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PREFORMULATION EXCIPIENT COMPATIBILITY TESTING. APPLICATION OF A DIFFERENTIAL SCANNING CALORIMETRIC METHOD VERSUS A WET GRANULATION SIMULATING, ISOTHERMAL STRESS METHOD

Francis A. Chrzanowski

Lucy A. Ulissi

Barry J. Fegely

Azarine C. Newman

Basic Pharmaceutics Section

McNeil Pharmaceutical

Spring House, PA 19477

ABSTRACT

The application of a differential scanning calorimetric (DSC) method versus an isothermal stress (IS) method, which utilizes HPLC analysis of simulated wet granulations stored for two months at 60°, was investigated as an excipient compatibility predictor for fenretinide and as a determinant of the most excipient compatible of three mefenidil salts. Stability of the simulated wet granulations after two years at 25° was the reference criterion.

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The DSC method was determined to be an unreliable compatibility predictor for fenretinide and could not be used with one of the mefenidil salts. Conversely, the IS method was an accurate compatiblity predictor for both compounds.

INTRODUCTION

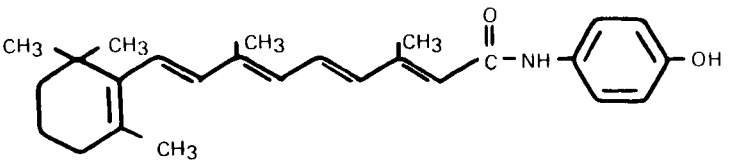
Drug-excipient compatibility testing is an important preformulation tool used to select excipients prior to large scale development trials, thereby improving the efficiency of dosage form development. Ideally, the method used should be relatively fast, easily interpreted, accurately predictive and require only small amounts of drug substance.

There are two general methods available, differential scanning calorimetry (DSC) and isothermal stress (IS) with quantitative assay (1). Recently, El-Shattawy et al. (2) developed a rapid DSC method which simplified test data interpretation, and required only a few milligrams of test compound and excipients. The compatibility is predicted from the differences in the heats of melting of the drug alone and in a mixture with an excipient. The method assumes the melting peak area and heat of melting of the drug in the mixture are decreased when an incompatibility occurs. The melting peak and heat of melting remain unchanged if the drug-excipient mixture is compatible. The potential for incompatibility is proportional to the decrease in the heat of melting (2). This particular DSC method was used to predict the

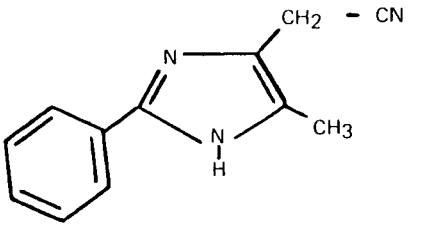
excipient compatibilities of aspartame (2,3), ampicillin (4), erythromycin (5), cephalexin (6) and nalidixic acid (7) with particular emphasis on direct compression excipients. The verification of these predictions has not been published.

The IS method takes a longer period of time to complete and requires a specific, quantitative assay method for either the test substance or its decomposition products. IS methods have been used in several compatibility studies. The compatibilities of amezinium methyl sulfate were studied by Moest et al. (8) at 20° to 80° storage temperatures, using thin layer chromatography (TLC) to detect decomposition. Boatman and Johnson (9) studied drug-excipient compatibilities at elevated storage temperatures, also using TLC. Water (5%) was sprayed onto one-half of each mixture to simulate wet granulation and the other half was left untreated to compare the compatibilities under methods comparable to wet granulation and direct compression (9).

This report describes attempted applications of the DSC method and successful utilizations of the IS method for determinations of excipient compatibilities of fenretinide, [N-(4-hydroxyphenyl)-retinamide] (Figure 1), and three mefenidil, [5-methyl-2-phenyl-1H-imidazole-4-acetonitrile], salts - mefenidil hydrochloride monohydrate, mefenidil fumarate and mefenidil mesylate (Figure 1). The results of the mefenidil salt evaluations were to aid in the selection of a salt for further development.



Fenretinide



Mefenidil

Figure 1: Structures of Fenretinide and Mefenidil.

MATERIALS AND METHODS

Materials

Fenretinide and the mefenidil salts (hydrochloride monohydrate, fumarate and mesylate) had a purity of >99% by HPLC and TLC, respectively. They were passed through an 80 mesh sieve prior to use. All excipients were of USP-NF quality. Fenretinide mixtures were prepared with the following excipients: microcrystalline cellulose,[1] dibasic calcium phosphate dihydrate, docusate sodium, lactose hydrous, sodium lauryl sulfate and powdered cellulose.[2] Mefenidil salt mixtures were prepared with the following excipients: starch, microcrystalline cellulose, pregelatinized starch, talc and magnesium stearate.

DSC Method

Samples of fenretinide, alone and in combination with the excipients, were analyzed by DSC[3] in unsealed aluminum sample pans with lids, in an atmosphere of nitrogen. The powders, fenretinide (100 mg) and excipient (150 mg), were mixed in a glass mortar. The DSC heating rate was 10°/min. The procedure was to scan a sample of fenretinide, the excipient, and the combination. At least two replicate scans were made. The areas under the endothermic melting peaks for fenretinide, alone and in excipient mixtures, were calculated by weighing a cut-out copy of the peak on a laboratory balance. The heats of melting were calculated from the area as described by El-Shattawy et al. (2).

Samples of the mefenidil salts were analyzed as described for fenretinide except that sealed sample pans were used.

IS Method

Fenretinide-Excipient Mixtures

The ratio of fenretinide to excipient (100:150) was the same for each excipient. The powders, fenretinide (240 mg) and excipient (360 mg), were mixed in a glass mortar. The mixtures were subdivided into 2 oz flint glass bottles, 50 ± 0.5 mg aliquots, each containing 20 mg of fenretinide. Fenretinide alone (20 mg aliquots) was also placed into bottles to serve as a control. Water (1 mL) was added to each bottle and the bottles were gently swirled to facilitate wetting of the mixtures. The fen-

retinide mixtures and controls were dried with the bottles uncapped in an oven at 49° for six hours. Duplicate samples of each mixture or control were assayed immediately after drying. The remaining sample bottles were capped and stored at 60° for up to two months and at 25° for two years.

Mefenidil-Excipient Mixtures

The drug-excipient mixtures were prepared using equivalent weights of the three salts (Table 1). The ratios were varied according to the excipients. The powders were mixed in a glass mortar and an aliquot containing the equivalent of 25 mg free base were added to 2 oz flint glass bottles. Water (1 mL) was added to each bottle and the bottles were gently swirled to facilitate wetting. The mixtures were dried with the bottles uncapped in an oven at 49° overnight (ca. 18 hours). Duplicate samples of each mixture or control were assayed immediately after drying. The remaining sample bottles were capped and placed at 60° for one month and at 25° for two years.

Assay

The test materials were assayed periodically during the 60° storage periods and after two years at 25° using HPLC methods specific for fenretinide (10) or mefenidil (11). The samples were assayed by adding 25 or 50 mL volumes of the mobile phase or another suitable solvent directly to the sample bottles avoiding further weighings. After appropriate dilutions and additions of internal standards, the amount of intact fenretinide or mefenidil

TABLE 1

Preparation and Subdivision of Mefenidil Salt-Excipient Mixtures

Excipient	Drug: Excipient Ratio	Mixture Preparation				Mixture Aliquots		
		Excipient Weight mg	Hydrochloride Hydrate mg	Fumarate mg	Mesylate mg	Hydrochloride Hydrate mg	Fumarate mg	Mesylate mg
None	--	--	--	--	--	31.9 ± 0.4	39.7 ± 0.4	37.2 ± 0.4
Starch	100:100	400	510.4	635.2	594.8	56.9 ± 0.5	64.7 ± 0.5	62.2 ± 0.5
Micro-crystalline cellulose	100:100	400	510.4	635.2	594.8	56.9 ± 0.5	64.7 ± 0.5	62.2 ± 0.5
Pregel Starch	100:20	80	510.4	635.2	594.8	36.9 ± 0.4	44.7 ± 0.4	42.2 ± 0.4
Talc	100:3	12	510.4	635.2	594.8	32.7 ± 0.4	40.5 ± 0.4	37.9 ± 0.4
Magnesium Stearate	100:2	8	510.4	635.2	594.8	32.4 ± 0.4	40.2 ± 0.4	37.7 ± 0.4

was determined using an HPLC[4] with an autosampler. The fenretinide mixture two-year, 25° samples were assayed by duplicate injections of single samples. All other assays of both fenretinide and mefenidil mixtures were performed by duplicate injections of duplicate samples.

RESULTS AND DISCUSSION

The DSC scans of the components and mixtures of the fenretinide compatibility study appear in Figure 2. The sample pans were not sealed because uncrimped pans gave better melting peaks and baselines. The mean heat of melting for fenretinide alone, from 12 determinations, was 25.3 ± 3.03 cal/g. The coefficient of variation was 12%. The addition of excipients generally resulted in a decrease in the intensity of the melting peaks.

For most of the mixtures there were no problems in establishing the base of the melting peak, calculating the area of the peak and the heat of melting. The fenretinide-lactose and fenretinide-microcrystalline cellulose mixtures had post melting exotherms (Figure 2) which did not affect the calculations. The fenretinide-dibasic calcium phosphate dihydrate mixture had multiple peaks in the fenretinide melting range because the melting ranges of the two components were so close. The heat of melting calculated for the first peak, coincidental with fenretinide melting, was 90 cal/g, 214% of the corresponding value obtained from fenretinide alone.

This type of problem had not been addressed by the originator of the method (2). The problem was resolved by using the total heat of melting from the mixture, 51.6 cal/g, and the combined heats for the components, 24.5 and 88.2 cal/g, respectively. A 54.2% reduction in heat of melting was calculated.

The mean differences in heats of melting are summarized in Table 2.

All six exceed the coefficient of variation for fenretinide alone. They ranged from 16.9% to 54.2%. The DSC method predicted that the most compatible of the excipients tested were hydrous lactose and sodium lauryl sulfate. The difference in heats of melting were 16.9 and 17.9%, respectively. The two-month, 60° stability data for the granulation simulating mixtures indicated that hydrous lactose was compatible. There was 93.4% fenretinide remaining in the hydrous lactose mixture and 92.6% for fenretinide alone (Table 2). The two-year, 25° data confirmed the compatibility of the fenretinide-lactose mixture.

The 60°, IS method did not support the compatibility of sodium lauryl sulfate predicted by the DSC method. Only 60% fenretinide remained after two months. The two-year, 25° data confirmed the incompatibility; 71.2% remained in the sodium lauryl sulfate mixture as compared to a 96.7% assay for fenretinide drug substance.

Powdered cellulose and microcrystalline cellulose, which had fairly high negative changes in heats of melting, had >88% fen-

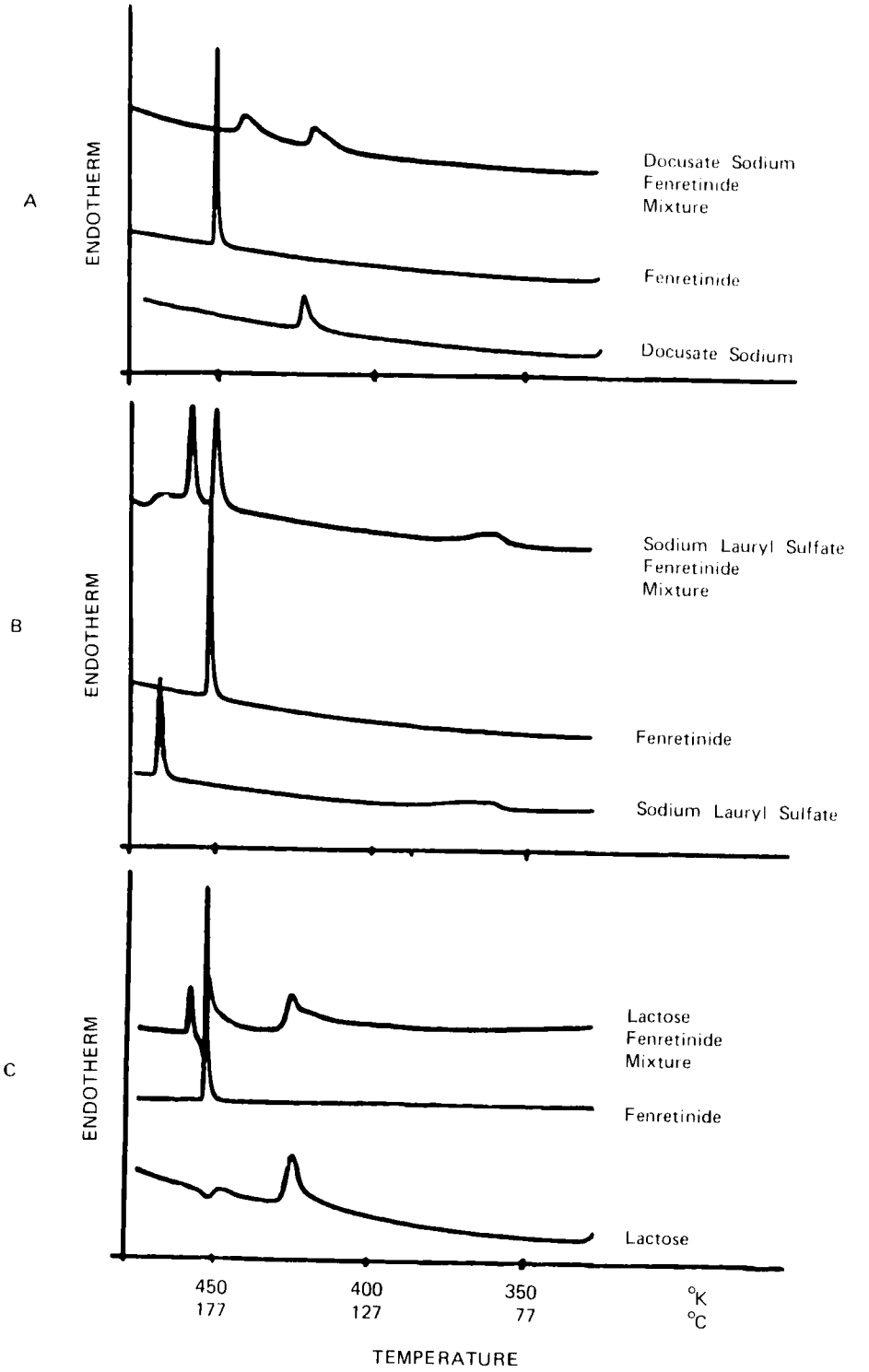


Figure 2: DSC Scans of Fenretinide, Excipients and Mixtures: A, Docusate Sodium; B, Sodium Lauryl Sulfate; C, Lactose Hydrous; D, Microcrystalline Cellulose; E, Powdered Cellulose; F, Dibasic Calcium Phosphate.

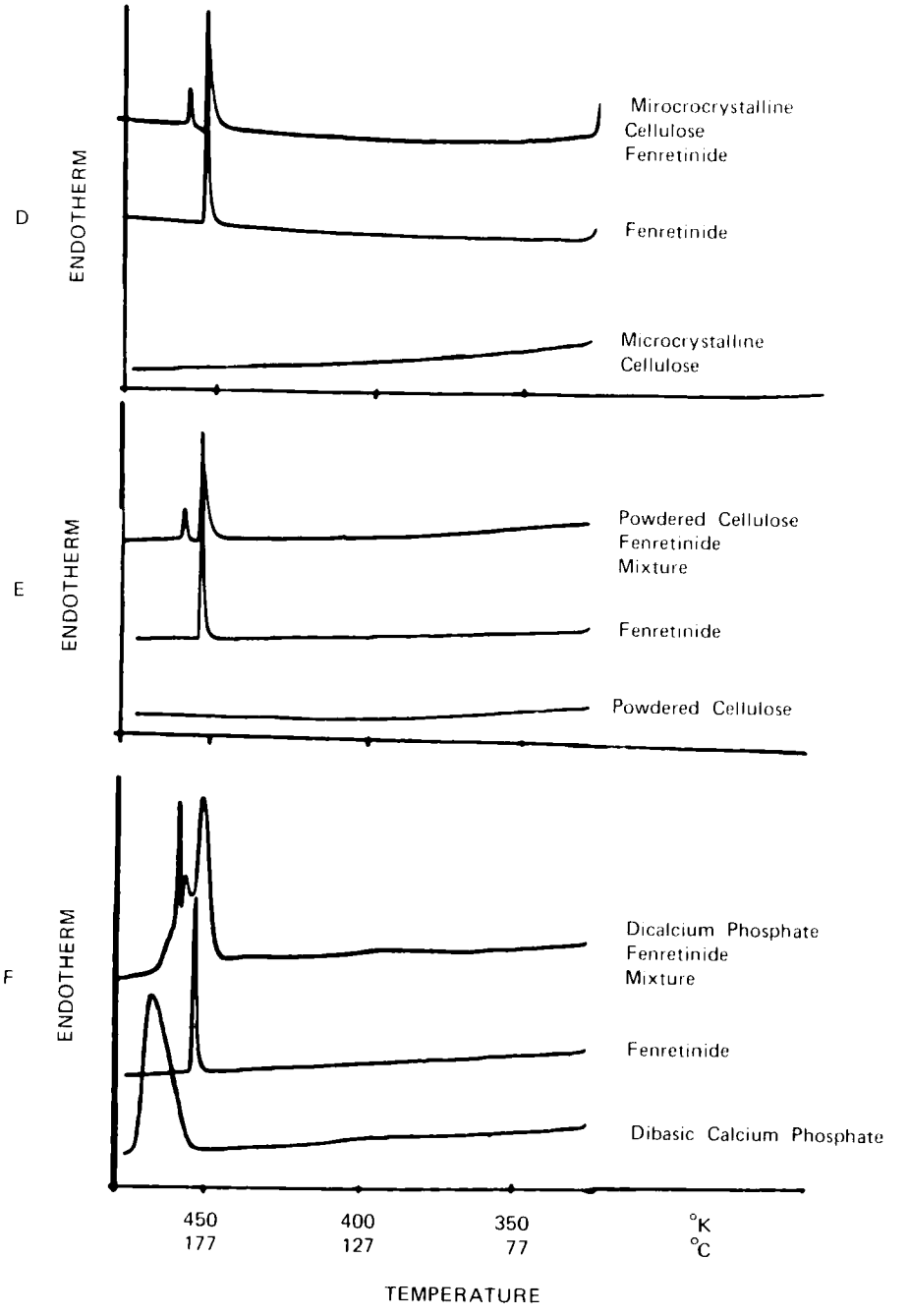


FIGURE 2 Continued. Parts D, E, and F.

TABLE 2

Comparison of DSC and IS Simulated Granulation Methods With Fenretinide-Excipient Mixtures

Excipient	Drug: Excipient Ratio	Heat of Melting Difference* %	Percent Remaining			
			Initial	60°** 1 mo	60°** 2 mos	25°*** 2 yr
None (Fenretinide only)	---	---	100.0	96.4	92.6	96.7
Docusate Sodium	100:150	53.2	102.2	94.5	91.8	97.6
Sodium laurylsulfate	100:150	17.9	98.0	67.0	60.0	71.2
Lactose, hyd.	100:150	16.9	99.0	95.4	93.4	97.8
Microcrystalline cellulose	100:150	38.0	99.0	92.8	88.7	94.2
Powdered cellulose	100:150	29.5	98.8	94.0	95.2	97.1
Dicalcium phosphate dihydrate	100:150	54.2	102.0	96.8	98.0	97.8

*mean of duplicate samples.
**mean of duplicate injections

retinide remaining after 60° for two months, and >94% after two years at 25°.

When docusate sodium and dibasic calcium phosphate dihydrate were mixed with fenretinide, the heats of melting were reduced 53.2% and 54.2%, respectively. The DSC method predicted that docusate sodium and dibasic calcium phosphate dihydrate were the least compatible. The IS method predicted that docusate sodium and dibasic calcium phosphate were compatible. After two months at 60°, 91.8% and 98.0% fenretinide remained, respectively, and after two years at 25°, the fenretinide assays in the mixtures

were within 1% of the assay for fenretinide drug substance stored at 25° for two years.

As for the mefenidil salt-excipient mixture evaluations, the DSC method could not be used because the hydrochloride salt produced a wide, shallow, assymetrical melting peak (Figure 3). However, the mefenidil salt-excipient mixtures were suitable for evaluation by the IS method. The data in Table 3 show that the three salts were equally compatible with the excipients and that there were no incompatibilities between the mefenidil salts and the excipients in the ratios tested and no basis for the selection of one salt over another. The four-week, 60° and two-year, 25° data were in agreement, again showing the accuracy of the IS method.

There are a number of advantages to the IS method. Unlike the DSC method, there was no presumption that heating the mixture through the melting range of the drug would reveal the compatibility of the drug-excipient mixture. Also, the chemical stability of the drug substance in the excipient mixtures was quantitated. The simulated wet granulation and subsequent drying procedure subjects the drug-excipient mixtures to conditions encountered during wet granulation, and utilizes the methodology used to establish drug substance stability. The authors have been misled as to the stability of other drug substances in wet granulations because dry mixtures were tested in preformulation. The dry granulations were stable, whereas the wetted granulations

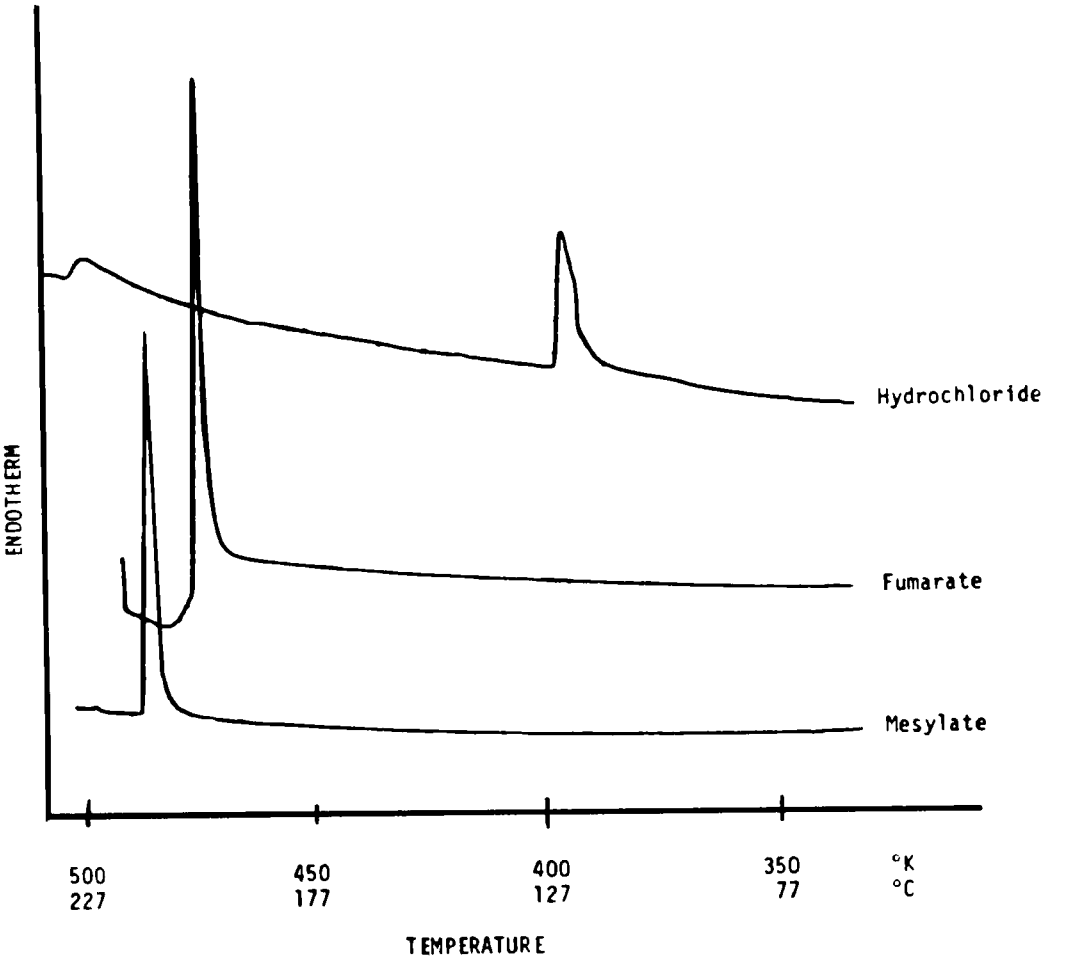


Figure 3: DSC Scans of Mefenidil Salts.

exhibited discoloration and chemical instability. This phenomenon has occurred even when both drug and excipients were hydrates. Using the proposed IS method, it would be possible to determine if a particular instability was occurring during the wet granulation step or afterward during the storage period.

Subdividing the test samples into individual aliquots in bottles prior to wetting, drying and storing at elevated tempera-

TABLE 3

Simulated Granulation Mefenidil-Excipient Mixtures Stability at 60° and 25°

Mefenidil Salt Excipient Mixtures	Drug: Excipient Ratio	Percent Remaining			
			60°		25°
		Initial	2 weeks	4 weeks	2 years
HYDROCHLORIDE HYD.	---	102.5	104.0	100.4	104.9
Starch	100:100	100.4	104.6	100.8	103.6
Micro. Cellu.	100:100	98.1	103.4	98.9	103.1
Pregel Starch	100:20	101.4	101.5	100.4	104.1
Talc	100:3	99.3	102.9	100.2	104.5
Mag. Stear.	100:2	99.5	104.0	99.2	103.9
FUMARATE	---	99.4	97.9	100.7	102.1
Starch	100:100	102.7	99.6	98.2	101.6
Micro. Cellu.	100:100	101.1	98.7	99.2	99.7
Pregel Starch	100:20	101.4	101.5	100.4	101.2
Talc	100:3	99.3	102.9	100.2	92.2
Mag. Stear.	100:2	99.5	104.0	99.2	100.5
MESYLATE	---	97.1	103.5	100.4	104.0
Starch	100:100	103.6	100.7	99.7	101.3
Micro. Cellu.	100:100	100.0	102.5	97.9	100.4
Pregel Starch	100:20	100.5	102.7	99.1	101.6
Talc	100:3	100.4	102.7	97.4	99.6
Mag. Stear.	100:2	100.9	101.9	100.8	102.4

tures, eliminated weighing errors due to the gain or loss of water by those treatments.

An excess of water (1 mL) was added to assure the drug-excipient mixture had ample opportunity for contact with water. A volume less than 1 mL may be adequate, but we have found 1 mL to be satisfactory and an excess is preferred. There may be difficulty in incorporating small amounts of water into drug-excipient mixtures such as the 5% water used by Boatman and Johnson (9). With a limited supply of drug substance and a number of excipients

to be tested, the uniform distribution of small amounts (5-20%) of water presents a problem. In this report, the largest drug excipient mixture (Table 1) was ca. 1 g. Adding 50 µL of water (5%) and distributing it uniformly in the mixture could have been a problem. It has been the authors experience that Karl Fischer water analyses have indicated uneven distribution of water in aliquots of drug-excipient mixtures prepared by adding up to 20% water in a mortar and pestle.

The selection of the IS temperature of 60° was made a priori, and was based on previous experiences with fenretinide, mefenidil salts and other test compounds. One to two months at 60° were satisfactory for fenretinide and the mefenidil salts. van Dooren (1) recommended three weeks at 55°, while Boatman and Johnson (9) used a two-week period. Moest et al. (8) detected incompatibilities at 60° and 80°, over a three month period. The selection of IS method conditions must be based upon the physical-chemical properties of the compounds and excipients.

CONCLUSIONS

This investigation demonstrated that the IS method is a preferred method for excipient compatibility studies over the DSC method. The long term stability data indicated that the DSC method was not predictive of fenretinide compatibilities and was not suitable for evaluating all salts of mefenidil. However, the

long term data did demonstrate that the IS method was predictive of the compatibilities of fenretinide and the mefenidil salts.

In addition, the IS method provided quantitative information, did not rely on the ability to obtain and interpret a DSC scan, and required less than a gram of drug substance per excipient tested.

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FOOTNOTES

1 Avicel PH 101; FMC Corp., Philadelphia, PA

2 Solka Floc; Edward Mendel, Carmel, NY

3 Model 2; Perkin Elmer, Norwalk, CT

4 Model 10818, Hewlett-Packard, Palo Alto, CA

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