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Stabilization of sulconazole nitrate in a topical powder formulation

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Summary

A mixture of sulconazole nitrate and talc appeared to be unstable under accelerated temperature conditions. The rate of degradation was influenced by temperature and the source of talc. Acid washing of the talc or addition of acidic compounds seemed to accelerate the degradation of sulconazole nitrate. The formulation was stabilized by the addition of basic metal salts of some inorganic or organic acids, such as sodium bicarbonate and sodium acetate. The stability was also influenced by the surface area of both the stabilizing agent and sulconazole nitrate.

Introduction

Sulconazole nitrate (I) is a new potent broad-spectrum antimycotic agent. A talc-based powder formulation was developed for topical use in a wide range of skin infections of fungal and yeast origin. Talc is widely used in the pharmaceutical and cosmetic industry. Although generally considered an inert material, talc has been known to influence the stability of the active ingredient in various formulations. Use of talc as lubricant was shown to stabilize aspirin in a tablet formulation containing aspirin, phenacetin and caffeine (Ribeiro et al., 1955; Nazareth and Huyck, 1961). Gold and Campbell (1964) found that different talcs varied significantly in their adverse effects on the stability of aspirin in tablets at elevated temperature and humidity. Autoxidation of drotaverine hydrochloride in the solid state was shown to be enhanced by the presence of talc in the preparation (Pawelczyk and Opielewicz, 1978). Other reports where talc was shown to adversely effect the stability of

pharmaceutical or cosmetic preparation include vitamin D_2 powder (Takahashi and Yamamoto, 1969), aspirin tablets (Delonca et al., 1975) powder preparations of cysteine derivatives (Nara et al., 1975) and talc compositions containing added perfumes (Augsburger et al., 1974; Zeitz, 1980). The purpose of this study was to evaluate the effects of elevated temperature on the stability of sulconazole nitrate in powder formulations containing talc.

Materials and Methods

Materials

Sulconazole nitrate, sulconazole free-base and the degradation products were obtained from the Institute of Organic Chemistry, Syntex Research. Talcs were USP or BP grade and purchased from various suppliers which are designated by A-L. Colloidal silicon dioxide USP/NF was supplied by Degussa (U.S.A.). All other chemicals were reagent grade and used as received.

Preparation of the powders

Powders were prepared by mixing sulconazole nitrate (1%), colloidal silicon dioxide (0–1%) and a portion of the talc in a small V-shaped blender until a homogeneous mixture was obtained (approximately 30 min). This premix was then mixed with the remainder of the talc in another V-blender. To prepare small amounts of mixtures of various additives and sulconazole nitrate powder, appropriate amounts of additives were added to about 20 g portions of the sulconazole nitrate powder. The powders were mixed for 5 min with a spatula, then transferred to large beakers, sealed tightly and shaken for 10 min.

Accelerated stability studies

Accurately weighed samples of the powder (0.2–2 g) were placed in tape-sealed scintillation vials and stored in ovens maintained at appropriate temperatures. The control samples were stored at 4°C or room temperature. The whole contents of the vials were assayed for sulconazole nitrate.

Analytical methods

Sulconazole nitrate was quantitated by either cation exchange or reversed-phase high-performance liquid chromatography (HPLC) described elsewhere (Lee et al., 1982). The whole contents of the vials was transferred completely into volumetric flasks using acetonitrile or methanol. Additional solvent was added until the flask was approximately 2/3 full. The flasks were sonicated to dissolve sulconazole nitrate. Then the flasks were filled up to the mark and a portion was centrifuged. Aliquots of the clear supernatant and the internal standard solution were diluted with mobile phase, filtered and injected into the HPLC.

Spectrographic analysis of talc samples was performed by American Spectrographic Laboratories, San Francisco, CA, and the elemental analysis of talc surface (ESCA analysis) was performed by Surface Science Laboratories, Palo Alto, CA.

Particle size distribution and mass median diameter of the talc were determined using a Coulter Counter apparatus. Moisture content of the talc was determined using Aquatest IV, automatic Karl Fischer titrator (Photovolt, U.S.A.). A suspension of talc in water (1 : 24) was agitated for at least 4 h and the pH of the supernatant measured on a standardized pH meter. The specific surface areas were measured using BET method from adsorption of nitrogen at low temperature.

Results and Discussion

Analytical methodology

The HPLC methods used to quantitate sulconazole nitrate in the samples have been shown to be accurate, linear, precise and specific. The relative standard deviations of replicate assays (performed by two analysts on two different days) were less than 1.5%. The specificity of the HPLC system was demonstrated by complete resolution between sulconazole nitrate, internal standard and possible degradation products. The details are afforded elsewhere (Lee et al., 1982). The

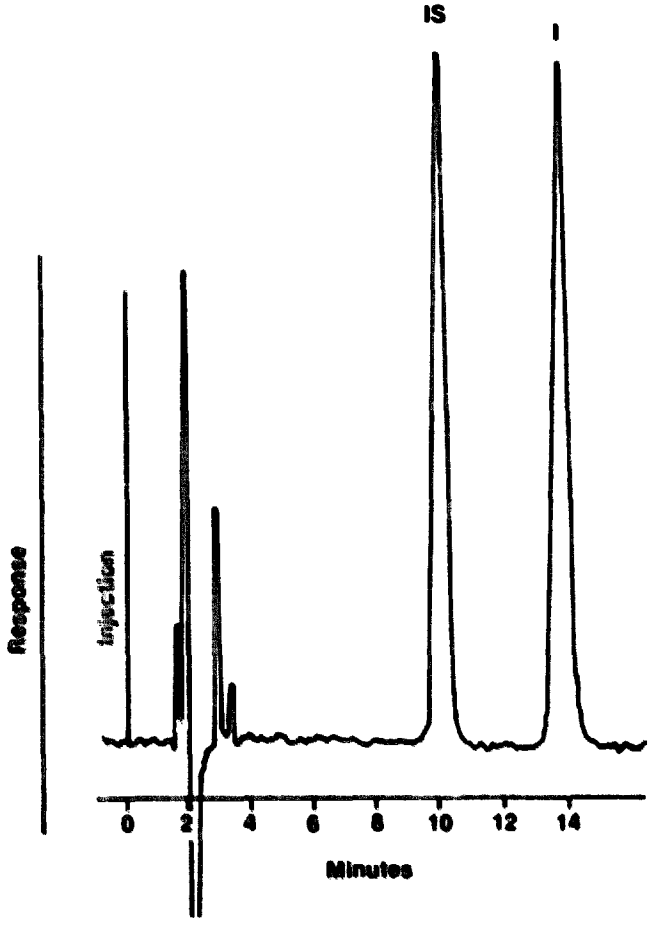


Fig. 1. HPLC traces of an undegraded sample of sulconazole nitrate powder showing sulconazole nitrate (I) and the internal standard (IS).

TABLE 1

ACCELERATED STABILITY OF SULCONAZOLE NITRATE, ITS FREE-BASE AND THEIR MIXTURES WITH TALC

Sulconazole	Talc [c]	% Labeled strength [a]		
	(%)	Initial	2 weeks 80°C	4 weeks 60°C
Nitrate	0	100	101, 101	101, 101
Nitrate [b]	q.s. 100	97, 97	76 [d], 79 [d]	86 [d], 80 [d]
Free-Base	0	100	98, 99	[e]
Free-Base [b]	q.s. 100	100, 101	101, 100	[e]

[a] Individual whole container assays.
[b] 1% w/w.
[c] Talc A used in this study.
[d] Degradation products observed.
[e] Not determined.

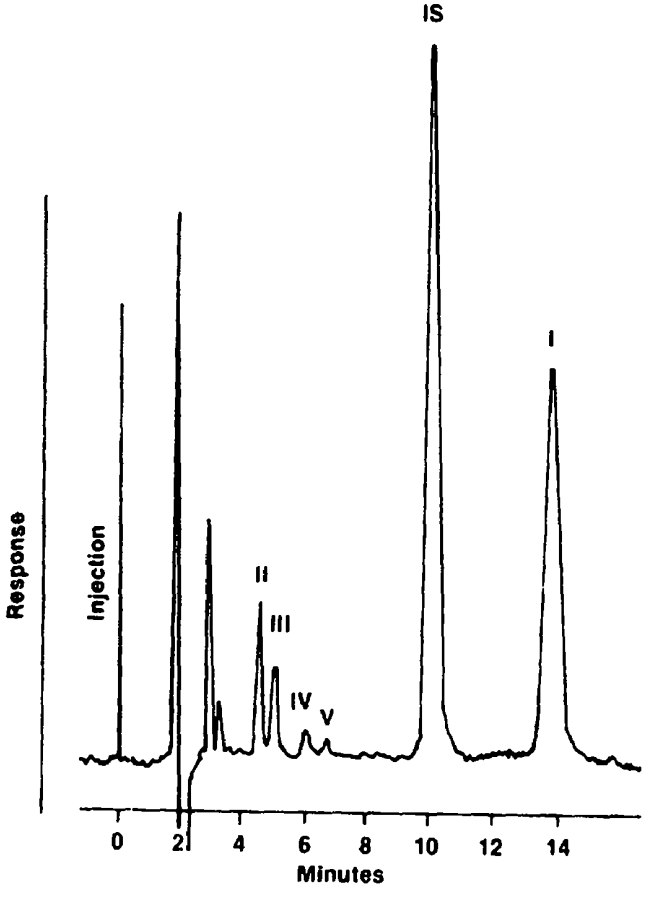


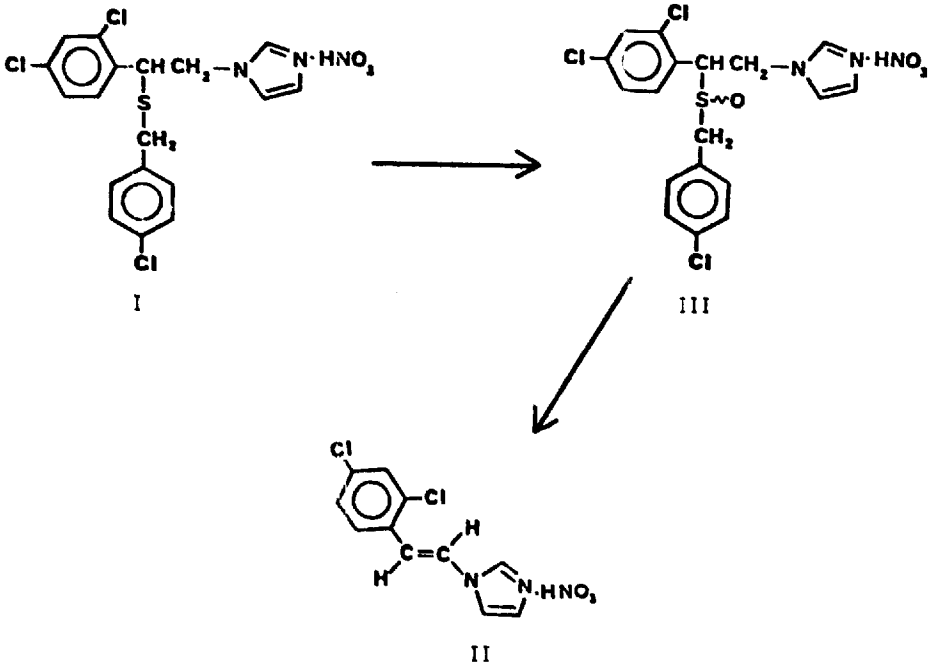
Fig. 2. HPLC traces of a degraded sample (16 days, 80°C, 45% of labeled strength) of sulconazole nitrate powder showing sulconazole nitrate (I), internal standard (IS) and the degradation products (II–V).

accelerated stability studies were set up in scintillation vials. After exposure to various storage conditions, the whole contents of the vials was analyzed for sulconazole nitrate. This procedure was used to maintain sample homogeneity (i.e. to eliminate sampling effects on the assay results).

Stability of sulconazole nitrate powder

The accelerated stability data for sulconazole nitrate, its free-base alone and their mixtures with talc are presented in Table 1. Pure solid sulconazole nitrate and its free-base showed excellent stability at elevated temperatures. However, a mixture of sulconazole nitrate and talc underwent 18–21% decrease in potency after two weeks at 80°C. The samples stored at 60°C for 4 weeks also showed marked degradation. It is interesting to note that sulconazole free-base appeared to be much more stable in the formulation. HPLC traces of intact and degraded samples are shown in Figs. 1 and 2, respectively. The chromatogram of the degraded sample showed the presence of degradation products (II–V), indicating that the decrease in potency was due to degradation of the drug rather than its adsorption on talc or incomplete recovery during extraction. The formation of degradation products also appeared to correlate with the decrease in potency of sulconazole nitrate, supporting the above conclusion.

The major degradation products have been identified to be the diastereomeric mixture of sulfoxides (III) and an olefin (II). The identity of these compounds were established by comparison of their retention times on both reversed-phase and cation exchange HPLC systems with those of authentic compounds. A possible mechanism of degradation of sulconazole nitrate in powder formulation is shown in Scheme 1.



SCHEME 1

TABLE 2

RESULTS OF ACCELERATED STUDIES TO EVALUATE THE EFFECTS OF COLLOIDAL SILICON DIOXIDE ON THE STABILITY OF SULCONAZOLE NITRATE IN TALC

Colloidal silicon [a] dioxide (%)	% Labeled strength sulconazole nitrate [b]		
	Initial (RT)	2 weeks 80°C [c]	4 weeks 60°C [c]
0.00	97, 97	76, 79	86, 80
0.01	100, 101	75, 71	92, 92
0.10	103, 100	75, 81	92, 94
0.50	104, 107	85. 80	97, 95
1.00	105, 102	84, 84	97, 96

[a] In addition the formulation contains 1% sulconazole nitrate and talc A q.s. 100%.
[b] Individual whole container assay.
[c] Degradation products observed in all elevated temperature samples.

The first step is postulated to be oxidation of sulfur atom to form a diastereomeric mixture of sulfoxides (III). Elimination of the sulfoxide-containing side-chain of III, in the subsequent step, generates the olefin (II). An alternate route for the formation of II could be elimination of the sulfur-containing side-chain of I. However, this reaction is expected to be much slower than the former, since sulfoxide is a better leaving group than sulfide. Whether these reactions are taking place in the solid state or a microenvironment of a solution has not been established.

Colloidal silicon dioxide was included in the formulation to improve the flow

TABLE 3

STABILITY OF SULCONAZOLE NITRATE POWDERS (1%) MANUFACTURED USING TALC FROM VARIOUS SOURCES

Talc	pH (1:24 dilution)	% LS [a] sulconazole nitrate	
		4°C [b]	2 weeks 80°C [c]
A	5.1, 6.4	99	77, 79, 86, 80
B	7.5, 7.6	102	60, 60
C	8.1, 7.9	100, 100	39, 48
D	8.1, 8.0	101, 102	39, 48
E	6.4, 6.7	102	28, 86
F	8.0, 7.8	104	81, 49
G	7.6, 7.4	100, 101	78, 68
H	7.6, 7.6	98, 100	65, 82
I	8.0, 8.0	107, 108	70, 54
J	7.0, 7.0	108, 109	73, 84

[a] Labeled strength, individual whole container assay.
[b] Represents initial assays.
[c] Degradation products observed in all 80°C samples.

TABLE 4

ANALYTICAL DATA ON TALC FROM VARIOUS SOURCES

Talc	Mass Med. Dia. (μm)	Moisture content (% $H_2O \pm$ S.D.)	pH (1 : 24 dilution)	Spectrographic analysis					Surface elemental analysis (atom %)					
				Mg	Al	Ca	Fe	Ti	Si	Mg	O	C	Zn	F
A	12.8	0.221 ± 0.079	8.9, 8.7	20	0.12	0.04	0.6	0.004	19.9	13.6	60.3	5.0	0.2	1.0
B	7.5	0.554 ± 0.065	8.7, 8.7	25	0.25	0.006	1.75	0.007						
C	10.6	0.307 ± 0.041	9.3, 8.9	25	0.4	0.07	0.85	0.25	19.7	14.2	62.1	4.0	–	–
D	9.8	0.394 ± 0.042	9.2, 8.9	20	0.4	0.15	0.85	0.025						
E	15.3	0.166 ± 0.029	9.0, 8.6	25	1.5	0.025	1.25	0.05						
F	15.3	0.178 ± 0.004	9.3, 9.3	20	0.2	0.05	0.75	0.01						
G	15.5	0.123 ± 0.021	9.3, 9.2	25	1.5	0.12	1.5	0.05						
H	15.9	0.173 ± 0.017	9.2, 9.2	25	0.6	0.1	1.25	0.04						
I	10.6	0.323 ± 0.056	9.2, 9.3	25	0.4	0.08	0.6	0.025						
J	16.3	0.195 ± 0.049	9.3, 9.3	20	0.08	0.007	0.4	0.004	20.3	12.3	60.4	7.0	–	–

characteristics of the powder mixture. An accelerated stability study was conducted to evaluate the effects of colloidal silicon dioxide on the stability of sulconazole nitrate in the powder. The results are presented in Table 2. Addition of colloidal silicon dioxide seemed to improve the stability of sulconazole nitrate slightly.

Effect of talc from various sources

Since pure solid sulconazole nitrate had excellent stability, the observed instability in the formulation strongly suggests adverse interaction with talc. Talc impurities such as heavy metals or alkalinity have been shown to affect the stability of various drugs (Asker et al., 1973). These talc impurities could vary from source to source (Gold and Campbell, 1964). Therefore, talc samples obtained from several different suppliers were used to prepare sulconazole nitrate powder formulations. The accelerated stability data for these powders after 2 weeks at 80°C are given in Table 3. The purpose of this study was to screen a large number of talc samples with respect to their relative stability effect on sulconazole nitrate. No attempts were made to extrapolate the 80°C data to predict shelf-life at room temperature. Although all the talc samples were USP/BP grade, varying the source of talc influenced the degradation of sulconazole nitrate profoundly.

The uniformity of initial assay results indicates that the powder blends were homogeneous. However, the analytical results of most of the samples exposed to 80°C show large scatter. This scatter could not be due to the analytical method, which has been proven to have excellent precision. Since each assay result represents

TABLE 5

EFFECTS OF ACID WASHED TALC AND ACIDIC COMPOUNDS ON THE ACCELERATED STABILITY OF SULCONAZOLE NITRATE IN POWDER FORMULATIONS [a]

Formulation	Acid wash procedure	Additive	pH (1:24 dilution)	% LS [b] sulconazole nitrate	
				4°C [c]	2 weeks 80°C [d]
1	None	None	5.1, 6.4	99	77, 79, 80, 86
2	Washed with HCl and dried over H_2SO_4	None	3.6, 3.8	99, 98	64, 3
3	Washed with HCl, heated at 160°C and dried under vacuum	None	3.6, 3.7	96, 98	2, 3
4	Washed with H_2SO_4 and heated at 160°C for 2 h	None	3.2	100	49, 66
5	None	0.5% citric acid	3.5	96, 97	22, 19, 13, 13

[a] Talc A used in this study.

[b] Labeled strength. Individual whole container assay.

[c] Represents initial assays.

[d] Degradation products observed in all 80°C samples.

the whole contents of a single container, non-homogeneity due to migration of sulconazole nitrate at elevated temperature can be overruled. One possible explanation for this high variance could be due to the nature of the degradation reaction (i.e. a non-homogeneous reaction as discussed later). This conclusion is supported by the observation that samples with low assay results also exhibited larger amounts of degration products.

Talcs A and J appear to provide the best stability, whereas talcs C and D poor stability. In order to explain these differences, the talc raw materials were extensively characterized with respect to particle size, pH, moisture content, elemental analysis of bulk talc as well as its surface (Table 4). In addition, the pH of the formulations (1 : 24 dilution) were also measured (Table 3). However, the stability data could not be qualitatively correlated with any of these talc properties.

Stabilization of sulconazole nitrate powder

Gold and Campbell (1964) reported that certain alkaline impurities in the talc adversely affected the stability of aspirin. Purification of talc by acid washing was shown to improve the stability of aspirin. However, in the present study the use of acid-washed talc seemed to accelerate the degradation of sulconazole nitrate in the finished product (Table 5). It should be noted that the apparent pH of the formulation (1 : 24 dilution) had dropped considerably after acid washing.

Earlier studies had shown that a mixture of sulconazole free-base (Table 1) and talc has an excellent stability at 80°C. The solubility of sulconazole nitrate in water at 25°C (0.6 mg/ml) is about 300 times higher than that of the free-base (Henes, 1979). Although it is possible that the poor aqueous solubility of the free-base may contribute to its superior stability, there is an intrinsic difference in the reactivity of the two species. A study of the effect of pH on the stability of sulconazole nitrate in a topical solution formulation (Benjamin et al., 1982) indicated that sulconazole nitrate undergoes rapid degradation in an acidic environment (pH < 4.5). The pH range for maximum stability was found to be pH 5–8. It is interesting to note that

TABLE 6

STABILIZATION OF SULCONAZOLE NITRATE POWDER BY BASIC METAL SALTS OF INORGANIC AND ORGANIC ACIDS [a]

Additives	pH (1:24 dilution)	% LS [b] sulconazole nitrate	
		4°C [c]	2 weeks 80°C
None	7.6	100, 100	39, 48
2.5% $NaHCO_3$	8.3	99	93, 94
1% Potassium acetate	7.6	90, 95, 97	94, 94, 92
1% Potassium citrate	8.0	83, 85, 104	38, 38, 39
1% Sodium carbonate	10.1	99, 103	95, 98, 95

[a] Talc C used in this study.
[b] Labeled strength. Individual whole container assay.
[c] Represents initial assays.

the major degradation products formed in the solution and powder formulations were the same, which would also indicate similar mechanism of degradation. These results strongly suggest that the protonated form of sulconazole nitrate is the chemically reactive species, which degrades rapidly in acidic environment. This is also supported by the fact that addition of acidic compounds (citric acid) to the powder formulation or use of acid-washed talc accelerated the degradation of sulconazole nitrate (Table 5). The apparent pH of the suspensions of these powder formulations indicated acidic environment.

Therefore, basic compounds were added to stabilize the powder formulation. As expected, the basic metal salts of organic and inorganic acids appear to stabilize the formulation under accelerated conditions (Table 6). When 1% sodium bicarbonate, potassium acetate or 2% sodium carbonate were included in the formulation, degradation was minimal after 14 days. However, addition of 1% potassium citrate to the powder did not improve the stability. The apparent pH (1 : 24 dilution) of these formulations are also included in Table 6. Except for sodium carbonate there was only a slight increase in pH. Sodium bicarbonate was selected as an additive of choice.

It is probable that basic metal salts of inorganic or organic acids exert their stabilization action by producing a basic microenvironment around sulconazole nitrate. Alternatively, there may be some acidic sites on the talc surface (Takahashi and Yamamoto, 1969), which catalyze the degradation of sulconazole nitrate. Basic

TABLE 7

EFFECT OF SODIUM BICARBONATE ON THE ACCELERATED STABILITY OF SULCONAZOLE NITRATE POWDER (IN TALC C)

% Sodium bicarbonate	Initial [a]		16 days at 80°C [a]	
	% LS [b]	pH [c]	% LS [b]	pH [c]
0.00	100	6.2	45	6.0
			36	6.0
0.05	99	6.6	93	6.7
			94	6.7
0.10	101	6.7	84	7.0
			96	7.2
0.25	100	7.1	95	8.0
			57	7.1
0.50	99	7.3	98	8.4
			51	7.4
1.00	99	7.8	96	8.6
			97	8.7
2.50	99	8.0	99	8.3
			99	8.4

[a] Same vial was sampled for pH and assay.
[b] % of labeled strength.
[c] pH of 1 : 10 dilution.

metal salts of acids would then act by neutralizing these acidic catalytic sites. The latter explanation is supported by Takahashi and Yamamoto (1969) who found that vitamin D_2 was readily isomerized in powders prepared with $CaHPO_4$ or talc and that this isomerization was catalyzed by surface acid of the excipients. Ethanolamines and poly(oxyethylene) compounds were found to stabilize the formulation by reducing the surface acidity of the excipients. This hypothesis may also explain the large variance of the analytical results (Table 3), when the catalytic sites are not uniformly distributed in the powder mixture.

In order to select the optimum level of sodium bicarbonate, the accelerated stability of powder formulations containing 0–2.5% sodium bicarbonate at 80°C was evaluated. The assay results and the apparent pH values (1 : 10 dilution) are presented in Table 7. Inclusion of as little as 0.05% sodium bicarbonate improved tremendously the stability of sulconazole nitrate. At higher levels of sodium bicarbonate, the stabilizing effect was even more dramatic. The data in Table 7 indicate that powders containing at least 1% sodium bicarbonate were highly stable. The stability data of powders containing less than 1% of this additive show considerable scatter. The scatter might have been due to lack of sample homogeneity with respect to the stabilizer, as reflected by the apparent pH values which were measured on the same samples. For example, one of the two samples containing 0.25% or 0.50% sodium bicarbonate degraded to about 50% labeled strength whereas the other sample underwent only a small amount of degradation. The pH of the former sample was also about 1 pH unit lower than the latter, indicating less sodium bicarbonate in the sample.

Similar stabilization effects due to 1% sodium bicarbonate, were found with the talcs obtained from other sources. Some of the data is presented in Table 8. This effect was also apparent at the lower temperature of 60°C. Activation energies for the solid state reaction are generally extremely high (Carstensen, 1974) and it is

TABLE 8

STABILIZING EFFECT OF SODIUM BICARBONATE ON SULCONAZOLE NITRATE POWDER (1%) AS A FUNCTION OF TEMPERATURE AND SOURCE OF TALC

Talc source	Sodium bicarbonate (%)	% Labeled strength sulconazole nitrate		
		Initial	1 Week 80°C [a]	1 Month 60°C [b]
C	0.0	99.0 ± 1.2	42 [a], 41 [c]	69 [c], 69 [c]
C	1.0	99.0 ± 1.2	98, 99	93 [c], 93 [c]
K	0.0	99.3 ± 1.0	4 [c], 4 [c]	59 [c], 65 [c]
K	1.0	99.8 ± 0.4	98 [c], 98 [c]	95 [c], 95 [c]
L	0.0	102.2 ± 1.5	13 [c], 16 [c]	86 [c], 82 [c]
L	1.0	100.5 ± 0.6	95 [c], 98 [c]	91 [c], 93 [c]

[a] Whole contents of vial was assayed.
[b] Sampled from 60 ml high density polyethylene bottles.
[c] Degradation products observed.

TABLE 9

EFFECT OF PARTICLE SIZE OF SULCONAZOLE NITRATE AND SODIUM BICARBONATE ON THE ACCELERATED STABILITY OF SULCONAZOLE NITRATE POWDER

For-mula-tion no.	Components [a]		% of labeled strength	
	Sulconazole nitrate 1%	Sodium bicarbonate 1%	5°C 2 weeks	80°C 2 weeks
1	Micronized [b]	Mesh 60/200 [d]	104, 101	13, 24 [f]
2	Micronized	Micromilled [e]	105, 100	98, 99
3	Milled [c]	Mesh 60/200	104, 101	53, 52 [f]
4	Milled	Micromilled	102, 103	100, 97

[a] Formulation also contains 0.5% colloidal silicon dioxide and talc C.
[b] Specific surface area 3.16 ± 0.12 m^2/g.
[c] Specific surface area 0.85 ± 0.01 m^2/g.
[d] 74–250 μm, specific surface area 0.60 ± 0.02 m^2/g.
[e] 99% by weight smaller than 75 μm, specific surface area 0.82 ± 0.11 m^2/g.
[f] Degradation products observed.

possible that these effects may not be significant under normal storage conditions for the product.

Effect of particle size on the stability

Most solid–solid interactions increase with increase in surface area. Therefore, the effect of particle size of sulconazole nitrate and sodium bicarbonate on the accelerated stability of sulconazole nitrate in the powder formulation was evaluated in order to select particle size for optimum stability. The formulations and the accelerated stability data are summarized in Table 9. Formulation no. 1 containing micronized sulconazole nitrate and sodium bicarbonate of larger particle size (mesh 60/200) showed the worst stability. As expected, reducing the surface area of sulconazole nitrate (formulation no. 3) improved the stability markedly. However, increasing the surface area of sodium bicarbonate, irrespective of the particle size of sulconazole nitrate (formulation nos. 2 and 4), improved the stability dramatically.

Conclusions

The accelerated stability of sulconazole nitrate powder formulation is affected by temperature and the source of talc. Basic metal salts of some inorganic or organic acids stabilize the formulation markedly. Optimum stabilization is obtained by the addition of 1% micromilled sodium bicarbonate. The exact nature of the interaction between talc and sulconazole nitrate and the mechanism of stabilization by sodium bicarbonate has not been established yet. Work is in progress to characterize and quantitate the catalytic sites on talc surface. In addition, the role of water in the reaction is being investigated.

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