# Spray-Congealed Formulations of Sulfaethidole (SETD) and Waxes for Prolonged-Release Medication

## Effect of Modifiers

By Y. RAGHUNATHAN and CHARLES H. BECKER

**An investigation was undertaken to examine the effects of the addition of certain substances—*viz.*, low molecular weight polyethylene, ethylcellulose 20 cps., and glyceryl ester of hydrogenated rosin, to carnauba wax, hydrogenated castor oil, and synthetic wax-like ester, on the *in vitro* dissolution patterns of spray-congealed particles of sulfaethidole (SETD) and wax-modifier combinations. The pneumatically atomized and congealed particles of the drug-wax-modifier suspensions were observed to possess log-normal particle-size distributions. These were characteristic for a particular wax. The addition of low molecular weight polyethylene was observed to increase the particle size significantly for all three wax formulations. The *in vitro* dissolution patterns appear to be second order, being functions of the effective surface area and the weight of drug available for dissolution. The dissolution patterns of SETD from the three wax formulations were observed to be characteristic for each wax and dissolution medium. The addition of low molecular weight polyethylene was observed to retard the dissolution rates of SETD from hydrogenated castor oil and synthetic wax-like ester formulations. The addition of ethylcellulose tended to increase the dissolution rate from carnauba wax and synthetic wax-like ester formulations. The addition of glyceryl ester of hydrogenated rosin tended to decrease the dissolution rate of the drug from carnauba wax and hydrogenated castor oil formulations.**

ALTHOUGH THE USE of spray-congealing techniques for modifying the physical, chemical, or physiological behavior of drugs has been in use for more than 10 years, information of direct value in the spray congealing of pharmaceutical systems has not appeared in the literature until very recently. Scott *et al.* (1) were probably the first pharmaceutical investigators to conduct an extensive study on the production factors influencing the size and distribution of spray-congealed particles. In their work, stearic acid-ethylcellulose mixtures were spray congealed using a specially instrumented spray dryer and a centrifugal wheel atomizer. The variables studied included atomizer wheel, feed rate, and feed viscosity.

A series of studies has been undertaken in these laboratories on spray-congealed particles prepared from a suspension of sulfaethidole (SETD) in melted waxes by atomizing through a compressed air-nozzle assembly. Cox (2) studied the effect of various production variables such as siphon height and atomizing pressure on the dissolution behavior and size of spray-congealed particles of SETD-white wax and SETD-synthetic wax-like ester. John and Becker (3) studied the effect of the surfactant sorbitan monooleate on the particle size and dissolution behavior of similar spray-congealed particles. Cusimano and Becker (4) prepared spray-congealed particles of SETD and different waxes and observed that their dissolution behavior depended on the chemical composition of the wax and the composition of the dissolution medium. The *in vitro* dissolution data obtained by using the rotating-bottle method (5) in these investigations could not be fitted to existing theoretical models for dissolution (6, 7) because these are based on the assumption that the total surface area of the dissolving solid does not change significantly during the period of observation. The dissolution model utilized was first proposed by Cox (2).

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

where $C$ is the weight of drug in solution at a particular time $t$, $C_e$ is the weight of drug in solution at equilibrium, and $c$ and $d$ are constants for a particular formulation.

The purpose of the present investigation was to

Received May 22, 1968, from the College of Pharmacy, University of Florida, Gainesville, FL 32601
Accepted for publication July 12, 1968.
Presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.
Abstracted in part from a dissertation presented by Y. Raghunathan to the Graduate School of the University of Florida, Gainesville, in partial fulfillment of Doctor of Philosophy degree requirements.
The authors express their appreciation to Dr. John I. Thornby, Statistical Consultant at the J. Hillis Miller Health Center, University of Florida, Gainesville, for his assistance in programming the dissolution data. The Assistance of the University of Florida Computing Center is also gratefully acknowledged.

determine the effect of the presence of certain modifiers in the spray-congealed particles of SETD and waxes on the *in vitro* dissolution behavior of the drug in acid pepsin medium pH 1.1 (simulated gastric fluid USP) and alkaline pancreatin medium pH 8.3 [test fluid B of Robinson and Swintosky (8)]. Additional experiments were also conducted to study the *in vitro* dissolution pattern of SETD from tablets made with these spray-congealed powders with and without disintegrants and from control tablets made with a mixture of SETD and spray-congealed powders of waxes with modifiers. The results of these will be reported separately.

## EXPERIMENTAL

**Experimental Design and Choice of Materials**—The main consideration given in the selection of the waxes for this investigation was that the resulting congealed particles should be free flowing, so that they could be added to tablet granulations, if needed. The candidate modifiers should dissolve completely in these waxes when melted. Accordingly, carnauba wax, hydrogenated castor oil,[1] and a synthetic wax-like ester[2] were selected as the waxes. They are designated $W_1$, $W_2$, and $W_3$, respectively. The three modifiers used were: a low molecular weight polyethylene,[3] ethylcellulose 20 cps.,[4] and glyceryl ester of hydrogenated rosin.[5] These are designated $M_1$, $M_2$, and $M_3$, respectively, and were used in three levels of concentration. The content of SETD was kept constant in all the formulations at 25% w/w. The exact drug content of each product was determined by subsequent assay. The content of wax in the different formulations varied depending upon the concentration of the modifier added. The concentrations of the modifiers expressed as % w/w were: 0, 5, and 10 of low molecular weight polyethylene ($M_1$); 0, 1, and 2.5 of ethylcellulose ($M_2$); and 0, 5, and 10 of glyceryl ester of hydrogenated rosin ($M_3$). The concentration levels are designated as $C_5$, $C_{10}$, $C_1$, $C_{2.5}$ *etc.*, where the subscript indicates the % w/w of the modifier.

**Preparation of Spray-Congealed SETD and Wax Particles**—The appropriate quantity of wax was first melted in a stainless steel beaker. The modifier was then added and dissolved in the wax by stirring over very low heat. The stainless steel beaker was then transferred to a constant-temperature bath and maintained at the desired temperature for spray congealing (100 ± 2° for carnauba wax and castor wax formulations and 80 ± 2° for synthetic wax-like ester formulations). A sufficient quantity of SETD was next added and mixed with a variable speed mixer until a homogeneous dispersion was achieved. The mixer ran constantly during the spray congealing operation so that any settling of the drug would be avoided. The batch size was maintained constant at 2,000 g. The melted mix was atomized through an external-mixing pneumatic nozzle having an orifice diameter of 0.25 cm. (0.1 in.). The apparatus has been described previously (3). A Teflon siphon tube, wrapped with a heating tape, maintained the melted wax-drug mixture at the desired temperature while it passed up to the pneumatic nozzle. Dry air was passed through the nozzle at a pressure of 40 p.s.i. This was sufficient to deliver the melted wax-drug mixture to the nozzle and then bring about atomization. Since the air was not heated prior to entering the nozzle, the latter was equipped with a heater and a thermocouple monitoring system so that it could be maintained at the desired temperature during the spraying operation. This prevented interruption due to clogging of the nozzle by the congealing of melted wax drug. The nozzle orifice was directed into the collection chamber such that the particles of melted wax-drug congealed in the air. This resulted in a very fine powder which was collected and then passed through a No. 30 U.S. Standard sieve before conducting any of the subsequent experiments.

**Particle-Size Measurements**—A microscope fitted with an ocular micrometer was used to determine the particle-size distribution of each sample. The ocular micrometer was calibrated using the 45 × objective and a stage micrometer, the scale of which was 2 mm. in length. The calibration was such that one division of the micrometer scale of the eyepiece was equal to 0.267 $\mu$.

A small sample of the material was withdrawn from the powder jar containing the product, after the latter had been thoroughly mixed by shaking for about 3 min. The sample was placed on a clean slide and a cover slip placed over it. The slide was mounted on the microscope and the 45 × objective brought into focus. In order to obtain a representative distribution, all particles within a microscopic field were measured and at least five different fields, each a representative of a particular section of the slide, were examined.

**Assay of Spray-Congealed SETD-Wax Particles**—Each product was formulated to contain about 25% SETD by weight. Chemical analyses were then performed on each product to determine the exact SETD content.

About 0.5 g. of the spray-congealed product, accurately weighed, was dissolved in 50 ml. of hot chloroform and the SETD was extracted with 5 portions of 0.10 *N* HCl. The acid extract was then assayed for SETD content by the Bratton-Marshall (9) procedure using a Klett-Summerson photoelectric colorimeter with a No. 54 filter.

A standard curve for SETD was also prepared and was found to be valid to a concentration of 2 mg. % SETD. Appropriate blank and standard solutions were run with all samples assayed.

**In Vitro Dissolution Studies**—The dissolution behavior of all spray-congealed products was determined using a rotating-bottle apparatus (5), and a procedure similar to that of Robinson and Swintosky (8). Rosen (10) has shown a direct rank relationship between *in vitro* dissolution data using the rotating-bottle method and the respective *in vitro* data in his studies on sustained-release preparations of prochlorperazine-$S^{35}$.

[1] Marketed as Castorwax M.P. 87 by Baker Castor Oil Co., Bayonne, N. J.
[2] Marketed as Glycowax S-932 by Glyco Chemicals, Inc., New York, N. Y.
[3] Marketed as Epolene E/10 by Eastman Chemical Products, Inc., Kingsport, Tenn.
[4] Marketed as Ethocel 20 CPS by Dow Chemical Co., Midland, Mich.
[5] Marketed as Stabelite Ester 5 by Hercules Powder Co., Wilmington, Del.

About 0.5 g. of the product, equivalent to 0.1200 g. of SETD as determined by prior assay, was accurately weighed into 90-ml. screw-capped bottles. Sixty milliliters of acid pepsin medium pH 1.1 (simulated gastric fluid USP), previously warmed to 37 ± 1°, was added to each bottle. Duplicate samples were allowed to rotate end over end at a speed of 40 to 45 r.p.m. in a water bath maintained at 37 ± 1°. The samples were removed at 0.25, 0.5, 0.75, 1, 1.25, 1.5, and 2 hr. The samples were filtered immediately and an appropriate aliquot of the filtrate was then assayed for SETD content. Samples were also run for extended periods of time, 24 and 48 hr. However, equilibrium concentration was not attained in acid pepsin medium during this period.

Dissolution studies were also conducted in an alkaline environment in a similar manner. Again, the equivalent of 0.1200 g. of SETD was weighed into each bottle, and 60 ml. of alkaline pancreatin medium (pH 8.3) was added. Samples were removed for assay at 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hr. Studies were also conducted for a period of 24 hr. at which time equilibrium was attained in most of the samples.

## RESULTS AND DISCUSSION

**Spray-Congealed SETD-Wax Products**—All the spray-congealed SETD-wax products were fine powders. Carnauba wax and hydrogenated castor oil products were more free-flowing than the synthetic wax-like ester products. The latter showed a tendency to become lumpy on storage. However, the lumps could be broken up easily by shaking the container for a few minutes.

An examination of the production rates of the various formulations showed that the synthetic wax-like ester products, in general, could be sprayed at a faster rate than hydrogenated castor oil and carnauba wax formulations, in that order. This correlates with the relative hardness of the waxes. The synthetic wax-like ester was found to be the least hard of the three waxes and carnauba wax, the hardest, as determined by penetrometer[6] studies. All three modifiers increased the hardness when added to the synthetic wax-like ester formulation. The additives also slowed the rate of production. The same type of behavior was also noticeable in hydrogenated castor oil formulations. However, the difference in hardness among the carnauba wax formulations with the addition of modifiers was not so clearly detectable by the penetrometer.

**Particle-Size Analysis**—The size frequency data of the spray-congealed formulations were converted to a weight basis by assuming the shape and density factors to be constant throughout the size range according to the procedure described by Edmundson (11). The relative weight in each size interval was obtained by cubing the midpoint value of the interval and multiplying by the frequency. The cumulative frequency distributions by weight were found to be log-normally distributed. Figure 1 is a plot of the particle sizes of SETD-carnauba wax and SETD-carnauba wax with 10% low molecular weight polyethylene. The effect of the addition of this modifier to the formulation on the particle size is evident.

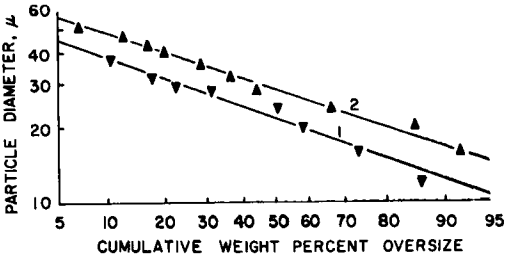


*Fig. 1—Particle-size distribution (by weight) of spray-congealed particles of SETD-carnauba wax (1) and SETD-carnauba wax with 10% low molecular weight polyethylene (2).*

A statistical analysis of the particle-size data of all the spray-congealed formulations showed that SETD-carnauba wax formulations were generally smaller particles with an average geometric weight mean diameter ($dg_w$) of 24.92 $\mu$ and an average geometric standard deviation ($\sigma$) of 1.52. SETD-hydrogenated castor oil formulations had an average $dg_w$ of 29.14 $\mu$ and an average $\sigma$ of 1.53, while SETD-synthetic wax-like ester formulations had an average $dg_w$ of 27.53 $\mu$ and $\sigma$ of 1.57. The addition of low molecular weight polyethylene to the waxes resulted in larger spray-congealed particles. As the modifier concentration was increased, the particle-size increase was observed to be linear and statistically significant. The average increase in $dg_w$ when 10% of low molecular weight polyethylene was added to the waxes was 6.75 $\mu$ with no significant change in the standard deviation. The increase in $dg_w$ with the addition of ethylcellulose or glyceryl ester of hydrogenated rosin was not very significant in the concentrations considered in the present study. There appeared, however, to be a decrease in the standard deviation in the formulations containing ethylcellulose, indicating the formation of uniform particles.

Microscopic examination of representative samples from the spray-congealed products showed that all the formulations yielded particles that appeared to be spherical in shape with smooth nonporous surface. Existence of some clusters of the particles was also noted in all the formulations.

**Analysis of Dissolution Data**—An inspection of the values of constant $c$ in Eq. 1 obtained in the previous studies from this laboratory showed that the values were close to unity. The substitution of the constant $c$ by 1 in Eq. 1 can simplify the equation as follows:

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

Equation 2 may be rearranged as follows:

$$\frac{C}{(C_e - C)} = \frac{t}{d} \qquad \text{(Eq. 3)}$$

Dividing Eq. 3 by $C_e$ gives the integrated form of a second-order equation

$$\frac{C}{(C_e - C)C_e} = \frac{t}{d \cdot C_e} = k_2 t \qquad \text{(Eq. 4)}$$

[6] Precision Universal Penetrometer, Precision Scientific Company, Chicago, Ill.

The first derivative of Eq. 4 being

$$\frac{dC}{dt} = k_2(C_e - C)^2 \qquad \text{(Eq. 5)}$$

The dissolution rate from a solid by the Noyes-Whitney equation (6) is given as follows:

$$\frac{dC}{dt} = k \cdot S[(X - C) - (X - C_e)] \qquad \text{(Eq. 6)}$$

where $S$ is the surface area of the dissolving solid, assumed constant, and $X$ is the initial weight of the solid present. It is reasonable to assume that the effective surface area available at any time is approximately proportional to the amount of solid drug remaining to be dissolved. Thus, effective surface area may be written in terms of $C$ as follows:

$$S = k_S[(X - C) - (X - C_e)] \qquad \text{(Eq. 7)}$$

where $k_s$ is the proportionality constant.

When $C = C_e$, then $S = 0$. Thus effective surface should be nil at equilibrium concentration and no more of the solid dissolves. Substituting the right-hand side expression of Eq. 7 into Eq. 6,

$$\frac{dC}{dt} = k \cdot k_S(C_e - C)^2$$

or,

$$\frac{dC}{dt} = k_2(C_e - C)^2 \qquad \text{(Eq. 8)}$$

Thus an apparent second-order rate of dissolution should be observed with changing surface area. The initial dissolution rate, $k \cdot C_e^2$, may be obtained from Eq. 8 by substituting the initial conditions: when $t = 0$, then $C = 0$.

Figure 2 shows the plot of $C/[(C_e - C)C_e]$ *versus* $t$ for the dissolution of plain SETD powder in acid pepsin medium. Figures 3, 4, and 5 show similar second-order plots of the dissolution data

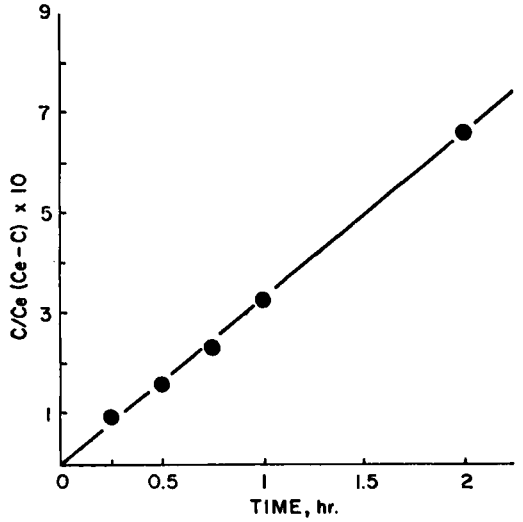


*Fig. 2—Plot of* $C/[(C_e - C)C_e]$ *as a function of time for the dissolution of plain SETD powder in acid pepsin medium.*

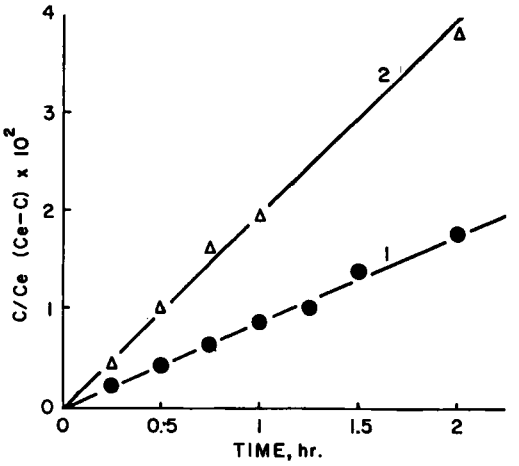


*Fig. 3—Plot of* $C/[(C_e - C)C_e]$ *as a function of time for the dissolution of SETD from spray-congealed particles of SETD-hydrogenated castor oil in acid pepsin medium (1) and alkaline pancreatin medium (2).*

of some of the spray-congealed formulations, indicating that the drug release pattern remains essentially the same as in the powder with only the rates being modified.

Figures represent cumulative percent of SETD released with time, of some of the spray-congealed formulations of hydrogenated castor oil showing the effect of the addition of low molecular weight polyethylene, ethylcellulose, and glyceryl ester of hydrogenated rosin, respectively. The points are experimental, whereas the lines are drawn from the predicted value obtained by fitting Eq. 2 by a modified Gauss-Newton nonlinear least-

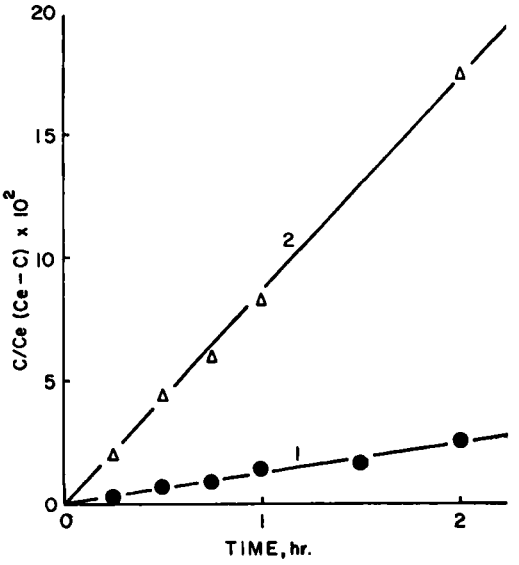


*Fig. 4—Plot of* $C/[(C_e - C)C_e]$ *as a function of time for the dissolution of SETD from spray-congealed particles of SETD-carnauba wax with 2.5% ethylcellulose in acid pepsin medium (1) and alkaline pancreatin medium (2).*

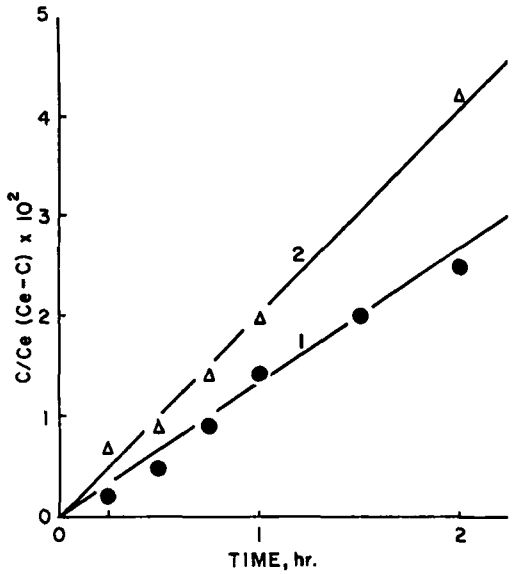


*Fig. 5—Plot of* $C/[(C_e - C)C_e]$ *as a function of time for the dissolution of SETD from spray-congealed particles of SETD-carnauba wax with 10% glyceryl ester of hydrogenated rosin in acid pepsin medium (1) and alkaline pancreatin medium (2).*

squares procedure (12). The mean standard deviation for the fit was 1.43% for the acid pepsin dissolution data and 1.90% for the alkaline pancreatin dissolution data.

**Effect of Modifiers on the Dissolution Pattern of SETD-Carnauba Wax Formulations**—Table I gives dissolution data of SETD-carnauba wax formulations with different modifiers. In general, it can be seen that the percentage of SETD released at equilibrium in alkaline pancreatin medium was higher than in acid pepsin medium. These observations are also reflected in higher second-order rate constants and higher initial dissolution rates. This may be mainly due to solubilizing or disintegrating effect of the alkaline pancreatin medium on carnauba wax, resulting in exposure of more effective surfaces of drug for dissolution. The effect of the addition of low molecular weight polyethylene in 10% concentration to the wax decreased the percentage of SETD released by about 5% in acid pepsin medium at the end of 2 hr. This is also reflected in the lower values observed for the second-order rate constant and the initial dissolution rate.

In alkaline pancreatin medium the percentage released at the end of 1 hr. was about 6% less, while at the end of 6 hr. the difference was more

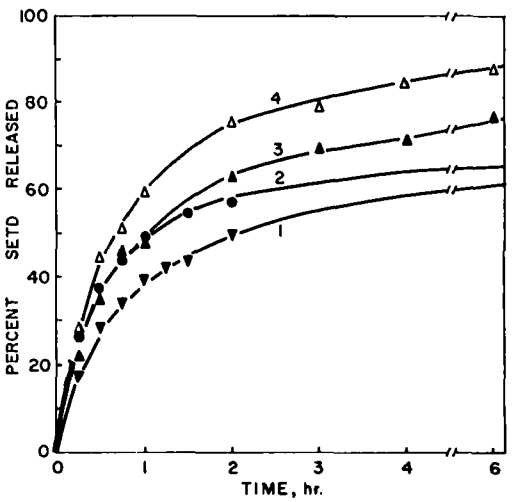


*Fig. 7—Plot of cumulative percent of SETD released versus time in acid pepsin medium (1, 2) and alkaline pancreatin medium (3, 4) from SETD-hydrogenated castor oil (2, 4) and SETD-hydrogenated castor oil with 2.5% ethyl cellulose (1, 3).*

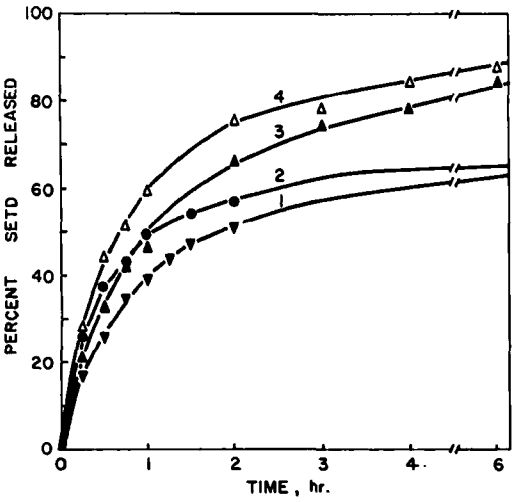


*Fig. 6—Plot of cumulative percent of SETD released versus time in acid pepsin medium (1, 2) and alkaline pancreatin medium (3, 4) from SETD-hydrogenated castor oil (2, 4) and SETD-hydrogenated castor oil with 10% low molecular weight polyethylene (1, 3).*

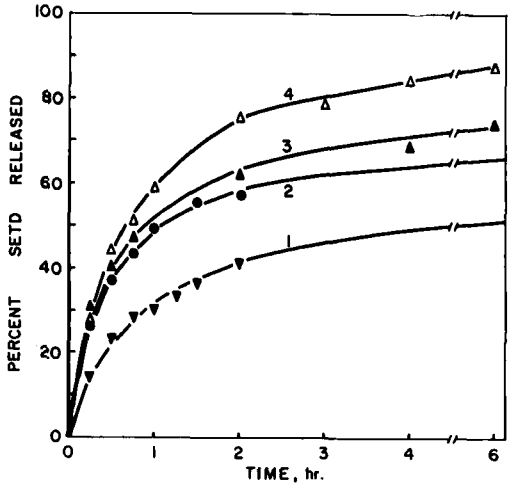


*Fig. 8—Plot of cumulative percent SETD released versus time in acid pepsin medium (1, 2) and alkaline pancreatin medium (3, 4) from SETD-hydrogenated castor oil (2, 4) and SETD-hydrogenated castor oil with 10% glyceryl ester of hydrogenated rosin (1, 3).*

TABLE I—DISSOLUTION DATA[a] EXPRESSED AS PERCENT SETD RELEASED FROM SETD-CARNAUBA WAX FORMULATIONS

| Time, hr. | $W_1$ | | $W_1M_1C_{10}$ | | $W_1M_2C_{2.5}$ | | $W_1M_3C_{10}$ | |
|---|---|---|---|---|---|---|---|---|
| | A[b] | B[c] | A | B | A | B | A | B |
| 0.25 | 11.9 | 45.31 | 9.89 | 47.30 | 14.01 | 58.22 | 7.88 | 40.98 |
| 0.50 | 20.48 | 61.06 | 17.34 | 59.29 | 23.42 | 69.22 | 14.15 | 54.40 |
| 1 | 32.05 | 73.91 | 27.80 | 67.89 | 35.25 | 76.44 | 23.47 | 65.06 |
| 2 | 44.66 | 82.59 | 39.83 | 73.19 | 47.16 | 80.65 | 35.03 | 72.12 |
| 4 | — | 87.75 | — | 76.16 | | 82.93 | — | 74.97 |
| 6 | — | 89.61 | — | 77.21 | | 83.71 | — | 78.51 |
| At equilibrium | 73.33 | 93.59 | 70.20 | 79.39 | 85.48 | 85.33 | 68.83 | 80.90 |
| $k_2$[d] | 0.872 | 3.343 | 0.778 | 6.196 | 1.146 | 8.388 | 0.626 | 4.230 |
| ID[e] | 68.13 | 421.69 | 55.25 | 562.36 | 83.75 | 879.27 | 42.74 | 398.58 |

[a] Predicted values from least-square line. [b] A = acid pepsin medium. [c] B = alkaline pancreatin medium. [d] Apparent second-order rate constant $\times 10^2$ mg.$^{-1}$hr.$^{-1}$. [e] Initial dissolution rate mg. hr.$^{-1}$.

than 12%. The addition of low molecular weight polyethylene appeared to decrease the solubility of the wax matrix by the alkaline pancreatin medium resulting in only 79.39% release at equilibrium. This results in a higher rate constant and higher initial dissolution rate. The addition of ethylcellulose in 2.5% concentration to the wax increased the release of SETD in acid pepsin medium slightly, as can be seen from the slightly higher values for the rate constant and the initial dissolution rate. The dissolution was not very significantly affected, as noted by the percent of SETD release at the end of 2 hr. The amount of SETD released at equilibrium in the alkaline pancreatin medium was lower than the value observed with no modifier. This is reflected by the higher rate constant and higher initial dissolution rate. Under the microscope the spray-congealed particles containing this modifier were observed to contain short fibers. The presence of these fibers appeared to have a wicking effect resulting in increased initial release.

The addition of 10% glyceryl esters of hydrogenated rosin decreased the release of drug in acid pepsin medium by about 9% at the end of 2 hr. Again, the rate constant and the initial dissolution rate reflect this decrease. The release was also observed to be more gradual in the alkaline pancreatin medium with lower equilibrium value resulting in a higher rate constant and lower initial dissolution rate.

**Effect of Modifiers on the Dissolution Pattern of SETD in SETD-Hydrogenated Castor Oil Formulations**—Table II gives the dissolution data of SETD-hydrogenated castor oil formulations with different modifiers. In general, it can be seen as in the previous table, the amount of SETD released at equilibrium in alkaline pancreatin medium was higher than in acid pepsin medium. However, the initial dissolution rates are generally about the same, so that these result in lower rate constants. This is a very desirable feature from the standpoint of sustained-release formulations. The presence of low molecular weight polyethylene in 10% concentration appeared to retard the release of SETD by about 10% in acid pepsin medium and alkaline pancreatin medium as seen from the 1-hr. data and with almost no retardation in equilibrium values. This is well brought out in the lower rate constants and initial dissolution rates. It is conceivable that a higher concentration of low molecular weight polyethylene may further retard the initial dissolution rate, yet giving a complete release at the end of 6 hr. and hence warrants further study.

The addition of 2.5% ethylcellulose also retarded the dissolution of drug in both acid pepsin medium and alkaline pancreatin medium so that a more uniform release resulted. This can be seen from the closer values of the rate constants in the two media.

The addition of 10% glyceryl ester of hydrogenated rosin resulted in a release pattern similar to that observed in the case of product containing 2.5% ethylcellulose. The initial dissolution rate and the equilibrium values in acid pepsin medium were lower than with ethylcellulose resulting in a rate constant that was slightly higher than with ethylcellulose products. The initial dissolution rate and the rate constant in alkaline pancreatin were also higher.

TABLE II—DISSOLUTION DATA[a] EXPRESSED AS PERCENT SETD RELEASED FROM SETD-HYDROGENATED CASTOR OIL FORMULATIONS

| Time, hr. | $W_2$ | | $W_2M_1C_{10}$ | | $W_2M_2C_{2.5}$ | | $W_2M_3O_{10}$ | |
|---|---|---|---|---|---|---|---|---|
| | A[b] | B[c] | A | B | A | B | A | B |
| 0.25 | 25.34 | 27.29 | 16.3 | 20.10 | 16.56 | 22.85 | 13.09 | 25.62 |
| 0.50 | 37.38 | 42.75 | 26.76 | 33.27 | 26.84 | 35.93 | 21.53 | 38.88 |
| 1 | 49.04 | 59.65 | 39.29 | 49.48 | 38.93 | 50.36 | 31.75 | 52.47 |
| 2 | 58.10 | 74.34 | 51.28 | 65.42 | 42.78 | 63.01 | 41.63 | 63.57 |
| 4 | — | 80.99 | — | 77.98 | — | 72.06 | — | 71.10 |
| 6 | — | 84.78 | — | 83.31 | — | 75.68 | — | 74.02 |
| At equilibrium | 71.29 | 98.63 | 73.83 | 96.50 | 70.80 | 84.14 | 60.45 | 80.64 |
| $k_2$[d] | 2.580 | 1.293 | 1.283 | 0.909 | 1.221 | 1.476 | 1.525 | 1.924 |
| ID[e] | 188.82 | 181.11 | 100.76 | 121.88 | 103.77 | 150.54 | 80.24 | 180.22 |

[a] Predicted values from least-square line. [b] A = acid pepsin medium. [c] B = alkaline pancreatin medium. [d] Apparent second-order rate constant $\times 10^2$ mg.$^{-1}$ hr.$^{-1}$. [e] Initial dissolution rate mg. hr.$^{-1}$.

TABLE III—DISSOLUTION DATA[a] EXPRESSED AS PERCENT SETD FROM SETD-SYNTHETIC WAX-LIKE ESTER FORMULATIONS

| Time, hr. | $W_3$ A[b] | $W_3$ B[c] | $W_3M_1C_{10}$ A | $W_3M_1C_{10}$ B | $W_3M_2C_{2.5}$ A | $W_3M_2C_{2.5}$ B | $W_3M_2C_{10}$ A | $W_3M_2C_{10}$ B |
|---|---|---|---|---|---|---|---|---|
| 0.25 | 10.83 | 23.5 | 2.49 | 5.24 | 14.59 | 29.90 | 16.07 | 37.21 |
| 0.50 | 18.74 | 36.08 | 4.62 | 9.90 | 24.03 | 44.19 | 26.38 | 53.99 |
| 1 | 29.53 | 49.26 | 8.09 | 17.85 | 35.52 | 58.06 | 38.86 | 69.71 |
| 2 | 41.46 | 60.27 | 12.95 | 29.80 | 46.67 | 68.87 | 50.99 | 81.59 |
| 4 | — | 67.85 | — | 44.78 | — | 75.94 | — | 89.19 |
| 6 | — | 70.82 | — | 53.80 | — | 78.62 | — | 92.04 |
| At equilibrium | 69.60 | 77.61 | 32.42 | 90.10 | 68.05 | 83.04 | 88.49 | 98.35 |
| $k_2$[d] | 0.883 | 1.865 | 0.854 | 0.228 | 1.337 | 1.463 | 1.260 | 2.063 |
| ID[e] | 61.58 | 161.81 | 12.93 | 26.71 | 89.17 | 222.02 | 98.61 | 287.36 |

[a] Predicted values from least-square line. [b] A = acid pepsin medium. [c] B = alkaline pancreatin medium. [d] Apparent second-order rate constant $\times 10^2$ mg.$^{-1}$hr.$^{-1}$. [e] Initial dissolution rate mg.hr.$^{-1}$.

**Effect of Modifiers on the Dissolution Pattern of SETD in SETD-Synthetic Wax-like Ester Formulations**—Table III gives the dissolution data of SETD-synthetic wax-like ester formulations with different modifiers. Here again, in general, the release of SETD was observed to be higher in the alkaline pancreatin medium than in the acid pepsin medium. The release in acid pepsin medium without modifier was about 41% in 2 hr. This was observed to be similar to the release pattern of carnauba wax. The rate constants and initial dissolution rates were also close. The release in alkaline pancreatin medium was, compared to the other two waxes, less complete being only about 70% at the end of 6 hr. This is reflected in a comparatively higher rate constant even though the initial dissolution rate is fairly low.

The addition of 10% low molecular weight polyethylene retarded the release of SETD in acid pepsin medium to about 13% in 2 hr. and about 54% in alkaline pancreatin medium in 6 hr. The retardation can also be seen in the lower values for the rate constant and initial dissolution rate.

The addition of 2.5% ethylcellulose to the synthetic wax-like ester increased the amount of SETD released by about 5% in 2 hr. in acid pepsin medium. The increase in release in alkaline pancreatin medium was also similar. These are also noticed by the higher rate constant in acid pepsin medium and higher initial dissolution rate in alkaline pancreatin medium.

The presence of 10% glyceryl ester of hydrogenated rosin in synthetic wax-like ester formulation resulted in more complete release in acid pepsin and alkaline pancreatin media as noticed by slightly higher rate constants and higher initial dissolution rates.

The analysis of the dissolution data reveals that for a good sustained-release effect from formulations such as spray-congealed particles for dissolution, the rate constant should be small and fairly unaffected by the pH or composition of the medium. They should also possess small initial dissolution rates and high equilibrium values. The purpose of this investiation has been, in addition to studying the effect of modifiers on SETD-wax formulations, to gain some insight into some of the factors controlling the dissolution process.

## SUMMARY AND CONCLUSIONS

1. Atomization through the use of pneumatic nozzle and siphon tube was found to provide discretely formed, apparently nonporous spheres which possessed a log-normal particle-size distribution. These were observed to be characteristic for a particular wax formulation. The addition of low molecular weight polyethylene was observed to increase the geometric weight mean diameter of the particles significantly for all the wax formulations. The geometric weight mean diameter was unaffected by the addition of ethylcellulose and glyceryl ester of hydrogenated rosin in the concentration used in this investigation.

2. The release pattern from drug-wax particles appears to be second order, being a function of the amount of drug remaining undissolved and the effective surface area of the drug particles, thus agreeing basically with the Noyes-Whitney equation for dissolution.

3. The release rates from SETD-carnauba wax formulations were generally observed to be higher in the alkaline pancreatin than in acid pepsin medium. The addition of 10% low molecular weight polyethylene and 10% glyceryl ester of hydrogenated rosin reduced the initial dissolution rates and the value of the second-order rate constant in acid pepsin medium. The rate constant and the initial dissolution rates were higher in the alkaline pancreatin medium. The addition of 2.5% ethyl cellulose increased the initial dissolution rate and the rate constants in acid pepsin medium and alkaline pancreatin medium.

4. The second-order rate constant for SETD-hydrogenated castor oil formulation was lower in alkaline pancreatin medium than in acid pepsin medium as a result of more complete release at equilibrium in the former medium. However, the initial dissolution rates were almost the same in both media. The addition of 10% low molecular weight polyethylene tended to bring the values for the rate constants in both the media closer to each other. The initial dissolution rates were also much reduced as compared to the product containing no modifier. The release value at equilibrium in alkaline pancreatin medium was also noted to be more than 96%. The addition of 2.5% ethylcellulose and 10% glyceryl ester of hydrogenated rosin also decreased the value of the rate constants and the initial dissolution rate in acid pepsin medium. The rate constants were higher in alkaline pancreatin medium. The initial dissolution rate for the product with ethylcellulose was slightly reduced while it was essentially the same for the product with glyceryl esters of hydrogenated rosin.

5. The release rates of SETD from SETD-synthetic wax-like ester formulations were higher in the alkaline pancreatin medium than in the acid pepsin medium. The initial dissolution rates and the rate constants were also similarly affected. The addition of 10% low molecular weight polyethylene decreased the dissolution rate in alkaline pancreatin medium considerably. The initial dissolution rates in both the acid and alkaline medium were also considerably reduced. The addition of 2.5% ethylcellulose resulted in higher initial dissolution rates with the values of the rate constants also higher and closer to each other. The addition of 10% glyceryl ester of hydrogenated rosin increased the initial dissolution rates and the values of the rate constants.

6. The analysis of the data suggests that for a good sustained-release effect from formulations such as spray-congealed particles, the rate constants should be small and independent of pH and composition of the medium with low initial dissolution rates and high equilibrium values in alkaline pancreatin medium. This investigation attempted to gain some insight in that direction.

## REFERENCES

(1) Scott, M. W., Robinson, M. J., Pauls, J. F., and Lautz, R. J., *J. Pharm. Sci.*, **53**, 670(1964).

(2) Cox, J. C., Doctoral Dissertation, University of Florida, Gainesville, Florida, 1967.

(3) John, P. M., and Becker, C. H., *J. Pharm. Sci.*, **57**, 584(1968).

(4) Cusimano, A. G., and Becker, C. H., *ibid.*, **57**, 1104 (1968).

(5) Souder, J. C., and Ellenbogen, W. C., *Drug Std.*, **26**, 77(1958).

(6) Noyes, A., and Whitney, W., *J. Am. Chem. Soc.*, **23**, 689 (1897).

(7) Higuchi, T., *J. Pharm. Sci.*, **52**, 1145(1963).

(8) Robinson, M. J., and Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 473(1959).

(9) Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, **128**, 537(1939).

(10) Rosen, E., *J. Pharm. Sci.*, **52**, 98(1963).

(11) Edmundson, I. C., "Advances in Pharmaceutical Sciences," Vol. 2, Bean, H. S., Beckett, A. H., and Carless, J. E., Eds., Academic Press, London, 1967, p. 95.

(12) Hartley, H. O., *Technometrics*, **3**, 269(1961).

*Keyphrases*

Spray-congealed formulations

Sulfaethidole–wax—prolonged release formulations

Modifiers, sulfaethidole-wax formulation—*in vitro* dissolution

Particle size—modifiers effect

Colorimetric analysis—spectrophotometer

# Preparation and Properties of Some Relatives of Noscapine

By J. SAM, A. V. LOPEZ*, and R. M. SHAFIK

**Fusion of phenylacetic acids with phthalic anhydrides resulted in the formation of benzylidenephthalides. Ammonolysis of the phthalides yielded 3-hydroxy-3-benzylphthalimidines which were easily dehydrated to 3-benzylidenephthalimidines. Bromination of 3-hydroxy-3-benzylphthalimidine with *N*-bromosuccinimide yielded 3-(α-bromobenzylidene)phthalimidine. Reaction of the latter with pyrrolidine gave the α-pyrrolidino derivative which on treatment with dilute hydrochloric acid resulted in 3-(α-hydroxybenzylidene)phthalimidine. Treatment of tetrahalobenzylidenephthalides with sodium methoxide produced 1,3-indandione derivatives. Mild sedative properties were noticed in compounds tested.**

NOSCAPINE (I), formerly known as narcotine (1), is the most abundant of the opium alkaloids after morphine. Despite the fact that it comes from a plant rich in narcotic alkaloids it possesses none of the undesirable effects of narcotics; however, it possesses mild central nervous system activity similar to that of papaverine (2). Winter and Flataker (3) during their search for antitussive agents, discovered that noscapine was very effective in this respect. Further studies (4, 5) showed that in addition to its central effect noscapine also has bronchodilation activity. These factors prompted the in-

Received July 24, 1967, from the Department of Pharmaceutical Chemistry, The University of Mississippi, University, MS 38677

Accepted for publication July 17, 1968.

This investigation was supported in part by grant MH 05293 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and in part during a tenure of a fellowship (R.M.S.) of the Mississippi Heart Association.

Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

* Present address: Mercer University, Southern School of Pharmacy, Atlanta, Georgia.