Release Study of Sulfaethylthiadiazole (SETD) from a Tablet Dosage Form Prepared from Spray-Congealed Formulations of SETD and Wax

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Abstract □ *In vitro* dissolution patterns of some spray-congealed products of sulfaethylthiadiazole–wax made into compressed tablets are reported. The tablets were made with a Carver laboratory press, employing a single force of compression and being approximately the same weight. The rate of release of sulfaethylthiadiazole (SETD) from the tablets was evaluated in acid pepsin medium and alkaline pancreatin medium using a rotating-bottle method. There was a gradual decrease in the amount of SETD released from the tablets as the concentration of sorbitan monooleate increased in the formulation, using acid pepsin medium. In alkaline pancreatin medium, an increase in the percentage of SETD released was noted as the concentration of surfactant increased. The mechanism of release of SETD appeared to be due to erosion, solubilization, and leaching of the drug from the tablet. The Higuchi model for drug release from inert matrices could describe the release pattern only for the initial few hours when apparently the variables other than the amount of drug released and time were essentially constant.

Keyphrases □ Sulfaethylthiadiazole–wax tablets—drug release □ Spray-congealed formulations—SETD–wax compressed tablets □ Dissolution, *in vitro*—SETD–wax compressed tablets □ Surfactant effect—SETD release, tablets □ Wax matrix effect—SETD release, tablets

The purpose of this investigation was to study *in vitro* the dissolution patterns of some spray-congealed sulfaethylthiadiazole–wax products made into compressed tablets. The spray-congealed products, in powder form, were prepared in this laboratory by John and Becker (1), and the dissolution patterns of the various powdered products were reported. Other workers (2–4) studied release patterns of tablet formulations which were simply made by mixing the active drug with inert matrices and compressing the materials into tablets.

Inasmuch as the release patterns of sulfaethylthiadiazole (SETD) from the spray-congealed drug–wax products, in powder form, were known in this study, with and without surfactant, it would be of value to know the release pattern of the drug from the same products when compressed into tablet form. Such factors as force of compression, possible fusion of the material on compression, and degree of disintegration or erosion (or both) of the tablets during dissolution should have decided effects on the release pattern of the drug. Other investigators (2–4) have reported dissolution patterns of drug from inert matrices in tablet form, but they did not report the release patterns of the drug imbedded in the matrices in the powder form.

EXPERIMENTAL

Materials—The spray-congealed SETD–wax products, in powder form, used to make the tablets in this study were prepared and reported by John and Becker (1). All other materials employed conformed to USP or NF specifications or were of analytical reagent quality.

White wax, a synthetic waxlike ester,[1] and a combination of equal parts of these waxes were employed in the formulations of John and Becker (1) as matrices, and these are designated as W_1, W_2, and W_3, respectively. The surfactant, sorbitan monooleate,[2] was used in some of the formulations in concentrations of 0, 1, 4, and 10%, and these are designated as S_0, S_1, S_4, and S_{10}, respectively. The tablets were made from three finenesses of spray-congealed powders, since these were atomized with three different nozzle sizes, namely, 0.05, 0.10, and 0.15. cm., and these are designated as N_2, N_4, and N_6, respectively.

Manufacture of Tablets—There were no additives incorporated in the tablets which were made with a Carver laboratory press. Accurately weighed, 0.5000 g. of the spray-congealed powder was put into the die. The die and the punches, 1.27 cm. in diameter, were previously lubricated with a small amount of talc to avoid sticking of the tablet to the punches. The 4000-p.s.i. gauge pressure was maintained for 1 min. All tablets were accurately weighed after compression, and they did not vary by more than 10 mg. It could be assumed that the surface area was essentially the same for a particular wax product made into tablets.

Assay Method—The SETD released was assayed by the Bratton-Marshall (5) procedure using a Klett-Summerson photoelectric colorimeter with a No. 54 filter.

***In Vitro* Dissolution Studies**—The rotating-bottle apparatus (6) was used to determine the dissolution behavior of the SETD from the tablets. Tablets weighing approximately 0.5000 g., accurately weighed, were put in 90-ml. screw-capped bottles, and to each bottle 60 ml. of acid pepsin medium (simulated gastric fluid USP, pH 1.1) was added. 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°. Samples were removed at specific time intervals, *i.e.*, at 0.25, 0.5, 1, 1.5, 2, 4, and 8 hr. Dissolution studies were also conducted in an alkaline pancreatin medium, test fluid B, pH 8.3, of Robinson and Swintosky (7), in a similar manner. Samples were removed for assay at 0.5, 1, 1.5, 2, 4, 8, and 12 hr.

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

RESULTS AND DISCUSSION

Spray-congealed products with white wax as the matrix were very tacky powders. The tackiness increased as the concentration of sorbitan monooleate in the formulations was increased, causing difficulty in transferring these powders into the die. The punches and the die had to be polished with a lubricant, talc, in order to obtain smooth and uniform tablets.

Spray-congealed products containing a combination of white wax and the synthetic waxlike ester in a 1 to 1 ratio were free flowing powders, but the ones with a higher concentration of the surfactant, sorbitan monooleate, were not free flowing. However, the tablets were easier to make from these products than those containing white wax alone as the matrix. In all of these instances, the punches and die had to be polished with talc to obtain smooth tablets.

All of the spray-congealed products containing the synthetic waxlike ester alone as the matrix, including the product having as high as 10% sorbitan monooleate, were free-flowing powders. However, the ones without surfactant could not be compressed into tablets at 4000-p.s.i. gauge pressure. This appeared to be due

[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.

Table I—*In Vitro* Dissolution Data Expressed as Percent SETD Released for SETD–White Wax Tablets and Powder Containing Sorbitan Monooleate and Atomized through a 0.15-cm. Pneumatic Nozzle

Time, hr.	Sample Symbol $W_1N_6S_0$ Tablet	Powder	Sample Symbol $W_1N_6S_4$ Tablet	Powder	Sample Symbol $W_1N_6S_{10}$ Tablet	Powder
			Dissolution in Acid Pepsin Medium			
0.25	0.28	8.00	0.32	10.05	0.25	3.66
0.50	0.35	9.76	0.33	16.91	0. 2	7.77
1.00	0.44	11.43	0.39	28.79	0.37	11.43
1.50	0.49	—	0.49	33.36	0.43	14.63
2.00	0.56	15.08	0.51	37.11	0.48	16.00
4.00	0.67	—	0.64	—	0.78	—
8.00	0.73	—	0.60	—	0.78	—
24.00	—	42.50	1.53	50.16	1.73	47.53
48.00	1.34	—	—	—	—	—
			Dissolution in Alkaline Pancreatin Medium			
0.50	1.60	38.16	3.41	74.04	3.74	65.81
1.00	2.15	53.47	4.37	80.44	6.48	74.73
1.50	4.03	—	9.42	—	11.70	—
2.00	7.00	74.79	11.59	83.18	14.08	87.75
4.00	12.60	90.27	21.31	85.50	25.61	89.81
6.00	22.50	90.72	33.25	87.29	39.50	—
8.00	31.40	—	34.99	—	43.78	95.52
12.00	50.80	—	56.54	—	64.02	—
24.00	—	94.15	—	—	—	—
48.00	86.50	—	91.00	92.32	97.52	96.89

to the friability of the finished tablet, as well as adherence or sticking of the tablet to the punch surface. The products with surfactant, on the other hand, could be compressed into tablets easily.

Tables I, II, and III give the dissolution data in acid pepsin medium and alkaline pancreatin medium from tablets with matrices of white wax (W_1), synthetic waxlike ester (W_2), and a combination of equal parts of these waxes (W_3) and varying concentrations of sorbitan monooleate. The tables also include dissolution data from the powder forms of the same formulations, reported earlier (1), for comparison.

Effect of Sorbitan Monooleate—There was an increase in the amount of SETD released with time from all tablets, with and without surfactant, in acid pepsin medium. However, there was a decrease in the rate of release of SETD from the tablets in acid pepsin medium as the concentration of surfactant in the tablets increased, particularly over the early dissolution testing periods, that is, from 0.25 to 4 hr. In most cases of powder forms of the same products (1) and for the same time period, there was an increase in the rate of release of SETD as the concentration level of sorbitan monooleate increased from 0 to 4%, but the rate of release decreased with the level of surfactant concentration at 10%. The magnitude of release of SETD was anywhere from 25 to 100 times less in tablet dosage form than in powder form. The decrease in the percent release of SETD from the tablets, as the concentration of sorbitan monooleate was increased, could be due to more cohesiveness of the products which increased as the concentration of surfactant was increased in the formulations. This can cause agglomeration of particles, which in turn can result in less surface area exposed to the dissolution medium. In addition, there could have been some fusion of particles under the compressional force used in tableting which could result in less porosity and more compactness of particles, thereby decreasing the release of SETD. Although sorbitan monooleate lowers surface tension and should theoretically increase the release of drug from a tablet, the surfactant apparently is not effective in an acid medium of low pH such as acid pepsin medium, nor is it as effective with tablets which are excessively compact.

An increase in the percentage of SETD released from tablets with time was noted in alkaline pancreatin medium, as the concentration of surfactant was increased in all the formulations of different waxes. This was also true for the same products in the powder form, except the percentage of release was of a larger magnitude (1). The release of SETD from white wax was anywhere from 35 to 60 times greater in powder form than that in tablet dosage form. The

Table II—*In Vitro* Dissolution Data Expressed as Percent SETD Released for SETD–Synthetic Waxlike Ester Tablets and Powder Containing Sorbitan Monooleate and Atomized through a 0.15-cm. Pneumatic Nozzle

Time, hr.	Sample Symbol $W_2N_6S_0$ Tablet	Powder	Sample Symbol $W_2N_6S_4$ Tablet	Powder	Sample Symbol $W_2N_6S_{10}$ Tablet	Powder
			Dissolution in Acid Pepsin Medium			
0.25	0.75	11.88	0.70	22.62	0.41	9.37
0.50	1.01	24.68	1.17	32.22	0.55	13.71
1.00	1.60	34.96	1.46	40.68	1.00	24.45
1.50	2.63	39.76	2.09	43.42	1.30	30.62
2.00	2.98	45.48	2.78	45.93	1.58	34.73
4.00	4.45	—	3.34	—	3.17	—
8.00	4.05	—	4.35	—	3.65	—
24.00	—	59.87	—	—	—	61.82
48.00	6.68	—	6.91	66.39	8.14	63.07
			Dissolution in Alkaline Pancreatin Medium			
0.50	2.70	30.00	2.42	69.70	2.85	56.44
1.00	3.20	45.25	2.59	80.40	4.45	65.36
1.50	3.80	—	4.00	—	6.21	—
2.00	4.40	48.67	4.88	85.01	7.64	76.78
4.00	6.00	53.70	6.70	90.95	9.76	92.32
6.00	7.80	65.36	7.09	95.06	12.46	94.61
8.00	9.50	—	9.72	—	19.09	—
12.00	9.57	—	12.89	—	22.14	—
48.00	18.22	97.81	20.79	97.35	46.67	96.89

Table III—*In Vitro* Dissolution Data Expressed as Percent SETD Released for SETD–Synthetic Waxlike Ester–White Wax (1:1) Tablets and Powder Containing Sorbitan Monooleate and Atomized through a 0.15-cm. Pneumatic Nozzle

Time, hr.	Sample Symbol $W_3N_6S_0$ Tablet	Powder	Sample Symbol $W_3N_6S_4$ Tablet	Powder	Sample Symbol $W_3N_6S_{10}$ Tablet	Powder
			Dissolution in Acid Pepsin Medium			
0.25	0.40	18.74	0.34	8.23	0.27	5.71
0.50	0.48	24.68	0.45	14.63	0.31	9.37
1.00	0.60	—	0.50	19.65	0.45	12.57
1.50	0.64	33.36	0.61	20.57	0.50	16.00
2.00	0.67	33.59	0.64	21.94	0.57	18.97
4.00	0.88	—	0.87	—	0.79	—
8.00	1.15	—	1.25	—	1.55	—
24.00	—	—	—	34.39	—	36.57
48.00	2.51	54.04	4.07	—	6.83	—
			Dissolution in Alkaline Pancreatin Medium			
0.50	2.15	38.19	1.99	31.54	3.50	55.30
1.00	2.19	58.27	3.26	46.39	5.16	68.78
1.50	3.01	—	5.61	—	8.30	—
2.00	4.00	58.73	8.10	56.67	9.89	78.38
4.00	8.60	82.27	13.52	69.24	15.50	86.61
6.00	14.88	82.50	17.88	74.73	20.00	90.27
8.00	17.99	—	23.68	—	29.00	—
12.00	33.99	—	37.63	—	30.31	—
48.00	76.50	96.89	62.32	95.98	70.99	95.06

increase in percent of SETD release in both tablet and powder forms may be due, partially, to surface tension lowering effect of sorbitan monooleate on the dissolution medium. Sorbitan monooleate probably enhances the action of alkaline pancreatin medium to accelerate softening and erosion of the wax-matrix tablets which did occur. It should be pointed out, also, that alkaline pancreatin medium contains ox bile extract which is a surfactant due to the presence of bile salts; this, combined with sorbitan monooleate, could have been more effective than either surfactant used alone.

Effect of Wax Matrix—Those tablets which could be made from formulations of spray-congealed SETD–synthetic waxlike ester powders gave the highest drug release of the three matrices investigated in an 8-hr. dissolution study in acid pepsin medium. Tablets with white wax alone as the matrix gave the lowest drug release. A combination of synthetic waxlike ester and white wax in a 1 to 1 proportion as the matrix ranged between the two above matrices in regard to release of SETD. This was true with and without surfactant. This effect may be due to the chemical composition of the two waxes. The synthetic waxlike ester contains a high percentage of glyceryl tristearate but no free fatty acids. The ester might have been hydrolyzed sufficiently in the acid pepsin medium to account for the highest percentage of SETD released of the three matrices studied On the other hand, white wax, not a glyceryl ester and not as easily hydrolyzed by acids, contains free fatty acids which are practically insoluble in the acid pepsin medium, hence showing the lowest drug release from this matrix. The products in powder form were also observed to possess similar characteristics (1).

As compared to the acid pepsin medium dissolution study, the percent of SETD released from tablets was found to be the highest from the white wax matrix in alkaline pancreatin medium over a 12-hr. period. Tablets with the synthetic waxlike ester alone as the matrix gave the lowest drug release. A combination of the synthetic waxlike ester and white wax in a 1 to 1 proportion was intermediate in release of SETD. Similar results were obtained when these products were studied in powder form by John and Becker (1). The high release of SETD from tablets containing the white wax matrix alone can most likely be attributed to the presence of free fatty acids in the wax which react with the alkalinity of the dissolution medium to form soaps that act as surfactants. The synthetic waxlike ester is apparently not as easily eroded and dispersed in alkaline pancreatin medium as white wax due to the lack of free fatty acids.

The percent of drug released from tablets of all the waxes, after any comparable time interval in alkaline pancreatin medium, was greater than in acid pepsin medium. One explanation is that the drug SETD is more soluble in an alkaline medium than in an acid medium. Secondly, the constituents of the waxes, both free fatty acids and the esters, are apparently more soluble and dispersible in an alkaline medium.

Effect of Nozzle Size—No definite conclusions could be drawn as to effect of nozzle size used in the pneumatic atomization of the various spray-congealed SETD–wax products and the influence of their particle sizes when made into tablets on the release of the drug in acid pepsin medium as well as in alkaline pancreatin medium. As reported earlier (1), the average particle size of SETD–white wax powders spray congealed with different nozzle sizes, namely, 0.05, 0.10, and 0.15 cm., was 9.2, 13.4, and 14.8 μ, respectively; for the SETD–synthetic waxlike ester powders, the average particle size was 7.8, 12.2, and 14.6 μ; and for the SETD–synthetic waxlike ester–white wax powders in a 1 to 1 proportion, the average particle size was 8.9, 13.1, and 18.8 μ, respectively. Apparently the difference in ranges of particle sizes was not sufficient to show any significant pattern in release of SETD from the respective tablets. It appears likely that the force of compression employed in making the tablets, resulting in some fusion of the waxy materials, removed any possible effects of particle size if such exist in this instance.

***In Vitro* Dissolution Pattern of SETD from Tablets Made from Inert Wax Matrices**—Higuchi (8) derived the following equation for drug release from granular inert matrices:

$$Q = A\left[\frac{DK}{r}(2 - KC_s)C_s t\right]^{1/2} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusitivity of drug in the homogeneous matrix media, A is the total amount of drug present in the matrix per unit volume, C_s is the solubility of the drug in the matrix system, r is the tortuosity factor of the capillary system, and K equals the specific

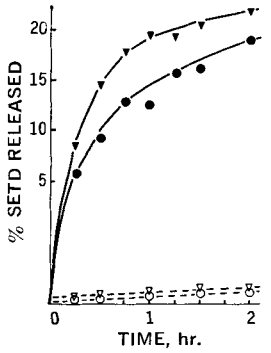

Figure 1—*Plot of percent SETD released as a function of time for dissolution from SETD–synthetic waxlike ester–white wax (1:1) tablets and powder in acid pepsin medium. Key:* ▼ ▽, $W_3N_6S_{10}$; ● ○, $W_3N_6S_4$. *Solid line: powder; dashed line: tablets.*

volume of the drug. Under the conditions where shape, size, weight, degree of compression, and surface area remain essentially unchanged, the above equation reduces to:

$$Q = kt^{1/2} \qquad \text{(Eq. 2)}$$

where k is a constant taking account of all the factors held constant in Eq. 1.

The percent of SETD released from the tablets after dissolution in the acid pepsin medium from all three matrices evaluated in this investigation was plotted as a function of square root of time. The linear relationship according to Eq. 2 was observed to be valid for a few hours where the release was less than 2%. After that the dissolution data did not follow this pattern, apparently due to considerable change in the effective surface area of the tablets. Similarly, the percent of SETD released from the tablets after dissolution in alkaline pancreatin medium from all three matrices was plotted as a function of square root of time. Likewise, in this instance, a deviation from linearity was observed after a few hours due to change in effective surface area of the tablets as erosion and some dispersion of the tablets occurred. Tablets compressed from spray-congealed products containing white wax alone as the matrix were observed to be more soluble than the other wax matrices employed and, hence, showed more deviation. After 6 hr. of exposure in the alkaline pancreatin medium, the SETD–white wax tablets were about half of the original size.

Dissolution of SETD from Spray-Congealed SETD–Wax Powders *versus* Dissolution of SETD from Tablets—It would be of interest to compare the dissolution of SETD from spray-congealed SETD–wax powders to the dissolution of SETD from tablets prepared from the same products. Figure 1 shows the percent of SETD-released against time from SETD-synthetic waxlike ester–white wax, in a 1 to 1 proportion, powder and tablets. It is apparent that the magnitude of release of SETD from the powdered forms is much greater than that in the tablet dosage form. The compressional force required in tableting resulted in some fusion, less porosity, and more compactness of the particles which seems to be responsible for the small amount of SETD release from the tablets.

Further work on tablets employing spray-congealed products of drug in wax matrices with modifier, which are free flowing, suitable for direct compression, and which release the active ingredient more completely, is presently under investigation. The results of this study will be reported separately in a later paper.

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Fitting a Double-Exponential Curve to Observed Salicylate Concentrations in Blood

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Abstract □ For interpretation of the results of blood concentration data to be meaningful, a very careful evaluation of the basic aspects of data collection, data description, and analysis is essential. The importance of these considerations is illustrated by the magnitude of observed differences in rate constants obtained under a variety of possible data-handling methods. The method of curve fitting presented, which minimizes squared logarithmic deviations, offers a different approach by utilizing relative error rather than absolute error. If truly equal weights are desired for data points, it is felt that this is the more appropriate definition of best fit. In any case, no mathematical technique for fitting a model to the data can compensate for an inadequate description of drug activity.

Keyphrases □ Blood concentration data—evaluation, basic aspects □ Rate constants—double-exponential curve fitting □ Salicylate concentration levels—rate constants, curve fitting, example

A desire to determine rate constants for drug absorption and elimination has resulted in the development of numerous analytical and mathematical techniques for pharmacokinetic analysis. In recent years, the applications of pharmacokinetic analysis have progressed rapidly from graphical solutions of concentration *versus* time plots to computer programs applied to increasingly sophisticated mathematical models. The latter yield apparent first-order rate constants for various processes of distribution and elimination [*e.g.*, Levy *et al.* (1) and Wagner (2)]. In many publications, the estimated values obtained for the parameters of the models have been presented without any indication that other values are possible. Where a number of apparent first-order rate constants are derived by a series of arithmetic manipulations from these estimated parameters, any inaccuracy in these estimates will be magnified in the subsequent computations. For a given set of observations, there are several important statistical considerations which merit careful attention before beginning the process of fitting a specific model to observed data.