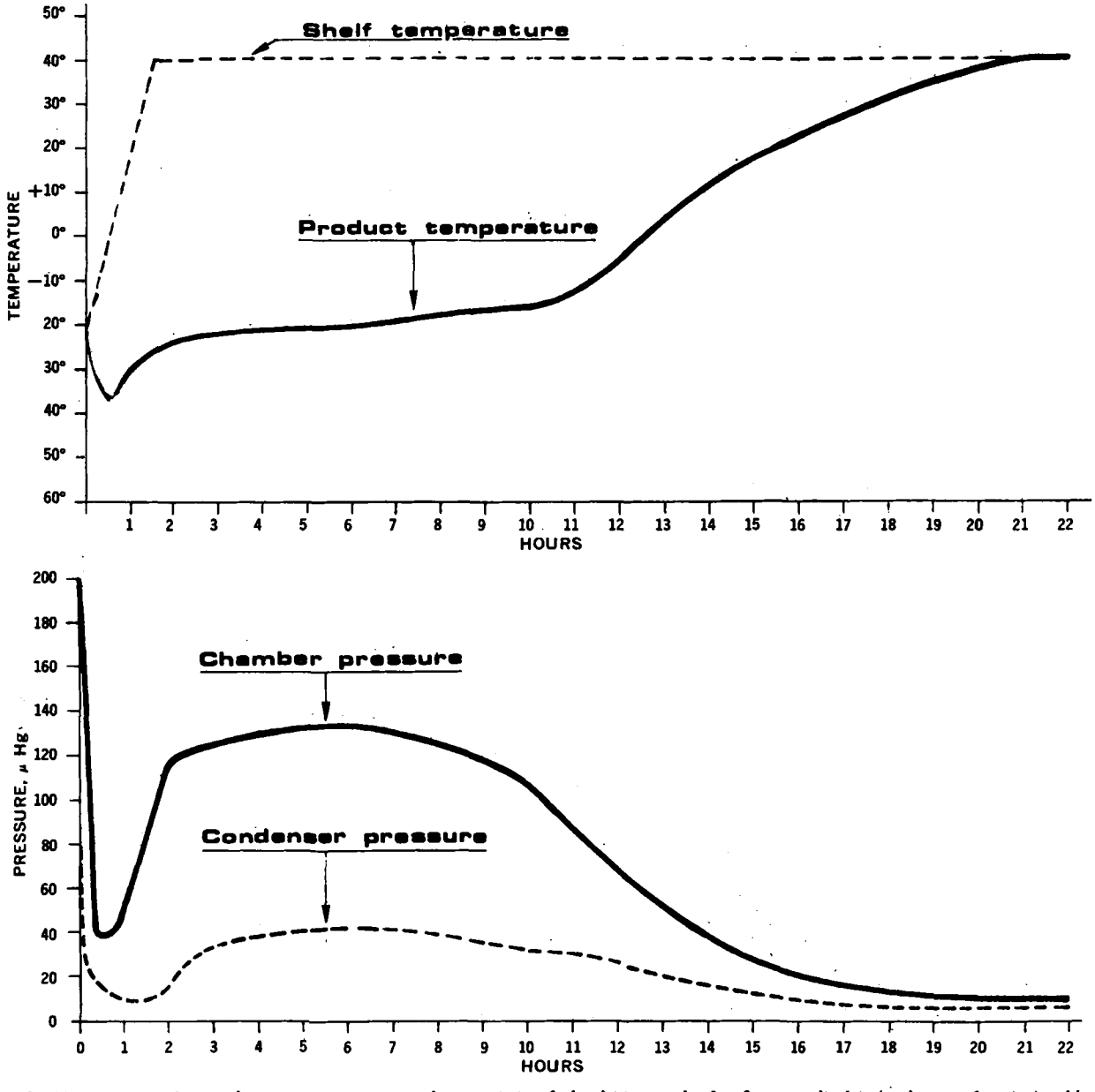

Figure 8—*Temperature–time and pressure–time curves characteristic of the drying cycle for frozen cylindric (or bottom freezing) tablets.*

on the freezer inclination and the volume of the liquid. With a different inclination of the freezer corresponds a different heat exchange surface which, therefore, can be changed according to the working conditions.

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Evaluation of Magnetic Basket Dissolution Apparatus I: Differences in Tablet Formulations

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Abstract □ The use of the magnetic basket dissolution apparatus as a means of following the dissolution of tablets was studied. Several different formulations of pentobarbituric acid tablets were manufactured and used to illustrate the ability of the magnetic basket dissolution apparatus to differentiate between the dissolution of tablets with differences in particle size of active ingredients, in formulation, and in hardness. The magnetic basket dissolution apparatus was compared with the USP XVIII and Levy beaker methods for following dissolution. Log probability plots were used as a means of providing a quick and accurate dimension for analyzing dissolution data.

Keyphrases □ Dissolution equipment—comparison of magnetic basket apparatus with compendial and Levy beaker methods for studying differences in tablet formulations □ Magnetic basket dissolution apparatus—differentiation between tablet formulations, compared with compendial and Levy beaker methods □ Tablet dissolution—magnetic basket apparatus used to study formulation differences, compared with compendial and Levy beaker methods □ Log probability plots—used to analyze dissolution data, magnetic basket apparatus compared with compendial and Levy beaker methods

In vitro dissolution profiles are of importance when they can be correlated to *in vivo* studies or when the results can be used to evaluate and examine relative differences in drug dissolution and, hence, availability for absorption between dosage forms or differences from batch to batch of the same formulation. Implied by these qualities is reproducibility of dissolution profiles for the dosage form and drug in question. An *in vitro* technique incorporating these capabilities is, of course, the ideal for which one strives.

In this quest, Levy and Hayes (1, 2) showed that the round-bottom beaker method in combination with slow agitation rates simulates, in physical appearance, the deposition of the dosage form in the stomach and mimics *in vivo* disintegration. In an earlier report (3), it was shown that the magnetic basket yielded reproducible dissolution results for both capsules and tablets. During the initial investigation of the magnetic basket, the concern was to ascertain the degree of reproducibility possible; in addition, it was found that certain characteristics of capsule disintegration and dissolution could be determined from the results. One type of tablet was examined, and it was determined that dissolution from this tablet could be reproducibly followed using the magnetic basket. No attempt at comparisons with other methods was made at that time.

This report delineates the reproducibility for dissolution of tablets, and it shows that the magnetic basket can be used to detect formulation differences in tablets. In this study, comparisons of the dissolution rate using the magnetic basket, the USP XVIII basket, and the Levy round-bottom beaker are discussed.

EXPERIMENTAL

Material—Pentobarbituric acid powder and pentobarbituric acid micronized were supplied by a commercial source[1]. The dissolution medium consisted of a buffer mixture (4) of hydrochloric acid and potassium chloride at pH 2. Fast flow lactose[2], microcrystalline cellulose[3], starch[4], and stearic acid[5] were purchased.

[1] Abbott Laboratories.
[2] Foremost Dairy, San Francisco, Calif.
[3] Avesil, FMS Corp., Newark, Del.
[4] Ruger Chemical Co., Inc., Irving, N. J.
[5] Fisher Chemicals, Fair Lawn, N. J.