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Drug–excipient interaction study of enalapril maleate using thermal analysis and scanning electron microscopy

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Summary

A drug-excipient interaction between enalapril maleate and microcrystalline cellulose, previously known to cause increased rates of degradation, has been studied using primarily thermal analysis and scanning electron microscopy. Results indicated apparent reduced heats of fusion for the drug in the presence of the excipient. This was related to the drug-excipient ratio and surface contact. Degradation under DSC conditions was monitored by thermogravimetric analysis (TGA) and high pressure liquid chromatography (HPLC) and shown not to explain the observed reduction in the apparent heats of fusion. The most probable explanation was a weak interaction of the drug with the excipient surface which significantly altered the crystal structure and provided additional low energy sites for melting in a matrix with increasing amorphous content.

Introduction

The study of drug–excipient interactions is an important element in preformulation activities. The classic procedure usually employed, involves preparing a powder sample containing the drug and the excipient, storing at elevated temperatures for several months and systematically analyzing the sample using a suitable stability-indicating method. This process is time-consuming and, generally, detects only chemical instability. The results are not necessarily indicative of possible problems with extraction, disintegration or dissolution.

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A recently employed alternative to study drug-excipient incompatibilities uses differential scanning calorimetry. Many such studies have been reported (Guillory et al., 1969; Jacobson and Gibbs, 1973; Eliasson, 1985; Lee and Hersey, 1977a; Liversidge et al., 1982; El-Shattawy et al., 1984) and the general application of thermal analysis to investigate drug-excipient interactions has been discussed in several reviews (Chiou and Riegelman, 1971; Hardy, 1982; Lee and Hersey, 1977b). Specific drug–excipient interactions studied include penicillin–stearic acid (Jacobson and Reier, 1969), sulfamethoxazole–lactose (Tarjanyi et al., 1971), sulfamethoxazole–sugars (Ford and Francomb, 1985) and ibuprofen–stearate lubricants (Gordon et al., 1984). If an interaction occurs, then it is likely that the thermal curve ob-

tained will have characteristics different from those of the excipients and drug superimposed. However, interactions observed at elevated temperatures should be cautiously interpreted because they may not always be relevant at ambient conditions.

To obtain insight into drug–excipient interactions and establish optimum conditions for observing these interactions, a model system was chosen in which a well-defined incompatibility had been observed by co-workers and was known to occur. The two components of the system were enalapril maleate (MK-421, mol. wt. 492.5), a potent angiotensin-converting enzyme inhibitor, and microcrystalline cellulose/sodium carboxymethylcellulose (Avicel RC-591). During preformulation studies. MK-421 was found to interact with many common excipients including microcrystalline cellulose. Previous data indicated that the rate of degradation of MK-421 was accelerated several orders of magnitude in the presence of microcrystalline cellulose. The final stable tablet formulation avoided these excipients. It contained only those ingredients in whose presence MK-421 was stable. In the present investigation, the physical nature of the drug-excipient interaction was examined using primarily differential scanning calorimetry (DSC) and scanning electron microscopy (SEM).

Materials and Methods

Materials

Enalapril maleate was pharmaceutical grade bulk chemical, L-154,739-01D45, manufactured by Merck, Sharp and Dohme. It exists as two thermodynamically similar crystal forms (Ip et al., 1986). Their very similar crystal energies were believed to have no significant effect on the drug–excipient interaction. Microcrystalline cellulose was NF quality from FMC Corporation. The excipient primarily investigated was Avicel RC-591, lot D8101, and is the material referred to in the text as microcrystalline cellulose (MCC) unless stated otherwise. Other grades of MCC studied included Avicel RC-581, PH101, PH103 and PH105. Other excipients used were all of USP or NF grade and included calcium phosphate dibasic, and sodium carboxymethylcellulose (NaCMC).

Thermal analysis: DSC studies

A Perkin-Elmer DSC-4 was used in conjunction with a System 4 and TADS 3600 data station. Samples were prepared by mixing a weighed portion of MK-421 with a weighed amount of MCC. Weight ratios examined were from two parts MK-421 and one part MCC to one part MK-421 and 10 parts MCC. The dry powder mixtures were tumbled in screw cap vials to obtain homogeneity. Sample pans used for DSC were either standard aluminum pans with crimped covers or sealed volatile aluminum pans. The standard pan was not thermetically sealed allowing volatile components to escape during the process of analysis. The volatile pan was hermetically sealed. This prevented the volatilization of components which would have escaped at atmospheric conditions. Both pans were obtained from Perkin-Elmer Corporation.

To examine different surface contacts between drug and excipient, samples were prepared in 4 different ways for DSC studies: (1) about 2–10 mg of the powder mixtures were weighed directly into standard aluminum sample pans, (2) small discs were prepared by compressing powder mixtures in a Carver press and a portion of each disc was gently broken up before weighing about 2–10 mg into standard sample pans, (3) powder mixtures were ground with mortar and pestle and the uniform, pulverized materials were weighed into either standard or volatile pans or (4) powder mixtures ground with mortar and pestle were compressed in a Carver press and broken portions of the discs were weighed into standard sample pans. The samples were preconditioned at 100 °C/30 min under a dry nitrogen purge before beginning the scan. Sample preparation for the pure drug was always identical to those of drug–excipient mixtures to ensure that the data obtained could always be related to the behavior of the pure drug under similar conditions. Preconditioning the samples removed adsorbed water and reduced interference from an excipient-related broad endothermic response. Thermal curves were obtained at a scanning rate from 1 to 40 °/min and a temperature range from 100 °C to 250 °C. They were

analyzed with the data station software to obtain the onset temperature and apparent heat of fusion for the MK-421 melting transition. Uniformity of the powder mixtures was demonstrated by obtaining thermal curves from 3 separate samples taken from the same powder mixture. The endothermic response for the melting of MK-421 was not significantly different among the 3 samples.

Thermal analysis: thermogravimetric analysis (TGA)

A Perkin-Elmer TGS 2 with a System 4 and TADS 3600 data station was used. Sample mixtures were prepared as described for the DSC analyses and weighed into platinum sample pans. Thermal curves were obtained isothermally at 100 °C and 150 °C under dry nitrogen purge. Samples also were run at conditions which simulated those used with the DSC. That is, samples were run isothermally at 100 °C/30 min followed by non-isothermal conditions with a scan rate of 10 °/min from 100 °C to 250 °C.

Thermal analysis: Thermomicroscopy

A Karl Zeiss universal microscope with a Mettler FP-82 hot stage was used. Samples were observed at a scan rate of 10 °/min from 130 to 200 °C.

Surface area analysis

Surface area of the MK-421 and MCC was determined using a BET method with nitrogen adsorption. The instrument was a Quantasorb surface area analyzer from Quantachrome.

Scanning electron microscopy (SEM)

Portions of samples prepared for DSC investigations were evaluated with an International Scientific Instruments ISI 40 electron microscope. Samples were gold sputter-coated prior to examination to render them electrically conductive.

Infrared spectroscopy (IR)

IR spectra were obtained using a Perkin-Elmer grating spectrophotometer model 457A. Samples were prepared by carefully weighing ingredients to ensure similar quantities of drug and excipient in drug–excipient and pure component samples. Each sample was mixed with KBr by grinding in a mortar and the intimate mixture compressed at 10,000 psi with a Carver press to obtain a KBr wafer. The IR spectra obtained were compared for similarities and differences.

High performance liquid chromatography (HPLC)

Analysis of MK-421 and its primary degradation product, the diketopiperazine (MK-421-DKP), was carried out using a method described by Kato, 1985. A Hewlett Packard 1084B instrument with variable-wavelength UV detection was employed with a Hewlett Packard RP-8 column (200 mm × 4.6 mm i.d., 10 μm packing material). The mobile phase was 30% acetonitrile in aqueous phosphate buffer (pH 2, 0.001 M). The flow rate was 2.5 ml/min, column temperature 80 °C, detection wavelength 215 nm and injection volume 50 μl.

Results and Discussion

Thermal analysis: DSC studies

The DSC thermal curve for MK-421 (Fig. 1) showed a single sharp endotherm at its melting point. At a scan rate of 10 °/min, the observed onset temperature was 149 °C and the apparent heat of fusion was 14.7 kcal/mol. This was in reasonable agreement with those results reported by Ip et al. (1986) of 13.6 ± 0.4 kcal/mol for Form I and 14.0 ± 0.5 kcal/mol for Form II. The thermal curve for MCC showed a broad endotherm attributable to water loss. Preconditioning at 100 °C/30 min allowed sufficient time to dehydrate the excipient and minimize the interference due to evaporation of moisture. No significant degradation of drug-excipient samples was observed by DSC, TGA or HPLC when examined at conditions of 100 °C/30 min. The endotherm obtained for powder mixtures of MK-421 and MCC was broader with an accompanying shift of the onset temperature to lower values. However, the most significant change was a reduction in the apparent heat of fusion (Fig. 1). The decrease in the apparent heat of fusion was enhanced by decreasing the drug–excipient ratio (Fig. 2). Re-

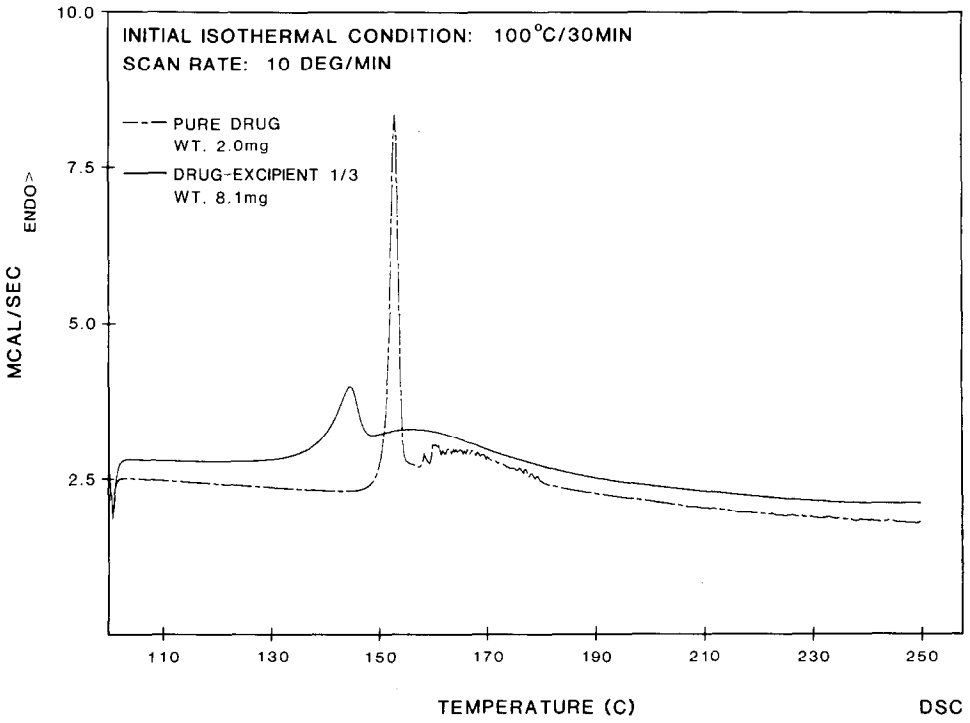


Fig. 1. DSC thermal curves for pure MK-421 (broken line) and for a MK-421/MCC mixture 1/3 (solid line) prepared in a mortar with comparable amounts of MK-421 (2 mg) in each sample. The thermal curve of the pure drug shows a single sharp endotherm. In the presence of the excipient the heat of fusion is reduced considerably.

sults shown in Table 1 are indicative of the apparent heats of fusion obtained on different days over a period of several weeks. The calculated standard deviations document the analytical error.

The reduced heats of fusion appeared to be related to the MK-421 contact with the surface of the MCC. Nakai et al. (1978) have examined the interaction of such compounds as benzoic acid, salicylic acid, and methyl *p*-hydroxybenzoate with MCC. They concluded that these compounds, when ground with MCC, formed a monomolecular layer on the excipient and were, presumably, hydrogen bonded to the cellulose molecule. A

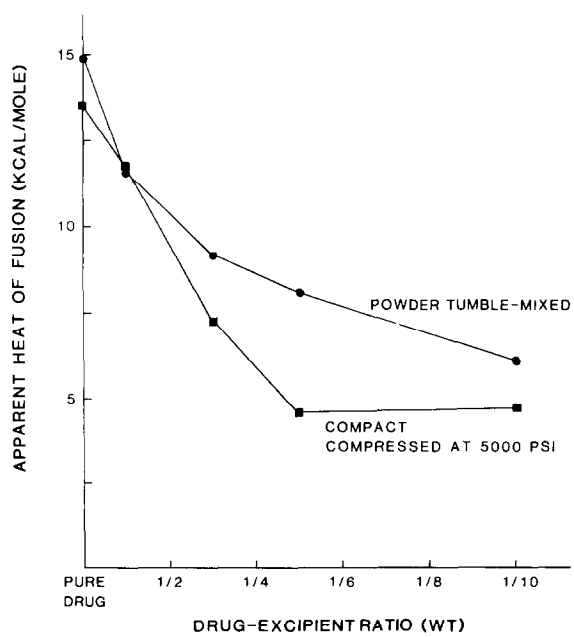


Fig. 2. The effect of excipient concentration on the apparent heat of fusion of MK-421 in powder samples and compressed discs. Since compression provides better surface contact between drug and excipient particles than simple physical mixing, the values obtained for compressed discs are consistently lower than those for the powder mixtures.

TABLE 1

The apparent heats of fusion for pure drug and drug–excipient mixtures (1/3)

	Pure drug (kcal/mol)	MK-421/MCC mixture (kcal/mol)
	14.0	6.1
	14.2	7.8
	14.6	6.1
	15.8	6.4
	14.3	6.8
	14.4	6.3
	15.4	8.1
Mean ± S.D.	14.7 ± 1.7	6.8 ± 0.8

Both samples were ground in a mortar and DSC thermal curves were obtained on different days.

similar type of interaction of MK-421 might explain the reduction in the apparent heats of fusion. The observed interaction was examined experimentally in an attempt to obtain evidence to validate this argument.

To evaluate the physical nature of the drug–excipient interaction 4 different methods of sample preparation resulting in a different degree of surface contact were examined by DSC and SEM. Samples were prepared by: (1) tumble blending of physical mixtures at different drug–excipient ratios, (2) compressing these blends, (3) grinding physical mixtures in a mortar or (4) grinding drug–excipient blends and compressing the ground samples. Since surface area appeared to be an important factor, the surface area of the MCC and MK-421 was determined (Table 2). The MCC is a very hard non-friable material and is unaffected by grinding with a mortar but the MK-421 surface area was greatly increased with grinding. Initially, choosing a compression of 5000 psi, (1 psi = 6.895

TABLE 2

The surface area of MCC and MK-421 as determined by a BET nitrogen adsorption method

Material	Surface area (m^2/g)
MCC (RC-591)	0.21
MK-421	0.94
MK-421 (after grinding)	8.10

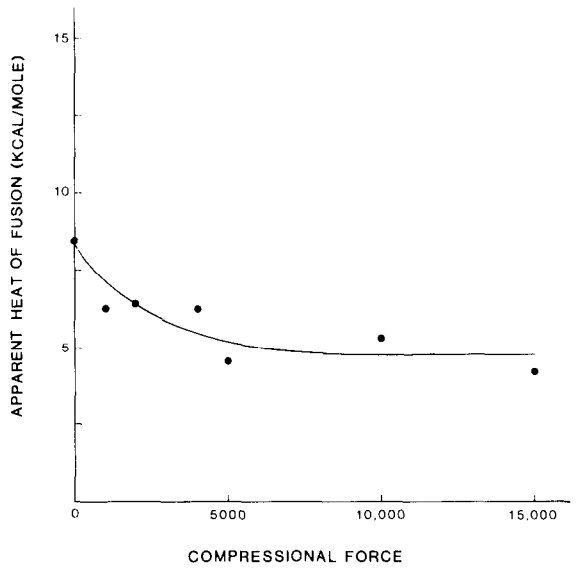


Fig. 3. The effect of compressional force (in psi) on the apparent heat of fusion of MK-421 at a constant excipient concentration. The dug-excipient ratio is 1/5.

MPa) discs were prepared at different drug–excipient ratios from 1/1 to 1/10. Results showed a marked decrease in the apparent heats of fusion (Fig. 2). Secondly, powder mixtures having a drug-excipient ratio of 1/5 were compressed at several compressional forces from 1000 to 15000 psi and examined by DSC at a scan rate of 10°/min. The apparent heats of fusion showed a small decrease with increasing compression (Fig. 3). The observed decrease was dependent upon the small drug–excipient ratio used (low intercept) and compressional force. The decrease in the apparent heats of fusion without compressing the sample was the result of drug–excipient surface contact obtained from physically mixing the components. Thirdly, improved surface contact was achieved by grinding the two components with a mortar and pestle. The intimate contact and increased drug surface area provided by grinding significantly reduced the apparent heats of fusion at drug-excipient ratios of about 1/3 (Fig. 4). Finally, ground samples compressed at 5000 psi were examined. The observed decrease in the apparent heats of fusion was not significantly different from those obtained with grinding but without compression. Since grinding with a mortar and

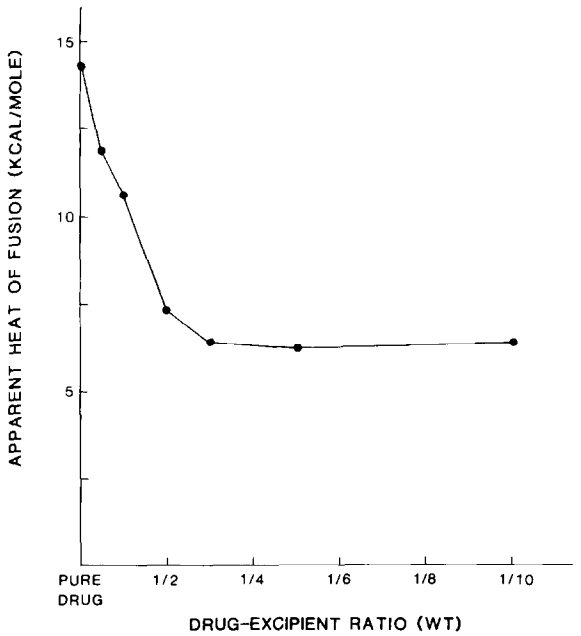


Fig. 4. The effect of excipient concentration on the apparent heat of fusion of MK-421 in samples prepared with a mortar and pestle. Samples ground in a mortar respond more effectively at high drug–excipient ratios

pestle appeared to maximize the effect on the MK-421 endothermic response at high drug–excipient ratios, further studies were conducted using this sample preparation technique. A 1/3 drug–excipient ratio was chosen where the observed decrease in the apparent heat of fusion reached a maximum and the high drug–excipient ratio ensured good sensitivity of the instrument to the MK-421 melting transition.

The nature of the drug–excipient interaction was examined further. Thermal curves were obtained at different scan rates from 1 to 40 °/min. The effect of scan rate on the apparent heat of fusion was not significant for ground pure MK-421 (14.3 kcal/mol). Drug–excipient samples (1/3 ratio) showed a rapid increase in the apparent heat of fusion with increasing scan rates approaching a limiting maximum value of 6.5 kcal/mol at about 10 °/min. This was indicative of MK-421 thermal degradation at scan rates of less than 10 °/min in the drug–excipient mixture. A scan rate of 10 °/min was chosen for further studies.

The role of moisture in the drug–excipient interaction was demonstrated by further exploration of DSC experimental conditions. Very different thermal curves could be obtained when sealed volatile sample pans were used rather than standard aluminum pans as shown in Table 3 (conditions 1 and 2). The endotherm obtained with volatile pans, where the evolved moisture was retained, was shifted to lower temperatures with an apparent heat of fusion similar to that observed for the pure drug. As expected, the endotherm for the drug–excipient mixture was very broad. Nevertheless, the drug–excipient sample

TABLE 3

Results obtained using standard aluminum pans and volatile pans

Condition	Apparent heat of fusion (kcal/mol)	Onset temperature (°C)
1. Sample: 1/3 drug–excipient sealed in volatile pan. Preconditioned at 100 °C/30 min.	13.8	121
2. Sample: 1/3 drug–excipient in standard pan with crimped cover. Preconditioned at 100 °C/30 min.	6.8	142
3. Sample: 1/3 drug–excipient sealed in volatile pan. No preconditioning.	15.2	104
4. Sample: 1/3 drug–excipient. Preconditioned in open volatile pan at 100 °C/30 min. Sample removed from DSC and sealed.	8.0	142
5. Sample: Pure MK-421 preconditioned in open volatile pan at 100 °C/30 min. Sample removed from DSC and sealed.	15.8	148
6. Sample: Pure MK-421 sealed in volatile pan. No preconditioning.	15.8	148

Thermal curves were obtained using 1/3 mixtures ground with a mortar or pure ground MK-421 at scan rates of 10 °/min under dry nitrogen purge.

run in the volatile pan without preconditioning at 100 °C/30 min gave similar results to those obtained with preconditioning, indicating that preconditioning was not responsible for the observed behavior (condition 3).

The thermal response with volatile pans appeared to be influenced by retained moisture in the MCC. This was evident from experiments in which a drug–excipient sample was first preconditioned in an open, unsealed volatile pan in the DSC, removed, sealed and a thermal curve obtained (condition 4). The data were similar to those obtained for a standard pan experiment with preconditioning. Both conditions remove moisture and permit the thermal curve to be obtained under anhydrous conditions. This was demonstrated further by obtaining thermal curves for pure MK-421 in volatile pans with and without preconditioning (conditions 5 and 6). Since in the absence of excipient no moisture had been introduced, results were the same for both conditions and similar to those obtained in the standard pan experiments. Having obtained similar results with standard aluminum pan experiments and volatile pan experiments when samples were preconditioned to remove water in each case, there appeared to be little advantage in using volatile pans. Further experimental work was done in standard aluminum pans.

Other grades of MCC were examined by DSC. These included Avicel RC-581 which is similar to RC-591 in its NaCMC content. Both grades of MCC contain 11% NaCMC. However, RC-581 contains NaCMC mechanically mixed rather than spray-dried onto the surface as is the case with RC-591. Avicel PH101, PH103 and PH105, with varying particle size and moisture content, are acid-treated, spray-dried MCC containing no NaCMC. Results, shown in Table 4, indicate that the apparent heats of fusion consist of two groups: those obtained in the presence of the pure MCC and those obtained with MCC containing NaCMC. The reduced values for the MCC/NaCMC system were about 15% lower than for the PH grade MCC. This would suggest that, under conditions at which the DSC thermal curves were obtained, a small, additional interactive effect may be operative with NaCMC present. However, interaction with MCC also can occur in the absence of NaCMC. The influence of particle size and moisture content over the range found in the PH grades of MCC examined is not a primary factor in the MK-421 interaction.

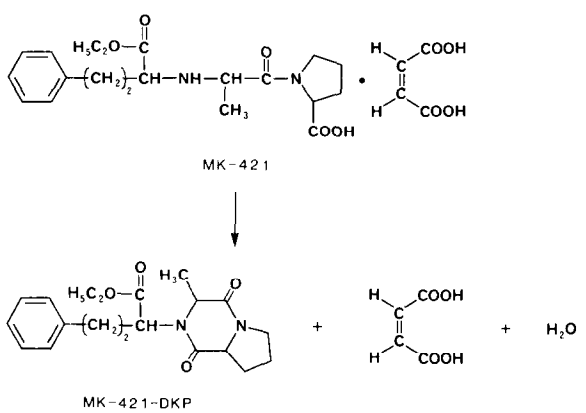
TABLE 4

The apparent heats of fusion obtained by DSC when drug was mixed with various grades of microcrystalline cellulose and carboxymethylcellulose at 1/3 ratio in a mortar

Excipient	Apparent heat of fusion (kcal/mol)	Onset temperature (°C)
Avicel RC-581	7.5	142
Avicel RC-591	8.1	142
Avicel PH101	9.2	147
Avicel PH103	9.1	147
Avicel PH105	9.1	147
NaCMC	7.5	147

Thermal analysis: TGA studies

Under acidic conditions, likely prevalent in samples of pure MK-421 or MCC mixtures, thermal degradation was known to generate MK-421-DKP by formation of an internal amide (Kato, 1985) (Scheme 1).



Scheme 1

From DSC data it was not sufficiently clear whether the observed decrease in the apparent heats of fusion in the presence of MCC was due to decomposition or other interactive effects. Because MK-421-DKP has a melting point of 90 °C,

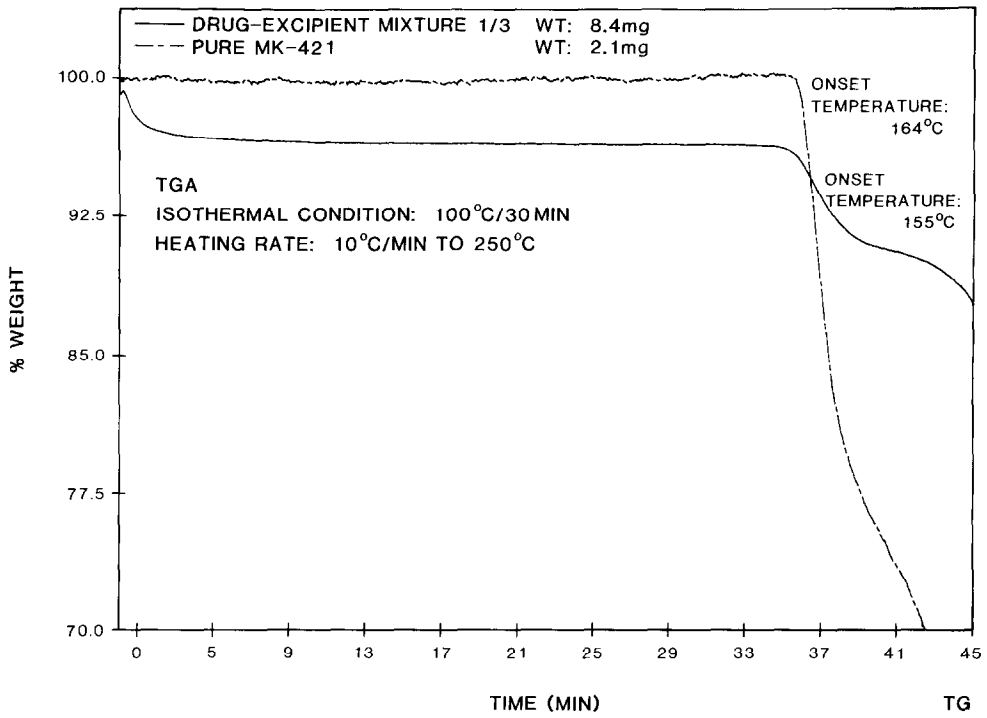


Fig. 5. TGA thermal curves of pure drug ground in a mortar and a drug–excipient sample prepared by grinding a 1/3 mixture in a mortar. Each curve was obtained at conditions used for the DSC experiments. Samples were run isothermally for 30 min, then heated at a rate of 10 °/min to 250 °C. Complete loss of moisture from the drug–excipient mixture and stable conditions for both samples are evident during the isothermal period. In both cases decomposition begins with an onset temperature above the melting transition observed by DSC.

it was not possible to detect its presence by DSC when operating from 100 °C to 250 °C. Any attempt to observe a second melt on cooling MK-421 samples to ambient and heating again was not possible because of glass formation upon cooling. Operating isothermally at temperatures below 90 °C for several hours, no melting transition for MK-421-DKP was observed because degradation was too slow to be significant during the time course of the experiment.

The effect of preconditioning on degradation under conditions of the DSC experiments was investigated by observing weight loss by TGA. To demonstrate loss of moisture during the preconditioning phase, a sample of MCC was run isothermally at 100 °C/30 min, then scanned at 10 °/min. The thermal curve obtained showed an initial loss of 5.5% complete in 25 min and attributable to water. Then, a constant weight was established which persisted through the scan until decomposition set in at 210 °C. Pure MK-421 under similar conditions showed no initial weight loss and an onset temperature for degradation of 164 °C, above the melting transition (Fig. 5). Drug-excipient 1/3 mixtures under similar TGA conditions showed a loss in moisture of 4.5%. Decomposition began at 155 °C, somewhat lower than for the pure drug (164 °C) but above the melting transition (Fig. 5).

When operating the TGA under conditions employed for DSC studies, decomposition observed in samples of pure drug and drug–excipient mixtures occurred as shown in Fig. 5. Estimated losses for pure drug and drug–excipient mixtures were 26.3% and 6.0%. These estimates are in reasonable agreement with calculated weight losses of 27% and 6.9% expected for conversion of MK-421 to MK-421-DKP with the subsequent loss of one mol of maleic acid and water. Operating only at isothermal conditions at 150 °C for 3 h, pure

MK-421 showed a total weight loss of 27.5%. Similar results were obtained for drug–excipient mixtures run isothermally under the same conditions with a weight loss of 26.4%. There was no significant difference in the rate of decay for pure drug or a 1/3 drug–excipient mixture suggesting that at 150 °C MK-421 had melted in the excipient matrix destroying any solid-state interaction that originally might have been present. Decomposition was unaffected by the presence of excipient and occurred primarily in the liquid phase. No significant weight loss was observed by TGA at 100 °C/3 h for either pure drug or drug–excipient mixtures.

Thermal analysis: thermomicroscopy

Samples of pure MK-421 were observed visually using a hot-stage microscope. The sample was heated from 130 °C to 200 °C at 10 °/min. A sharp melt was apparent at 147 °–148 °C. At 170–185 °C the melt became agitated indicative of degradation with the evolution of volatile components. Upon cooling to 130 °C, then to ambient conditions, the sample solidified but showed no indication of crystallization. The glassy material remaining on the slide was reddish-brown. Drug–excipient mixtures prepared by grinding with a mortar were observed under similar conditions. A melt occurred at 143 °–149 °C. Above the melting temperature the sample appeared as clusters of MCC particles interdispersed with droplets of liquid. Cooled samples appeared as off-white particles coated with a solid glass. No melt was observed on reheating the sample. These observations supported previous observations by DSC and TGA.

Scanning electron microscopy

In an attempt to understand the processes involved in sample preparation, the compressed discs and the powder mixtures prepared in a mortar were examined by SEM. Fig. 6 shows MK-421 and MCC tumble-mixed in equal proportions. Both the drug and excipient particles are readily recognizable with well-preserved morphology.

Evaluation of compressed discs resulted in two major observations. The lamellar drug particles collected in the interstitial spaces formed by the

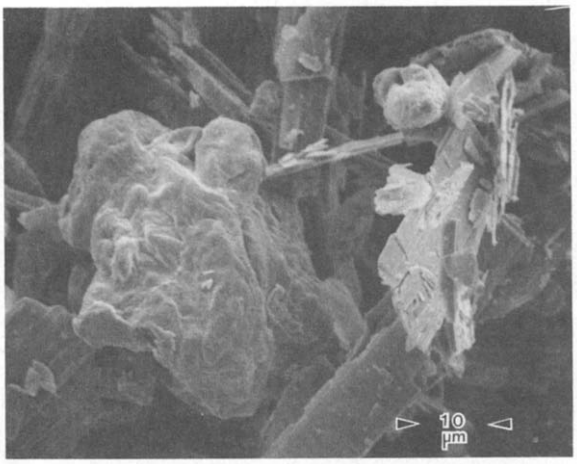


Fig. 6. A scanning electron micrograph of a 1/1 powder mixture of MCC and MK-421 (lamellar particles) showing the well-preserved integrity of both components. The contact between particles is loose and superficial.

excipient particles, particularly at high drug–excipient ratios. The morphology of the individual components gradually disappeared on the surfaces of the compressed discs with increasing compressional force. Examination of the fracture faces, however, revealed remarkable preservation of the integrity of the individual components in the bulk of the compressed material. Both segregation of the drug particles and preservation of morphology were apparent in 1/1 sample mixtures compressed at 1000 psi when the surface of the disc (Fig. 7a) and its fracture face (Fig. 7b) were examined. At 5000 psi, the same sample mixture showed a complete obliteration of particle integrity at the surface of the disc (Fig. 8a) in contrast to the inside of the disc (Fig. 8b) where some of the original morphology could be recognized.

These observations provided a probable explanation for the effect of increasing compressional force on the apparent heat of fusion of MK-421 when compared with the effect of increasing drug–excipient ratios. The non-random distribution of drug particles after compression effectively reduced the surface contact between drug and excipient, particularly at high drug–excipient ratios and low compressional forces. Intimate contact at high compressional forces oc-

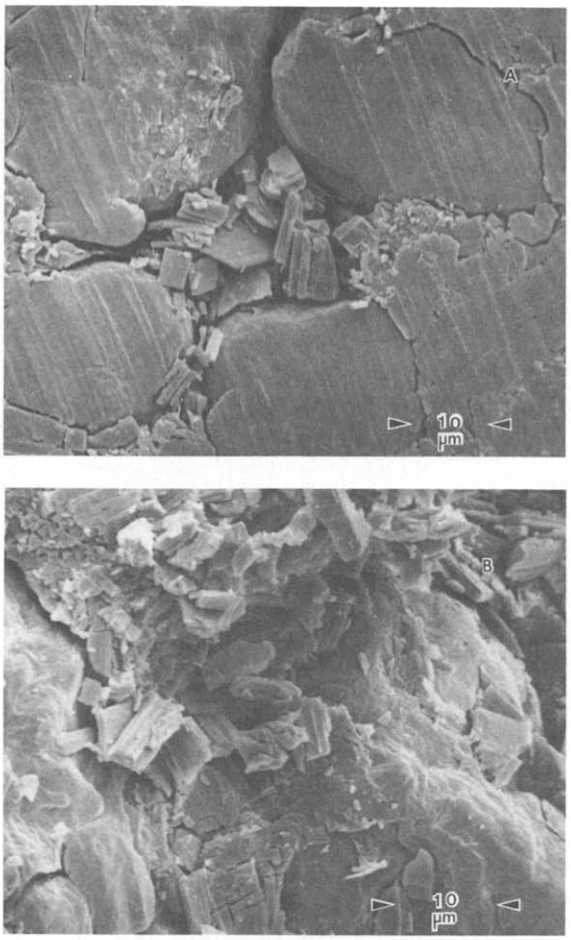


Fig. 7. Scanning electron micrographs of a 1/1 mixture of MCC and MK-421 compressed at 1000 psi. A: the disc surface showing the drug particles filling the interstitial spaces created between the excipient particles upon compression. Note some loss of particle morphology. B: the fracture face showing complete preservation of particle integrity inside the compressed disc.

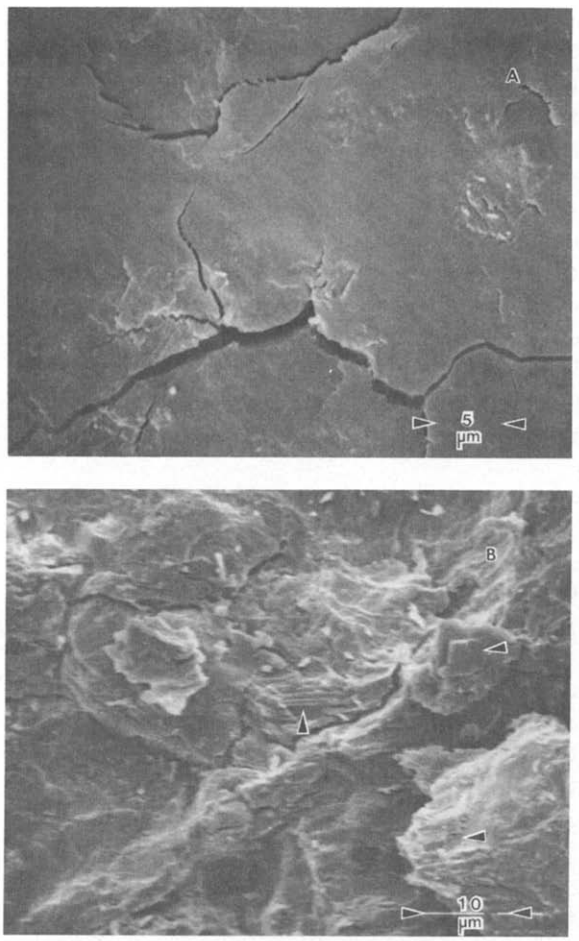


Fig. 8. Scanning electron micrographs of a 1/1 mixture of MCC and MK-421 compressed at 5000 psi. A: the disc surface showing complete loss of particle integrity. B: the fracture face showing how particle integrity is partially preserved within the compressed disc despite the high compressional force. The arrows indicate the lamellar MK-421 particles.

curred only at the surface of the disc and to a much lesser extent in the bulk of the compressed material. Drug segregation into the interstitial spaces of the excipient was more important at high drug–excipient ratios resulting in a non-random distribution of the drug in the excipient. When the drug was diluted with the excipient to low drug–excipient ratios greater uniformity of drug distribution occurred on the surface of the excipient. This was reflected in reduced apparent heats of fusion.

Grinding with a mortar and pestle provided the most intimate surface contact. Breaking up the drug particles resulted in an increase in surface area available for drug–excipient contact. A scanning electron micrograph illustrated how the finely divided MK-421 particles covered the surface of the excipient after grinding (Fig. 9).

IR spectroscopy

The spectrum of a 1/3 drug–excipient mixture showed no gross differences from that of the drug

and excipient obtained separately under similar conditions especially in areas where hydrogen bonding is likely to affect the spectrum (1600–1800 cm^{-1}).

Analysis of thermal degradation by HPLC

Drug degradation was investigated further using HPLC to monitor quantitatively the MK-421 and MK-421-DKP under conditions similar to those used on the DSC. Samples containing drug and excipient in a 1/3 ratio were run by DSC under conditions used to obtain thermal curves. All samples were preconditioned at 100 °C/30 min prior to obtaining the thermal curve. The samples were heated at 10 °/min to a predetermined temperature and rapidly cooled to room temperature when the target temperature was attained. Target temperatures ranged from 135 to 155 °C. Analysis of these samples by HPLC was used to determine the amount of degradation occurring under conditions at which the apparent heats of fusion were obtained. In effect, these experiments allowed an examination of the sample at different slices of time through the portion of the thermal curve where the melting transition occurred. At least 3 consecutive experiments were run at a given condition to obtain sufficient material for the HPLC assay. Results from standard aluminum pans and volatile pans are shown in Table 5.

Good material accountability was obtained in the volatile pan assuming degradation primarily to MK-421-DKP. However, in the standard pan, material accountability was increasingly poor with increasing degradation. This was attributed to loss of the volatile MK-421-DKP from standard pans. Results were obtained for pure MK-421 only in the volatile pan where material accountability was good. Previous DSC data indicated that results should be similar with either volatile or standard pans. Estimated degradation during the melting transition for pure MK-421 and 1/3 drug–excipient mixtures melting over the temperature range of 149–152 °C and 139–147 °C, respectively, was 15–20%. These results are probably high because of the finite time required to cool the sample during which the degradation of the sample will continue. The TGA results discussed earlier also suggest that decomposition is likely to be lower than that indicated by HPLC. The thermal curves obtained by TGA (Fig. 5) show that degradation

TABLE 5

The amount of degradation occurring under conditions used to obtain the DSC thermal curves determined by HPLC quantitation of MK-421 and MK-421-DKP

Sample	Pan used	Target temperature	Intact drug remaining (% of initial drug)	MK-421 -DKP present (% of initial drug)	Recovered (% of initial drug)
1/3 drug–excipient	standard aluminum	130	97.7	1.5	99.2
		140	92.3	2.1	94.4
		145	89.4	4.2	93.6
		150	83.7	6.3	90.0
		155	50.3	29.3	79.6
1/3 drug–excipient	volatile pan	135	79.0	19.7	98.7
		140	69.3	28.3	97.6
		145	52.2	44.0	96.2
		150	33.4	61.4	94.8
Pure drug	volatile pan	135	100.0	–	100.0
		140	97.2	–	97.1
		145	95.0	2.7	97.7
		150	88.0	9.7	98.0
		155	53.8	40.4	94.2

Samples were prepared in standard aluminum or volatile pans, preconditioned isothermally at 100 °C/30 min, heated in the DSC at 10 °/min to a given target temperature, cooled rapidly to ambient conditions, the pans removed and samples extracted and analyzed by HPLC.

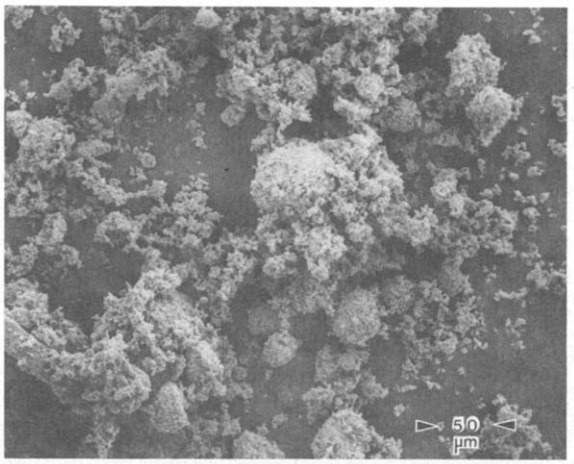


Fig. 9. A scanning electron micrograph of a 1/1 mixture of MCC and MK-421 ground with a mortar and pestle. The broken, finely dispersed MK-421 particles completely cover the excipient surface resulting in a very efficient surface contact. Compare this surface contact with Fig. 6.

is less than 10% prior to the temperature of onset, although it is 9 degrees lower for the drug–excipient mixture than for the pure drug. The degradation observed probably occurs primarily in the liquid melt rather than in the solid state. It is similar to that of the pure drug and cannot account for the reduced heats of fusion observed for drug–excipient mixtures.

Results from drug–excipient studies in volatile pans indicate substantial degradation over the same range of temperature examined with the standard pan. DSC data indicated that the drug melted prior to 135 °C under these conditions. Therefore, the drug was in the liquid state where decomposition was observed to occur shortly after melting (see Fig. 5).

Conclusion

The reduction in the apparent heats of fusion observed in the presence of various grades of MCC appeared to be the result of an interactive effect at the polar surface of the MCC. This effect caused reductions in the apparent heats of fusion of about 50% (from 14.5 kcal/mol to 6.8 kcal/mol). This was in contrast to DSC data obtained with other excipients such as calcium phosphate. In the latter case the melting endotherm for MK-421, obtained at a drug–excipient ratio of 1/3, had a heat of fusion not significantly different from the pure drug.

Further evidence for a probable interaction with MCC affecting the apparent heats of fusion was obtained by varying the heating rate in the DSC experiments. Results suggest increased degradation at low heating rates for drug–excipient mixtures. However, the limiting heat of fusion obtained at high heating rates was considerably lower in the presence of excipient than that obtained for the drug alone. Although some drug degradation did occur during the melting transition and in the presence of MCC, decomposition could not completely account for the observed reduction in the apparent heats of fusion. This was clearly defined by TGA thermal curves which monitored the weight loss due to decomposition under conditions at which the DSC thermal curves were obtained.

Further support for this contention was obtained by monitoring degradation by HPLC. From these data the drug appears to degrade in the liquid melt rather than in the solid-state under DSC conditions. The shift in the onset of degradation in the TGA thermal curves for drug–excipient mixtures parallels the broadening and shift of the melting transition observed by DSC. Assuming decomposition occurs primarily to MK-421-DKP, the HPLC data have provided good material accountability. These data indicate that the reduced heats of fusion are not the result of lost or otherwise unaccounted for material.

A probable explanation for the reduction in the apparent heats of fusion in the presence of MCC is the contact and interaction or weak adsorption of drug on the MCC surface. The results of Fig. 4 may be explained in terms of the surface areas of the drug and excipient limiting contact and, hence, interaction. At high drug–excipient ratios where ample drug is present, the interaction is limited by the available surface area of the MCC. With increasing amount of MCC the interaction increases and the apparent heats of fusion continue to decrease. However, at low drug–excipient ratios the process is limited by the available surface area of the drug. Continuing to increase the MCC content

relative to drug has no affect on the apparent heat of fusion.

The surface interaction of drug and excipient is supported by SEM. The surface contact obtained with grinding is clearly visible by SEM (Fig. 9). The non-random distribution of drug in compacts at high drug concentrations (Fig. 7) indicates the effect of drug–excipient ratio on surface contact. In this case, at high concentrations of the drug, it collects in the interstitial spaces of the excipient minimizing contact. At low drug concentrations relative to the excipient the drug disperses evenly, maximizing surface contact.

The results obtained by IR spectroscopy do not indicate hydrogen bonding. However, if bonding occurs only on the particle surface in contact with the microcrystalline cellulose this may represent a small portion of the total drug. Thus, small spectral shifts indicative of hydrogen bonding would not be observed.

The drug–excipient interaction described appears not to be easily categorized into any of the 6 classifications for solid dispersion systems originally proposed by Chiou and Riegelman (1971) and discussed by Grant and Abougela (1982). The closest category into which this phenomenon fits is complexation, although that is not what appears to be occurring. Rather, the drug appears to be weakly adsorbed onto the surface of the excipient and, because of this process, its heat of fusion is reduced. No evidence for a strong interaction corresponding to complexation at the molecular level appears to exist. The IR spectrum is unchanged before and after grinding the drug with excipients. Evidence from SEM observations indicates the presence of an interdispersed particulate rather than a monomolecular layer of drug on excipient. This suggests that the physical state of the drug, dispersed on the polar excipient surface, has less order and the contact of the drug with excipient causes a sufficient change to provide low energy sites for nucleation during the initial melting phase. This may reflect disruptions in crystal structure or a weak physical adsorptive interaction. The reduced heats of fusion reflect the reduced amount of energy required to melt the drug in this altered condition.

Reduced crystallinity of a drug–excipient interaction has been reported recently for at least one other system (Kim et al., 1985). A further consequence of increasing amorphous content will reduce chemical stability. It is likely a primary contributor to the observed increase in the rate of degradation with drug–excipient mixtures.

General guidelines for the study of drug–excipient interactions are difficult to define. Each potential interactive effect must be evaluated on its own merits. Although DSC and SEM are not a substitute for long-term stability studies, they nevertheless can provide considerable insight into the nature of molecular interactions. They also can provide supplemental information to help define a drug–excipient interaction. Interactions observed at elevated temperatures must be interpreted cautiously. Interactive effects observed by DSC may not be relevant at ambient conditions.

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