Preparation and *In Vitro* Evaluation of a Sustained-Action Suspension of Dextromethorphan

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Abstract □ A stable suspension having a prolonged *in vitro* release was prepared by synthesizing a poorly water-soluble salt of dextromethorphan, crystallizing this salt as a hydrate, coating the crystals in a solid particle-coating device with a triglyceride fatty acid mixture, and dispersing the coated crystals in an aqueous vehicle. Dramatic differences in physical and release-rate stability were encountered with the same chemical salt when it was coated by different methods and crystallized from different solvent systems.

Keyphrases □ Dextromethorphan—sustained-action suspension □ Sustained action—dextromethorphan suspension □ Suspension—triglyceride fatty acid-coated dextromethorphan salt □ Spray-congealed coating—dextromethorphan crystals □ Release-rate stability—dextromethorphan suspension □ Thermal analysis, differential—dextromethorphan salt

Numerous oral sustained-action products have been marketed in the past 16 years. For most of these products, sustained action has been obtained by coating compressed tablets or large pellets, or by compressing drug in admixture with water-insoluble fillers. Very little data have been presented on the use of coated subsieve-sized particles in the formulation of sustained-action dosage form. Bakan (1) has outlined the use of the coacervation process for preparing sustained-action powders. Several investigators (2–5) have reported on the use of spray-congealing procedures for preparing sustained-action powders.

Coacervation coating and spray-congealing methods have not been widely used to prepare sustained-action products, possibly because these methods require expensive, specialized equipment not commonly utilized by the pharmaceutical industry. A simple, relatively inexpensive, solid particle-coating device (PCD) developed in this laboratory may have greater utility for the preparation of sustained-action dosage forms (6). This report presents an example of subsieve-sized crystals coated in the PCD and use of these coated crystals in the formulation of a stable, liquid, sustained-action suspension of dextromethorphan. It also presents the differences found in physical and release-rate stability which illustrate the importance of certain physical and chemical properties of drug and coating components in the formulation of this dosage form.

EXPERIMENTAL

Materials—A poorly water-soluble form of dextromethorphan was obtained by reacting *d*-methorphan with *o*-(*p*-hydroxybenzoyl) benzoic acid (7). The resulting salt (DMHB) was crystallized from ethanol–chloroform and dimethylformamide–water solvent systems. Mixtures of glyceryl tristearate (GTS)[1] and 12-hydroxystearic acid (12-HSA)[2] or GTS and behenic acid (BA)[3] were used as coating materials. Chloroform and carbon tetrachloride were used as solvents for these coating materials. The aqueous vehicle for the sustained-action powders contained tragacanth, sorbitol, methylcellulose, sodium cyclamate, saccharin, methyl and propyl paraben, sorbic acid, and imitation black currant flavor.

Table I—Composition and Typical Release Rates for Coated DMHB Prepared by Spray Congealing

A.	Theory, %—DMHB = 25.0, 12-HSA = 37.5, GTS = 37.5
	Actual, %—DMHB = 24.4
	Release rate, %[a]—0.5 = 4, 1.5 + 0.5 = 11, 1.5 + 3 = 55, 1.5 + 5.5 = 86
B.	Theory, %—DMHB = 20.0, 12-HSA = 40.0, GTS = 40.0
	Actual, %—DMHB = 19.7
	Release rate, %[a]—0.5 = 4, 1.5 + 0.5 = 13, 1.5 + 3 = 62, 1.5 + 5.5 = 87

[a] First number indicates hours in USP gastric fluid and second, where given, indicates hours in modified USP intestinal fluid.

Table II—Composition and Typical Release Rates for Coated DMHB Crystals Prepared in PCD

A.	Theory, %—DMHB = 33.0, 12-HSA = 33.5, GTS = 33.5
	Actual, %—DMHB = 33.1
	Release rate, %[a]—0.5 = 17, 1.5 + 0.5 = 37, 1.5 + 3 = 70, 1.5 + 5.5 = 78
B.	Theory, %—DMHB = 35.0, BA = 6.5, GTS = 58.5
	Actual, %—DMHB = 32.0
	Release rate, %[a]—0.5 = 19, 1.5 + 0.5 = 27, 1.5 + 3 = 70, 1.5 + 5.5 = 89

[a] First number indicates hours in USP gastric fluid and second, where given, indicates hours in modified USP intestinal fluid.

Equipment and Methodology—Spray-congealed, sustained-action powders were prepared by suspending DMHB crystals in a molten mixture of the coating materials and spraying the resulting suspension in a Niro laboratory model spray drier.[4] Procedures analogous to those described in previous publications were followed (3, 8). DMHB crystals were coated in the PCD, using solvent solutions of the coating materials and techniques generally in accord with those previously described for use with this apparatus (6). A Fisher subsieve size analyzer[5] was used to determine the volume-surface mean diameter (d_{vs}) of DMHB, the spray-congealed powders, and the coated DMHB crystals. Coating uniformity and integrity were checked by microscopic examination of a glycerin–H_2O or mineral oil mull of the sustained-action powders. An L & R ultrasonic bath[6] operating at 73 kc./sec. was used to crystallize the DMHB from the dimethylformamide solvent system. DMHB release was measured using the method described by Souder and Ellenbogen (9), with the exception that the USP intestinal fluid was prefiltered and the undissolved particles containing DMHB were collected on 1.2-μ filter paper.[7]

[1] Hydrofol Glycerides T57L, Ashland Chemical Co., Columbus, Ohio.

[2] Baker Castor Oil Co., Bayonne, N. J.
[3] Hydrofol Acid 560, Ashland Chemical Co., Columbus, Ohio.
[4] Nichols Engineering and Research Corp., New York, N. Y.
[5] Fisher Scientific Co., Pittsburgh, Pa.
[6] L & R Manufacturing Co., Kearny, N. J.
[7] Millipore Corp., Bedford, Mass.

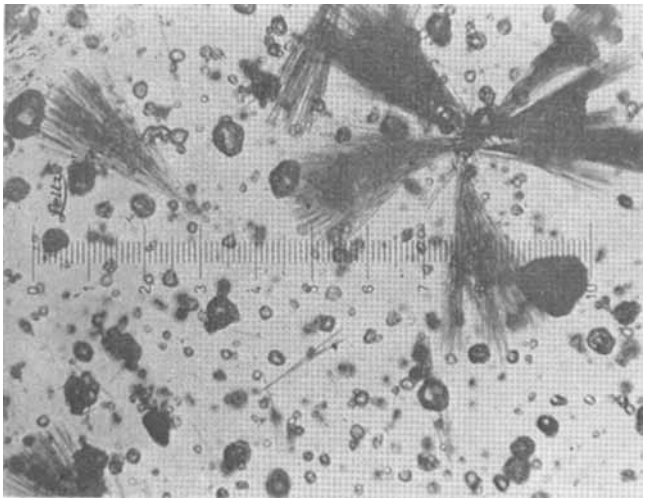

Figure 1—*Crystal growth from DMHB "ethanolate"-coated particles in an aqueous suspension (magnification: 0–1 equals 63.9 μ).*

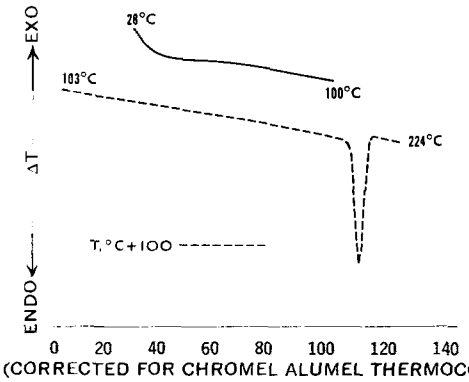

Figure 2—*A typical thermogram for the anhydrous form of DMHB.*

RESULTS AND DISCUSSION

The solubility of DMHB in the aqueous vehicle was about 0.9 mg./ml. at 25°. At a concentration below saturation, uncoated DMHB crystals dissolved completely in USP gastric or intestinal fluid in less than 5 min. At the same concentration, the spray-congealed and the coated crystals released DMHB slowly over time in USP gastric and intestinal fluid. Typical release values and the composition of these powders are given in Tables I and II. The d_{vs} was about 15 μ for the spray-congealed powders and about 30 μ for crystals coated in the PCD. These results suggested that powders prepared by either process should be suitable for the preparation

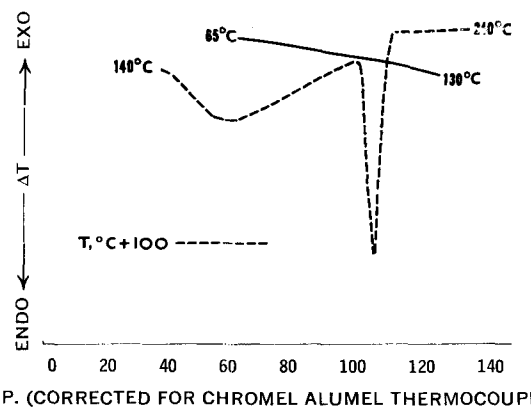

Figure 3—*A typical thermogram for the "ethanolate" form of DMHB.*

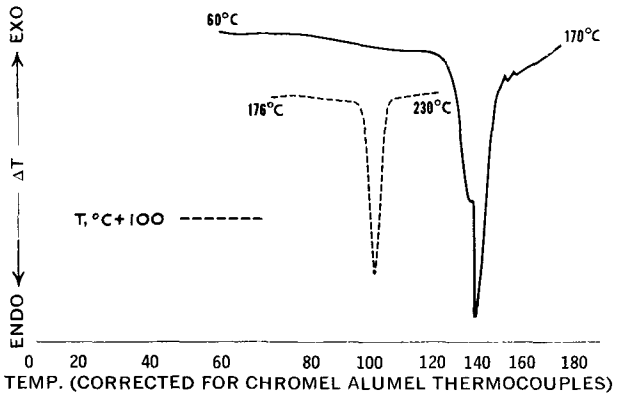

Figure 4—*A typical thermogram for the hydrate form of DMHB.*

of a sustained-action suspension. The particle size was low enough to minimize grittiness and sedimentation propensity. The theoretical density was in a range where the addition of a small amount of sorbitol permitted a match between particle and vehicle density. Only about 10% of the DMHB dose (9.0 mg./ml.) would be needed to saturate the aqueous vehicle, permitting formulation of a suspension with a desirable balance between initial and prolonged release. The *in vitro* release rates of the spray-congealed and the coated DMHB crystals suggested that a suspension of these powders would provide sustained antitussive activity *in vivo*.

An additional requirement for the sustained-action powders is the absence of significant change in chemical potency and release rate over time. This was determined for these formulations by storing them at 37° and under ambient conditions. The results obtained after several months' storage are given in Table III. It is evident that the release rate of the spray-congealed formulation has increased

Table III—Chemical and Release-Rate Stability of DMHB Sustained-Action Powders

Sample	Storage Temp.	Storage Time, month	Assay, %	Release Rate, %[a] Hours 0.5	1.5 + 0.5	1.5 + 3	1.5 + 5
Spray-congealed	Ambient	0	24.4	4	11	55	86
	Ambient	1	24.6	—	15	75	—
	37°	1	24.6	12	30	86	94
	37°	2	24.6	9	40	91	96
Spray-congealed	Ambient	0	19.7	4	13	62	87
	Ambient	1	19.7	—	23	74	—
	37°	1	19.9	9	32	84	92
	37°	3	19.9	7	40	88	94
PCD	Ambient	0	33.1	17	37	70	78
	Ambient	2	34.0	16	34	69	80
	37°	1	34.1	13	34	69	80
	37°	3	34.2	16	36	66	76

[a] First number indicates hours in USP gastric fluid and second, where given, indicates hours in modified USP intestinal fluid.

Table IV—Release-Rate Stability of a Sustained-Action Suspension of DMHB "Ethanolate"

Release Rate, %[a]	After 25° Storage, days 1	4	6
0.5	40%	59%	73%
1.5 + 0.5	52%	68%	77%
1.5 + 3	66%	78%	83%
1.5 + 5.5	79%	89%	—

[a] First number indicates hours in USP gastric fluid and second where given, indicates hours in modified USP intestinal fluid.

markedly, whereas that of the coated crystals has not. Microscopic examination of the spray-congealed powders suggested some change in the crystal form in the GTS–12-HSA matrix. This possibility was confirmed by X-ray diffraction which showed that spray-congealed GTS solidified in the polymorphic α-form. This form is unstable and on storage transformed into the stable β-modification. In contrast, GTS could be obtained in the β-form by spraying from chloroform or carbon tetrachloride. Since there was no other discernible physical change in these powders, it is considered likely that the release-rate increase of the spray-congealed powders was related to polymorphic transition of the GTS. In any event, the changes in release rate of the spray-congealed formulation indicated that only the DMHB crystals coated in the PCD would be acceptable for use in formulating a sustained-action suspension.

DMHB crystallized from the chloroform–alcohol solvent system had a d_{vs} of less than 20 μ, and the shape of the individual particles approached sphericity. The particle size and shape were considered optimal for formulation. However, when these crystals were coated and the resultant powder dispersed in the aqueous vehicle, DMHB underwent marked crystal growth. The effect of this crystal growth on coating integrity is shown in Fig. 1 and the resultant increase in release rate is given in Table IV. Chemical analysis of DMHB indicated that, prior to coating, the crystals were either anhydrous or contained varying amounts of alcohol. In contrast, crystals taken from the aqueous suspension contained 3.5–3.8% H_2O. Typical thermograms obtained by differential thermal analysis for the anhydrate, "ethanolate," and hydrate are given in Figs. 2–4. These results indicate that DMHB crystallized from the chloroform–alcohol solvent system as an "ethanolate" of varying composition (possibly unstable) and, in some instances, was converted to the anhydrate by drying at high temperatures. In aqueous media, these more soluble forms recrystallized in the form of the monohydrate.

It was found that crystals of the monohydrate could be obtained by use of a dimethylformamide–water solvent system, but these crystals were excessively large and acicular in shape. Experimentation with various crystallization techniques established the fact that crystals of a desirable size and shape could be obtained by rapid nucleation through the use of insonation and by slowing crystal growth by careful temperature control. Photomicrographs of the DMHB monohydrate crystals obtained by this procedure appear in Fig. 5. The release rates for an aqueous suspension of coated DMHB monohydrate crystals are listed in Table V. Also given in this table are the release-rate values after 6 months' storage at 37° and 1 year's storage at ambient conditions. Photomicrographs of coated crystals alone and in an aqueous dispersion after 1 year's storage at ambient conditions appear in Figs. 6 and 7. No evidence of change in appearance, potency, or release rate was found for this formulation during this storage time.

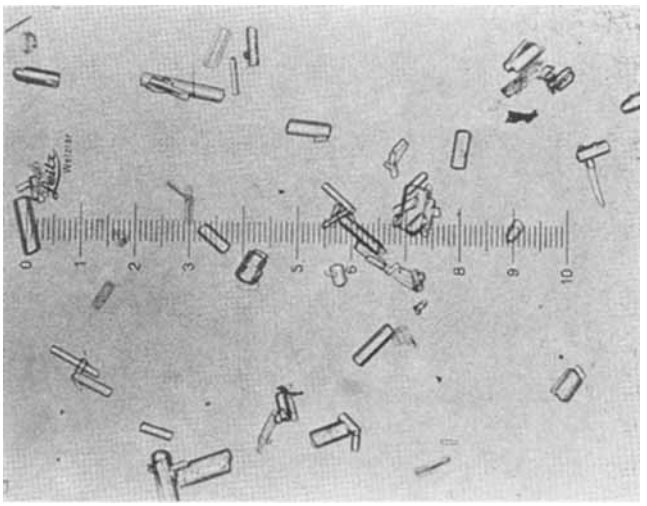

Figure 5—*DMHB crystals obtained from a dimethylformamide–water solvent system (magnification: 0–1 equals 63.9 μ).*

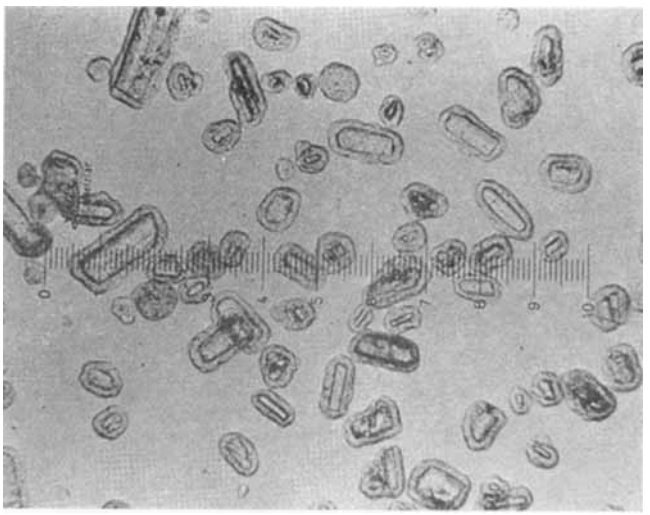

Figure 6—*DMHB crystals coated with a mixture of GTS and BA (magnification: 0–1 equals 63.9 μ).*

Although this formulation was not tested *in vivo* for antitussive activity, the *in vitro* release values suggest that this preparation would release a desirable amount of dextromethorphan for immediate absorption and the remainder would be released for absorption slowly over time.

In this report, dramatically different behavior has been described for the same chemical salt coated by two different methods and crystallized from two different solvent systems. It is likely that the implications of these observations are not only applicable to the formulation of liquid sustained-release dosage forms but also should be considered in the formulation of other dosage forms. This study

Table V—Chemical and Release-Rate Stability of a Sustained-Action Suspension of DMHB Hydrate

Release Rate, %[a]	Original	3 Months RT	3 Months 37°	6 Months RT	6 Months 37°	1 Year, RT
	Assay, mg./ml.					
	8.9	8.9	8.7	9.0	8.8	8.9
0.5	23%	24%	26%	25%	26%	25%
1.5 + 0.5	35%	32%	36%	—	37%	35%
1.5 + 3	70%	71%	71%	73%	81%	80%
1.5 + 5.5	94%	91%	94%	93%	97%	95%
Solubility in vehicle	10–11%	—	—	—	—	—

[a] First number indicates hours in USP gastric fluid and second, where given, indicates hours in modified USP intestinal fluid.

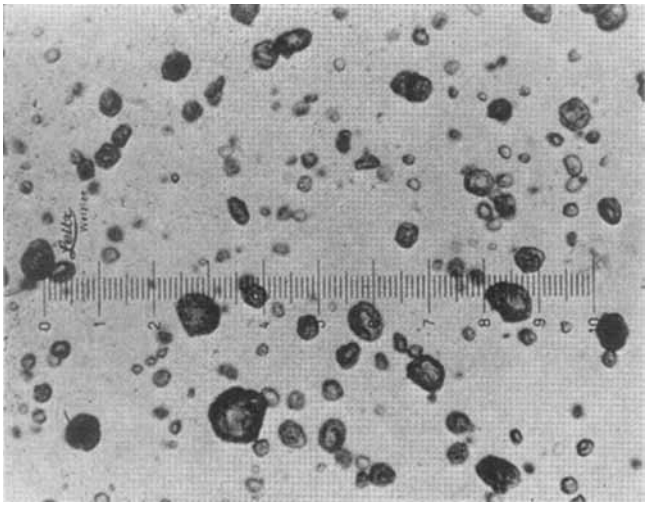

Figure 7—*An aqueous suspension of coated DMHB crystals after 1 year's storage at ambient conditions (magnification: 0–1 equals 63.9 μ).*

illustrates the value of having a choice of materials and processes which can be used to arrive at the best formulation prior to clinical testing. In this instance, the PCD proved to be a useful addition to equipment available in these laboratories for the formulation of a suspension having a prolonged *in vitro* release.

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Correlation and Prediction of Rates of Alkaline Hydrolysis of Some Benzoate Esters

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Abstract □ Rate constants have been determined for the alkaline hydrolysis of 36 *p*-substituted alkyl benzoates, and it is shown that these esters can be characterized on the basis of their rates of alkaline hydrolysis. Application of linear free-energy relationships allows calculation of alkaline hydrolysis rate constants for alkyl or aromatic *p*-substituted benzoate esters not included in this study. It is demonstrated that rates can be predicted for esters whether substituent variation is in the acyl or alkyl portion of the molecule by using the conventional Hammett treatment and the more recent alcohol dissociation model.

Keyphrases □ Benzoate esters—alkaline hydrolysis rates □ Alkaline hydrolysis rates—benzoate ester identification □ Linear free-energy relationships—alkaline hydrolysis rate prediction □ UV spectrophotometry—reaction monitoring

Earlier papers in this series (1–4) demonstrated that precise kinetic measurements can be a powerful tool in the identification of organic compounds. In addition, the large number of rate constants generated in these studies, under constant conditions, provides the necessary data for structure–reactivity relationships, mechanistic interpretations, *etc.* The classes of organic compounds previously considered were: alcohols [rates of alkaline hydrolysis of their 3,5-dinitrobenzoate esters (1)], sugars [rates of oxime formation (2)], aliphatic amines [rates of cinnamoylation (3)], and aliphatic esters [rates of alkaline hydrolysis (4)]. The present study demonstrates that rates of alkaline hydrolysis can be used to identify aromatic esters and presents linear free-energy relationships to predict rates of alkaline hydrolysis for esters not included in the study.

EXPERIMENTAL

Chemicals—Fisher certified acetonitrile was used without further purification after it was established that it was spectrally pure (from 220–300 mμ) and that it had no anomalous effect on the rate of alkaline hydrolysis. All other chemicals were either analytical or reagent grade. Water was double distilled from acid permanganate in an all-glass distillation apparatus.

All esters were prepared according to procedures outlined by Shriner *et al.* (5) with slight modification. The acyl chloride was reacted with the appropriate alcohol by heating under reflux for 30 min. The reaction mixture was then taken up in chloroform and extracted with 5% Na_2CO_3 followed by water and finally dried with $MgSO_4$. After removing the chloroform under vacuum, the ester remaining was purified by repeated recrystallization from water or from the alcohol representing the alkyl portion of the ester or, in the case of liquids, by vacuum distillation.