Some Spray-Dried Formulations of Sulfaethylthiadiazole for Prolonged-Release Medication

By AHMED F. ASKER* and CHARLES H. BECKER

Aqueous and organic solvent solutions containing sulfaethylthiadiazole and dissolution-retarding materials were spray dried with the purpose of preparing sulfaethylthiadiazole in prolonged-release form. Shellac, cellulose acetate phthalate, Glycowax S-932, Castorwax MP 80, aluminum monostearate, and glyceryl monostearate were used as the dissolution-retarding materials. Microscopic examination and infrared spectral analysis were carried out on some of the spray-dried products. An *in vitro* evaluation of the antibacterial activity of spray-dried sulfaethylthiadiazole was compared with an original sample. Dissolution characteristics of the products were studied *in vitro,* and one product was evaluated *in vivo* by urinary excretion data.

THE PHARMACEUTICAL industry has in the last decade become increasingly active in the manufacture of oral dosage forms intended to impart prolonged, sustained, or long-acting therapeutic effects. Spray drying as a method of processing such products has received little attention. Although the process is mentioned in the patent literature, detailed information is not given.

Spray drying usually results in the production of free-flowing monodispersible particles which could be directly compressed into tablets, filled into capsules, or made into suspensions.

The technique of spray drying suspensions, as shown by literature reports, necessitates the use of micronized drug, the maintenance of stirring the feed throughout the operation, and the use of suspending agents to maintain a uniform suspension. There also appears to be a limitation concerning the amount of solids which can be suspended to give a satisfactory spray. Therefore, solutions rather than suspensions were used in this study. The use of solutions also adds simplicity to the process of manufacture, thus insuring better reproducibility of product.

Aqueous ammonia has been widely used as a solvent for shellac. Ammonia was reported to volatilize when an ammoniacal solution of shellac was used in coating tablets (1). For some sulfonamides, such as sulfadiazine and sulfathiazole, Higuchi *et al.* (2) demonstrated that, when their ammonium salt solutions were spray dried, ammonia volatilized, and the drug reverted to its original form. Use was made, therefore, of the solvent action of aqueous ammonia on shellac and sulfaethylthiadiazole to prepare clear solutions, which were then spray dried.

Malm *et al.* (3) reported the formation of soluble sodium and triethanolamine salts of cellulose acetate phthalate. Its ability to form an ammonium salt was utilized in this study for the same reasons mentioned for shellac.

In the case of Glycowax S-932,[1] Castorwax MP 80,[2] and glyceryl and aluminum monostearate, a solvent mixture of 1 part by volume of absolute alcohol and 3 parts of chloroform was used to dissolve both the drug and the dissolution-retarding material with the aid of gentle heat.

EXPERIMENTAL

Materials.—Sulfacthylthiadiazole (SETD) was obtained from the American Cyanamid Co. The dissolution-retarding materials used included white dewaxed shellac,[3] cellulose acetate phthalate,[4] Glycowax S-932, Castorwax MP 80, aluminum monostearate U.S.P., and glyceryl monostearate N.F.

Preparation of Solutions.—In the case of shellac and cellulose acetate phthalate, their ammonium salt solutions were mixed with solutions of the ammonium salt of SETD prepared by essentially the same method described by Higuchi *et al.* (2). Glycowax S-932 and Castorwax MP 80 were dissolved in warm solutions of a mixture of 1 part by volume of absolute alcohol and 3 parts of chloroform in which the SETD was previously dissolved.

Preparation of Spray-Dried Materials.—The solutions were spray dried in a Bowen table model spray dryer. The solutions were fed by gravity and the feed rate controlled by means of a glass stopcock. The resulting products were screened through a 100-mesh sieve, transferred to tight containers, and stored at room temperature. Table I

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[1] Glycowax S-932 is a product of Glyco Chemicals, Williamsport, Pa.
[2] Castorwax MP 80 is a product of the Baker Castor Oil Co., Bayonne, N. J.
[3] Bradshaw-Praeger and Co., Chicago, Ill.
[4] Marketed as C-A-P by Eastman Kodak Co., Rochester, N. Y.

TABLE I.—OPERATING CONDITIONS FOR SPRAY DRYING THE SOLUTIONS OF SETD AND DISSOLUTION-RETARDING MATERIALS

Soln.	SETD-Dissolution-Retarding Material Ratio	Feed Solids, % w/v	Feed Rate, ml./min.	Temp. Ranges, °C. Inlet	Outlet	Cooling Ports
SETD–shellac	1:1	3.8	12	210–216	38–40	Partially open
	1:2	4.3	18	210–216	38–40	Partially open
	1:3	4.0	13	210–216	37–39	Partially open
SETD–cellulose acetate phthalate	1:1	5.7	30	220–223	36–38	Partially open
	1:2	5.0	30	216–221	37–38	Partially open
	1:3	4.7	42	216–221	38–40	Partially open
SETD–Castorwax MP 80	1:1	8.0	16	138–149	36–38	Open
	2:3	8.0	18	143–149	37–38	Open
	1:2	6.8	20	143–149	37–38	Open
SETD–Glycowax S-932	1:1	6.7	12	171–174	38–40	Open
	2:3	7.5	20	171–173	37–39	Open
	1:2	4.7	18	171–175	36–39	Open

shows feed concentrations and operating conditions for spray drying the solutions made.

Microscopic Examination of the Spray-Dried Materials.—Microphotographs were taken of the spray-dried formulations which consisted of 1 part of the drug and 2 parts of the dissolution-retarding material. The characteristic particle shape and size are seen in Figs. 1–4.

In Vitro Evaluation of the Antibacterial Activity of SETD.—The agar cup-plate method of assay (4) on samples of original SETD and spray-dried ammonium salt of SETD was carried out against *E. coli* and *S. aureus*. A microstatistic advocated by Dixon and Massey (5) was utilized in the evaluation of the results at $\alpha = 0.05$. The results obtained are shown in Table II.

Infrared Spectral Analysis.—Infrared spectral analysis of original SETD, shellac, cellulose acetate phthalate, and their spray-dried ammonium salts was performed by the potassium bromide pelleting technique on a Perkin-Elmer Infracord model 137.

In Vitro Dissolution Studies.—The *in vitro* release patterns of the spray-dried products were determined in 0.1 *N* HCl (pH 1.1) and alkaline pancreatin solution (pH 8.3). The method used is essentially the same as that given by Robinson and Swintosky (6). The rotating-bottle apparatus described by Souder and Ellenbogen (7) operating at 40 r.p.m. in a 30 ± 0.5° water bath was employed. The amount of SETD released at various time intervals was determined in the filtrate by the Bratton and Marshall (8) colorimetric assay.

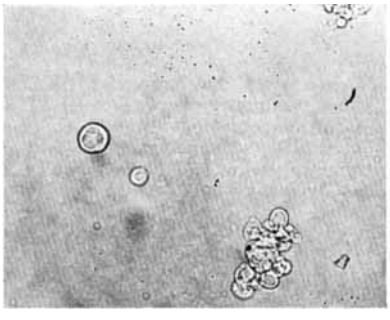

Fig. 1.—Spray-dried SETD (1 part)–cellulose acetate phthalate (2 parts).

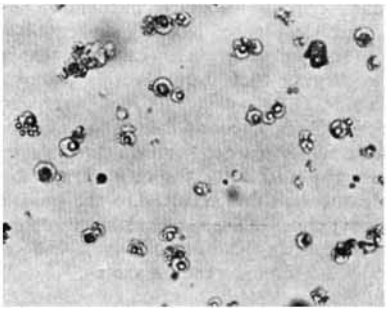

Fig. 3.—Spray-dried SETD (1 part)–Glycowax S-932 (2 parts).

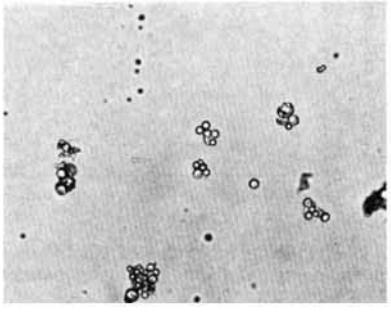

Fig. 2.—Spray-dried SETD (1 part)–shellac (2 parts).

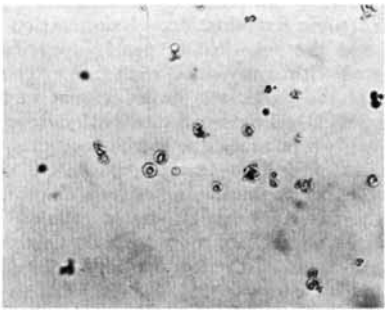

Fig. 4.—Spray-dried SETD (1 part)–Castorwax MP 80 (2 parts).

TABLE II.—COMPARATIVE INHIBITORY ACTI OF ORIGINALVITY AND SPRAY-DRIED SETD USING *E. coli* AND *S. aureus*—EXPERIMENTAL DATA AND STATISTICAL EVALUATION

Sample	*E. coli* Zones of Inhibitions, mm.	*E. coli* Av. Diam., mm.	*E. coli* Range, mm.	*S. aureus* Zones of Inhibition, mm.	*S. aureus* Av. Diam., mm.	*S. aureus* Range, mm.
SETD	37 35 39 39 38	37.6	4	40 40 39 38 39	39.2	2
SETD (spray-dried)	37 36 37 35 38	36.6	3	37 38 39 39 38	38.2	2
	$t_d = 0.286$			$t_d = 0.5$		
	Critical region $t_d > \pm 0.613$			Critical region $t_d > \pm 0.613$		
	Significant difference No			Significant difference No		

The *in vitro* release curves of products consisting of 1 part of SETD by weight and 2 parts of the dissolution-retarding materials are shown in Figs. 5 and 6.

In Vivo Evaluation.—The method is basically the same as that described by Nicholson *et al.* (9) for the clinical evaluation of sustained-release tablets of SETD using urinary excretion studies. Four healthy adult male subjects were utilized in the evaluation of the spray-dried formulation of SETD–Glycowax S-932 which gave a satisfactory *in vitro* release pattern as compared with a sustained-release powder of SETD.[5] Urine samples were collected at various time intervals, and the amounts of free SETD excreted were determined by the Bratton and Marshall method (8).

RESULTS AND DISCUSSION

Preparation of Spray-Dried Materials.—Solutions of the dissolution-retarding materials were spray dried in order to study their behavior during the operation. The spray-dried material also served as blanks for the *in vitro* dissolution studies.

Shellac, cellulose acetate phthalate, Glycowax S-932, and Castorwax MP 80 presented no difficulties in spray drying. This behavior was reflected in spray drying their formulations containing the drug (Table I).

Difficulty was encountered in spray drying an aluminum monostearate solution due to its gelatinization in the feed line. Spray drying of a glyceryl monostearate solution resulted in the production of sticky particles. These difficulties were not overcome by operating the dryer over a wide range of feed rates and inlet gas temperatures.

The ammonium salt solution of sulfaethylthiadiazole was spray dried to serve as a control. The spray-dried material was found to have a melting point of 185–186.5° which is in agreement with the literature value for sulfaethylthiadiazole.

Microscopic Examination.—Examination of Figs. 1–4 shows the spherical or nearly spherical shape associated with spray-dried materials. The porous nature of the particle is quite evident in the case of the SETD–cellulose acetate phthalate combination. This is possibly due to the good film-forming properties of cellulose acetate phthalate with the result that a case-hardening effect was produced.

In the case of formulations of cellulose acetate phthalate and shellac, more isolated particles were obtained than with formulations of Glycowax S-932 and Castorwax MP 80, of which a greater portion was in the form of aggregates. This may be expected from wax or wax-like materials because of the tendency of wax particles to adhere to each other.

In Vitro Evaluation of the Antibacterial Activity of Spray-Dried SETD.—Although it is accepted that heat degradation does not occur during spray drying, Smith (10) pointed out that the spray of the smallest particles is dried faster than the main portion of the spray; therefore, the smallest par-

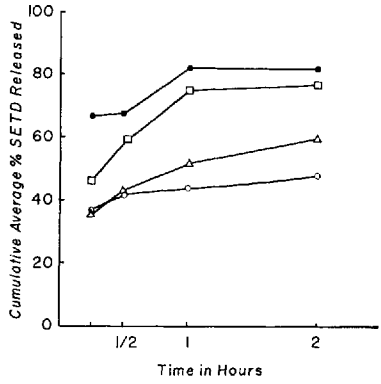

Fig. 5.—*In vitro* dissolution of SETD in 0.1 *N* HCl from products consisting of SETD (1 part) and dissolution-retarding materials (2 parts). Key: ○, SETD–shellac; ●, SETD–cellulose acetate phthalate; □, SETD–Castorwax MP 80; △, SETD–Glycowax S-932.

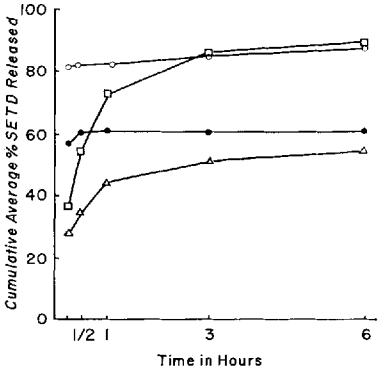

Fig. 6.—*In vitro* dissolution of SETD in alkaline pancreatin solution from products consisting of SETD (1 part) and dissolution-retarding materials (2 parts). Key: ○, SETD–shellac; ●, SETD–cellulose acetate phthalate; □, SETD–Castorwax MP 80; △, SETD–Glycowax S-932.

[5] Supplied by Smith Kline & French Laboratories, Philadelphia, Pa.

TABLE III.—PHYSIOLOGIC AVAILABILITY OF SETD BASED ON FREE SETD FROM SETD–GLYCOWAX S-932 (1:2) COMBINATION IN FOUR SUBJECTS

Collection Time Interval, hr.	Plain SETD — SETD Excreted, mg. Subj. A	B	C	D	SETD–Glycowax S-932 — SETD Excreted, mg. Subj. A	B	C	D
0–3	486	676	150	495	8	...	...	8
3–6	810	323	414	931	22	247	36	53
6–9	429	1001	544	522	23	635	223	275
9–12	293	707	359	343	88	[a]	354	125
12–15	214	[a]	297	203	95	128	244	63
15–24	386	233	477	358	552	328	376	445
24–48	387	321	386	184	1129	383	202	481
48–72	52	...	101	37	289	120	...	224
Total	3057	3261	2728	3073	2206	1841	1435	1674
Physiologic availability based on the 72-hr. period					72.2%	56.5%	52.6%	54.5%

Av. physiologic availability = 59%
S. D. ± 8.97%

[a] No urine was voided.

ticles approach the inlet gas temperature and could be damaged by heat. In order to study the effect spray drying might have on the antibacterial activity of SETD, the agar cup-plate method was carried out. The results obtained appeared to show no significant difference between original SETD and spray-dried ammonium salt of SETD when tested against *E. coli* and *S. aureus* (Table II).

Infrared Spectral Analysis.—The infrared spectrum of the spray-dried ammonium salt of SETD compared well with that of the original sample of SETD, suggesting no apparent changes in the chemical constitution of the drug during spray drying. This was also confirmed by the melting point determination. Spectra of the spray-dried ammonium salts of shellac and cellulose acetate phthalate, however, were not comparable with the original materials. The complex constitution of shellac, the possibility of its polymerization during spray drying, and the polymeric nature of cellulose acetate phthalate may account for these differences.

The spectral analysis provided by this study was not sufficient to support a conclusion of more significance, but it gives some insight of the apparent changes produced by spray drying.

In Vitro Dissolution Studies.—The *in vitro* screening test was carried out in order to identify products worthy of *in vivo* evaluation (Figs. 5 and 6).

SETD–shellac formulations gave substantial retardation of release when tested in 0.1 *N* HCl. The higher the proportion of shellac to the drug, the more retardation was obtained. However, no significant retardation was demonstrated by formulations of SETD–shellac in alkaline pancreatin solution, regardless of the amount of shellac to drug used in this study. This may be attributed to the formation of highly soluble salts of shellac in alkaline pancreatin solution. This insignificant retardation was amplified by the use of dewaxed shellac and the small porous particles obtained in spray drying.

SETD–cellulose acetate phthalate formulation demonstrated more release of the drug in 0.1 *N* HCl as compared to those of SETD–shellac combinations. However, less dissolution of drug was obtained in alkaline pancreatin solution.

No appreciable retardation of drug release was demonstrated by SETD–Castorwax MP 80 in either 0.1 *N* HCl or alkaline pancreatin solution. This may be attributed to the slightly hydrophilic nature of Castorwax MP 80 as compared to other waxes due to hydroxy acid esters present.

SETD-Glycowax S-932 formulations showed a significant retardation of release of the drug in 0.1 *N* HCl and in alkaline pancreatin solution especially at a concentration of 1 part of the drug and 2 parts of the wax. The *in vitro* release pattern of this combination compared within a reasonable range with that of a sustained-release control sample (supplied by Smith Kline & French Laboratories) consisting of 2 parts of SETD and 3 parts of Castorwax MP 80. This formulation was therefore utilized in the *in vivo* evaluation.

In Vivo Evaluation.—Evaluation of SETD–Glycowax S-932 (1:2) by urinary excretion data showed that an insignificant amount of drug appeared to be released in the first 3 hr. after drug administration (Table III and Fig. 7).

Results also showed that less drug appeared to be released *in vivo*, contrary to what was expected from the *in vitro* screening results. This emphasizes the fact that *in vitro* testing does not necessarily reflect *in vivo* response. This was also reported by Blythe (11), who found that although sulfaethylthiadiazole in sustained liquid or tablet form

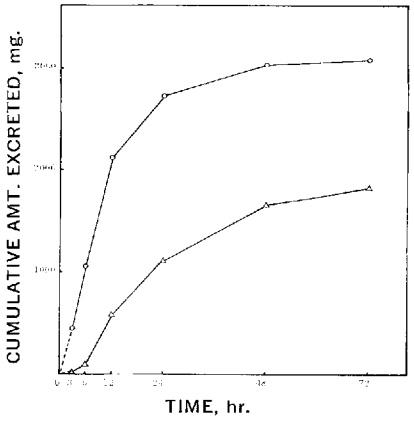

Fig. 7.—Average cumulative urinary excretion of free SETD for 4 humans receiving a 3.9-Gm. oral dose of SETD in plain form (○) and SETD–Glycowax S-932 combination (△).

gave substantially different release rates *in vitro*, yet both gave practically identical blood levels when tested in humans.

The fact that little or no drug was released in the first 3 hr. after drug administration, suggests that plain SETD can be added to the initial dose of the SETD–Glycowax S-932 combination without complications as far as product design is concerned.

Since less drug was released from the SETD–Glycowax S-932 (1:2) combination, a lower proportion of the wax appears necessary to obtain a medication that would meet the requirements for a more desired prolonged-release product.

The average physiologic availability of the drug from SETD–Glycowax S-932 combination tested *in vivo* was 59% after 72 hr. This low physiologic availability would reflect the incomplete release of the drug as indicated by urinary excretion data.

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Automated Differential Amperometric Analyzer

Application to Penicillin Determination

By JOSEPH BOMSTEIN, J. M. SHEPP, S. T. DAWSON, and W. J. BLAEDEL*

An automated, differential amperometric analyzer has been constructed, based on the tubular platinum electrode and a differential signal detection system. Its chief advantages are sensitivity to species which are oxidizable or reducible at the platinum electrode, and a linear relationship between concentration and signal. As applied to the iodimetric determination of several penicillins, precision is 0.7–2.6 per cent and accuracy ranges from 1.0 to −3.0 per cent.

CONSIDERABLE progress has been made in recent years in automating analytical laboratory processes. A number of reports deal with automation of 1 or more steps of analytical procedures, and outstanding success has been achieved industrially with the AutoAnalyzer (Technicon Instruments Corp., Chauncey, N. Y.), generally applying spectrometric techniques. A greater range of applications might be handled by combining the instrument's continuous-flow and chemical-physical processing capabilities with an electrometric detector. Redox analyses could then be performed. Such a system has been designed, constructed, and evaluated for the iodimetric determination of penicillins.

The method involves degradation of the penicillin with alkali or penicillinase, followed by iodimetric determination of the resulting penicilloic acid (1). A published procedure, in which a penicillin stream after hydrolysis and dialysis reacts with iodine to cause an absorbance decrease (2), has been modified and used to prove the practicality of an amperometric technique.

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EXPERIMENTAL

Differential Electrode Detection System.—The detector is a differential electrode system based on the tubular platinum electrode (TPE) (3, 4). Figure 1 shows the pair of platinum electrodes and the saturated calomel reference electrode. The sample stream enters one side of the Y-tube, flowing past a pulse suppression overflow tube, then through 0.5 in. length of platinum tubing (i.d. 0.06 in., o.d. 0.07 in.) which serves as 1 arm of a Wheatstone bridge. (See TPE_1 in Fig. 2.) The reference stream, which serves the purpose of blank compensation, flows past a second overflow tube, then through a second TPE identical to the first. This is the arm of the bridge TPE_2, in Fig. 2. The two streams combine to give a conducting path for current flow through the saturated-calomel reference electrode (SCE), physically separated from the flowing stream by a porous glass wall (code 7730 Vycor, Corning). Impurities introduced by diffusion into the SCE are displaced by a flow of saturated KCl/Hg_2Cl_2. The ground connections are added to improve electrical stability.

Bridge Circuit.—Figure 2 shows the schematic diagram of the bridge to which the signal from the electrodes is applied. Except for the replacement of the microvoltammeter and recorder by the VOM-6 recorder (Bausch & Lomb, Rochester, N. Y.) alone, it is identical to the bridge discussed by Blaedel and Olson (3). Initial balance is obtained