Sulfaethylthiadiazole (SETD) Release from Synthetic Wax Prolonged-Release Particles I

Effect of Dispersant Concentration

By IRA C. ROBINSON* and CHARLES H. BECKER

Synthetic wax particles containing sulfaethylthiadiazole (SETD) dispersed throughout and on the surface were made by a method of aqueous dispersion using various concentrations of polysorbate 80 USP and sorbitan monooleate each alone and in combination as dispersants. The *in vitro* release of SETD from 50–70 mesh wax particles was investigated with a rotating bottle dissolution apparatus, using simulated gastric and intestinal fluids. The dispersant factor was found to affect both the release rate and the proportion of total drug apparently constituting the prolonged-release fraction.

THE LITERATURE contains numerous examples of investigations of factors affecting the dissolution of drugs from both dosage forms and ideal experimental matrices effecting retarded drug release. Most of these studies were conducted on granules, pellets, or beads prepared by conventional means, by spray-drying, or by spray-congealing, or on dosage forms comprised of such particles.

In studies of drug release from various dosage forms Wagner (1) and Wiegand and Taylor (2) reported that the percent released time data followed apparent first-order rates. Lazarus *et al.* (3) observed the influence of drug particle size, drug concentration, and granule size on the *in vitro* release rate of drug from a compressed waxy granular tablet matrix and reported that drug concentration and crystal size exerted greater effects on the rate than matrix granule size.

Apparent first-order release rates for drug were found to be inversely proportional to drug–wax particle size in one investigation by Draper and Becker (4).

Higuchi attempted to relate the rate of drug release from one surface of sustained action solid matrices to physical constants based on simple laws of diffusion and obtained the following mathematical relation for the case where drug particles are incorporated into a granular matrix from which release is by a leaching action of penetrating solvent (5):

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released after time, t, per unit exposed area; D, the diffusivity of the drug in the permeating fluid; τ, the tortuosity factor; A, the total amount of drug present in the matrix per unit volume; C, the solubility of the drug in the permeating fluid; and ϵ, the porosity of the matrix.

Desai *et al.* (6) showed the applicability of the Higuchi theory in a study of drug release from planar surfaces of plastic matrices.

The effects of concentration of drug and water solubility on release rates were investigated by Sjorgren and Fryklof (7) with tablets prepared from granules. The use of water-soluble substances to increase the rate of release of water-soluble drugs from a compressed plastic tablet was suggested in a patent by Endicott (8).

Saski and Shah (9) studied the effects of three oxyethylene oxypropylene polymers on the availability of hexetidine and observed enhancement of activity with concentrations below the CMC's for two and a decrease in activity at the CMC for all three. Desai *et al.* (6) reported that the addition of benzalkonium chloride and sodium lauryl sulfate increased the rate of release of sodium salicylate from tablets, presumably by an increase in the effective porosity of the tablets.

In the present investigation, the authors prepared synthetic wax particles containing dispersed sulfaethylthiadiazole and dispersant, if used, by a method of aqueous dispersion and considered the effects of two nonionic surfactants, polysorbate 80 USP[1] and sorbitan monooleate,[2] when used singly and in combination as dispers-

Received November 22, 1966, from the College of Pharmacy, University of Florida, Gainesville, FL 32602
Accepted for publication August 29, 1967.
Abstracted in part from a thesis presented by Ira C. Robinson to the University of Florida, Gainesville, in partial fulfillment of Doctor of Philosophy degree requirements.
This investigation was supported in part by a grant from the University of Florida Computing Center, Gainesville, Fla.
* Present address: Pharmaceutical Research and Development Department, Chas. Pfizer and Co., Inc., Brooklyn, NY 11206

[1] Marketed as Tween 80 by Atlas Chemical Corp., Wilmington, Del.
[2] Marketed as Span 80 by Atlas Chemical Corp., Wilmington, Del.

ing agents, on the *in vitro* rates of drug release from the wax matrices. The procedure was to manufacture the particles under controlled conditions, characterize or examine, classify, and assay, and to use such particles in *in vitro* release studies.

DISCUSSION

The general method of aqueous dispersion consists of blending subdivided drug in a melted waxy material and dispersing this mixture by controlled agitation in either a heated or cooled aqueous bath, with or without the aid of a surface-active agent. The end product may be spherical or irregularly shaped particles, all containing drug over the surface as well as dispersed throughout the wax matrix. Drug dispersed on the surface would be expected to enter into the dissolution medium more rapidly than drug dispersed within the matrix since solvent must first penetrate the matrix and dissolve the medicament therein before diffusion from within can take place.

Factors which may affect matrix particle size and/or geometry include type and concentration of dispersant, temperature to which the initial melt and aqueous bath are heated, rate of cooling, and rate and type of agitation. Particle size and geometry and dispersant type and concentration would be expected to affect the drug release rate.

If the Higuchi relation (Eq. 1) applies to the systems under study, drug release data when plotted *versus* the square root of time should produce linearity for that portion of drug dispersed within the wax matrix. However, the fact that these percent released square root of time data plots are linear does not in itself prove that the equation applies to this study. Such proof is obtainable only from controlled studies specifically designed to test the effect of variables in Eq. 1.

It was theorized that altering the concentration of surfactant used as dispersing agent would result in altered release rates for SETD from within the synthetic wax–drug particles when tested in simulated digestive fluids. This result would presumably be due to a combination of the wetting effect of the dispersant and the consequent increase in availability of more channels to permit leaching to take place. Further, the linear portion of the release curve should not go through the origin when extrapolated to zero time.

EXPERIMENTAL

Official drug, or reagent grade materials were used throughout this work. Sulfaethylthiadiazole was obtained from American Cyanamid Co. Glyceryl tristearate[3] was supplied by Glyco Chemicals. The term SETD–glyceryl tristearate is employed to designate an approximate ratio of 1 part sulfaethylthiadiazole to 3 parts of glyceryl tristearate in completed products. Where reference is made to a mesh size range, it indicates that the particles passed through the lower-numbered sieve but were retained on the higher-numbered sieve.

[3] Glycowax S-932.

Table I—Dispersant Concentrations Employed in Preparation of SETD–Glyceryl Tristearate Particles

Product No.	% Dispersants Used[a] Sorbitan Monooleate	Polysorbate 80 USP
1	8.56[b]	0.07[g]
2	5.87[c]	0.11[g]
3	3.03[d]	0.23[g]
4	3.01[d]	0.63[e]
5	8.56	...
6	5.87	...
7	3.03	...
8	...	0.78[e]
9	...	0.47[f]
10	...	0.16[g]

[a] Used per 24 Gm. glyceryl tristearate and 8 Gm. SETD: [b] 3.0 ml. [c] 2.0 ml. [d] 1.0 ml. [e] 0.25 ml. [f] 0.15 ml. [g] 0.05 ml.

The USP XVII method of determining uniformity of fineness (10) was employed in a particle size analysis of the SETD powder reserved for this study, the mean diameter of which was determined to be 47 μ.

Preparation of SETD–Glyceryl Tristearate Particles—The basic formula for products manufactured was: glyceryl tristearate, 3 parts; SETD, 1 part; dispersing agent, a predetermined quantity (Table I); and distilled water, 50 parts. The glyceryl tristearate was melted in a glass beaker on a water bath and heated to a temperature of 75°. The SETD was uniformly dispersed in the melted glyceryl tristearate. In order to minimize loss, distilled water, generally containing a dispersant, was heated to 80° and added slowly to the SETD–wax dispersion with stirring provided by a "Lightnin" mixer, laboratory type, model F. Stirring was continued at an optimum rate until the temperature reached 45°. The SETD–glyceryl tristearate particles were separated from the aqueous phase by filtration and washing with three 250-ml. portions of distilled water to remove free SETD. These products were then air dried. A 50–70 mesh fraction was separated on a Ro-Tap sieve shaker by the official USP method (10) to represent a mean diameter of 203 μ, assuming spherical shape. Visual and microscopic examination of the particles was made. Bulk densities of the SETD–glyceryl tristearate particles were determined by the method of Butler and Ramsey (11) using the relationship:

$$\rho_b = W/V \qquad \text{(Eq. 2)}$$

where V is the volume in ml., W is the quantity of Gm. of material in the cylinder, and ρ_b, the bulk density expressed as Gm./ml. with the modification that the graduate was dropped 20 times/min. for better uniformity of results.

In the preparation of all drug–wax particles, it was desired that as many variables as possible be held constant. Therefore, the ratio of drug to wax (1:3), the volume of aqueous phase, the rate of addition of aqueous phase to melted wax–drug mixture, the temperature to which the wax–drug and the aqueous phases were initially heated, mixing container type and size, method of mixing, and position of stirrer in container were held constant throughout the manufacturing operations. Opti-

mum rates of stirring were determined and kept constant thereafter.

Assay for SETD Content—Duplicate samples of exactly 0.5000 Gm. of each air-dried product were placed in 25-ml. portions of chloroform heated on a water bath. These were then extracted with several 30-ml. portions of warmed 3.5% HCl using a separator. The combined extracts were made up to volume and an aliquot portion was assayed by the Bratton and Marshall colorimetric procedure (12). A Klett-Summerson colorimeter equipped with a No. 54 filter was employed.

In Vitro Release Studies—A rotating bottle dissolution apparatus[4] similar to that described by Souder and Ellenbogen (13) and constructed by the Bioelectronic and Instrument Department, J. Hillis Miller Health Center, was employed in release studies. It consisted of a rotating machine with spring clamps for holding sixteen 90-ml. screw-capped bottles in alternately perpendicular pairs along the rotating axis. A speed of rotation of 40 r.p.m. and a constant-temperature water bath were used.

The two dissolution fluids used were simulated gastric fluid (0.1 *N* HCl, pH 1.1) and simulated intestinal fluid (alkaline pancreatin solution, pH 8.3). For studies in the simulated gastric fluid, duplicate samples of each product equivalent to 120.0 mg. of SETD and one sample of an equivalent amount of blank glyceryl tristearate particles prepared in the same manner as the product were provided for each time interval and withdrawn for analysis after 15, 30, 45, 60, 90, and 120 min., and at appropriate intervals thereafter to determine when equilibrium of release was achieved. A similar procedure was followed with simulated intestinal fluid except that samples equivalent to 600.0 mg. of SETD were used and intervals after which withdrawals were made were 15, 30, 45, 60, 120, 180, 240, 360, 480, and 720 min., and additional ones to determine when equilibrium of release had been attained. With all samples, at withdrawal the contents of each bottle was filtered and 0.5 or 1 ml. of the filtrate was diluted to an appropriate volume with distilled water in a volumetric flask. One milliliter of the dilution was assayed for SETD by the colorimetric procedure previously mentioned.

RESULTS

Production of SETD–Wax Particles—Preliminary investigations showed the maximum workable ratio of sorbitan monooleate to wax to be 1:8 and higher proportions resulted in excessively soft masses. It was also found that a small proportion of polysorbate 80 USP to sorbitan monooleate gave particles with more desirable surface properties than particles prepared with larger proportions. Increasing the concentration of either dispersant when used singly or in combination with the other facilitated the production of finer particles.

In the preparation of particles from the dispersant mixtures employing the smallest amount of sorbitan monooleate along with polysorbate 80 USP, water-in-oil emulsions developed during the early stages of mixing. With cooling and further addition of aqueous phase containing dispersant, inversion took place. Resultant particles were less smoothly surfaced than were products made from formulas employing sorbitan monooleate alone in all proportions under investigation. Particles prepared with polysorbate 80 USP alone as dispersant had more irregular surfaces than those prepared with sorbitan monooleate alone. It was apparent from these results that the spherical and surface smoothness properties of completed products should be properly attributed to the surface activity of sorbitan monooleate. Observations by visual and microscopic examination of particles prepared and studied are presented in Table II along with the bulk densities for these products.

Increasing the concentration of sorbitan monooleate in combination with a constant amount of polysorbate 80 USP resulted in slightly increased bulk densities of the drug–wax particles. Products made with varying concentrations of each surfactant alone showed no trend with respect to bulk density differences. However, the bulk densities for these latter products were greater than for either product made with a combination of surfactants as dispersant.

SETD Release Rate Comparison—From plots of percent SETD released in alkaline pancreatin solution *versus* the square root of time (in min.), the slopes for the linear portions of the curves were calculated and compared for the various products. Most of the following discussion pertains to these results.

It was found that from 50–60% of the total SETD provided in the wax matrices was released in the simulated gastric fluid at equilibrium, and this amount was released quite rapidly during the first 15 min. as can be seen in Table III. The percentages of SETD released in the alkaline pancreatin solution during the first 15 min. was of the same relative order except for products 3 and 4 where the lowest percentage of sorbitan monooleate was used with polysorbate 80 USP. In the alkaline pancreatin solution, however, drug continued to be extracted from the wax particle after this initial period due not only to diffusion but also in part to a gradual disintegration of the wax matrix in this test fluid. Thus it appears that the SETD released in the simulated gastric fluid during the initial period (and at equilibrium) was drug from the particle surface, indicating negligible diffusion of drug from within the wax matrix. During dissolution studies in alkaline pancreatin solution, both the porosity and tortuosity factors were constantly changing. Nevertheless, the release data plots as square root of time results were reasonably well approximated.

Increasing the concentration of sorbitan monooleate approximately twofold in combination with constant amount of polysorbate 80 USP decreased the rate at which SETD was released in alkaline pancreatin solution by a factor of 4 (Fig. 1). The additional increase in sorbitan monooleate in a third product caused no further reduction in the SETD release slope, indicating that a minimum had been attained. Figure 2 shows that increases in sorbitan monooleate as singular dispersant promoted the release of SETD after the initial period. Rates are presented in Table III. Increased

[4] Subsequent to this work, this type of apparatus was made official in NF XII, 2nd supplement, March 1, 1967, p. 15.

TABLE II—PHYSICAL PROPERTIES OF SETD–GLYCERYL TRISTEARATE PARTICLES

Product No.	Bulk Density, Gm./ml.	Visual and Microscopic Examination
1	0.5611	Free-flowing, spherical particles, tan-colored with characteristic odor
2	0.5337	Free-flowing, spherical tan-colored granules with characteristic odor
3	0.5000	Free-flowing, nearly spherical granules of light tan color and characteristic odor
4	0.4939	Light tan-colored, free-flowing granules of slightly irregular shape and characteristic odor
5	0.5882	Free-flowing, spherical particles, cream-colored with faint characteristic odor
6	0.5574	Free-flowing, cream-colored spherical particles with faint characteristic odor
7	0.5864	Free-flowing, spherical cream-colored particles with faint characteristic odor
8	0.5769	Irregularly shaped, free-flowing, cream-colored granules with faint characteristic odor
9	0.5660	Free-flowing, irregularly shaped, cream-colored particles with faint characteristic odor
10	0.5882	Irregularly surfaced, free-flowing, cream-colored particles with characteristic odor

TABLE III—*In Vitro* DATA FOR SETD RELEASE FROM SETD–WAX PARTICLES

Product No.	Simulated Gastric Fluid —% SETD Released— 15 min.	Simulated Gastric Fluid —% SETD Released— Equilibrium	Simulated Intestinal Fluid —SETD Release Profile Data— Zero Intercept	Slope, min.$^{-1/2}$	% at Equilibrium
1	52.42	52.67	62.34	0.2648	91.19
2	52.67	52.67	63.09	0.2787	96.35
3	54.92	55.58	27.01	1.0631	82.23
4	57.17	56.00	17.00	1.8390	81.78
5	55.07	55.07	61.18	0.2053	65.65
6	57.10	57.10	63.98	0.1897	67.77
7	55.74	56.22	64.14	0.1780	67.88
8	51.08	52.00	56.51	0.3060	67.75
9	52.83	53.09	53.96	0.2389	60.95
10	49.25	50.60	53.52	0.1897	59.60

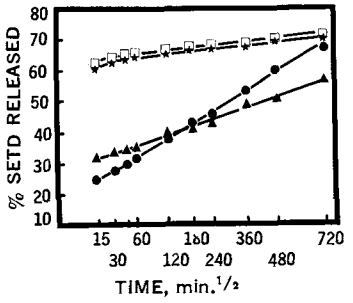

Fig. 1—Effect of dispersant concentration on SETD release in simulated intestinal fluid from SETD–wax particles. Key: ★, 8.56% sorbitan monooleate with 0.07% polysorbate 80 USP; □, 5.87% sorbitan monooleate with 0.11% polysorbate 80 USP; ▲, 3.03% sorbitan monooleate with 0.23% polysorbate 80 USP; ●, 3.01% sorbitan monooleate with 0.63% polysorbate 80 USP.

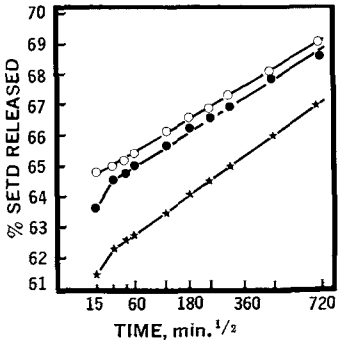

Fig. 2—Effect of singular dispersant sorbitan monooleate concentration on SETD release in simulated intestinal fluid from SETD–wax particles. Key: ★, 8.56%; ●, 5.87%; ○, 3.03%.

SETD release rates were observed with each raise in polysorbate 80 USP concentration when this dispersant was used both singly and in combination with constant amount of sorbitan monooleate (Figs. 1 and 3).

In addition to their effects on drug release rate and in the observable physical characteristics of the drug–wax particles, zero intercept values calculated from the linear portion of the dissolution curve for SETD in alkaline pancreatin solution suggest that variation in both the type and amount

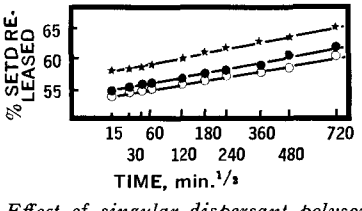

Fig. 3—Effect of singular dispersant polysorbate 80 USP on SETD release in simulated intestinal fluid from SETD–wax particles. Key: ★, 0.78%; ●, 0.47%; ○, 0.16%.

of dispersant influenced the amount of drug concentrating on or near the wax particle surface. A glance at the zero intercept values presented in Table III will show that more drug was apparently present on or near the surface of the drug–wax particles produced with the aid of sorbitan monooleate alone than on those prepared with polysorbate 80 USP alone; that increasing the concentration of sorbitan monooleate twofold with constant amount of polysorbate 80 USP gave a marked increase in this portion of drug rapidly released in the alkaline pancreatin solution; and that increasing the concentration of polysorbate 80 USP, while holding constant the amount of sorbitan monooleate in the formula, caused a marked decrease in the amount of SETD representing this value.

For all products except those prepared with use of polysorbate 80 USP singly as dispersant, where a larger portion of the total drug was apparently embedded within the wax matrix (total drug minus apparent surface drug), an increased rate of SETD release in the simulated intestinal fluid was observed.

SUMMARY

SETD–glyceryl tristearate particles were manufactured by a method of aqueous dispersion for prolonged-release application using various concentrations of polysorbate 80 USP and sorbitan monooleate singly and in combination as dispersants. The effects of variation in the type and concentration of surfactant used as dispersant were studied by *in vitro* release tests, physical testing, and visual and microscopic examination. Rates of release of SETD constituting the prolonged dissolution portion were calculated for results in simulated intestinal fluid using square root of time relationships and compared. Percent released square root of time plots gave reasonable linear approximations of prolonged-release SETD dissolution data.

REFERENCES

(1) Wagner, J., *Drug Std.*, **27**, 178(1959).
(2) Wiegand, R., and Taylor, J., *ibid.*, **27**, 165(1959).
(3) Lazarus, J., Pagliery, P., and Lachman, L., *J. Pharm. Sci.*, **53**, 798(1964).
(4) Draper, E., and Becker, C. H., *ibid.*, **55**, 376(1966).
(5) Higuchi, T., *ibid.*, **52**, 1145(1963).
(6) Desai, S., Simonelli, A., and Higuchi, W. I., *ibid.*, **54**, 1459(1965).
(7) Sjorgren, J., and Fryklof, L., *Farm. Revy*, **59**, 171 (1960).
(8) Endicott, C., U. S. pat. 3,087,860(1963).
(9) Saski, W., and Shah, S., *J. Pharm. Sci.*, **54**, 277 (1965).
(10) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 916.
(11) Bratton, A., and Marshall, E., Jr., *J. Biol. Chem.*, **128**, 537(1939).
(12) Butler, A. Q., and Ramsey, J. C., *Drug Std.*, **20**, 217(1952).
(13) Souder, J. C., and Ellenbogen, W. C., *ibid.*, **26**, 77 (1958).

Keyphrases

Drug release from wax prolonged-release particles
Sulfaethylthiazole–wax particle preparation
Surfactant effect on wax particle formation
Dispersant effect on wax particle formation
In vitro release studies
Colorimetric analysis

Complexation of Sodium Fluorescein with Polyvinylpyrrolidone

By RUSSELL E. PHARES, JR.

The complexation of sodium fluorescein (NaFluor) with polyvinylpyrrolidone (PVP) was studied at four pH values using a method similar to that of Benesi and Hildebrand. It was found that fluorescein can exist in four forms, each of which is capable of complexing. The results tend to indicate that at low pH values PVP exists in more than one form and that not all forms of the PVP are capable of complexing with NaFluor. When the ratio of NaFluor to PVP is small, a 1 : 1 complex is favored; but as the ratio increases, higher complexes predominate. The stability of the 1 : 1 complex seems to increase as the negative charge on the fluorescein decreases.

IT WAS recently discovered that polyvinylpyrrolidone (PVP), which for a long time has been known to complex with many substances, would form a sodium fluorescein complex possessing some interesting properties (1). By utilizing the unique properties of this complex, Krezanoski (1) has been able to formulate a stable and effective applanation tonometry diagnostic aid[1] con-

Received April 10, 1967, from the Research Laboratories, Barnes-Hind Pharmaceuticals, Inc., Sunnyvale, CA 94086
Accepted for publication August 23, 1967.
The author gratefully acknowledges the invaluable assistance of Mr. F. A. Caligiuri and Mr. F. D. Dreier.
Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

[1] Fluress, Barnes-Hind Ophthalmic Products.