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

Effect of Wax

By ANTHONY G. CUSIMANO* and CHARLES H. BECKER

Various spray-congealed SETD-wax products were prepared by pneumatic atomization using six waxes (white wax USP, glyceryl tristearate, carnauba wax, hydrogenated castor oil, cetyl alcohol NF, and glyceryl monostearate), two nozzle sizes, 0.20 and 0.25 cm. (0.08 and 0.10 in.) i.d., and three concentrations of the surfactant sorbitan monostearate (0, 1, and 5 percent w/w). The geometric mean diameters and the volume-surface diameters were affected primarily by the wax and the nozzle size used. All of the main effects, *i.e.*, wax, nozzle size, and concentration of surfactant, had a significant effect on the percent of SETD released in acid pepsin and alkaline pancreatin media. In general, the dissolution rate increased as the concentration of surfactant was increased. Faster dissolution rates were noted with formulations atomized through the smaller of the two nozzles. The most important factor that had an effect on the dissolution behavior of these products was the wax used in a particular formulation. This effect depends upon the following factors: the physical properties of the wax and the drug–wax particles, the chemical composition of wax, and the composition of the dissolution medium.

THE USE of spray-congealing techniques for modifying the physical, chemical, or physiological behavior of drugs has gained increasing attention within recent years. This process has proved to be an effective means of controlling the particle size of drug–wax particles. Therefore, spray congealing may be quite useful in controlling the dissolution behavior of drugs intended for prolonged-release medication.

In 1958, the utilization of this process was reported for the first time in the pharmaceutical literature (1). A sustained-release powder of sulfamethylthiadiazole (SMTD) was prepared by mixing the drug with molten hydrogenated castor oil and atomizing the resulting suspension. The same workers prepared a sustained-release powder of sulfaethylthiadiazole (SETD) by spray congealing a suspension of the drug using a centrifugal wheel atomizer (2).

Spray congealing has also been employed by others for enhancing the stability and palatability of such compounds as iron salts, vitamin A, and the B vitamins (3–7).

Scott *et al.* (8), 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 speed, feed rate, and feed viscosity.

Recently, Cox (9) studied the effect of various production variables, *i.e.*, siphon height and atomizing pressure, on the particle size and dissolution behavior of spray-congealed particles of SETD-beeswax and SETD-glyceryl tristearate.[1] John and Becker (10) studied the effect of surfactant, *i.e.*, sorbitan monooleate, on the particle size and dissolution behavior of similar spray-congealed particles.

The purpose of this investigation was to determine the effect of several production and formulation variables on the particle size and dissolution behavior of various spray-congealed particles. This work was intended primarily to evaluate the effect of various waxes on the parameters studied. The experimental work conformed to a factorial design such that all of the possible combinations of the treatment variables were formulated and investigated.

EXPERIMENTAL

Materials—All materials used in this study, except some of the waxes, conformed to USP or NF specifications, or were of analytical reagent quality. The drug, sulfaethylthiadiazole (SETD) was obtained from American Cyanamid Co.

The six waxes used were white wax USP, glyceryl

Received January 8, 1968, from the College of Pharmacy, University of Florida, Gainesville, FL 32601

Accepted for publication April 19, 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 Anthony G. Cusimano 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 Glyco Chemicals, Inc., for supplying the Glycowax S-932 and the Aldo MS, Edible used in this study, and to Dr. John I. Thornby, 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.

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[1] Marketed as Glycowax S-932 by Glyco Chemicals, Inc., New York, N. Y.

tristearate, carnauba wax, hydrogenated castor oil,[2] cetyl alcohol NF, and glyceryl monostearate,[3] and these were designated as W_1, W_2, W_3, W_4, W_5, and W_6, respectively.

The surfactant, sorbitan monostearate,[4] was used in some of the formulations in concentrations of 0, 1, and 5% w/w, and these were designated as S_0, S_1, and S_5, respectively. Sorbitan monostearate was used rather than some of the more commonly employed surfactants because it is a solid at room temperature. This would eliminate or reduce the tendency of the spray-congealed products to become tacky.

Preparation of Spray-Congealed SETD-Wax Particles—Spray-congealed formulations were prepared using the six waxes as the carrier for the drug SETD. All formulations contained about 25% SETD by weight. These were atomized through one of two external-mixing pneumatic nozzles[5] having orifice diameters of 0.20 and 0.25 cm., and the latter were designated as N_8 and N_{10}, respectively. The apparatus used has been described previously (10).

The wax for a particular formulation was melted in a stainless steel beaker which was immersed in an oil bath maintained at 100 ± 2°. The sorbitan monostearate, where included, was dissolved in the melted wax after which the SETD was added. Suspension of the SETD was maintained by means of a variable speed mixer. A Teflon siphon tube, wrapped with a heating tape, maintained the melted wax–drug mixture at the desired temperature (100 ± 2°) 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 to bring about atomization. A higher pressure could not be used since this would have caused the molten mixture to congeal on the sides of the collection chamber rather than within it. Since the air was not heated prior to entering the nozzle, the latter was equipped with a heater and a thermocouple monitoring system. Thus, the spraying operation could be performed without interruption due to clogging of the nozzle by melted wax–drug congealing inside. 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—Particle-size measurements were conducted on each of the 36 products using a microscopic method. The microscope was equipped with a calibrated ocular micrometer. Calibration was performed with a stage micrometer, and each division of the ocular micrometer was equivalent to 1.175 μ at a magnification of 10×.

In order to measure the individual particles, deagglomeration of the samples was necessary. Adequate deagglomeration was attained by briefly shaking a small amount of the sample in a test tube with an aqueous solution of polysorbate 80[6] and washed sand.

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.

Each sample was dissolved in hot chloroform, and the SETD was extracted with five portions of 0.10 *N* HCl. The acid extract was then assayed for SETD content by the Bratton-Marshall (11) 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 up to a concentration of 2.0 mg.% in 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 (12), and a procedure similar to that of Robinson and Swintosky (2).

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. To each bottle 60 ml. of acid pepsin medium (pH 1.1) was added. Duplicate samples were allowed to rotate end over end at a speed of 46 r.p.m. in a water bath maintained at 37 ± 1°. Samples were removed at specified time intervals, *i.e.*, at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, and 2 hr.

The samples were filtered, and an appropriate aliquot of the filtrate was then assayed for SETD content. If all of the SETD were released during the dissolution run, then the solution assayed would be equivalent to 2.0 mg.% in SETD.

Samples were also run for extended periods of time, *i.e.*, 24 and 48 hr., although equilibrium was not attained in acid medium.

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, 1.0, 2.0, 3.0, 4.0, and 6.0 hr. Studies were also conducted for a period of 12 hr. at which time equilibrium was attained in most of the samples.

RESULTS AND DISCUSSION

Manufacture of Spray-Congealed SETD-Wax Products—Most of the spray-congealed SETD-wax products were fine powders that initially were free flowing. The SETD-carnauba wax products were the best from an esthetic viewpoint since they were very fine, free-flowing powders that were not tacky. In addition, they showed no tendency to become lumpy in storage. The SETD-glyceryl monostearate products showed the greatest tendency to become lumpy.

The ease with which the products were sprayed depended primarily upon the wax and the nozzle size used. The production rates were greatest when white wax, glyceryl tristearate, and cetyl alcohol were used as the drug carrier. Formulations con-

[2] Marketed as Castorwax MP-70 by the Baker Castor Oil Co., Bayonne, N. J.
[3] Marketed as Aldo MS, Edible by Glyco Chemicals, Inc., New York, N. Y.
[4] Marketed as Span 60 by Atlas Chemical Industries, Inc., Wilmington, Del.
[5] Available from Spraying Systems Co., Bellwood, Ill.
[6] Marketed as Tween 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

taining glyceryl monostearate were the most difficult to spray, and these became increasingly difficult to spray as the concentration of sorbitan monostearate in the formulation was increased. This was due primarily to an increase in the viscosity of the melt when sorbitan monostearate was added. Sorbitan monostearate had little effect on the ease of production of the other formulations.

As one would expect, the larger nozzle (0.25 cm.) gave higher production rates for a given wax formulation.

Particle-Size Analysis—The particle sizes of the various spray-congealed SETD-wax products were found to be log-normally distributed. The particle-size distributions of the SETD-white wax products are shown in Fig. 1. These linear log-probability plots are typical of those obtained with all of the waxes used in this study. Other investigators have observed the log-normal distribution of spray-congealed SETD-wax particles (9, 10).

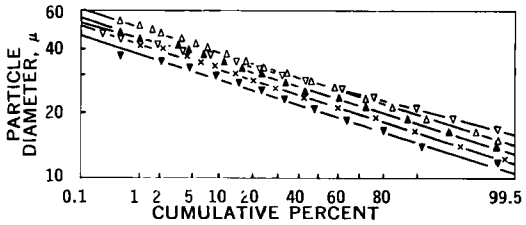

Fig. 1—Particle-size distributions by number of several spray-congealed SETD-white wax products. Key: ▼, $N_8S_0W_1$; ×, $N_8S_1W_1$; ▲, $N_8S_5W_1$; Δ, $N_{10}S_0W_1$; ▽, $N_{10}S_1W_1$.

TABLE I—ANALYSIS OF VARIANCE FOR GEOMETRIC MEAN DIAMETER ($\bar{d}$)

Source of Variation	*df*	*SS*	*MS*	*F* Value
Main effects				
W (Wax)	5	158.69	31.74	9.83[a]
N (Nozzle size)	1	190.85	190.85	59.09[a]
S (Sorbitan monostearate)	2	6.68	3.34	1.03
Interactions				
W × S	10	23.10	2.31	0.72
W × N	5	41.74	8.35	2.58[b]
N × S	2	4.76	2.38	0.74
Error	10	32.29	3.23	
Total	35	458.11		

[a] Significant at $p < 0.01$. [b] The wax–nozzle interaction was not significant at the 5% level.

The geometric mean diameters ($\bar{d}$) and the volume-surface diameters (d_{vs}) of these particles were affected primarily by the wax and the nozzle size used. Sorbitan monostearate had no significant effect on these parameters (Table I).

The smallest particles, in terms of the geometric mean diameter, were produced from the SETD-glyceryl monostearate formulations atomized through the 0.20-cm. nozzle. These averaged about 20 μ. The SETD-white wax and the SETD-glyceryl tristearate formulations gave the smallest particles from the 0.25-cm. nozzle. These averaged about 25–26 μ. The largest particles were produced from the SETD-cetyl alcohol and the SETD-hydrogenated castor oil formulations atomized through the 0.25-cm. nozzle (Table II).

The results obtained in this study are in qualitative agreement with those reported by Scott *et al.* (8). These workers found that the volume-surface diameter of spray-congealed stearic acid particles varied inversely with the feed viscosity. In the present study, the SETD-cetyl alcohol formulations gave the highest values for the volume-surface diameter, *i.e.*, about 32 μ for the 0.20-cm. nozzle, and about 42 μ for the 0.25-cm. nozzle. These formulations, prior to atomization, were observed to be the least viscous of all the waxes used. The SETD-glyceryl monostearate formulations were found to be the most viscous, and these gave relatively low values for the volume-surface diameter. This was particularly the case with the glyceryl monostearate formulations atomized through the 0.20-cm. nozzle where the volume-surface diameter was about 23 μ.

The wax and nozzle size used also had a significant effect on the other micromeritic parameters, *i.e.*, bulk density, percent porosity, and specific surface. Sorbitan monostearate had no significant effect on these parameters (Table III).

TABLE II—GEOMETRIC MEAN DIAMETERS ($\bar{d}$), GEOMETRIC STANDARD DEVIATIONS (σ), AND VOLUME-SURFACE DIAMETERS (d_{vs}) OF SEVERAL SPRAY-CONGEALED SETD-WAX PRODUCTS

Wax	Sample Symbol	Geometric Mean Diameter ($\bar{d}$), μ	Geometric Standard Deviation (σ)	Volume-Surface Diameter (d_{vs}), μ
Hydrogenated castor oil	$N_8S_0W_4$	25.4	1.2	28.1
	$N_8S_1W_4$	27.4	1.2	30.3
	$N_8S_5W_4$	23.4	1.2	25.6
	$N_{10}S_0W_4$	27.4	1.3	32.0
	$N_{10}S_1W_4$	33.7	1.3	38.2
	$N_{10}S_5W_4$	32.6	1.2	36.5
Cetyl alcohol	$N_8S_0W_5$	25.8	1.4	34.2
	$N_8S_1W_5$	25.2	1.4	32.6
	$N_8S_5W_5$	25.3	1.3	30.0
	$N_{10}S_0W_5$	32.7	1.4	43.8
	$N_{10}S_1W_5$	31.7	1.4	43.3
	$N_{10}S_5W_5$	28.5	1.4	39.1
Glyceryl monostearate, edible	$N_8S_0W_6$	19.3	1.2	21.8
	$N_8S_1W_6$	19.1	1.3	22.4
	$N_8S_5W_6$	20.7	1.3	23.9
	$N_{10}S_0W_6$	27.2	1.3	33.0
	$N_{10}S_1W_6$	27.4	1.3	32.3
	$N_{10}S_5W_6$	28.7	1.3	33.2

TABLE III—ANALYSIS OF VARIANCE FOR SPECIFIC SURFACE (S_w)

Source of Variation	*df*	*SS*	*MS*	*F* Value
Main effects				
W (Wax)	5	1,534,170	306,834	19.35[a]
N (Nozzle Size)	1	1,486,774	1,486,774	93.76[a]
S (Sorbitan monostearate)	2	39,947	19,974	1.26
Interactions				
W × S	10	137,458	13,746	0.87
W × N	5	359,716	71,943	4.54[a]
N × S	2	6,383	3,192	0.20
Error	10	158,567	15,857	
Total	35	3,723,015		

[a] Significant at $p < 0.01$.

The SETD-carnauba wax products were the least porous, and these gave relatively low values for the specific surface. In addition, the SETD-white wax products were the most porous, and these gave relatively high values for the specific surface. In general, products atomized through the smaller of the two nozzles gave higher percent porosities.

In Vitro Dissolution Behavior of Spray-Congealed SETD-Wax Products—The drug SETD is much more soluble in an alkaline medium than in an acid medium. Therefore, the dissolution rate was much less in acid pepsin medium than that in alkaline pancreatin medium. In all samples, the percent of SETD released in the alkaline medium was much greater than that in the acid medium during the same time interval (Table IV).

A greater amount of SETD was released during the initial 15-min. period than in any subsequent 15-min. period. The percent of SETD released, from samples containing no sorbitan monostearate, during the initial 15-min. period in acid pepsin medium may be taken as an estimate of the amount of drug partially exposed on the surface of the particles and any free drug present in the samples. However, in all samples, the percent of SETD released during the initial 15-min. period in alkaline pancreatin medium was greater than that in acid pepsin medium. This may be due to the nature of the medium itself, as well as to the solubility factor mentioned previously. The alkaline medium contains ox bile extract which is a powerful surfactant due to the presence of bile salts. Apparently, a significant amount of the spray-congealed particles are emulsified, disintegrated, or solubilized during the initial 15-min. exposure to the alkaline medium. A similar effect was noted, even in the acid medium, for those samples containing sorbitan monostearate.

All of the main effects, *i.e.*, wax, nozzle size, and concentration of sorbitan monostearate, had a significant effect on the percent of SETD released in both media (Table V).

Effect of Sorbitan Monostearate—In general, the dissolution rate increased significantly as the concentration of sorbitan monostearate was increased. This was noted with four of the six waxes used, *i.e.*, white wax, glyceryl tristearate, carnauba wax, and hydrogenated castor oil (Figs. 2 and 3). The surfactant lowers the interfacial tension between the drug–wax particles and the dissolution medium, particularly since some sorbitan monostearate may be extracted into the medium. Therefore, wetting of the drug–wax particles is promoted, and the amount of drug released increased with the concentration of surfactant. In addition, the dissolution medium can more readily enter the porous, waxy clusters and dissolve the drug within the matrix. The drug is then transported away from the matrix into the medium. Some of the drug–wax particles may actually be emulsified, disintegrated, or solubilized, allowing the drug to be more readily dissolved due to an increase in the total surface area available to the medium.

An unusual surfactant effect was noted in the case of the SETD-cetyl alcohol and the SETD-glyceryl

TABLE IV—*In Vitro* DISSOLUTION DATA FOR SETD-WHITE WAX PARTICLES CONTAINING 5% SORBITAN MONOSTEARATE AND ATOMIZED THROUGH a 0.20-cm. PNEUMATIC NOZZLE[a]

Time, Hr.	Colorimetric Readings of Two Determinations		Mg. SETD Released	% SETD Released	% Predicted Released
			Dissolution in Acid Pepsin Medium		
0.25	35	32	20.13	16.77	14.36
0.5	39	37	22.83	19.03	20.43
0.75	41	45	25.84	21.53	23.97
1.0	51	50	30.34	25.29	26.36
1.25	55	58	33.95	28.29	28.11
1.5	63	61	37.25	31.04	29.47
2	66	66	39.66	33.05	31.45
			Dissolution in Alkaline Pancreatin Medium		
0.25	86	85	51.37	42.81	40.96
0.5	109	112	66.39	55.33	56.61
0.75	128	125	76.01	63.34	65.14
1.0	142	143	85.62	71.35	70.61
2.0	159	163	96.74	80.61	81.34
3.0	171	175	103.95	86.62	86.03
4.0	180	181	108.45	90.38	88.73
6.0	187	184	111.46	92.88	91.78

[a] Sample number 19 ($N_8S_8W_1$); each sample weighed 0.4630 g.

TABLE V—ANALYSIS OF VARIANCE FOR PERCENT SETD RELEASED DURING INITIAL 15-MIN. PERIOD IN ALKALINE PANCREATIN MEDIUM

Source of Variation	*df*	*SS*	*MS*	*F* Value
Main effects				
W (Wax)	5	12,679.684	2,535.937	107.99[a]
N (Nozzle size)	1	391.314	391.314	16.66[a]
S (Sorbitan monostearate)	2	612.111	306.056	13.03[a]
Interactions				
W × S	10	833.060	83.306	3.55[b]
W × N	5	175.688	35.138	1.50
N × S	2	44.206	22.103	0.94
Error	10	234.832	23.483	
Total	35	14,970.895		

[a] Significant at $p < 0.01$. [b] The wax–sorbitan monostearate interaction was not significant at the 2.5% level.

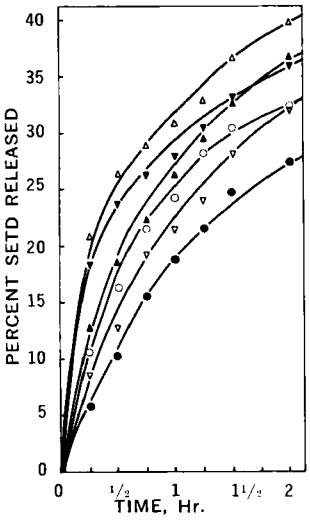

Fig. 2—In vitro *dissolution behavior of SETD-carnauba wax particles in acid pepsin medium. Key:* ▽, $N_8S_0W_3$; ▲, $N_8S_1W_3$; △, $N_8S_5W_3$; ●, $N_{10}S_0W_3$; ○, $N_{10}S_1W_3$; ▼, $N_{10}S_5W_3$.

monostearate particles, especially in acid pepsin medium. The amount of drug released from these particles decreased as the concentration of sorbitan monostearate increased (Fig. 4). This phenomenon may be explained in the following manner.

Although all of the waxes used in this study are insoluble in water, cetyl alcohol and glycerol monostearate differ from the others, with the exception of hydrogenated castor oil, in that they are somewhat hydrophilic. That is, cetyl alcohol and glyceryl monostearate are capable of being hydrated in an aqueous medium. The presence of sorbitan monostearate in the formulation reduces the tendency of these particles to become hydrated. This is to be expected since sorbitan monostearate has an HLB value of 4.7 and would make the drug–wax matrix more lipophilic than the one containing no sorbitan monostearate.

Effect of Nozzle Size—The nozzle used in atomizing the SETD-wax formulations also had a significant effect on the dissolution behavior of the spray-congealed particles. Faster dissolution rates were noted with formulations atomized through the 0.20-cm. nozzle than with the same formulations atomized through the 0.25-cm. nozzle.

This effect was apparently due to a difference in the total surface area of the particles prepared from

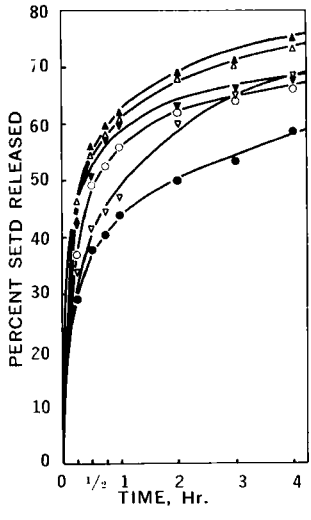

Fig. 3—In vitro *dissolution behavior of SETD-carnauba wax particles in alkaline pancreatin medium. Key:* ▽, $N_8S_0W_3$; ▲, $N_8S_1W_3$; △, $N_8S_5W_3$; ●, $N_{10}S_0W_3$; ○, $N_{10}S_1W_3$; ▼, $N_{10}S_5W_3$.

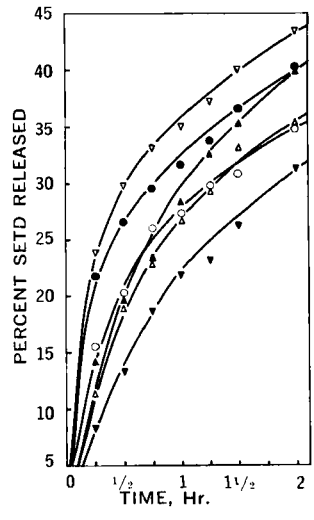

Fig. 4—In vitro *dissolution behavior of SETD-cetyl alcohol particles in acid pepsin medium. Key:* ▽, $N_8S_0W_5$; ▲, $N_8S_1W_5$; △, $N_8S_5W_5$; ●, $N_{10}S_0W_5$; ○, $N_{10}S_1W_5$; ▼, $N_{10}S_5W_5$.

the two nozzles. Particles having smaller volume-surface diameters, and therefore larger specific surfaces, were those prepared with the smaller of the two nozzles. For example, the SETD-white wax particles prepared with the 0.20-cm. nozzle had an average specific surface of 2,124 cm.²/g., whereas those prepared with the 0.25-cm. nozzle had an average specific surface of 1,858 cm.²/g. Similar results were obtained with the other waxes.

Effect of Wax—The most important factor that had an effect on the dissolution behavior of the spray-congealed SETD-wax particles was the wax used in a particular formulation. The effect of wax apparently depends upon the following factors: the physical properties of the wax and the drug–wax particles, the chemical composition of the wax, and the composition of the dissolution medium. For all waxes the amount of drug released after a certain time interval in alkaline pancreatin medium was greater than that in acid pepsin medium. This effect is due to three factors. The drug SETD is much more soluble in the alkaline medium than in the acid medium. Secondly, the alkaline medium can emulsify, disintegrate, or solubilize the particles much more readily. Finally, the constituents of these waxes, notably the fatty acids and fatty alcohols, would be expected to be more soluble in the alkaline medium. In addition, the fatty esters, present in some of the waxes, may be more readily degraded or hydrolyzed in the alkaline medium.

SETD-White Wax Particles—The SETD-white wax particles released between 10 to 33% of the drug after a 2-hr. exposure to acid pepsin medium. In alkaline pancreatin medium these particles released between 55 to 80% of the drug after 2 hr. and between 80 to 95% of the drug after 6 hr. Sorbitan monostearate had a significant effect in increasing the dissolution rate from these particles.

The primary constituents of white wax are cerotic acid and the fatty ester, myricyl palmitate. The fatty acid would be more soluble in the alkaline medium than in the acid medium. In addition, the ester may be more readily hydrolyzed in the alkaline medium. These factors would facilitate the disintegration of these particles and increase the dissolution rate in the alkaline medium.

SETD-Glyceryl Tristearate—The SETD-glyceryl tristearate particles released between 20 to 42% of the drug after 2 hr. in acid pepsin medium. In alkaline pancreatin medium these particles released between 25 to 60% of the drug after 2 hr. and between 38 to 80% of the drug after 6 hr. Again sorbitan monostearate significantly increased the amount of drug released after a certain time interval.

The dissolution rate was greater in the alkaline medium than in the acid medium. It is possible that the ester is more susceptible to alkaline-catalyzed hydrolysis than to acid-catalyzed hydrolysis.

In general, the SETD-glyceryl tristearate particles gave the slowest dissolution rates of the six waxes used. This was the case in both media, and it is not surprising since glyceryl tristearate consists essentially of the triglyceride ester of stearic acid. Triglyceride esters of fatty acids are less susceptible to either acid- or alkaline-catalyzed hydrolysis than are the corresponding di- or monoglyceride esters.

However, the SETD-glyceryl tristearate particles released more drug in the acid medium than the SETD-white wax particles, whereas the former released less drug in the alkaline medium. This effect is also believed to be due to the chemical composition of the two waxes. White wax contains a high percentage of free fatty acids, notably cerotic acid. These fatty acids are essentially insoluble in the acid medium, but are readily soluble in the alkaline medium. Glyceryl tristearate contains no free fatty acids, but does contain a high percentage of glyceryl tristearate. The latter is slowly hydrolyzed in acid and alkaline media, and therefore the glyceryl tristearate particles disintegrate quite slowly. In addition, these particles were not readily wetted by the dissolution media.

SETD-Carnauba Wax Particles—The SETD-carnauba wax particles released between 27 to 40% of the drug after 2 hr. in acid pepsin medium (Fig. 2). In alkaline pancreatin medium these particles released between 50 to 70% of the drug after 2 hr. (Fig. 3) and between 65 to 78% of the drug after 6 hr. Sorbitan monostearate increased the amount of drug released from these particles in both media.

Carnauba wax consists chiefly of myricyl cerotate with smaller amounts of myricyl alcohol, ceryl alcohol, and cerotic acid. Its fatty alcohol and fatty acid content probably accounts, in part, for the higher dissolution rates in the alkaline medium.

Again it was noted, just as with the SETD-glyceryl tristearate particles, that the SETD-canauba wax particles released more drug in acid pepsin medium than the SETD-white wax particles, whereas the former released less drug in alkaline pancreatin medium than the SETD-white wax particles. Carnauba wax contains a lower percentage of free fatty acids (acid value from 2 to 10) than white wax (acid value from 17 to 24), but the former contains a somewhat higher percentage of fatty esters (ester value from 75 to 85) than white wax (ester value from 72 to 79).

For the same reason, the SETD-carnauba wax particles released more drug in the alkaline medium than the SETD-glyceryl tristearate particles since glyceryl tristearate contains no free fatty acids.

SETD-Hydrogenated Castor Oil Particles—The SETD-hydrogenated castor oil particles released between 35 to 48% of the drug after 2 hr. in acid pepsin medium. In alkaline pancreatin medium these particles released between 75 to 92% of the drug after 2 hr. and between 92 to 100% of the drug after 6 hr. Sorbitan monostearate also increased the amount of drug released from these particles in both media.

Hydrogenated castor oil consists primarily of partially hydrogenated glyceryl triricinoleate. It contains very little free fatty acids (acid value of 2) but a significant amount of hydroxyl groups (hydroxyl value of 158). A relatively large proportion of its fatty ester content is in the form of triglycerides of unsaturated fatty acids (iodine value of 38). These factors may account, in part, for the observed dissolution behavior of these particles.

The hydroxyl groups in this wax make it somewhat hydrophilic such that the particles were easily wetted, particularly in the alkaline medium. This would also account for the relatively high dissolution rates in the acid medium. The latter effect is also due to the relatively low free fatty acid content. In addition, the unsaturated fatty esters present in this wax are apparently more susceptible to acid- and

alkaline-catalyzed hydrolysis than the saturated fatty esters present in some of the other waxes.

SETD-Cetyl Alcohol Particles—The SETD-cetyl alcohol particles released between 32 to 44% of the drug after 2 hr. in acid pepsin medium (Fig. 4). In alkaline pancreatin medium these particles released between 85 to 93% of the drug after 2 hr. and between 90 to 96% of the drug after 6 hr. (Fig. 5). In these products the amount of drug released decreased as the concentration of sorbitan monostearate increased.

The official alcohol is a mixture of solid, fatty alcohols consisting chiefly of cetyl alcohol. Although it is insoluble in water, it is capable of being hydrated. Thus, of the waxes used in this study, cetyl alcohol is one of the most hydrophilic. Glyceryl monostearate and hydrogenated castor oil are also somewhat hydrophilic. This property is evident from the fact that these particles were readily wetted by the dissolution media, particularly in the alkaline medium.

Nearly complete removal of the drug was attained from these particles after about 6 hr. in the alkaline medium. The dissolution rates in the acid medium were relatively high also, that is, compared with the SETD-white wax and the SETD-glyceryl tristearate particles. The latter effect is due to the hydrophilic character of cetyl alcohol and also to the fact that this material contains no free fatty acids or fatty esters.

SETD-Glyceryl Monostearate Particles—The SETD-glyceryl monostearate particles released between 45 to 51% of the drug after 2 hr. in acid pepsin medium. In alkaline pancreatin medium these particles released between 83 to 97% of the drug after 2 hr. and between 86 to 100% of the drug after 6 hr. In these products the amount of drug released decreased slightly as the concentration of sorbitan monostearate increased. This phenomenon was not as pronounced as in the case of the SETD-cetyl alcohol particles.

Glyceryl monostearate is a wax-like ester. It has an acid value of less than 5, and is somewhat hydrophilic since each molecule of the pure ester contains two hydroxyl groups. For this reason, this material was readily wetted in both media. The dissolution behavior of these particles was quite similar to that of the SETD-cetyl alcohol particles since both are somewhat hydrophilic. They differ in that the SETD-glyceryl monostearate particles released more drug in the acid medium.

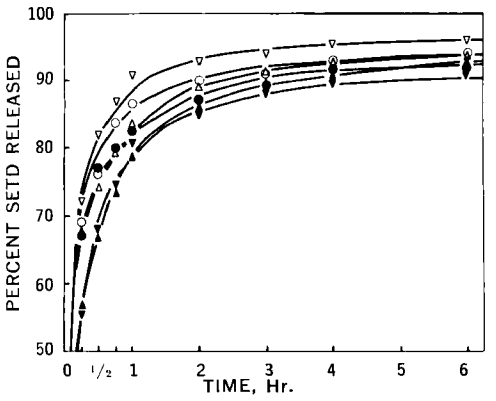

Fig. 5—In vitro *dissolution behavior of SETD-cetyl alcohol particles in alkaline pancreatin medium. Key:* ▽, $N_8S_0W_5$; ▲, $N_8S_1W_5$; △, $N_8S_5W_5$; ●, $N_{10}S_0W_5$; ○, $N_{10}S_1W_5$; ▼, $N_{10}S_5W_5$.

It is interesting to note the tremendous difference in the dissolution behavior between these particles and the SETD-glyceryl tristearate particles. In both media, the SETD-glyceryl monostearate particles released significantly greater amounts of the drug than the SETD-glyceryl tristearate particles. This may have been due to the combined effect of the following factors: the hydrophilic character of glyceryl monostearate, the fact that the SETD-glyceryl monostearate particles can be readily emulsified or disintegrated, and that glyceryl monostearate may be more readily hydrolyzed in acid and alkaline media than glyceryl tristearate.

In Vitro Dissolution Model for Spray-Congealed SETD-Wax Products—The dissolution data obtained in this investigation did not give a linear relationship when plotted in accordance with existing theories (13, 14). For example, a plot of the percent of SETD remaining in the particles ($C_e - C$) *versus* time was not linear. This would indicate that the dissolution kinetics were not zero order. In addition, a plot of the logarithm of the percent of SETD remaining in the particles *versus* time was not linear. Therefore, the dissolution process did not conform to first-order kinetics either. In accordance with the theory of Higuchi (14), the percent of SETD remaining in the particles was also plotted *versus* the square root of time. Again nonlinear relationships were obtained for all of the waxes used.

The nonlinear relationships obtained are not surprising in view of the assumptions involved in these theories. The most important assumption in both the Noyes-Whitney (13) dissolution rate law and the theory of Higuchi (14) is that the total surface area of the tablet or particles does not change significantly during the dissolution run. Therefore, it is presumed that the drug–wax matrix is completely inert or unaffected by the dissolution medium. However, this was not the case in the present study. For all of the waxes used, the particles were emulsified, disintegrated, or solubilized by the dissolution medium. This was particularly true in the alkaline medium.

A dissolution model previously proposed by Cox (9) was utilized in the present study. This model is represented by the equation

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

where C is the percent of drug in solution at a particular time (t), C_e is the percent of drug in solution at equilibrium, and c and d are constants for a particular formulation. This dissolution model is not a linear function of the unknown parameters c, d, and C_e. Therefore, a nonlinear least-squares curve fitting procedure was used to estimate the above parameters. Different values for c, d, and C_e were used in a computer program, and the estimated percent of drug in solution ($\hat{C}$) at a particular time (t) was calculated. The experimental values of the percent of drug in solution (C) at a particular time (t) were compared with the estimated values. The quantity $\Sigma\ (C - \hat{C})^2$ was minimized by adjusting the values of the three parameters, c, d, and C_e (Table VI).

TABLE VI—ESTIMATED[a] PARAMETERS FOR DISSOLUTION MODEL IN ACID PEPSIN MEDIUM

Wax	Sample Symbol	$C = C_e[1 - (1 + t/d)^{-c}]$ C_e	c	d	SS for Error	Instantaneous Dissolution Rate, $(c/d)C_e$
White wax	$N_8S_0W_1$	37.81	0.6630	1.7350	4.26	14.45
	$N_8S_1W_1$	46.68	0.3054	0.1894	16.09	75.27
	$N_8S_5W_1$	45.60	0.5160	0.2311	21.66	101.82
	$N_{10}S_0W_1$	45.00	0.3732	1.5000	14.65	11.20
	$N_{10}S_1W_1$	33.84	0.5669	0.5495	5.72	34.91
	$N_{10}S_5W_1$	69.85	0.1181	0.0537	2.20	153.60
Glyceryl tristearate	$N_8S_0W_2$	69.77	0.1971	0.1644	8.83	83.65
	$N_8S_1W_2$	66.27	0.2317	0.0809	9.76	189.80
	$N_8S_5W_2$	67.16	0.2389	0.0448	24.04	358.14
	$N_{10}S_0W_2$	76.00	0.1958	0.4845	7.59	30.71
	$N_{10}S_1W_2$	68.61	0.2039	0.1228	19.22	113.92
	$N_{10}S_5W_2$	75.53	0.1754	0.0366	14.75	361.97
Carnauba wax	$N_8S_0W_3$	45.30	2.8258	3.7450	4.93	34.18
	$N_8S_1W_3$	47.97	1.4304	1.2591	7.84	54.50
	$N_8S_5W_3$	54.24	0.4260	0.1341	13.64	172.31
	$N_{10}S_0W_3$	42.22	4.1761	6.6859	1.75	26.37
	$N_{10}S_1W_3$	46.91	1.0864	0.9886	3.13	51.55
	$N_{10}S_5W_3$	53.23	0.3834	0.1383	7.23	147.57
Hydrogenated castor oil	$N_8S_0W_4$	85.36	0.1664	0.0344	7.65	412.90
	$N_8S_1W_4$	81.04	0.1716	0.0172	3.35	808.52
	$N_8S_5W_4$	77.43	0.2012	0.0179	3.84	870.33
	$N_{10}S_0W_4$	86.80	0.1885	0.1338	3.95	122.29
	$N_{10}S_1W_4$	73.36	0.2726	0.0933	2.44	214.34
	$N_{10}S_5W_4$	75.06	0.2264	0.0284	1.91	598.37
Cetyl alcohol	$N_8S_0W_5$	64.39	0.3179	0.0808	13.37	253.34
	$N_8S_1W_5$	53.50	1.2642	1.1429	14.90	59.18
	$N_8S_5W_5$	58.40	0.5815	0.5311	13.08	63.94
	$N_{10}S_0W_5$	71.23	0.2144	0.0605	18.57	252.42
	$N_{10}S_1W_5$	74.59	0.2396	0.1678	48.77	106.51
	$N_{10}S_5W_5$	75.00	0.3151	0.5000	47.28	47.27
Glyceryl monostearate edible	$N_8S_0W_6$	78.23	0.1705	0.0056	14.75	2,381.82
	$N_8S_1W_6$	83.80	0.1420	0.0071	4.76	1,676.00
	$N_8S_5W_6$	60.06	0.3041	0.0216	5.40	845.57
	$N_{10}S_0W_6$	68.27	0.2518	0.0154	17.24	1,116.26
	$N_{10}S_1W_6$	68.83	0.2060	0.0086	6.02	1,648.72
	$N_{10}S_5W_6$	57.65	0.4379	0.0590	6.02	427.88

[a] Modified Gauss-Newton least-squares method (15).

Specifically, the procedure used in performing the nonlinear least-squares fit was a modified Gauss-Newton least-squares method (15). Setting up of the computer program and subsequent operations with the computer were performed in cooperation with the University of Florida Computing Center using an IBM 360 computer.

Equation 1 can be shown to be equivalent to

$$\log (C_e - C) = \log C_e + c \log d - c \log (t + d) \quad \text{(Eq. 2)}$$

Therefore, a plot of the logarithm of the percent of drug remaining in the particles $(C_e - C)$ *versus* the logarithm of $(t + d)$ should give a straight line.

In general, the agreement between the experimental and the predicted values for the dissolution data was good. The experimental data for the dissolution of SETD from the SETD-carnauba wax particles in acid pepsin medium are plotted on the lines predicted from the dissolution model in Fig. 6. The plot of the logarithm of the percent of SETD remaining in the particles *versus* the logarithm of $(t + d)$ was found to be reasonably linear. A similar plot for the dissolution of SETD from the SETD-cetyl alcohol particles in alkaline pancreatin medium is shown in Fig. 7. Again a reasonably good linear relationship was obtained.

Thus, the data obtained in this investigation, both in acid pepsin and in alkaline pancreatin media, agreed reasonably well with those predicted from a dissolution model in accordance with Eq. 1.

However, it should be pointed out that no correlation could be demonstrated between the instantaneous dissolution rates, *i.e.*, $(c/d)C_e$, and the parameters obtained from the particle-size studies, notably the specific surface. A possible explanation for this is as follows. In the particle-size studies, only individual particles were measured and not clusters of particles. In the samples used for the dissolution studies, many clusters of particles were also present in addition to the individual, spherical

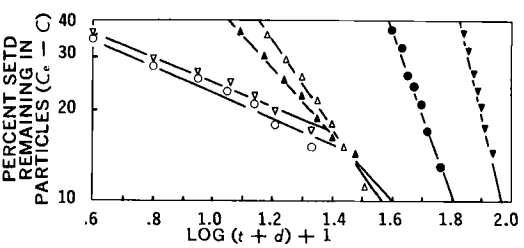

Fig. 6—Experimental data for percent SETD released from SETD-carnauba wax particles in acid pepsin medium, plotted on lines predicted from dissolution model. Key: ●, $N_8S_0W_3$; △, $N_8S_1W_3$; ○, $N_8S_5W_3$; ▼, $N_{10}S_0W_3$; ▲, $N_{10}S_1W_3$; ▽, $N_{10}S_5W_3$.

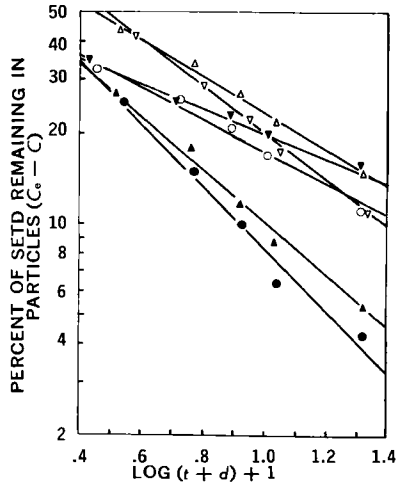

Fig. 7—Experimental data for percent SETD released from SETD-cetyl alcohol particles in alkaline pancreatin medium, plotted on lines predicted from dissolution model. Key: ●, $N_8S_0W_5$; Δ, $N_8S_1W_5$; ○, $N_8S_5W_5$; ▼, $N_{10}S_0W_5$; ▲, $N_{10}S_1W_5$; ▽, $N_{10}S_5W_5$.

particles. This would be the case particularly for those products that were somewhat tacky. Another factor is that many of the spray-congealed SETD-wax products were not easily wetted by the dissolution medium, at least initially. Some of the particles tended to agglomerate upon coming in contact with the dissolution medium, particularly in acid pepsin medium. As the dissolution process continued, these agglomerates were subsequently emulsified, disintegrated, or solubilized as were the individual particles.

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Keyphrases

Prolonged release dosage forms—spray congealed
Sulfaethylthiadiazole–wax formulations
Spray-congealed products—*in vitro* dissolution model
Particle size—wax, nozzle size effect
Dissolution rates—parameters affecting

Tumor-Inhibitory Activity of Pyrrolizidine Alkaloids

By C. C. J. CULVENOR

Eighteen pyrrolizidine alkaloids and several derivatives have been examined for tumor-inhibitory properties. Of these, 10 compounds show significant activity against one or more test tumors. Heliotrine, lasiocarpine, monocrotaline, spectabiline, and senecionine are highly active against the Walker 256 (intramuscular) system. The activity pattern is consistent with the tumor-inhibitory action being associated with the allylic ester function which imparts alkylating ability and is also responsible for hepatotoxicity.

PYRROLIZIDINE ALKALOIDS are found typically in species of *Senecio* (family *Compositae*, tribe *Senecioneae*), *Crotalaria* (family *Leguminosae*, tribe *Genistae*) and the subfamilies *Heliotropioideae* and *Boraginoideae* of the family *Boraginaceae* (1). They occur also in other genera of the tribes *Senecioneae* [*e.g.*, *Cacalia*, *Emilia* (2), *Erechtites*] and *Genistae* [*e.g.*, *Adenocarpus* (3), *Cytisus* (4)] as well as in the unrelated genera *Eupatorium* (*Compositae*) (5), *Thesium* (*Santalaceae*) (6), *Planchonella* (*Sapotaceae*) (7), *Lolium* (8), and *Festuca* (9) (*Gramineae*). The ability of some alkaloids of the group to cause an unusual chronic liver disease in animals (10) has promoted extensive study of their chemical and toxicological properties (*e.g.*, *References 1, 11, 12*). Platyphylline (I) (13) has no hepatotoxic action and has found use in the U.S.S.R. as an antispasmodic.

Received May 15, 1967, from the Division of Applied Chemistry, C.S.I.R.O. Chemical Research Laboratories, Melbourne, Australia.
Accepted for publication October 9, 1967.
This work has been carried out partly in collaboration with Cancer Chemotherapy National Service Center, Bethesda, Md., and partly in collaboration with Abbott Laboratories, North Chicago, Ill. Thanks are due to both organizations for permission to publish the screening results.