

Spray Congealing: Particle Size Relationships Using a Centrifugal Wheel Atomizer

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Stearic acid-ethylcellulose mixtures were spray congealed using a specially instrumented Niro laboratory model spray dryer. Thirty-five runs were conducted under various operating conditions. The variables studied included atomizer wheel speed (11,900 to 43,100 r.p.m.), feed rate (32 to 280 Gm. per minute), and feed viscosity (0.098 to 1.995 poise). The volume-surface mean diameter, D_{vs} , for each congealed product was obtained from Fisher subsieve sizer measurements. The influence of each variable on the mean particle size is correlated by simple exponential equation which relates D_{vs} to feed viscosity, peripheral wheel velocity, and to feed rate per unit wetted wheel periphery. Predicted particle sizes closely agree with those determined experimentally.

THE USE OF spray congealing techniques for modifying the physical, chemical, and/or physiological behavior of pharmaceutical materials has gained increasing attention within recent years. Robinson and co-workers, in their development of sustained-release sulfonamides (1, 2), extended the conventional spray congealing or "prilling" unit operation (3) to pharmaceutical formulations. The general technique was applied by others in the preparation of tasteless forms of several water-soluble vitamins (4) and iron salts (5) and in formulating stabilized, sugar-based flavoring agents (6). The use of spray congealing in conjunction with fluidization procedures for the manufacture of free flowing particles containing vitamin A and other liquid materials has been reported (7). Spray congealing methods also have been applied to citric acid, sodium bicarbonate, and other pharmaceutical materials in order to modify their moisture sensitivity, rate of solubility, and compatibility (8).

These spray congealed products generally are prepared by suspending the active ingredient in a melt of a suitable "coating" or matrix material, then atomizing the hot liquid mixture into a cool chamber. Conventional spray dryers operating with a cool inlet air often are used for this purpose. Feed rates and temperature conditions are adjusted to insure rapid congealing of the atomized liquid droplets. The powder collected as product consists of individual, more or less, spheri-

cal particles, each of which contains bits of active ingredient suspended in a matrix of the coating agent (8).

Waxes, fatty acids and alcohols, plastics, sugars, and other materials which are solids at room temperature and melt without decomposition can be used as matrix agents. The behavior of the final congealed product depends in part on the properties (solubility, hydrophobicity, permeability, etc.) of the specific matrix selected. The characteristics of the congealed material also are governed by the particle size of the product. This factor is particularly important in controlling the bulk density, grittiness, and the distribution and coverage of the active ingredient in the matrix.

The engineering literature includes a number of reports in which relationships between the particle size characteristics of atomized materials and the conditions of atomization have been studied (9-13). The majority of work has concerned nozzle-type atomizers (14-17). Centrifugal wheel-type atomizers of the type commonly used in pharmaceutical operations have been studied, but usually in connection with spray



Fig. 1.—Centrifugal wheel atomizer. Wheel has radius = 2.50 cm., 24 vanes, vane height = 5.82 mm., width of vane opening = 3.51 mm.

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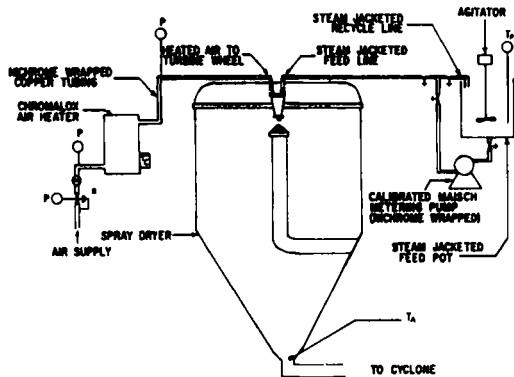


Fig. 2.—Schematic diagram of equipment used for spray congealing. Instruments and controls include: T_p , pot thermometer; P , pressure gauge; R , reducer valve; N , needle valve; T_C , thermostatic control; T_A , outlet air thermocouple; \boxplus jacketed gate valve.

drying applications (18–21). Information of direct value in the spray congealing of pharmaceutical systems has not appeared in the literature previously.

The object of the present study was to develop the relationships between the average particle size of a spray congealed product and several of the more important process variables. A centrifugal wheel-type atomizer was used, and the variables studied included liquid feed rate, feed viscosity, and atomizer wheel speed. The experimental system was designed so that the results would have particular application to spray congealing procedures of interest in pharmacy.

EXPERIMENTAL

Materials.—Molten stearic acid (single-pressed) thickened with various proportions of dissolved ethylcellulose¹ was used as the test system. Melt viscosities for each mixture were determined using an Epprecht viscometer.² Over the range of ethylcellulose concentrations (0 to 4.0% w/w) and temperature (68.0 to 72.0°) studied, all systems showed Newtonian flow characteristics. Measurements of surface tension at 68 to 72° were obtained with a Du Nouy tensiometer using a hot water jacketed Petri dish as a sample holder.

Equipment.—A Niro laboratory spray dryer³ operating with inlet air at ambient temperature (25–27°) was used for the spray congealing studies. The Niro unit employs an air-driven, rotating, vaned wheel for atomization of the liquid feed. A single wheel of the type shown in Fig. 1 was used for all runs

A calibrated Maisch metering pump,⁴ electrically heated by nichrome wire windings, was used to deliver feed material to the atomizer. Flow rates were calculated by measuring the liquid volume

pumped per unit time through the steam-traced feed line leading to the atomizer. This measure of flow rate was repeated at the start and end of each run. The rates obtained by these measurements agreed with each other within $\pm 1.0\%$. Cyclone losses were estimated from material balance calculations. The over-all equipment setup used in these studies is illustrated in Fig. 2.

Continuous readings of atomizer wheel speeds during each run were obtained using a Minitron proximity impulse generator⁵ mounted opposite a steel extension of the wheel shaft. A small hole was drilled through this extension to break the magnetic field of the generator, thus creating two impulses per wheel revolution. The signals from the generator were amplified and fed to a Hewlett-Packard tachometer indicator⁶ which gave direct dial readings of wheel speed in revolutions per minute.

Wheel speeds were controlled by regulating the turbine air pressure through a pressure reducer and needle valve assembly which is standard equipment on the Niro unit. Wheel speed was maintained substantially constant (± 200 r.p.m.), during each run.

Feed temperature at the wheel was obtained from a thermocouple which had been introduced down the atomizer feed tube and terminated at the liquid entrance to the wheel. In all cases, this temperature measurement was within $\pm 0.5^\circ$ of the feed temperature measured at the feed pot.

Figure 3 presents a schematic diagram of the

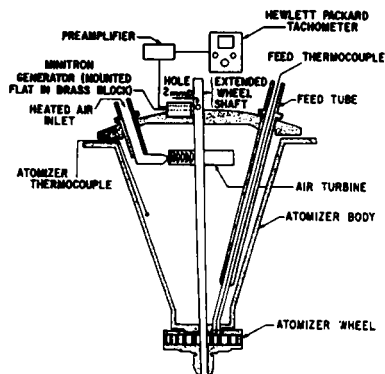


Fig. 3.—Schematic diagram of atomizer and instrumentation.

atomizer head and its accompanying instrumentation.

Operating Procedure.—At the start of each run the atomizer head was brought to approximately 75° by using heated air at 80° to drive the air turbine. This preheating prevented the melt from congealing in the atomizer feed lines or on the wheel during the run. Molten feed then was circulated through the pump and feed lines until a constant flow rate and a constant melt temperature in the range of 68–72° was obtained. The atomizer wheel was brought to approximately the desired speed, and feed to the wheel started. Slight corrections in the turbine air pressure, which were required to compensate for the increased load on the wheel, were made immediately. The small amount of product (5–10 Gm.) collected in the cyclone during this start-up period was dis-

¹ Ethocel, 50 cps., Dow Chemical Co., Midland, Mich.

² American Optical Co., Pittsburgh, Pa.

³ Nichols Engineering and Research Corp., New York, N. Y.

⁴ Mechanical Product Corp., Chicago, Ill.

⁵ Minatron Corp., Belle Mead, N. J.

⁶ Model 500 C, Hewlett-Packard, Inc., Palo Alto, Calif

carded. Approximately 2000 Gm. of product was prepared in each test. The entire equipment assembly was dismantled and cleaned between runs.

For these studies, feed rates were varied from 32 to 280 Gm. per minute. Wheel speeds ranged from 11,900 to 43,100 r.p.m. The viscosities examined were from 0.098 to 1.995 poise. Viscosity values were obtained from predetermined relationships between viscosity and temperature for each stearic acid-ethylcellulose mixture and from the measured temperature of the feed at the wheel.

The order in which the operating variables were changed from run to run followed a predetermined randomized design so that experimental bias would be minimized. Four sets of duplicate experiments were conducted to establish the reproducibility of the results.

The experimental conditions used in each run are listed in Table I.

Particle Size Determinations.—Samples taken for particle size analysis were obtained as coned and quartered aliquots of the total product collected in each run. To confirm the reliability of this sampling procedure, analyses were occasionally performed on duplicate samples obtained by repeating the cone and quartering procedure. In all cases examined, the agreement of the results was within $\pm 2\%$.

The particle size was determined with the Fisher subsieve sizer. Density values required for these determinations were obtained for each composition by the (liquid) pycnometer method.

TABLE I.—EXPERIMENTAL CONDITIONS USED IN SPRAY CONGEALING RUNS

Run	System (Wt. % Ethylcellulose Combined with Stearic Acid)	Feed Rate, F (Gm./Min.)	Feed Temp., °C.	Wheel Speed, W_s (r.p.m.)
1	0.0	47	67.5	20300
2	0.0	170	68.0	20500
3	0.0	168	68.0	31900
4	0.0	32	68.5	41300
5	0.0	280	70.5	17600
6	0.0	32	69.0	43100
7	0.0	33	69.0	22300
8	0.0	33	71.0	30400
9	0.0	110	68.5	38200
10	0.0	110	69.0	25300
11	0.0	170	69.5	33200
12	0.0	110	69.5	16800
13	0.0	112	68.5	28900
14	0.0	272	69.5	18500
15	0.0	46	68.5	11900
16	0.0	111	69.0	35600
17	0.0	46	72.0	29600
18	0.0	46	71.5	20300
19	0.0	272	72.0	21600
20	0.0	168	70.0	23600
21	0.0	168	70.0	29400
22	0.0	46	71.0	39000
23	0.0	32	70.5	18400
24	0.0	110	70.0	25200
25	0.0	168	70.0	31800
26	0.0	46	70.0	29600
27	2.5	110	72.0	34300
28	2.5	46	71.5	38500
29	2.5	110	70.5	20300
30	2.5	168	71.5	30700
31	2.5	272	72.0	27900
32	1.5	32	72.0	24500
33	1.5	46	70.5	30500
34	4.0	32	70.5	37100
35	4.0	110	69.5	24000

TABLE II.—VALUES FOR THE EXPERIMENTAL OPERATING VARIABLES AND AVERAGE PARTICLE SIZES

Run	Feed Rate Per Unit Wetted Wheel Periphery, ^a F_p (Gm./Sec./cm.)	Peripheral Wheel Velocity, ^b V_p (cm./Sec.)	Feed Viscosity, μ (poise)	Mean Surface-Volume Particle Size of Product, ^c D_{vs} (μ)
1	0.0174	5300	0.108	25.4
2	0.0630	5400	0.107	31.6
3	0.0622	8300	0.107	25.7
4	0.0118	10800	0.106	17.4
5	0.104	4600	0.102	38.2
6	0.0118	11300	0.105	18.2
7	0.0122	5800	0.105	26.5
8	0.0122	8000	0.100	19.3
9	0.0408	10000	0.106	22.3
10	0.0408	6600	0.105	26.4
11	0.0630	8700	0.104	25.8
12	0.0408	4400	0.104	32.2
13	0.0415	7600	0.106	25.1
14	0.101	4800	0.106	39.7
15	0.0170	3100	0.106	35.6
16	0.0412	9300	0.105	23.5
17	0.0170	7700	0.098	22.1
18	0.0170	5300	0.099	26.5
19	0.101	5700	0.098	39.7
20	0.0622	6200	0.102	31.5
21	0.0622	7700	0.102	26.9
22	0.0170	10200	0.100	18.1
23	0.0118	4800	0.102	28.4
24	0.0408	6600	0.102	27.3
25	0.0622	8300	0.102	25.8
26	0.0170	7700	0.102	23.1
27	0.0408	9000	0.613	23.4
28	0.0170	10100	0.619	18.1
29	0.0408	5300	0.671	30.9
30	0.0622	8000	0.624	25.7
31	0.101	7300	0.613	29.0
32	0.0118	6400	0.328	22.0
33	0.0170	8000	0.341	18.8
34	0.0118	9700	1.845	17.9
35	0.0408	6300	1.940	28.4

^a Calculated from feed rate, F , as listed in Table I by

$$F_p = \frac{F \text{ (Gm./min.)}}{60 \text{ (sec./min.)} \times P \text{ (cm.)}}$$

where P is the total periphery of vane openings of the wheel, $P = 18.66$ (mm./vane opening) $\times 24$ (vane openings) = 45 cm. ^b Calculated from wheel speed, W_s , listed in Table I by

$$V_p = \frac{2\pi R \text{ (cm./rev.)} \times W_s \text{ (r.p.m.)}}{60 \text{ (sec./min.)}}$$

where R = wheel radius = 2.5 cm. ^c Fisher subsieve sizer values.

Particle size distributions were obtained also using the Sharples Micromerograph.

RESULTS

To establish a correlation between the operating variables (feed rate, F , feed viscosity, μ , and wheel speed, W_s) and the average particle size, a simple exponential equation was assumed to apply.⁷ Equation 1 served as the starting point

$$D_{vs} = K(F)^\alpha(W)^\beta(\mu)^\epsilon \quad (\text{Eq. 1})$$

where D_{vs} is the mean volume-surface diameter of the product,⁸ F is the feed rate, μ is the feed viscos-

⁷ It was assumed thereby that effects produced by the interaction of the variables would not be significant. This assumption appears to be justified by the results.

⁸ Average particle sizes obtained by Fisher subsieve sizer analysis are D_{vs} values.

ity, W , is the wheel speed, a , b , c are dimensionless constants, and K is a constant (proportionality factor) with dimensions necessary to make the equation dimensionally correct.

It was considered desirable to include appropriate terms in the final correlation to account for the differences in atomizer wheel size which may be employed with units of different production capacities and which have been studied by other workers (18, 20). Equation 1 confined itself to data obtained with a single wheel size. To remove this limitation, various methods of expressing feed rate, F , and the wheel speed, W , which were independent of wheel size, were tested in Eq. 1. Equation 1 was best modified by expressing wheel speed in terms of peripheral wheel velocity and feed rate in terms of feed rate per unit wetted wheel periphery. Equation 2 shows this form of the relationship

$$D_{50} = K(F_p)^a (V_p)^b (\mu)^c \quad (\text{Eq. 2})$$

where F_p is the feed rate per unit wetted wheel periphery, grams per second per centimeter, V_p is the peripheral wheel velocity, centimeters per second, and K , a , b , c , and μ are as defined in Eq. 1.

The values of F_p , V_p , and feed viscosity for each experimental run are listed in Table II. The average particle size of the product obtained in each run is given in Table II also.

Equation 2 was set in logarithmic form and the constants K , a , b , and c calculated from the experimental data by the method of least squares. The best fit to the experimental data was obtained by Eq. 3

$$D_{50} = 5240 F_p^{0.171} V_p^{-0.539} \mu^{-0.017} \quad (\text{Eq. 3})$$

where F_p is the feed rate per unit wetted wheel periphery, grams per second per centimeter, V_p is the peripheral wheel velocity, centimeters per second, and μ is the feed viscosity, poise.

D_{50} values were calculated from Eq. 3 using the values of F_p , V_p , and μ established in each run (Table II). These calculated average particle sizes are compared with those determined experimentally in Fig. 4.

DISCUSSION

The instrumentation developed for this study allowed close control of the spray congealing process. As a result, essentially constant operating conditions

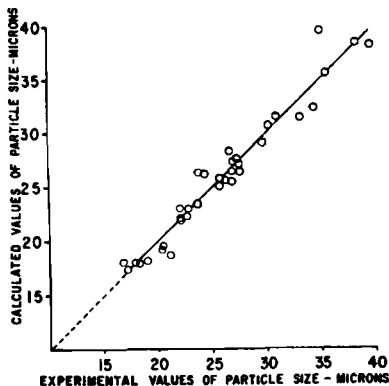


Fig. 4.—Comparison of experimental values of average particle size (D_{50}) with values predicted by Eq. 3.

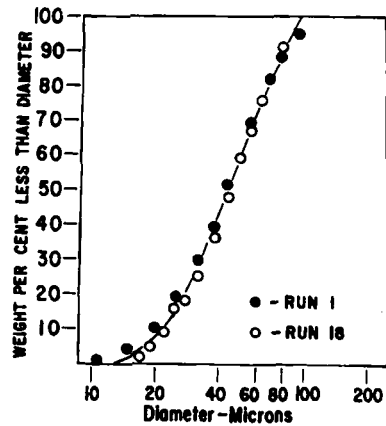


Fig. 5.—Micromerograph data for runs 1 and 18 illustrating reproducibility of results.

could be maintained during the course of each run. It was also possible to set each variable at its predetermined level quickly at the start of each run and thereby minimize product contamination during the start-up period. The Minitron generator and Hewlett-Packard tachometer system for measuring wheel speed was particularly useful, since preliminary trials showed that neither friction tachometers nor stroboscopic techniques could be applied for measuring this variable.

The particle size characteristics of the spray congealed products appear to be reproducible. This is indicated, for example, by comparison of the average particle size values obtained in duplicate runs 3 and 25 (25.7 and 25.8 μ , respectively), duplicate runs 17 and 26 (22.1 and 23.1 μ , respectively), and duplicate runs 4 and 6 (17.4 and 18.2 μ , respectively). Particle size distributions obtained with the Sharples Micromerograph are shown in Fig. 5 for duplicate runs 1 and 18 and further demonstrate the reproducibility of results.

Cyclone losses in the present experiments were estimated to be less than 0.3%. The particles passing the cyclone were most probably those with the smallest diameters. While the presence of these particles would modify average particle size values if calculated on the basis of particle count,⁹ their influence on Fisher D_{50} averages would not be significant.¹⁰

In developing final relationships between the particle size and the operating variables, several techniques of measuring and expressing the average particle size were tested. Correlations were generated using average particle size values obtained by Micromerograph analysis and expressed both in terms of D_{50} and D_{mm} (mass median diameter). These correlations, however, did not fit the experimental data so closely as the correlation obtained using Fisher D_{50} values (Eq. 3).

The final correlation derived in this study is given by Eq. 3 and shows that particle size increases with

⁹ As obtained from microscopic analysis for example.

¹⁰ This was shown by calculation of D_{50} values for an extreme hypothetical system containing 99.7% (by weight) of particles with diameter equal to 10 μ plus 0.3% of particles with diameter equal to 1 μ . This D_{50} value differed by only 2.5% from the value calculated assuming no small particles were present in the system. The conclusion also was confirmed experimentally. This was done by blending 2.0% by weight of particles having a measured Fisher D_{50} of 17.4 μ with 98% of particles having a D_{50} of 39.7 μ . The Fisher value obtained with the mixture was 39.6 μ .

decreasing wheel speed (peripheral velocity), increasing feed rate, and decreasing feed viscosity. The present results indicate that particle size varies inversely as the 0.54 power of the peripheral velocity. This value is in reasonable agreement with Wallman and Blyth's value of 0.6 (21) and Meyer's value of 0.69 (20). However, Friedman, *et al.*, found that particle size varied inversely as the 0.9 power of the peripheral velocity (18).

The present correlation also shows that particle size varies directly as the 0.17 power of feed rate. This result closely agrees with the results of Wallman and Blyth (0.11), Friedman, *et al.* (0.2), and Meyer (0.21). Thus, feed rate appears to exert less influence on particle size than wheel speed. This points to the relative importance of controlling wheel speed to obtain spray congealed products with reproducible size characteristics.

The correlation expressed in Eq. 3 shows that feed viscosity has little if any influence on particle size. The negative value of the exponent, however, is surprising in view of the reports of others which indicate that particle size tends to increase with increasing viscosity (13, 18).

The close agreement of the particle sizes calculated by Eq. 3 and the experimentally determined

values are evident in Fig. 5. Table III summarizes data on the deviation of calculated and experimental values. The average deviation for all runs was 1.0μ . The deviation was less than 1.8μ in 31 of the 35 runs.

These results also suggest that second and higher order interactions of the variables are not involved in the atomization.

Changes in surface tension of the liquid feed have been reported to have a small but significant effect on particle size (18). In the present study, surface tension was relatively constant at 27.8 dynes per cm. and did not vary by more than $\pm 1.0\%$ for any of the test systems. The correlation, therefore, could not be extended to include this variable. The influence of surface tension is contained, however, in the statement of the constant K in Eq. 3. This constant would be expected to take higher numerical values with increasing surface tension.

The stearic acid-ethylcellulose system selected for this study is representative of other wax mixtures which may be used as matrix agents in spray congealing operations. The system exhibited Newtonian flow characteristics over the complete range of test conditions. This simplified the estimation of feed viscosity at the point of atomization, *i.e.*, at the wheel periphery. It should be noted, however, that concentrated suspensions of active ingredients in molten wax often are of interest in spray congealing processes. These systems may show non-Newtonian behavior. For such cases, the viscosity at the wheel will vary with shear rate, and therefore with wheel speed. Viscosity is not in effect an independent variable and must be estimated independently for each wheel speed used.

CONCLUSIONS

The results of this study show that the average particle size (D_w) of spray congealed stearic acid varies directly with the 0.17 power of the feed rate, inversely with the 0.54 power of the peripheral wheel velocity, and inversely with the 0.02 power of feed viscosity. Except for the latter variable, the correlations developed here are in general agreement with those previously reported for spray drying operations. The lack of agreement regarding the influence of feed viscosity is of little practical concern since changes in viscosity over the limits studied in this report (and in the reports of others) exerted negligible effects on particle size.

Average particle sizes calculated by the equations derived in this report showed excellent agreement with the experimental values. The average deviation of the predicted values from the experimental values was $\pm 1.0 \mu$. The results of duplicate runs indicate that products with reproducible particle size characteristics are obtainable.

In the absence of other information, the correlation developed here should be useful in arriving at first estimates of the wheel speed and feed rate required to obtain a given desired particle size. When specifications for the product have been established in laboratory runs, the correlating equation (Eq. 3) may help in approximating scale-up factors for the pilot and production level operations.

The instrumentation developed in the study was reliable, simple to construct, and provided close control of the congealing process.

TABLE III.—COMPARISON OF EXPERIMENTALLY DETERMINED AVERAGE PARTICLE SIZE WITH PREDICTED VALUES

Run	Exptl. Value of Particle Size ^a (μ)	Predicted Value of Particle Size ^b (μ)	Deviation (μ)
1	25.4	26.9	1.5
2	31.6	33.2	1.6
3	25.7	26.3	0.6
4	17.4	17.2	0.2
5	38.2	39.4	1.2
6	18.2	16.8	1.4
7	26.5	24.1	2.4
8	19.3	20.3	1.0
9	22.3	22.1	0.2
10	26.4	27.7	1.3
11	25.8	25.7	0.1
12	32.2	34.4	2.2
13	25.1	25.7	0.6
14	39.7	38.3	1.4
15	35.6	35.8	0.2
16	23.5	23.0	0.5
17	22.1	22.0	0.1
18	26.5	26.9	0.4
19	39.7	35.0	4.7
20	31.5	30.8	0.7
21	26.9	27.4	0.5
22	18.1	18.9	0.8
23	28.4	26.6	1.8
24	27.3	27.7	0.4
25	25.8	26.3	0.5
26	23.1	22.0	1.1
27	23.4	22.7	0.7
28	18.1	18.4	0.3
29	30.9	30.1	0.8
30	25.7	26.0	0.3
31	29.0	29.6	0.6
32	22.0	22.3	0.3
33	18.8	21.1	2.3
34	17.9	18.0	0.1
35	28.4	27.0	1.4

Av. Dev. = $\pm 1.0 \mu$

^a Fisher subsieve sizer values. ^b Values predicted by Eq. 3.

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Change of Ethylene Oxide Concentration During Gaseous Sterilization Process

By D. SATAS

The change of ethylene oxide concentration during the operation of laboratory and production sterilizers is reported. The rate of sorption is high at the beginning and decreases toward the end of a sterilization cycle.

ETHYLENE OXIDE (ETO) gas and its mixtures with carbon dioxide and fluorocarbons are widely used in the chemical sterilization of various pharmaceutical and hospital products. The principal use is for the sterilization of products which cannot be sterilized by steam without damage to their appearance or functionality. With an increasing utilization of heat-sensitive plastic materials, the importance of ETO as an efficient and economical sterilizing agent is growing.

This paper considers the change of ETO concentration during sterilization in laboratory and production size sterilizers, and discusses some of the experiences with a 10% ETO 90% CO₂ mixture at the Chicago Division of the Kendall Co.

Methods of ETO Analysis.—Chemical and infrared gas analyses were employed to assay the ETO concentration in the gaseous phase.

The reaction between epoxide compounds and hydrochloric acid to form the corresponding chlorohydrin was utilized to determine the ETO concentration (1). The reagent was prepared by dissolving 810 Gm. of CaCl₂·H₂O and 95 ml. of concentrated HCl in 1400 ml. of water. Although several gas sampling techniques provided adequate accuracy, it was most convenient to bubble the gas

slowly through gas washing bottles equipped with fritted glass cylinders and filled halfway with 150 ml. of reagent. Two wash bottles in series were used. At bubbling rates of 150–200 ml./minute and ETO concentrations of 10% or below, practically all ETO was absorbed in the first bottle. The gas flow rate was measured by a rotameter in series with the washing bottles. The amount of ETO absorbed was determined by titration of the excess acid with NaOH.

Infrared gas analysis is especially suitable for quick continuous determination of ETO and has been successfully used also by other workers (2). A known mixture of ETO and N₂ was used for calibration of the instrument. Such mixtures should be prepared carefully to assure their homogeneity. If any ETO is condensed in the calibration gas container, the discharge concentration will vary and might result in erroneous calibration of the instrument. For this reason, other more difficultly condensible gas mixtures (*n*-butane in N₂) can be used more conveniently for checking the analyzer once it has been calibrated with ETO.

ETO Changes in the Laboratory Sterilizer.—The change of ETO concentration in an 80-L. laboratory sterilizer manufactured by American Sterilizer Co.

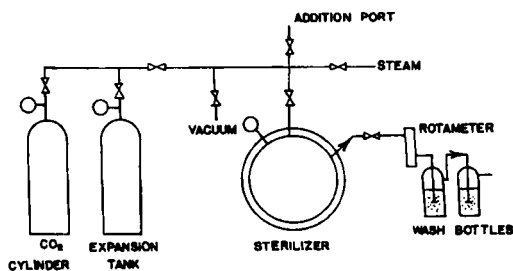


Fig. 1.—Schematic diagram of the equipment used for the laboratory sterilizer tests.

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