Surfactant Effects on Spray-Congealed Formulations of Sulfaethylthiadiazole–Wax

By PHILLIP M. JOHN* and CHARLES H. BECKER

An investigation was undertaken to examine the effects of selected formulation and production variables on the physical characteristics and dissolution patterns of spray-congealed particles of sulfaethylthiadiazole (SETD)–wax. Melted suspensions of SETD in wax formulations contained various concentrations of the lipophilic surfactant, sorbitan monooleate. Particle size was found to correspond to the size of nozzle used; smaller particles were characterized by faster rates of SETD release. Depending upon the concentration employed, sorbitan monooleate may increase or depress the rate of SETD released from the particles in 0.1 *N* HCl; the surfactant consistently promoted faster release rates in alkaline pancreatin solution. A log–log dissolution model was used to predict the release patterns of the products, and the model showed good agreement with the experimental data.

VERY LITTLE WORK of a research nature has been done in the area of spray congealing. Although the technique of spray congealing is used by many industries, the pharmaceutical industry has not accepted this process as quickly as expected. This unit operation (prilling) offers an expedient method of producing a fairly uniformly sized particulate product from a melted wax suspension or solution of a medicament without the difficulties often encountered with a comminution step. Spray-congealed particles may be combined into a tablet granulation, encapsulated, or incorporated into a liquid suspension (1). A variety of suitable matrix materials have been spray congealed to produce essentially tasteless products of iron compounds (2) and water-soluble vitamins (3).

A very complete enumeration of available atomization techniques and equipment has been reported by Marshall (4) in the engineering literature. The particle-size relationships of centrifugal-disk atomizers have been examined by Scott *et al.* (5). Single-fluid pressure nozzles are frequently used to spray congeal drug and lipid material mixtures; Lantz and Robinson (6) used such a nozzle located at the top of a spray-dryer tower. Although less commonly used on a commercial scale, pneumatic atomizing nozzles are particularly useful for producing very fine powders. Such a two-fluid nozzle was used by Cox (7) in a study of the effects of wax matrix, siphon height, and air pressure.

The dissolution rates of spray-congealed products of sulfamethylthiadiazole (SMTD) and hydrogenated castor oil in 0.1 *N* HCl and alkaline pancreatin solution were determined by Robinson, Bondi, and Swintosky (8). They showed that the release in humans of a single 4.0-Gm. dose of the spray-congealed product was extended over a 12-hr. period. In a later work (9), the drug release of a SETD-hydrogenated castor oil spray-congealed product was compared to that of crystalline SETD administered to human subjects; this study showed that approximately 50% of the sustained-release dosage form was available for early absorption, with the balance being absorbed over a prolonged time.

The purpose of the present investigation was to determine the effects of wax matrix material, atomizing nozzle orifice size, and surfactant concentration on the resulting *in vitro* dissolution patterns of spray-congealed products of SETD–wax intended for sustained- or prolonged-release medication. Generalizations concerning the effect of these three treatment variables on rate of production, resulting particle size, density, and porosity were also sought. White wax USP, a synthetic wax-like ester,[1] and a 1:1 combination of these two waxes were used as matrices. These waxes were chosen to obtain a range of plasticity between the pliability of white wax and the brittleness of the synthetic wax-like ester. Three distinct particle-size ranges were obtained by using three sizes of fluid nozzle orifices. The effect of the nonionic lipophilic surfactant sorbitan monooleate[2] was studied over the range of concentrations from 0 to 10% by weight.

EXPERIMENTAL

Throughout this investigation analytical reagent chemicals were used for the assay procedures, and waxes of food grade were employed in the spray-

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[1] Marketed as Glycowax S-932 by Glyco Chemicals, Inc., New York, N. Y.
[2] Marketed as Span 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

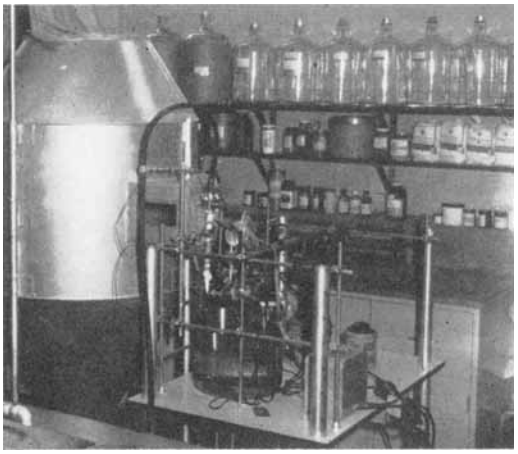

Fig. 1—Collection chamber attached to pneumatic atomizing nozzle of spray-congealing apparatus.

congealed samples. Sulfaethylthiadiazole (SETD) was obtained from American Cyanamid Co.

Manufacture of Spray-Congealed Samples—Ingredients totaling 2,000 Gm. for each formulation were combined and melted in a stainless steel beaker immersed in an 80 ± 0.5° constant-temperature oil bath. Suspension of the SETD was maintained through the use of a Lightnin model F laboratory-type mixer. A Teflon siphon tube wrapped with silicone-treated heater tape brought the melted wax mixture at the desired temperature from the beaker to the spraying nozzle. The 1/4 JCO pneumatic atomizing nozzle[3] was equipped with a specially designed nichrome wire heater and a copper-constantan thermocouple and monitor.[4] The nozzle was maintained at a temperature of 80 ± 3° throughout the spraying operation. Dry air at 60 p.s.i. provided the suction necessary to lift the melted formulation from the beaker through a constant siphon height of 30.5 cm. (12 in.) to the nozzle where atomization took place. The cloud of congealing wax droplets was directed into a galvanized steel collection chamber through the spraying port, and the product was collected from the base of the chamber's lower cone. A vortex was created during spraying operations by having the spraying port located 15 cm. (6 in.) left of center; the swirling flow of air inside the collection chamber helped to prevent the waxy particles from adhering to the walls of the chamber.

The assembled apparatus is shown in Fig. 1. The collection chamber was approximately 274.3 cm. (9 ft.) high. A cloth sleeve joined the atomizing nozzle to the spraying port, a cloth air-escape bag was attached to the upper cone, and a plastic collection bag was joined to the lower cone. The equipment was assembled as shown and preheated to 80° for 20 min. before atomization was begun. After a sufficient amount of product had been collected, the air and heaters were turned off. The product was then removed, weighed, and stored in glass jars. The remaining portion of the 2,000-Gm. formulation melt was allowed to cool in the beaker, then removed, weighed, and stored.

Problem Design—All formulations contained approximately 25% by weight SETD; the exact drug content of each product was determined by subsequent extraction and assay. Three wax bases were chosen that had been shown to release the drug favorably over an extended period of time (10). These bases were: white wax USP, a synthetic wax-like ester, and a combination of equal parts of these two waxes. Four levels of the surfactant sorbitan monooleate were used: 0, 1, 4, and 10% by weight. Each of these 12 different formulations was sprayed once through three fluid nozzle sizes; 0.02(~0.5 mm.), 0.04(~1 mm.), and 0.06(~1.5 mm.), in. diameter. This factorial design led to 36 samples, each with a unique set of the three treatment variables.

Particle-Size Analysis—Microscopic analysis, using a Zeiss filar ocular and a haemocytometer test cell, was selected as the best method of particle-size analysis. Mechanical sieving was not possible since the particles were too fine and too tacky in some instances to flow through the screens. Adequate deflocculation could not be maintained to enable the use of an electronic counter or a sedimentation technique.

Density Determinations—True density data were obtained from measurements made on the congealed portions of each formulation remaining in the beaker after spraying. Apparent bulk densities were determined by a standardized tapping method using a 100-ml. cylindrical graduate. Porosities and specific surfaces for each sample were then calculated from the results of the particle-size analysis and the density determinations.

Assay for SETD Content of Spray-Congealed Products—The test drug was extracted from the product by placing exactly 0.5000 Gm. of the spray-congealed sample in a 40-ml. portion of warm chloroform and washing several times with warm 0.1 *N* HCl, the washings being combined and made to volume in a 250-ml. volumetric flask with distilled water. An aliquot was assayed for SETD content by the Bratton-Marshall (11) colorimetric procedure for sulfonamides. The absorbance of the resulting solutions was determined on a Klett-Summerson colorimeter using a No. 54 filter and compared to a prepared standard curve. Duplicate extractions and assays were conducted on each spray-congealed sample.

Dissolution Studies—The release characteristics of the spray-congealed SETD–wax particles were examined by the method of Robinson and Swintosky (9). For the acid studies, 14 aliquots of the product were weighed and placed in 90-ml. glass vials. Each aliquot contained 0.1200 Gm. SETD, as determined by prior assay, and weighed between 0.4 Gm. and 0.5 Gm. Sixty milliliters of simulated gastric fluid (0.1 *N* HCl, pH 1.1) was added to each vial, and the vials were clamped into the rotating-bottle apparatus described by Souder and Ellenbogen (12). A constant-temperature water bath was used to maintain a temperature of 37 ± 1°, and filtered into 250-ml. conical flasks after 1/4, 1/2, 3/4, 1, 1 1/4, 1 1/2, and 2-hr. intervals. One milliliter of the filtered eluant was transferred to a 100-ml. volumetric flask and made to volume with distilled water. The samples were then assayed for SETD content by the Bratton-Marshall method. Duplicate samples were also eluted in the HCl for extended time periods from 20 to 60 hr. These later points were

[3] Manufactured by Spraying Systems Co., Bellwood, Ill.
[4] Built by the Bioelectronics and Instrument Dept., J. Hillis Miller Health Center, University of Florida.

used to estimate the amount of SETD that would eventually be released if extracted for an infinite period of time.

Similar studies were conducted in simulated intestinal fluid (alkaline pancreatin solution, pH 8.3) with the following differences: Each aliquot contained 0.6000 Gm. SETD and weighed between 2.2 and 2.5 Gm. Two samples were withdrawn from the rotating-bottle device after 1/4, 1/2, 3/4, 1, 2, 3, 4, and 6 hr. had elapsed. Two-tenths milliliter of the filtrate was transferred by pipet to 100-ml. volumetric flasks and made to volume with distilled water. In all other respects, the procedures for the acid and the alkaline dissolution studies were identical.

Mathematical Calculations for Estimating Drug Released—A log–log model first developed by Cox (7) for spray-congealed particles of white wax and the synthetic wax-like ester containing no surfactant showed good agreement with the experimental data of this investigation. It may be written in the following forms:

$$\log (1 - C/C_e) = -c \log (1 + t/d) \quad \text{(Eq. 1)}$$

$$C = C_e [1 - (1 + t/d)^{-c}] \quad \text{(Eq. 2)}$$

where C is the amount of drug released in time t, C_e is the equilibrium solubility, and c and d are parameters specific for a given formulation determined by minimizing the quantity $\Sigma(\hat{C} - C)^2$ utilizing the experimental data of a completed dissolution study. A least-squares solution in terms of $\log (1 - C/C_e)$ (from Eq. 1) would not be the solution of choice in terms of C. Since experimental errors were approximately of equal variance along the dissolution curve, it is best to find the least-squares fit in terms of C, Eq. 2. This second equation is not a linear function of the unknown constants; therefore, there is no explicit formula for the calculations of the least-squares estimates of the parameters. An iterative procedure must be used that will converge to the best-fitting values. A number of such procedures exist; the method used was a modified Gauss-Newton nonlinear least-squares procedure (13).

RESULTS AND DISCUSSION

Production Rates—Of the three treatment variables considered, nozzle orifice size almost entirely determined the rate of production. The average rate for the 0.02-in. nozzle was 3.9 Gm./min., for the 0.04-in. nozzle the rate was 54.0 Gm./min., and for the 0.06-in. nozzle, 127.4 Gm./min. The rate of production of the largest nozzle was approximately of the same order as those reported by Scott and co-workers (5) using a centrifugal-disk atomizer 5 cm. in diameter.

Frequent clogging occurred when the smallest nozzle was used, and almost continuous operation of a built-in nozzle clean-out needle was required to remove obstructions from the fluid nozzle orifice. These obstructions appeared to be congealed wax plugs which formed in the orifice. The 1/4 JCO nozzle operates on an external-mixing principle with the atomizing air passing through a small annular around the fluid nozzle orifice. It was impossible to heat the tip of the fluid nozzle sufficiently to compensate for the cooling effects of the atomizing air. Clogging seldom occurred with the two larger

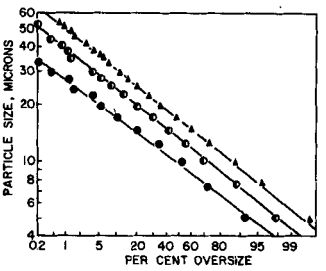

Fig. 2—Particle-size distribution comparison (by number) of spray-congealed products of SETD-white wax atomized through three different nozzles. Key: ●, 0.02-in. nozzle; ◐, 0.04-in. nozzle; ▲, 0.06-in. nozzle.

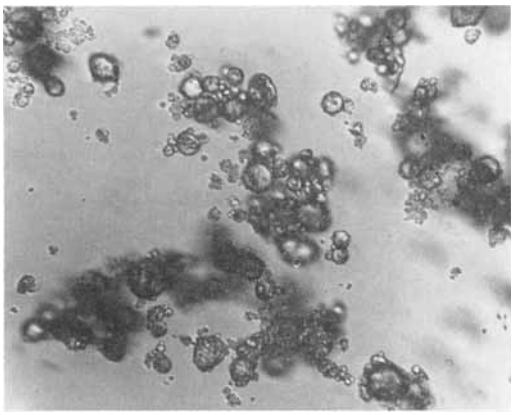

Fig. 3—Spray-congealed particles of SETD–white wax and a synthetic wax-like ester (1:1) containing 4% sorbitan monooleate atomized through a 0.02-in. pneumatic nozzle. Magnification, 210×.

nozzles, and the greater amount of hot wax passing through the nozzle apparently heated the inner surfaces of the nozzle sufficiently to prevent congealing. The use of steam-jacketed nozzles and positive-pressure pumps would likely have eliminated the clogging problems experienced.

Surfactant concentration had no significant effect on the production rate, but the 1:1 combination wax matrices averaged production rates approximately twice those of synthetic wax-like ester matrices.

Particle-Size Analysis—The size of the nozzle used to atomize the melted wax formulations was found to largely influence the volume-surface mean diameter (d_{vs}) of the product; the type of wax matrix used was also found to be significant at the 5% level. The average d_{vs} was approximately linearly related to the nozzle size: 14.18 μ for the 0.02-in. nozzle, 21.23 μ for the 0.04-in., and 29.34 μ for the 0.06-in. nozzle. Figure 2 is a plot of the particle sizes obtained by spraying an identical formulation through three sizes of nozzles used in this investigation. Unusually close compliance with the log-normal distribution was found for each sample. Figures 3 and 4 are photomicrographs of the same formulation atomized through the 0.02-in. and the 0.06-in. nozzles, at the same magnification. The pronounced effect of the nozzle size can be seen in these photographs.

Synthetic wax-like ester formulations produced the smallest particles, and the 1:1 combination

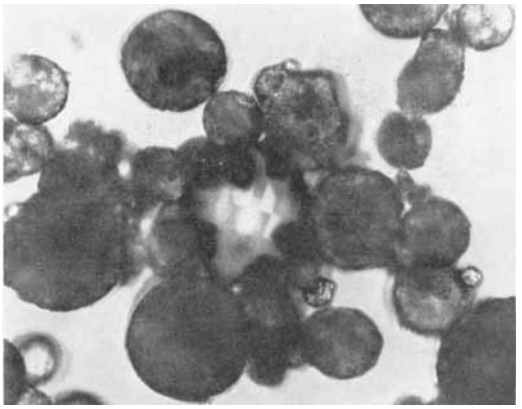

Fig. 4—Spray-congealed particles of SETD–white wax and a synthetic wax-like ester (1:1) containing 4% sorbitan monooleate atomized through a 0.06-in. pneumatic nozzle. Magnification, 210×.

matrix resulted in particles approximately 50% larger. The brittleness of synthetic wax-like ester was thought to be responsible for the small size of the particles since this wax shatters when stressed. The 1:1 combination matrix was more plastic than the synthetic wax-like ester alone and not as tacky as white wax alone. Sorbitan monooleate concentration had no significant effect on particle size.

Density Results—The true density of all formulations was almost the same: 1.063 average. Nozzle size and wax matrix were both important considerations in the bulk densities of the products. Bulk density increased with increasing particle size, as did flowability. White wax had the lowest bulk density as a result of its inherent tacky qualities, and the 1:1 combination had the highest.

Dissolution Studies in 0.1 N HCl—The amount of SETD released during the first 15 min. in 0.1 *N* HCl was taken as a measure of the partially exposed drug on the particles and possibly some free SETD. More drug was released in the first 15-min. period than in any later quarter-hour period, and it was found that all three treatment variables exerted a significant effect on this initial amount of released drug. The specific surface of the product was in part responsible for the amount of drug released in this initial period. Figure 5 shows the effect of the nozzle size on the dissolution patterns of the products; the largest nozzle produced particles with the lowest specific surfaces and lowest rates of dissolution.

White wax formulations released an average of half as much drug as either of the other two matrices within the first 15 min. of exposure to the acid fluid. White wax products tended to agglomerate more than the other matrices, thus presenting less surface to the eluant. Also, white wax, being very pliable, was thought to have insulated the drug particles from the eluting fluid through film formation around each particle. The addition of the brittle synthetic wax-like ester may have so reduced the pliability of white wax that such films were not formed, or were ruptured after formation, with the result that the drug was left exposed on the surface.

Sorbitan monooleate had a very pronounced effect upon the dissolution which occurred in the initial 15-min. period (Fig. 6). From this study, it appears that in concentrations up to 4%, this surfactant softens the particles, promotes wetting, and thus increases the amount of drug released. However, in 35 out of 36 samples prepared, 10% surfactant produced the lowest release. The particles were generally very tacky when this much surfactant was present. If the particles had agglomerated extensively, the total surface area exposed to the fluid would have been considerably reduced. Another possible explanation is that the w/o emulsion-forming tendencies of this lipophilic surfactant (HLB 4.3) may have entrapped the eluant and prevented the dissolved drug from being transported away from the wax particle into the solution.

The initial dissolution rate was obtained from the first derivative of Eq. 2 by setting $C = 0$ when $t = 0$. It was found that comparisons of the initial dissolution rate $(c/d)(C_e)$ closely paralleled the results of the 15-min. analysis. The initial dissolution rates of products atomized through the 0.06-in., 0.04-in., and 0.02-in. nozzles were in the ratios of 1:2:4, respectively. The average initial rate of synthetic wax-like ester formulations was twice that of white wax; the 1:1 combination rate was three times that of the white wax formulations. Increases in the surfactant concentration up to 4% resulted in higher initial rates of dissolution; at 10% concentration, the rate was about one-third that of products containing no surfactant.

There was little change in the effects of nozzle size, wax matrix, and surfactant concentration up

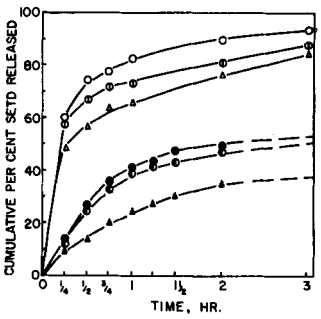

Fig. 5—Dissolution patterns of SETD in 0.1 N hydrochloric acid and alkaline pancreatin solution from spray-congealed particles of SETD–synthetic wax-like ester containing 10% sorbitan monooleate. Key: ○, 0.02-in. nozzle; ◑, 0.04-in. nozzle; △, 0.06-in. nozzle in alkaline pancreatin solution; ●, 0.02-in. nozzle; ◐, 0.04-in. nozzle; ▲, 0.06-in. nozzle in 0.1 N HCl.

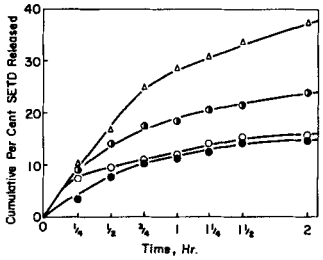

Fig. 6—Effect of sorbitan monooleate concentration on the dissolution patterns of SETD in 0.1 N hydrochloric acid from spray-congealed particles of SETD–white wax atomized through a 0.06-in. pneumatic nozzle. Key: ○, 0%; ◑, 1%; △, 4%; ●, 10% sorbitan monooleate.

to 2 hr. in the acid fluid. After 22 hr., however, it was found that the synthetic wax-like ester formulations had released approximately 50% more drug than had the white wax formulations. As the drug was removed, the wax bead would likely become porous, channeled, and less able to resist the attritional forces of agitation in the vial. White wax, being pliable, would perhaps be more resistant to crumbling when used as a matrix than would the brittle synthetic wax-like ester. After 22 hr., sorbitan monooleate no longer exerted a significant repressant effect upon the total amount of drug dissolved.

Dissolution in Alkaline Pancreatin Solution—An examination of Fig. 5 shows that much more drug was released in a given time period to the alkaline pancreatin eluant than to 0.1 *N* HCl. This increase in dissolution was probably due to partial solubilization and disintegration of the wax particles by the surfactant action of bile and pancreatin, and by the alkalinity of the sodium bicarbonate. When the sample contained sorbitan monooleate, essentially complete solubilization or emulsification of the wax beads was noted after 24 to 48 hr.

After 15 min. in alkaline pancreatin solution, the effects of all three variables could be seen in the amounts of SETD released from the various samples. Products made with the largest (0.06-in.) nozzle released considerably less drug than the smaller particles. White wax showed the highest release, synthetic wax-like ester the lowest, and the 1:1 combination was intermediate. The acids present in white wax are believed to be responsible for the large release observed; synthetic wax-like ester was not as easily disintegrated and solubilized in the alkaline pancreatin solution due to the apparent lack of acids. In the alkaline medium, sorbitan monooleate promoted faster rates of release, and 10% surfactant concentration led to greater releases of drug in 6 hr.

Model Predictions—Figures 7 and 8 are compound log–log plots of $(C_e - C)$ against $(t + d)$. The lines and data points are derived from separate sources and do not represent a least-squares fit of the data in the usual sense. The lines were plotted using the estimated parameters from Eq. 2. Superimposed upon these lines are the data points of the indicated samples. The fit appears to be uniform, and the discrepancies are random. The slopes of the plotted lines $(-c)$ have been assigned no significance since c was determined through adjustment with trial values of C_e and d. Attempts to correlate these three parameters with the treatment variables or with other quantitated properties of the products were not successful.

Higuchi and Hiestand (14) proposed that diffusion-controlled systems released drug from the insoluble matrix according to the square root of time. A relationship to apparent zero- or first-order release patterns was demonstrated by Wagner (15) using previously published dissolution data. Considerable work has been done on idealized systems of solid drug dispersed in solid matrices. Higuchi (16) enumerated several complicating factors which must be considered before any dissolution model can be assumed to apply. He pointed out that break-up or dissolution of the matrix substances would result in erratically changing exposed surface area; also, the possibility of drug on the surface of the particle being released more rapidly than drug imbedded in the matrix must be considered.

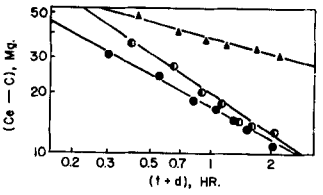

Fig. 7—Experimentally determined dissolution data for SETD in 0.1 N hydrochloric acid plotted on predicted lines for SETD–white wax and synthetic wax-like ester (1:1) formulations containing 1% sorbitan monooleate. Key: ●, 0.02-in. nozzle; ◐, 0.04-in. nozzle; ▲, 0.06-in. nozzle.

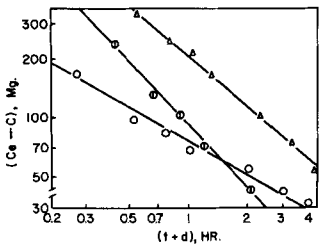

Fig. 8—Experimentally determined dissolution data for SETD in alkaline pancreatin solution plotted on predicted lines for SETD–white wax and synthetic wax-like ester (1:1) formulations containing 10% sorbitan monooleate. Key: ○, 0.02-in. nozzle; ◑, 0.04-in. nozzle; △, 0.06-in. nozzle.

This project dealt with wax particles which clumped, disintegrated, dissolved, and became emulsified; the exposed area was constantly changing. The surfactant concentration of the eluant continuously increased as sorbitan monooleate was extracted along with the drug from the wax particles. The parameters of the log–log model are likely related to the surface area, or to the rate of change of surface area; however, no relationship of this type was discovered during the course of the investigation.

SUMMARY AND CONCLUSIONS

1. Atomization through the use of a pneumatic nozzle and siphon tube was found to provide an expedient method of producing spray-congealed particles of drugs suspended in melted lipid materials.

2. Nozzle size largely determined the rate of production of the spray-congealed products.

3. The resulting particle size of the product was a function of the size of nozzle used for atomization; the particle-size distribution was found to be approximately log-normal.

4. The spray-congealed particles were discretely formed, apparently nonporous spheres; addition of sorbitan monooleate generally impaired flow properties and caused agglomeration.

5. In 0.1 *N* HCl, white wax matrices and large atomizing nozzles produced particles which had the slowest dissolution rates; sorbitan monooleate in concentrations up to 4% increased the solution rate; at 10%, the rate was markedly depressed. There was no noticeable surfactant effect upon the

total amount of drug dissoluted in a 22-hr. period.

6. In alkaline pancreatin solution, white wax matrices had the fastest rates of release, the largest particles had the slowest rates, and sorbitan monooleate consistently promoted faster release rates.

7. Good agreement was obtained between the model predictions and experimentally determined amounts of drug released from a formulation in a particular length of time. Determination of the model parameters adequately characterized the dissolution curve over the time period studied.

8. Sorbitan monooleate, when present in concentrations of 10%, was found to repress the dissolution rate of SETD in 0.1 *N* HCl, and to augment the rate in alkaline pancreatin solution. This behavior could be of use to formulators wishing to insure efficient release of the drug in the intestines after an initial delay.

REFERENCES

(1) Robinson, M. J., and Svedres, E. V., U. S. pat. 2,805,977 (Sept. 1957).
(2) Stoyle, L. E., Jr., Quellette, P. A., and Hanus, E. J., U. S. pat. 3,035,985 (May 1962).
(3) Stoyle, L. E., Jr., Quellette, P. A., and Hanus, E. J., U. S. pat. 3,037,911 (June 1962).
(4) Marshall, W. R., Jr., "Atomization and Spray Drying," Chemical Engineering Progress Monograph Series, 50, No. 2, American Institute of Chemical Engineers, New York, N. Y., 1954.
(5) Scott, M. W., Robinson, M. J., Pauls, J. F., and Lantz, R. J., *J. Pharm. Sci.*, **53**, 670(1964).
(6) Lantz, R. J., Jr., and Robinson, M. J., U. S. pat. 3,146,167 (Aug. 1964).
(7) Cox, J. C., Doctoral. Dissertation, University of Florida, Gainesville, Fla., 1967.
(8) Robinson, M. J., Bondi, A., Jr., and Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 874 (1958).
(9) Robinson, M. J., and Swintosky, J. V., *ibid.*, **48**, 473(1959).
(10) Draper, E. B., and Becker, C. H., *J. Pharm. Sci.*, **55**, 376(1966).
(11) Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, **128**, 537(1939).
(12) Souder, J. C., and Ellenbogen, W. C., *Drug Std.*, **26**, 77(1958).
(13) Hartley, H. O., *Technometrics*, **3**, 269 (1961).
(14) Higuchi, W. I., and Hiestand, E. N., *J. Pharm. Sci.*, **52**, 67(1963).
(15) Wagner, J. G., *Drug Std.*, **27**, 178(1959).
(16) Higuchi, T., *J. Pharm. Sci.*, **52**, 1145(1963).

Keyphrases

Sulfaethylthiadiazole—wax formulations
Spray-congealed particles
Apparatus, particle preparation—described
Nozzle orifice size—dissolution rate
Sorbitan monooleate—dissolution rate
Waxes—dissolution rate

Effect of Gibberellic Acid on the Growth, Alkaloid Production, and VLB Content of *Catharanthus roseus*

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***Catharanthus roseus*, treated for 7 weeks with weekly doses of 100 mcg. of gibberellic acid (GA) and harvested biweekly, showed a significant increase in height and in stem dry weight. While GA treatment had a favorable effect on growth and did not affect the rate of flowering, it had an unfavorable effect on the concentration of total alkaloids in the plant organs. At final harvest the concentration of total alkaloids in the leaves was 55 percent of controls; that of the roots, 39 percent. Total alkaloid content per plant was greater than controls at the second harvest, but decreased at the fourth harvest. Detectable quantities of vincaleukoblastine (VLB) were not found in the stems or roots of both treated and untreated groups, but an increase of VLB concentration was noted in the leaves of the treated group. Gibberellic acid treatment had no affect on chlorophyll content, but markedly reduced the petroleum ether and ether extracts of plant organs.**

THE FOLLOWING GENERAL gibberellin effects have been reported in the solanaceous plants producing tropane alkaloids: increased internodal elongation, taller and spindlier plants, increased stem growth, variable effects on total plant growth depending upon the stage of the plant when treated and the concentration of growth hormone applied as well as environmental factors, chlorotic leaves and reduced chlorophyll content, an increased sugar content of the leaf tops, and a reduction in the concentration of alkaloids of the aerial parts (1–6). Many of these effects have been reported for other alkaloid pro-

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