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DIFFERENTIAL SCANNING CALORIMETRY AS A QUICK SCANNING TECHNIQUE FOR SOLID STATE STABILITY STUDIES

S. Venkataram[#+], M. Khohlokwane[+] and S.H. Wallis[*]
[+] Faculty of Pharmacy, University of Manitoba, Winnipeg, R3T 2N2, Manitoba, Canada and [*] Biovail Corporation International, 100 Life Sciences Parkway, P.O.Box 21390 Steinbach, R0A 2T3, Manitoba, Canada.

ABSTRACT

The potential compatabilities of various commonly used excipients with Indomethacin (IMC) were compared using differential scanning calorimetry (DSC). Some agents were found to have no solid state interaction whereas others showed major changes in the thermograms signifying possible interactions in the solid state. The results show that DSC can be employed in preliminary preformulation studies for the evaluation of solid state interactions as an aid to excipient selection.

Key Words: Solid state interactions, DSC, Preformulation, Excipient compatability.

INTRODUCTION

Researchers have used thermal methods of analyses such as differential scanning calorimetry (DSC) and differential thermal analysis (DTA) for studying interactions between drugs and excipients in the solid state (1-5). In

Author to whom all correspondence should be addressed

preformulation studies, it is possible to derive information about potential physical or chemical incompatabilities between the active ingredient and the so called "inert" excipients. Additional information regarding the effects of storage at elevated temperatures can also be obtained. These reactions may or may not lead to inactivation of the active ingredient in the formulation. In general, DSC can distinguish between those excipients that are unlikely to cause problems and those that may cause problems in the formulation. This allows a more rational approach to be established in early formulation designs . However, to substantiate DSC findings other more direct and conclusive techniques have to be used in conjunction. The following report describes a study aimed at determining the potential incompatabilities of Indomethacin (IMC) with various pharmaceutical excipients.

MATERIALS AND METHODS

The following agents were included in the study (abbreviations, if any, and the sources are included in paranthesis):
Hydroxypropylmethylcellulose (Methocel®, K4M Premium grade, Dow Chemical Co., Midland, MI, USA); Anhydrous Lactose (D.M.V., Vehgel, Holland); Corn Starch (Staley, Decatur, IL, USA); Carbomer®-934P (Goodrich, Cleveland, OH); Sucrose (Special fine grade, Redpath, Toronto, ON, Canada); Magnesium stearate (Mallinckrodt Specialty Chemicals, Paris, KY, USA); Opadry® Enteric Yellow (Colorcon, Westpoint, PA, USA); Microcrystalline cellulose (Avicel® PH101, FMC Corp., Newark, DE, USA); Dicalcium phosphate dihydrate (DCP(dihyd), Monsanto, St.Louis, MO, USA); Dicalcium phosphate anhydrous (DCP (anhyd), Emcompress®, from Mendell, New York, NY, USA); Polyethy-leneglycol 8000 (PEG 8000, Carbowax® from Union Carbide, Danbury, CT, USA); Stearic acid (Triple pressed, BDH, Toronto, ON, Canada); Indomethacin USP (IMC, I.C.F.I., Italy); *p*-Chlorobenzoic acid (CBA, Aldrich Chemicals, Milwaukee, WI, USA).
The following experimental protocol was used for the stability studies:

Sample Preparation: Equal weights of IMC and each excipient were individually weighed into amber glass vials to give composite weights of 5 grams. The mixture was mixed well by tumble mixing and shaking and the vials were sealed. Four samples were prepared for each excipient. Two samples each were stored at 27°C (reference) and 50°C for 30 days protected from light. One sample of each pair was removed at the end of this period and the remaining samples were left on reference test.

Differential Scanning Calorimetry: About 3.0 to 4.0 mg of the drug-excipient mixture or 1.5 to 2.0 mg of pure drug or pure excipient samples were weighed into aluminum DSC pans and hermetically sealed capsules were prepared with

TABLE I. Summary of IMC Peak Positions and Heats of Transitions from Pure Samples and Physical Mixtures with Various Excipients.

	Storage conditions			
1:1 mix of IMC and excipient	30 days at 27°C		30 days at 50°C	
	T_m(°C)	ΔH_{corr}(J/g)	T_m(°C)	ΔH_{corr}(J/g)
Pure IMC	160.49	112.2	161.01	115.7
Methocel-K4M	157.78	98.6	158.80	102.1
Lactose(anhyd)	159.88	103.1	160.25	103.4
Corn Starch	156.19	111.4	157.23	112.1
Carbomer-934P	159.94	107.1	160.70	108.1
Sucrose	160.09	90.9	160.43	102.3
Mag.Stearate	NoPeak	-----	NoPeak	-----
Opadry Yellow	149.48	90.9	150.35	93.6
Avicel (PH101)	157.33	102.8	157.89	105.3
DCP (dihyd)	135.25	112.6	136.12	115.0
Carbowax 8000	NoPeak	-----	NoPeak	-----
DCP (anhyd)	158.96	101.4	159.56	109.7
Stearic acid	144.27	66.20	145.26	46.3

$\Delta H_{corr} = (\Delta H_{obs}/\%\text{IMC in sample}) * 100$

aluminum lids. A Dupont Differential Scanning Calorimeter (Model 910) with a thermal analyzer and a data acquisition unit (Series 9900) was used. The instrument was calibrated using Indium and all experiments were run at a heating rate of 10°C per min and a sensitivity setting of 1x. An initial ramp was used to jump the temperature to 25°C and then a constant heating rate of 10°C was used up to 300°C under nitrogen atmosphere. The area under the curve was measured by integrating the peaks and the heat of transition was automatically calculated by the analyzer.

RESULTS AND DISCUSSION

The heats of fusion and peak transition temperature of the IMC peak (T_m) in various samples are summarized in Table I. The thermogram of pure IMC (Fig. Ia) showed a sharp endothermic transition at 160.49°C and the heat of transition was 112.2 J/g. The onset of transition was at 158.93°C. Several polymorphic

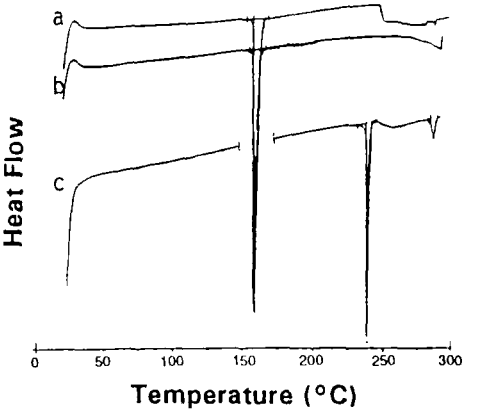

FIGURE I. DSC thermograms of pure Indomethacin stored for 30 days at 27°C (a), 50°C (b), and pure *p*-chlorobenzoic acid (c).

forms of IMC along with their melting points have been reported (6). The observed peak temperature corresponds to the melting point of Form I (Type γ). Storage of IMC at 50°C for 30 days did not have any detrimental effect on its stability as shown in Fig. Ib. The main endotherm remained at 161.01°C and the heat of transition of 115.7 J/g was almost identical to the value obtained for the reference sample (112.2 J/g). No degradation products could be detected, the principle expected one is *p*-chlorobenzoic acid (CBA).

The thermogram of CBA (Fig. Ic) showed a sharp endothermic transition beginning at 239°C and reaching a peak at 240°C corresponding to its melting point of 243°C (Merck Index, 9th ed., p. 2099). The heat of transition was relatively high, 185.8 J/g. Previous experiments showed that the detection limit of CBA by this technique was 0.05 mg.

Avicel®, Carbomer®, DCP (anhydrous) and Methocel® did not show any characteristic transitions as shown in Fig. II A, II B, II C and II E respectively. Lactose (anhydrous), Opadry®, Starch, and Sucrose by themselves showed some major and minor transitions as shown in Fig. II D, II F, II G, and II H respectively. However, these peaks were not in the region where IMC transition occurred. The 1:1 physical mixtures of these excipients with IMC showed the characteristic IMC peak. The samples stored at 50°C also behaved similarly. The heats of fusion in all cases were close to the expected values. None of the samples showed any major additional or new peaks. The minor peak variations seen in the case of starch are perhaps due to differences in the moisture contents of samples as reported by Biliaderis (7). Hence these excipients can be considered compatable with IMC. There have been previous reports of incompatabilities of

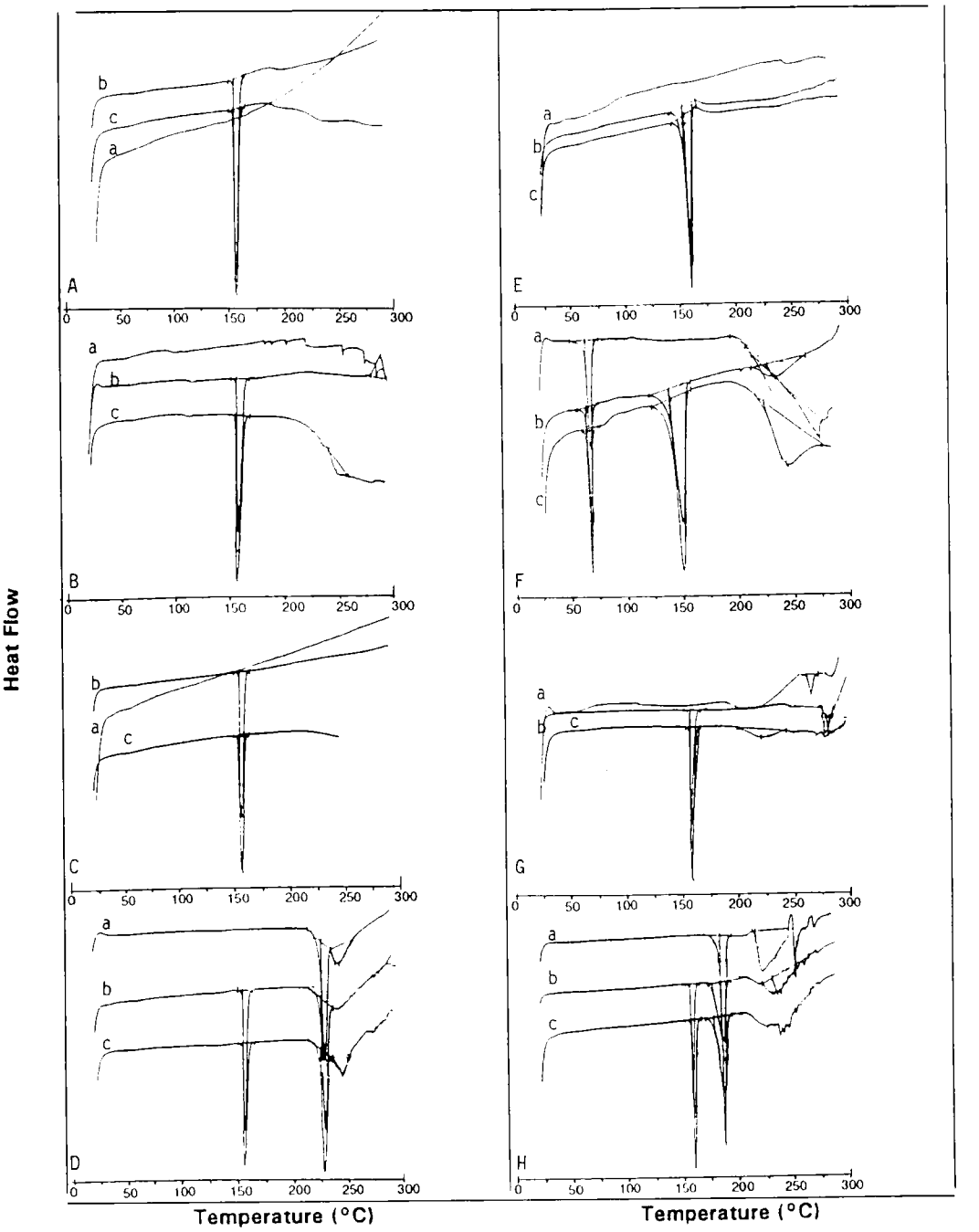

FIGURE II. DSC thermograms of pure excipients (a), and 1:1 physical mixtures of Indomethacin with various excipients stored for 30 days at 27°C (b), or 50°C (c). Section A:Avicel®; B:Carbomer®; C:Dicalcium phosphate (anhydrous); D:Lactose (anhydrous); E:Methocel®; F:Opadry®; G:Starch; and H:Sucrose. Endotherms are pointing downwards and exotherms upwards.

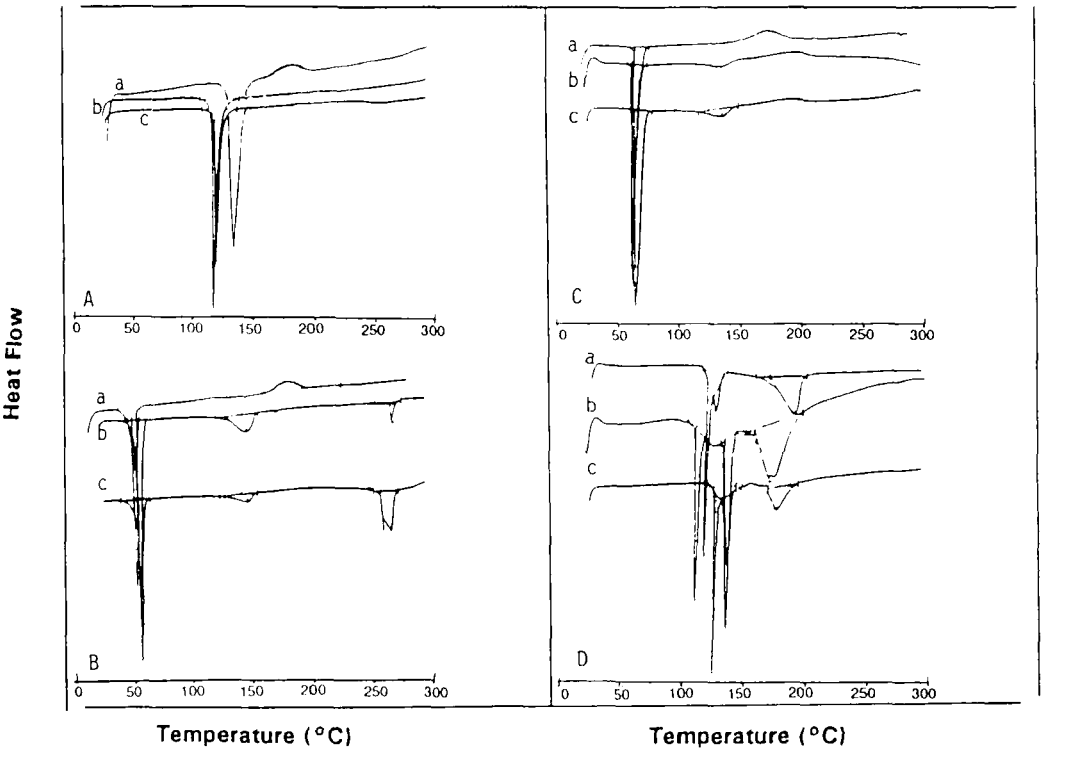

FIGURE III. DSC thermograms of pure excipients (a), and 1:1 physical mixtures of Indomethacin with various excipients stored for 30 days at 27°C (b), or 50°C (c). Section A:Magnesium stearate; B:Stearic acid; C:PEG 8000; and D:Dicalcium phosphate (dihydrate).

lactose with other drug candidates particularly the ones having a primary or secondary amine functionality (8). This is not applicable to IMC since it has a tertiary amine group. Lactose has also been shown to interact with ketoprofen (9).

As shown in Fig. III Aa, magnesium stearate by itself showed a major endothermic transition at 128.03°C (149.9 J/g) and a broad exothermic transition at 182.63°C (52.76 J/g). A similar exotherm was seen in stearic acid (Fig. III Ba) suggesting that this could be the degradation of the fatty acid moeity. A 1:1 physical mixture of magnesium stearate and IMC stored at reference temperature showed an endothermic peak at 116.83°C (Fig. III Ab) which is neither characteristic of IMC nor of magnesium stearate. The heat of fusion was 109.9 J/g. The sample stored at 50°C behaved almost identically (Fig. III Ac), with only one endothermic transition at 118.89°C (112.7 J/g). This temperature does not match with the melting points of any of the reported polymorphic forms of

IMC (6). This suggests that a new product, perhaps a eutectic compound has been formed between the two ingredients *in-situ*. It is also possible that as the magnesium stearate melts with the applied heat, the IMC present in the sample dissolves, hence not showing any endotherm corresponding to its melt. This solubility of IMC in liquid magnesium stearate has to be confirmed by other experiments. The results strongly suggest that IMC could have potential interaction with magnesium stearate. These findings are supported by other workers (9,10).

As seen in Fig. III Ba, stearic acid by itself showed a major endothermic transition at 55°C corresponding to its melting point (176.7 J/g) and a broad exothermic transition at 182°C (36.08 J/g) perhaps signifying degradation. A 1:1 physical mixture of stearic acid and IMC stored at reference temperature showed an endothermic peak at 57°C (Fig. III Bb) which is characteristic of stearic acid. The heat of fusion was close to the expected value. A broad endothermic transition occured at 144°C, perhaps corresponding to the melting endotherm of IMC. The heat of transition was lower than the expected value. This shows that the cooperativity in IMC transition has been lost (leading to lower degree of crystallinity) in the presence of stearic acid. In addition a very sharp, but small, endothermic transition appeared at 265.33°C which could not be identified with the available information. Similar behaviour was seen with the sample stored at 50°C which showed an endothermic transition at 55°C that can be attributed to stearic acid. However, the accompanying enthalpy, much higher than the expected value, can not be readily explained. There was only a broad peak at 145°C attributable to IMC. The results strongly suggest that IMC could have potential incompatability with stearic acid. Similar results have been reported by others (11).

PEG 8000 by itself showed a major endothermic transition at 59.38°C (187.1 J/g, Fig. III Ca). An exothermic transition at 170.86°C (27.72 J/g) was also observed. A 1:1 physical mixture of PEG 8000 and IMC stored at reference temperature showed an endothermic peak at 59.53°C, characteristic of PEG 8000 with an accompanying heat of fusion very close to the expected value. The exothermic transition shown by PEG 8000 alone was abolished. Some very broad transitions in the 125-135°C range were seen, but, could not be accurately integrated. No peak characteristic of IMC was detected. This shows that IMC has a high degree of solubility in molten PEG 8000. The sample stored at 50°C behaved similarly, with an endothermic transition at 63.57°C which is 4°C higher than the characteristic peak of PEG 8000, but with the expected heat of fusion value. It also showed a broad transition at 132.13°C (of a very low heat of fusion) perhaps representing the transition of IMC. The exothermic transition shown by pure PEG 8000 was abolished. The results demonstrate that IMC has a high degree of solubility in liquid PEG 8000 and therefore can be expected to show strong interactions in the solid state as well.

DCP(dihyd) by itself had several major transitions occuring at 113.06°C, 123.50°C and 169.38°C. The heats accompanying these transitions were 71.47 J/g, 30.20 J/g and 223.70 J/g respectively. Characterization of DCP(dihyd) alone after storage at 50°C showed all the three transitions with some changes in the peak positions (116.82°C, 124.83°C and 188.98°C with accompanying heats of transition of 15.22 J/g, 70.44 J/g and 144.8 J/g respectively). This is shown in Fig. III Da. A 1:1 physical mixture of DCP(dihyd) and IMC stored at reference temperature showed the characteristic IMC peak, but, shifted to a lower temperature of 135.25°C that perhaps, can be attributed to Form IV IMC (6). The heat of transition was the expected value. Only two of the three DCP(dihyd) peaks appeared at 109.32°C and 168.77°C. The other peak was suppressed by the presence of IMC. These results suggest possible interactions between DCP(dihyd) and IMC. The sample stored at 50°C behaved differently, with the peak IMC transition at 136.12°C, a downward shift as compared to pure IMC as seen above. Again, only two transitions could be attributed to DCP(dihyd), at 124.77°C and 175.80°C. As a result of some overlapping, suppression and obscured peaks, it is difficult to draw any conclusions from these results. Although no new peak has been generated, because of the changes in peak positions and heats a strong interaction between DCP(dihyd) and IMC is possible. A similar incompatability has been reported before with this agent (12).

CONCLUSIONS

In summary, DSC can be used as a quick screening tool for preformulation studies to study the potential incompatabilities of ingredients in the solid state. Several excipients were found to be potentially incompatible with IMC and the extent of interaction varied from just a shift in the IMC melting endotherm to total abolition of the peak. Some other excipients were found to be very suitable for IMC.

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