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Some Wax Formulations of Sulfaethylthiadiazole Produced by Aqueous Dispersion for Prolonged-Release Medication

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Drug–wax particles were prepared by pouring heated aqueous solutions of surfactants into melted wax which contained dispersed sulfaethylthiadiazole (SETD). The systems then were slowly cooled to room temperature with stirring. The SETD–wax particles were recovered, washed, dried, and sieved into predetermined mesh size ranges. There appeared to be a direct relationship between drug release rate and average theoretical surface area of the SETD–Glycowax S-932 particles *in vitro*. This relationship was not seen in the SETD–beeswax particles. The dissolution rates of all the mesh ranges of particles studied seemed to be pseudo first order after the first 15 min. of testing. SETD–Glycowax S-932, 50- to 60-mesh particles, showed reasonably good prolonged-release properties in an *in vivo* urinary excretion study.

A NUMBER of methods and techniques have been used in the manufacture of oral dosage forms intended to impart prolonged, sustained, or long-acting therapeutic effect. The production of prolonged release of a drug in a wax matrix by means of aqueous dispersion or an emulsification process is mentioned in the literature, but detailed information is not given. Spray-congealing and spray-drying methods using wax with drugs have received quite a bit of attention.

Yamamoto and Baba (1) describe in their patent an aqueous dispersion method for producing wax pearls containing drug for prolonged-release medication. As an example, a melted wax containing dispersed drug is poured into a 2% polyvinyl alcohol aqueous solution, previously heated to 80°, and stirred until cool. The wax pearls that form are strained, washed with water, and dried. In this patent, several suitable dispersing agents are recommended and a number of wax or wax-like dissolution retardants are illustrated.

Kowarski *et al.* (2) describe a similar process in the preparation of prolonged-release sulfamethazine in small size batches. In this method, 2 parts of Japanese synthetic wax was melted with 1 part of sulfamethazine and poured into a running Waring blender containing cold water. After a few minutes of blending, the resulting suspension was filtered and dried. The particles were then washed with hydrochloric acid to remove sulfamethazine embedded on the outside of the granules, which was determined to be about 58% of the total drug in and on the granule.

The purpose of this investigation was to study some wax formulations of sulfaethylthiadiazole (SETD) produced by an aqueous-dispersion method for prolonged action. Bleached beeswax and Glycowax S-932 were used as the dissolution retarding materials. Beeswax was selected because it is a natural product and has plastic properties, whereas Glycowax S-932, a synthetic wax-like product is brittle. Both materials are edible, and the melting points of both are about the same, approximately 63°.

It was hoped that this study might reveal some

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generalizations pertaining to the preparation of prolonged-release drug–wax particles produced by the aqueous-dispersion method, such as effect of temperature, emulsifier and rate of mixing, as well as to the release pattern of the drug from several specific mesh sizes of drug–wax particles.

The present study involves 3 parts: first, the preparation of the drug–wax particles; second, the study of their *in vitro* release patterns; and third, the *in vivo* evaluation using a urinary excretion study of 1 drug–wax product that proved satisfactory by the *in vitro* screening test.

EXPERIMENTAL

Throughout this investigation official or drug grade materials were employed wherever feasible, except for some chemicals used for test or assay purposes which were usually reagent grade. Sulfaethylthiadiazole (SETD) was obtained from American Cyanamid Co. Wherever the term SETD–beeswax or SETD–Glycowax is employed, this means an approximate ratio of 1 part of SETD to 3 parts of Glycowax S-932 or beeswax. Drug–wax particles designated 16 to 20, 30 to 40, and 50 to 60 mesh mean that the particles passed through the lower-numbered sieve but were retained or did not pass through the higher-numbered sieve.

Preparation of Various Mesh Sizes of SETD–Beeswax and SETD–Glycowax Particles.—Preliminary work showed that many factors had an influence on the production of various mesh sizes of SETD–wax particles as well as the release rate of the SETD from the wax matrix. A combination of sorbitan monooleate[1] and polysorbate 80[2] was found to be a suitable dispersant. To minimize variables as much as possible the following SETD–beeswax formula was used: bleached beeswax, 24.0 Gm.; SETD, 8.0 Gm.; sorbitan monooleate, 1.0 ml.; polysorbate 80, 1.15 ml.; and distilled water, 400.0 ml. The SETD–Glycowax formula employed was: Glycowax S-932, 24.0 Gm.; SETD, 8.0 Gm.; sorbitan monooleate, 1.0 ml.; polysorbate 80, 0.25 ml.; and distilled water, 400.0 ml.

The bleached beeswax or Glycowax S-932 and SETD were placed in a 1000-ml. beaker, heated on a water bath to 75°, and well dispersed. The sorbitan monooleate, polysorbate 80, and distilled water were combined in another beaker and heated to 80°. The aqueous phase was added slowly to the SETD–wax phase while hot with continuous stirring at a predetermined speed, using a Lightnin laboratory type, model F mixer, until the resulting dispersion reached a temperature of about 45°. Cooling the product to this temperature took about 25 min. When the combined hot SETD–wax and aqueous phase was stirred at about 150 r.p.m., the majority of the resulting SETD–wax particles produced were in the range of 12 to 30 mesh. When the mixture was stirred at about 300 to 400 r.p.m., most of the SETD–wax particles were in the range of 30 to 100 mesh.

The SETD–wax particles were separated from the aqueous phase by means of filtration through filter paper and washed with distilled water to remove any free SETD. The SETD–wax particles were then dried.

The air-dried SETD–beeswax and SETD–Glycowax particles were classified into 3 mesh sizes, namely, 16 to 20, 30 to 40, and 50 to 60, using U.S.P. sieves and the U.S.P. XVII method (3) for determining uniformity of fineness.

Assay of SETD Content in Wax Particles.—The SETD–beeswax particles were assayed for SETD by placing exactly 0.5000 Gm. of the air-dried sample in a 25-ml. portion of warm benzene and extracting the SETD with several portions of warm 3.5% HCl using a separator. The SETD–Glycowax particles were similarly treated, except the organic solvent employed was chloroform. In each case, the acid extract was made up to 100 ml. with distilled water in a volumetric flask. An aliquot portion was assayed for SETD content by the Bratton-Marshall colorimetric method (4). A Klett-Summerson colorimeter with a No. 54 filter was employed to determine the color intensity, which was compared to that of standard solutions.

In Vitro Dissolution Studies.—The *in vitro* evaluation of the various mesh sizes of SETD–beeswax and SETD–Glycowax particles for prolonged release was essentially the same as that described by Robinson and Swintosky (5). Using simulated gastric fluid (0.1 *N* HCl, pH 1.1), exactly 0.5000 Gm. of the air-dried SETD–wax samples was employed, 2 for each time interval. Likewise, an equivalent amount of the wax formation particles without SETD was treated similarly to serve as a blank. Three bottles (1 for the blank and 2 for the product) were withdrawn for analysis after intervals of 0.25, 0.5, 1, and 2 hr. and at appropriate times to determine when equilibrium of release was reached. For evaluation of dissolution in simulated intestinal fluid (alkaline pancreatin solution, pH 8.3), exactly 2.000 Gm. of the air-dried SETD–wax samples was used, 2 for each time interval. Similarly, a blank was employed, and test bottles were withdrawn for analysis after intervals of 0.25, 0.5, 1, 3, and 6 hr. and at appropriate times to determine when equilibrium of release of SETD was reached. With all samples, the content of each bottle was filtered and 1 ml. of the filtrate was diluted to an appropriate volume with distilled water in a volumetric flask. Then 1 ml. of the dilution was assayed for SETD content by the Bratton-Marshall colorimetric method (4) as described above. The rotating bottle dissolution apparatus employed was the same as that described by Souder and Ellenbogen (6). The temperature of the water bath was 30 ± 0.5°.

In Vivo Evaluation.—The method used in this study was basically the same as that described by Nicholson *et al.* (7) for the clinical evaluation of sustained-release tablets of SETD using urinary excretion studies. Four healthy adult males were utilized in the clinical evaluation of a 50- to 60-mesh formulation of SETD–Glycowax consisting of approximately 1 part of SETD and 3 parts of Glycowax S-932, which gave a satisfactory *in vitro* release pattern. As a control, 3.9 Gm. of plain SETD was administered in a suspension form in a sweetened, flavored, methylcellulose solution using the following 2-part formula: (*a*) methylcellulose,[3]

[1] Marketed as Span 80 by the Atlas Powder Co., Inc., Wilmington, Del.

[2] Marketed as Tween 80 by the Atlas Powder Co., Inc., Wilmington, Del.

[3] Marketed as Methocel.

400 cps., 3.0 Gm.; methyl salicylate, 0.2 ml.; distilled water, to 200.0 ml.; and (*b*) SETD, 3.9 Gm.; and sucrose, 20.0 Gm. Each subject was told to add the solid ingredients of part (*b*) to solution (*a*), mix well for several minutes, and drink. It was instructed that the bottle be rinsed well with about 2 fluid ounces of water to assure ingestion of all the SETD. Two weeks after the control was run, each subject received the same amount of SETD in a SETD–Glycowax combination, 50 to 60 mesh, in a suspension prepared from the 2-part formula described above.

Concentrations of the free and of the total (free plus conjugated) SETD in urine were determined colorimetrically as described by Bratton and Marshall (4).

Mathematical Calculation of Rates of Dissolution and Excretion.—The rates of dissolution and excretion were determined by use of the Noyes-Whitney equation: $dc/dt = k(C_e - C)$, where C is the concentration at time t, C_e is equilibrium solubility at the experimental temperature, and k is the rate constant.

C_e was determined in the *in vitro* tests to be the concentration at which there was no change with time. C_e in the *in vivo* tests was the cumulative amount excreted at the end of 72 hr.

From plots of log $(C_e - C)$ *versus* time,

$$k = -2.303 \frac{[\log(C_e - C)_2 - \log(C_e - C)_1]}{(t_2 - t_1)}$$

$$k = 2.303 \frac{[\log(C_e - C)_1 - \log(C_e - C)_2]}{(t_2 - t_1)}$$

RESULTS AND DISCUSSION

Preparation of Drug–Wax Particles.—In preliminary work, various nonionic emulsifiers and dispersants were tried. Yamamoto and Baba (1) recommended polyvinyl alcohol (PVA) in a similar process. The partially hydrolyzed PVA,[4] 50–42 grade, was evaluated in this study in varying concentrations, from 0.25 to 4.0%. Regardless of amount used, however, over 50% of the particles produced were of size 40 to 80 mesh. Not enough of the 20- to 40-mesh size could be produced. This investigation required a greater range and a more uniform distribution of particle size than was obtained with PVA.

The effect of the HLB of some surfactants upon particle size was studied. The required HLB values of beeswax (8) are 5 for a w/o emulsion and 10 to 16 for an o/w emulsion. Various proportions of sorbitan monooleate and polysorbate 80 were used with beeswax; and the combination which produced bead-like particles of satisfactory texture and the most desirable range and distribution of particle size had a HLB of 10 and was 1 part of sorbitan monooleate to 1.15 parts of polysorbate 80. The required HLB values of Glycowax S-932 were not available. However, the most satisfactory combination was 1 part of polysorbate 80 to 4 parts of sorbitan monooleate, having an HLB value of 6.44. The proportion of emulsifier to the total volume of dispersion made was less than 1% for both waxes because too much emulsifier would have had a pronounced effect on dissolution of SETD from the wax matrix.

[4] Marketed as Elvanol.

The temperature of the drug–wax phase and of the dispersion solution, the rate of cooling and the speed of mixing of the combined phase during the cooling period, and the ratio of dispersion medium to dispersed phase were all important factors in influencing the size of particles produced. The higher the temperature, the smaller the particles. Slower rates of cooling, increased amounts of dispersion medium in relation to dispersed phase, and higher speeds of mixing yielded smaller particles. Optimum conditions were determined and were kept constant thereafter.

In Vitro Dissolution Studies.—One of the objectives of this investigation was to study the effect of particle size upon rate of release of SETD from the wax matrix. For this reason the drug–wax particles were classified into size ranges of 16 to 20, 30 to 40, and 50 to 60 mesh. The average diameter of these would be 1050, 505, and 230 μ, respectively, assuming spherical shape, which is a ratio of approximately 4, 2, 1. Since specific surface area is inversely proportional to diameter of the particles, S_w = surface of particles/weight of particles = $\pi\Sigma nd^2/(\pi/6)_p\Sigma nd^3 = 6/pd$ (9), the ratio of specific surface area for the samples in all 3 groups is 1, 2, and 4.

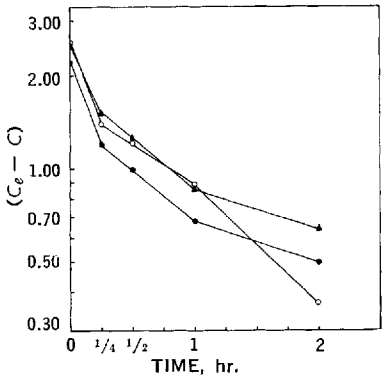

Fig. 1.—*In vitro* dissolution rates of SETD from various mesh sizes of SETD–beeswax particles in 0.1 *N* HCl. Key: ●, 16 to 20 mesh; ▲, 30 to 40 mesh; ○, 50 to 60 mesh.

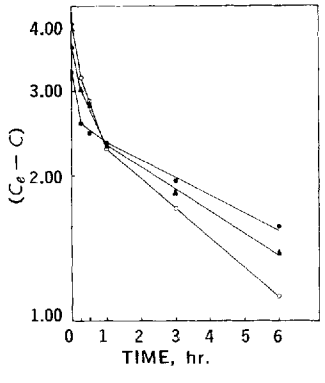

Fig. 2.—*In vitro* dissolution rates of SETD from various mesh sizes of SETD–beeswax particles in alkaline pancreatin solution. Key: ●, 16 to 20 mesh; ▲, 30 to 40 mesh; ○, 50 to 60 mesh.

It was theorized that the rate of dissolution of drug from the particles during the first 15-min. period in the test solutions would be in direct relation to specific surface area, since the particles were assumed to have a uniform distribution of drug on the surface. This theory proved to be correct for just the SETD–Glycowax product (Figs. 3 and 4). The SETD–beeswax particles showed a slower rate of release of SETD for the medium size range than for the smaller or larger (Figs. 1 and 2). The fact that this was slower than the smaller size range follows the theory. The fact that it was slower than the larger sized particles seemed very likely to be due to the aggregation of smaller particles to form some larger ones. Microscopic examination revealed that most of the larger particles were aggregates of smaller ones.

After the first 15-min. period, the rate of dissolution of SETD from the wax matrix varied in all cases (Figs. 1–4). The rate was constant from the end of the first hour to the termination of the test period, and was pseudo first order. The rate of dissolution should change as surface area changes. Some of the groups of particles showed dissolution rates of different ratio to apparent particle size during the last period of dissolution than during the first period. This could be due to the fact that some of the particles were more porous than others, the porosity being due to the speed of stirring causing some air to be trapped in the particles during preparation.

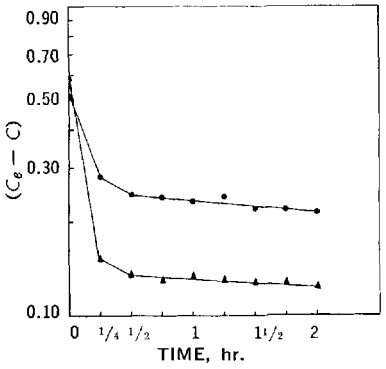

Fig. 3.—*In vitro* dissolution rates of SETD from various mesh sizes of SETD–Glycowax particles in 0.1 *N* HCl. Key: ●, 16 to 20 mesh; ▲, 30 to 40 mesh; ○, 50 to 60 mesh, $(C_e - C) = 0$.

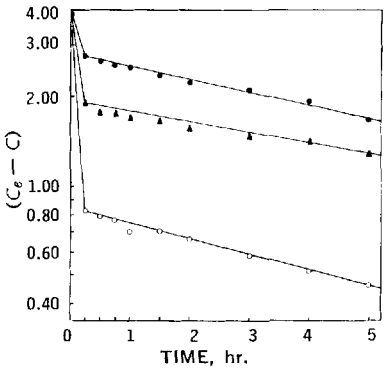

Fig. 4.—*In vitro* dissolution rates of SETD from various mesh sizes of SETD–Glycowax particles in alkaline pancreatin solution. Key: ●, 16 to 20 mesh; ▲, 30 to 40 mesh; ○, 50 to 60 mesh.

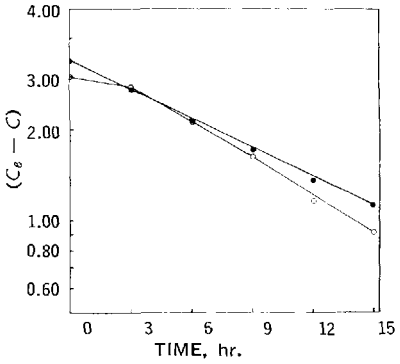

Fig. 5.—Average urinary excretion rates of free SETD for 4 humans receiving a 3.9-Gm. oral dose of SETD in (*a*) plain form and (*b*) SETD–Glycowax combination. Key: ●, plain SETD; ○, SETD–Glycowax combination.

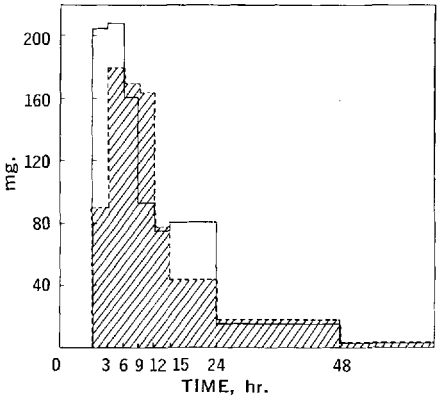

Fig. 6.—Average urinary excretion pattern of free SETD/hr. for 4 humans receiving a 3.9-Gm. oral dose of SETD in (*a*) plain form and (*b*) SETD–Glycowax combination. Key: □, plain SETD; ▨, SETD–Glycowax combination.

The per cent of SETD released in 0.1 *N* HCl (Figs. 1 and 3) was less than that in alkaline pancreatin solution (Figs. 2 and 4) for the same type sample and for the same time period. The rate of release was greater in the 0.1 *N* HCl, however. In alkaline pancreatin solution the peripheral portion of drug was apparently released at about the same rate as in the 0.1 *N* HCl. The increase in amount of release of SETD in the alkaline pancreatin solution could most likely be due to the fact that the wax matrix is partially solubilized, emulsified, and disintegrated by the surfactants and alkalinity of this solution.

It was theorized that the first part of dissolution of SETD from the drug–wax particle in both test solutions involved the simultaneous dissolution of drug by 2 first-order rates, $c = a_1e^{-k_1t} + a_2e^{-k_2t}$ (10). Dissolution data for 30- to 40-mesh SETD–beeswax particles were used in an attempt to test

this theory. From the semilog plot of $(C_e - C)$ *versus* time, the difference in $(C_e - C)$ values as obtained by the data during the first 0.75 hr. in the solution and that which would be obtained if the rate of dissolution was the same as that for the last period of the test was plotted semilogarithmically *versus* time. Since this gave a straight line, one rate appears to be that of the dissolution of the drug on the surface of the particle and the other that of the drug within the particle. Of course, the

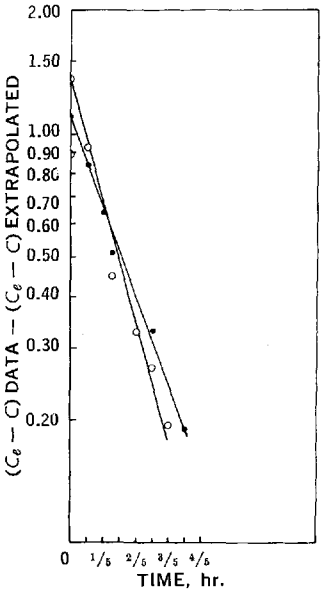

Fig. 7.—$(C_e - C)_{data}$ minus $(C_e - C)_{extrapolated}$ *vs.* time in hr. for 30- to 40-mesh SETD–beeswax particles in 0.1 *N* HCl and in alkaline pancreatin solution. Key: ○, in 0.1 *N* HCl; ●, in alkaline pancreatin solution.

rate during the last period of the test is also that of the drug within the particle. The rate calculated in Fig. 7 and theorized to be that of the surface SETD was 3.44 in 0.1 *N* HCl and 2.51 in alkaline pancreatin solution. It appears logical that this difference in rate may be due to the decrease in rate of diffusion in alkaline pancreatin solution caused by a partially emulsified layer, and possibly a concentration of colloidal particles around the SETD–wax beads.

In Vivo Study.—The SETD–Glycowax product of 50- to 60-mesh size was chosen because the *in vitro* results were most similar to the *in vitro* data of a well-known commercial prolonged-release preparation of SETD (11). Although *in vivo* release does not follow that of *in vitro*, it can be predicted from it by various patterns which can be correlated by experienced diagnosis.

From Figs. 5 and 6, it can be seen that the SETD–Glycowax particles as compared with plain SETD did show a decrease in the rate of release of SETD by about 50% during the first 3 hr. The rates were about the same for the second 3-hr. period. After this time, the rate increased for the SETD–Glycowax particles so that at the end of 24 hr. 71% of the total SETD had been excreted from the SETD–Glycowax particles as compared to 85% from plain SETD. The total free plus conjugated SETD excreted within 72 hr. after ingestion of SETD–Glycowax was 85%, whereas that released *in vitro* at equilibrium was 81%, a fairly close relationship. Since the ideal prolonged-release preparation maintains a proper therapeutic blood level for a 12- or 24-hr. period, the 50- to 60-mesh SETD–Glycowax product evaluated in this study appears to be a reasonably good prolonged-release preparation. Previous work (7) using SETD in urinary excretion studies showed the biological half-life to be about 6 hr. The present work showed a similar half-life period for SETD.

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