

## **CONTROL OF THE NON-CRYSTALLINITY OF MIOKAMYCIN (9,3"-DIACETYLMIDECAMYCIN) BY DIFFERENTIAL THERMAL ANALYSIS**

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A mixture of 9,3"-diacetylmidecamycin with 9.1% (by weight) ethylcellulose is used for its antibiotic properties, but it is only active in a non-crystalline state, which is a glassy one: DTA shows  $T_g$  at  $99 < T < 106$ .

DTA has been used to develop a quantitative method of non-crystallinity control based upon a linear relation between the crystallinity percentage and the computed algebraic sum of the enthalpies of recrystallization and fusion.

It is shown that for binary mixtures with liquidus-type melting curves this procedure is to be preferred to the measurement of recrystallization enthalpy vs. crystallinity percentage.

Miokamycin or 9,3"-diacetylmidecamycin (MOM),  $C_{45}H_{71}NO_{17}$  (MW = 897.07), is an antibiotic of the macrolide series, which has a much higher bioavailability in the non-crystalline state than in the crystalline state [1]. In consequence, use of the antibiotic in human therapeutics necessitates methods of control of non-crystallinity which are not only qualitative, but above all quantitative.

The authors who have described the physico-chemical properties of MOM recommend control by radiocrystallographic analysis based on the absence of X-ray diffraction patterns [1].

This paper puts forward a qualitative control based on the observation of a glass transition ( $T_g$ ), that has not hitherto been reported, and on the behaviour of the raw material when subjected to differential thermal analysis (DTA). A quantitative method of evaluation of the degree of non-crystallinity is also described and is linked to the thermal effects of the fusion and recrystallization which occurs before melting.

A control based on the absence of a signal (radiocrystallography) could be complemented by or even replaced by a control that positively demonstrates non-crystallinity.

## I. Technical section

Samples of between 5 and 15 mg were weighed to  $\pm 0.02$  mg. Thermal analyses were effected using the FP85 heating cell of the computer-aided METTLER FP800 analyser. The enthalpies of the thermal effects can thus be determined by summing the heat fluxes recorded.

The non-crystalline commercial product used (MOM : EC, NC) contains 9.1% (by weight) of ethylcellulose. The latter compound is added to enhance maintenance of the non-crystalline state [1]. The crystalline reference (MOM : EC) used contained the same percentage of ethylcellulose.

## II. Preliminary thermal analyses

Curves A, B and C (Fig. 1) show the records obtained by heating MOM : EC, NC at different rates ( $v = 5, 10$  or  $20 \text{ deg} \cdot \text{min}^{-1}$ ). In all three cases a first signal, "a", that has not previously been reported [1], was observed. The signal resembles that which is conventionally [2, 3] observed during the glass transition. Two effects

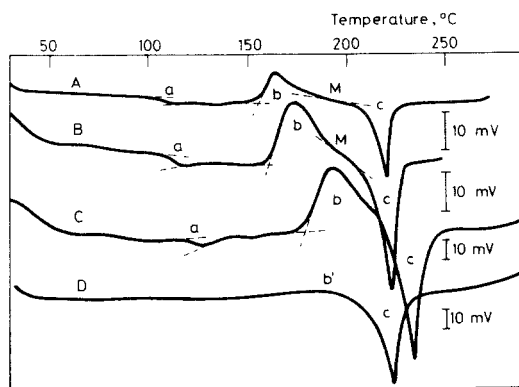


Fig. 1 DTA curves of non-crystalline (A, B, C) and crystalline (D) MOM : EC. A:  $v = 5 \text{ deg} \cdot \text{min}^{-1}$ ,  $m = 5.00 \text{ mg}$ , B:  $v = 10 \text{ deg} \cdot \text{min}^{-1}$ ,  $m = 5.90 \text{ mg}$ , C:  $v = 20 \text{ deg} \cdot \text{min}^{-1}$ ,  $m = 7.01 \text{ mg}$ , D:  $v = 10 \text{ deg} \cdot \text{min}^{-1}$ ,  $m = 8.90 \text{ mg}$ . The endothermic direction is shown in accordance with the recommendations of I.C.T.A. [7], from top to bottom

which have already been described [1] are then observed: exotherm "b", corresponding to recrystallization of the metastable liquid forming after  $T_g$ , and endotherm "c", reflecting melting of the crystalline solid. Curve D (Fig. 1) corresponds to the crystalline reference MOM:EC. A glass transition was not observed, only melting being recorded.

These results are identical to those obtained using a DuPont 990 thermal analyser.

The presence of ethylcellulose results in the endotherm "c" of curve D being more closely related to a liquidus-type peak than to a pure-compound melting peak [1]. It should also be noted that the general shape of curve D does not allow clear determination of a base-line. Peak "c" seems to be preceded by an exotherm "b" of low intensity, which is found in a constant manner in all tests run between approximately 120 and 190°. Moreover, peak "c" is followed by the beginning of the exothermic chemical decomposition around 240°, in other words, shortly after the end-melting.

The above is all reflected in the non-crystalline sample DTA curves rendering both the choice of temperature at the end-recrystallization and that at the beginning-melting not precise. While the DTA curve for pure non-crystalline MOM [1] shows a clear horizontal plateau between the recrystallization exotherm and the melting endotherm, for MOM:EC, NC only a point of inflexion, is observed. The position of this point varies with the rate of heating.

Figure 2 shows the temperature variation from the beginning ( $T_1$ ) and the end ( $T_2$ ) of the glass transition and from the beginning ( $T_3$ ) of recrystallization and from the summit ( $T_4$ ) corresponding to the end of melting. By extrapolation to 0

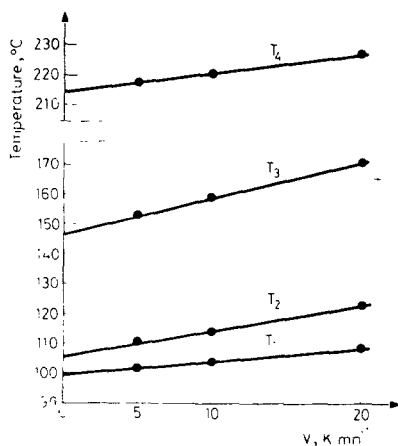


Fig. 2 Extrapolation of temperatures of different thermal effects at 0 heating rate.  $T_1$  = beginning  $T_g$  (effect a),  $T_2$  = end  $T_g$ ,  $T_3$  = beginning recrystallization exotherm (effect b),  $T_4$  = summit of the peak of fusion (effect c)

heating rate, the values are as follows:  $T_1 = 99.5^\circ$ ,  $T_2 = 105.5^\circ$ ,  $T_3 = 147^\circ$ , and  $T_4 = 214.5^\circ$ .

The fact that MOM:EC, NC presents a  $T_g$  under DTA requires its connection to the vitreous state. In other words, MOM:EC, NC is able to change towards the crystalline state by itself during time. This fact is considered an additional justification for the control of non-crystallinity by DTA. When the sample quenched after melting is immediately subjected to DTA, no thermal signal is observed between room temperature and the beginning of exothermic chemical decomposition.

However, it seems unlikely that in a time compatible with the therapeutic use of the product, recrystallization of MOM:EC, NC could take place at room temperature. In fact, we presume, in accordance with Mazières [3], that in media for which  $T_g(\text{K}) > 2/3 T_f(\text{K})$ , if recrystallization is unlikely in the absence of artificial seeding, then for MOM:EC, NC  $T_g/T_f = 371 \text{ K}/487 \text{ K} = 0.76$ , in other words, a value comparable to that for silica glass (0.75). However, given possible prolonged contact with an excipient or an aqueous solution in the course of therapeutic use, a quantitative evaluation of any crystallinity that appears in a non-crystalline sample was developed.

### III. Preliminary quantitative tests

#### A. Enthalpy of fusion of crystalline MOM:EC

According to [1], the enthalpy of fusion  $\Delta H_c$  of pure MOM is  $15.3 \pm 0.5 \text{ kcal} \cdot \text{mol}^{-1}$  ( $64 \text{ kJ} \cdot \text{mol}^{-1}$ ). For non-crystalline MOM an enthalpy of recrystallization  $\Delta H_b = -13.9 \text{ kcal} \cdot \text{mol}^{-1}$  ( $-58 \text{ kJ} \cdot \text{mol}^{-1}$ ) and an enthalpy of fusion  $\Delta H_c = 14.0 \text{ kcal} \cdot \text{mol}^{-1}$  ( $58.5 \text{ kJ} \cdot \text{mol}^{-1}$ ) are given. For MOM:EC, NC the

**Table 1** Enthalpy of fusion  $\Delta H_c$ : values obtained with a crystalline sample of MOM:EC between different summing limits (heating rate =  $10 \text{ deg} \cdot \text{min}^{-1}$ ). Sample decomposition beginning between  $240$  and  $250^\circ$  gives higher results for the summing effected between  $180$  and  $250^\circ$

Heating rate, $10 \text{ deg} \cdot \text{min}^{-1}$	Weight (in MOM) of samples tested, mg						mean $\Delta H_c$	$\sigma$
	8.82	12.99	7.81	6.75	7.24	9.02		
Summing limits, $^\circ\text{C}$	Enthalpy of fusion, $\text{kJ} \cdot \text{mol}^{-1}$							
170–240	65.30	58.22	61.08	60.38	60.25	58.08	60.55	2.63
180–240		60.38	62.28	62.20	63.45	59.44	61.55	1.61
180–250	68.58	69.70	66.48	66.86	68.73		68.07	1.35

authors reported  $\Delta H_c = -\Delta H_b = 8.7 \text{ kcal} \cdot \text{mol}^{-1}$  ( $36.4 \text{ kJ} \cdot \text{mol}^{-1}$ ). Given the difference between the values measured for MOM, NC and MOM:EC, NC, we first proceeded to verify the results.

The main difficulty encountered consisted in the choice of limit temperatures for summing the heat fluxes corresponding to endotherm "c" in curve D (Fig. 1). Tables 1 and 2 list the data obtained with two heating rates and different summing intervals. It will first be observed that the mean  $\Delta H_c$  values obtained with  $v = 10 \text{ deg} \cdot \text{min}^{-1}$  between 170 (or 180) and  $240^\circ$  are practically identical to those obtained with  $v = 5 \text{ deg} \cdot \text{min}^{-1}$  between 160 (or 170) and  $230^\circ$ . The  $\Delta H_c$  values thus obtained are in line with the values previously found [1] for pure crystalline MOM ( $64 \text{ kJ} \cdot \text{mol}^{-1}$ ) and recrystallized MOM ( $58.5 \text{ kJ} \cdot \text{mol}^{-1}$ ).

In both series of tests it will also be noted that the beginning chemical decomposition strongly influences the results, but the values given in Table 2 show that the same applies for effect "b", which seems to precede peak "c".

### B. Enthalpies of recrystallization and fusion of MOM:EC, NC

According to [5], Burros [4] mentions the use of differential scanning calorimetry (DSC) in the determination of the degree of crystallinity of semi-crystalline

**Table 2** Enthalpy of fusion  $\Delta H_c$ : values obtained with a crystalline sample of MOM:EC between different summing limits ( $v = 5 \text{ deg} \cdot \text{min}^{-1}$ ). This Table shows that lowering the summing limits by  $10^\circ$  gives the same results as using  $v = 10 \text{ deg} \cdot \text{min}^{-1}$ . In each measurement series (*a*, *b*, or *c*), the results increase with the upper summing limit. This is linked to the exothermic decomposition of the sample

Heating rate $5 \text{ deg} \cdot \text{min}^{-1}$	Weight (in MOM) of samples tested, mg				mean $\Delta H_c$	$\sigma$
	6.22	7.09	7.34	5.47		
Summing limits, $^\circ\text{C}$	Enthalpy of fusion, $\text{kJ} \cdot \text{mol}^{-1}$					
160–230 <i>a</i>	60.21	59.40	62.26	55.75	59.40	2.72
170–230 <i>b</i>	62.64	63.25	66.51	60.09	63.12	3.00
180–230 <i>c</i>	70.61	66.89	69.65	66.11	68.31	2.16
160–235 <i>a</i>	65.89	63.08	66.71	60.88	64.14	2.67
170–235 <i>b</i>	69.53	67.06	70.75	64.24	67.89	2.88
180–235 <i>c</i>	74.52	70.54	72.33	69.37	71.69	2.24
160–240 <i>a</i>	67.94	68.02	67.99	63.55	66.87	2.22
170–240 <i>b</i>	72.98	70.63	72.92	67.00	70.88	2.81
180–240 <i>c</i>	77.48	72.73	73.71	72.63	74.14	2.28
180–250 <i>c</i>	83.00	83.61	76.77	78.15	80.38	3.43

polymers. He illustrates this application with a curve that is fully comparable with curves A, B and C of Fig. 1, and reports that the recrystallization exotherm area is proportional to the non-crystalline fraction and equal to that of the fusion endotherm when the sample is not crystalline.

These indications, verified with pure non-crystalline MOM [1], were initially used with regard to the MOM:EC, NC sample.

It was decided not to use results obtained with  $\nu = 20 \text{ deg} \cdot \text{min}^{-1}$ . Curve C (Fig. 1) shows that the separation of M from the exo- and endothermic effects "b" and "c" is not appreciable at that rate of heating. The results reported in Table 3 indicate the values of  $\Delta H_b$  and  $\Delta H_c$  determined by varying the limits of summing, the temperature at point M being read on curves comparable to curve A (Fig. 1). Given the approximate character of point M localization, summing was effected with  $T_M$  lying between  $193$  and  $195^\circ$ , when  $\nu = 5 \text{ deg} \cdot \text{min}^{-1}$ , and between  $201$  and  $206^\circ$ , when  $\nu = 10 \text{ deg} \cdot \text{min}^{-1}$ .

*Enthalpy of recrystallization  $\Delta H_b$ .* Whatever the summing limits at the heating rates used, results were obtained with extreme values of  $-33$  and  $-48 \text{ kJ} \cdot \text{mol}^{-1}$  (i.e. a dispersion of  $15 \text{ kJ} \cdot \text{mol}^{-1}$ ) around a mean value of  $-41 \text{ kJ} \cdot \text{mol}^{-1}$ . This result seems to be in agreement with that already given [1].

*Enthalpy of fusion  $\Delta H_c$ .* The same does not apply for  $\Delta H_c$ . While the mean value,  $+48 \text{ kJ} \cdot \text{mol}^{-1}$ , is very close to that found for  $-\Delta H_b$ , the results obtained lie between  $+37$  and  $+60 \text{ kJ} \cdot \text{mol}^{-1}$  (i.e. a dispersion of  $23 \text{ kJ} \cdot \text{mol}^{-1}$ ), without the value distribution being gaussian, which is the case for  $\Delta H_b$ .

These results only provide a very rough confirmation of those already cited [1]. The differences between the enthalpies  $\Delta H_c$  measured with MOM:EC and with MOM:EC, NC seem to be an artefact linked to the choice of the summing limits. In the first case, summing could be started at  $170$  or  $180^\circ$ . This is not possible in the second case, since MOM:EC, NC recrystallizes at these temperatures. The dispersion of the  $\Delta H_c$  values measured with a non-crystalline sample seems much higher than would be expected considering the accuracy of the apparatus ( $\pm 10\%$ ). In all probability, this dispersion is also linked to the choice of the summing limits, but also perhaps to the fact that the recrystallization exotherm is superimposed on an endotherm of liquidus type. A further reason might be variations in specific heat accompanying the changes of state.

### C. Exothermic effect "b" preceding the fusion of crystalline MOM:EC

It has already been indicated that a low-intensity exotherm "b" seems to precede endotherm "c" in the DTA curve for MOM:EC (curve D, Fig. 1). In order to enhance the demonstration of "b" and measure the corresponding enthalpy, the following procedure was used, as illustrated in Fig. 3A. Figure 3A shows

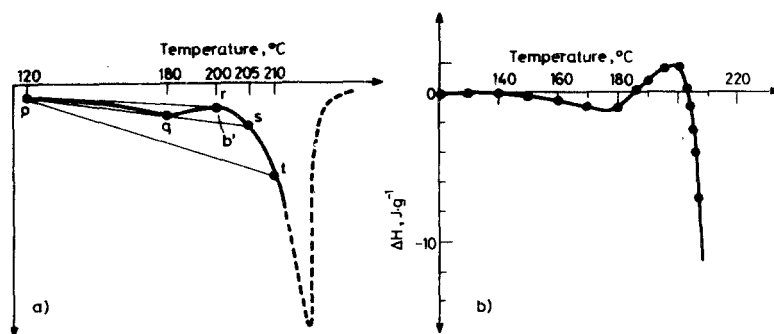
**Table 3** Enthalpy of recrystallization ( $-\Delta H_b$ ) and enthalpy of fusion  $\Delta H_c$ : values obtained with a non-crystalline sample of MOM: EC, NC for heating rates  $\nu = 5$  and  $10 \text{ deg} \cdot \text{min}^{-1}$ , with different summing intervals.  $T_0$  = initial temperature,  $T_1$  = final temperature,  $T_M$  = temperature at point of inflexion  $M$  between exotherm  $b$  and endotherm  $c$

Heating rate:  $5 \text{ deg} \cdot \text{min}^{-1}$

Weight MOM in MOM:EC samples	Interval $T^\circ\text{C}$ $T_0 \leftrightarrow T_1 = T_M$	$-\Delta H_b$ , $\text{kJ} \cdot \text{mol}^{-1}$	Interval $T^\circ\text{C}$ $T_0 \leftrightarrow T_1 = T_M$	$\Delta H_c$ , $\text{kJ} \cdot \text{mol}^{-1}$
3.64 mg	135-193	38.08	193-235	40.81
	135-194	39.04	194-235	40.42
	135-195	40.02	195-235	39.38
	140-195	42.41	195-240	41.16
4.47 mg			193-230	38.59
			194-230	37.98
			195-230	37.95
			193-235	54.38
			194-235	54.06
			195-235	53.66
			195-240	55.79
			193-230	50.79
			194-230	50.61
			195-230	50.55
5.94 mg	135-193	36.67	193-235	57.60
	135-194	38.16	194-235	57.06
	135-195	39.76	195-235	56.44
	140-195	41.64	195-240	60.32
			193-230	54.49
			194-230	52.62
			195-230	53.45

Heating rate:  $10 \text{ deg} \cdot \text{min}^{-1}$

4.09 mg	160-206	42.59	206-240	36.82
	150-206	44.26		
5.91 mg	160-206	45.39	206-240	49.90
5.78 mg	150-201	40.04	201-240	48.25
	150-202	41.94	202-240	46.97
	150-204	45.00	204-240	45.98
	150-206	48.02	206-240	44.06
	160-201	40.06		
	160-202	41.74		
	160-204	44.21		
	160-206	46.59		
4.50 mg	150-201	33.39	201-240	43.52
	150-202	35.12	202-240	42.72
	150-204	37.69	204-240	41.84
	150-206	40.37	206-240	39.93
	160-201	33.63		
	160-206	39.15		



**Fig. 3 A:** Determination of enthalpy corresponding to exotherm "b". Schematic representation of endotherm of fusion of MOM:EC: exotherm "b" is exaggerated. Point *p*, *q*, *r* and *t* define four types of surface, the areas of which are delimited by the segments connecting the points on the curve corresponding to the extreme temperatures selected

**Fig. 3 B:** Determination of enthalpy corresponding to exotherm "b". The apparent enthalpy is a function of the upper limit of summing (constant lower limit  $T_p = 120^\circ$ ). For  $T_s = 205^\circ$ , points *p*, *q* and *s* are in a straight line: summing between 120 and 205° yields  $\Delta H_b$ .

schematically the 4 possible types of areas delimitable on the DTA curve by summing, when the lower limit is constant ( $120^\circ$ ).

First case: summing from  $120^\circ$  and  $T \leq 180^\circ$

This case corresponds to the interval in which the endothermic departure from the base line remains small for the DTA curves showing a liquidus peak. The measured enthalpy is 0 or slightly negative.

Second case: summing from  $120^\circ$  to  $180 < T \text{ }^\circ\text{C} \leq 200^\circ$ .

The presence of exotherm "b" results in the measured enthalpy becoming positive.

Third case: summing between  $120^\circ$  and  $T = 205^\circ$ .

The point corresponding to  $T = 205^\circ$  in the DTA curve is situated on the straight line joining the points  $T = 120^\circ$  and  $T = 180^\circ$ . The enthalpy is then  $-2.5 \text{ J}\cdot\text{g}^{-1}$ . The latter value may be attributed to "b".

Fourth case: summing between  $120^\circ$  and  $T > 205^\circ$ .

The upper limit being situated on the first slope of endotherm "c", the values obtained are all more negative, as the upper summing limit becomes closer to the summit of peak "c".

Figure 3B shows graphically the results of this procedure, allowing "amplification" of curve D in Fig. 1. It also permits the conclusion of the unambiguous existence of exotherm "b". The presence of this exotherm must be explained.



#### D. Thermal study of ethylcellulose

As noted, ethylcellulose is an ingredient of the commercial sample, present at 9.1% by weight. The DTA curve in Fig. 4 is that of a sample of Hercules ethylcellulose, grade N50. An exothermic effect "d" is observed between 120 and 190°, corresponding to the enthalpy  $\Delta H_d = -25 \text{ J} \cdot \text{g}^{-1}$ . This effect occurs in the same temperature interval as exotherm "b'" and it is observed that  $\Delta H_{b'}$  and  $\Delta H_d$  have a ratio similar to that of ethylcellulose in MOM : EC, NC. Thus, "b'" may be linked to the presence of ethylcellulose in the commercial sample.

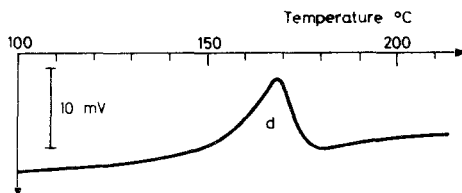


Fig. 4 DTA curve of Hercules ethylcellulose grade N 50.  $\nu = 10 \text{ deg} \cdot \text{min}^{-1}$ ,  $m = 4.11 \pm 0.02 \text{ mg}$

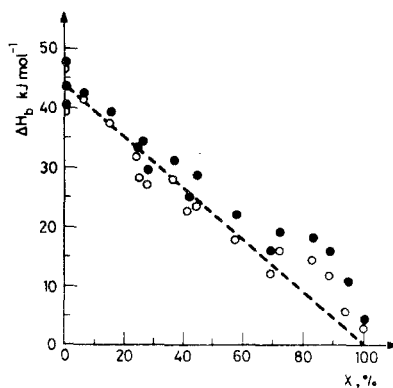


Fig. 5 Recrystallization enthalpy ( $\Delta H_b$ ) vs percentage crystallinity  $X\%$ . Summing limits: ● 150 to 206° ; ○ 160 to 206°

#### E. Testing the correlation between enthalpy of recrystallization and degree of crystallinity

Samples forming a "standardization range" were prepared by trituration of appropriate proportions of MOM : EC and MOM : EC, NC. Each sample was subjected to DTA with  $\nu = 10 \text{ deg} \cdot \text{min}^{-1}$ . Summing limits were fixed at 150 to 206° and 160 to 206°, whatever the degree of crystallinity. The results are given in Fig. 5. The relationship between  $\Delta H_b$  and the degree of crystallinity,  $X\%$ , is

reasonably linear when the latter lies between 0 and 60%. Conversely, when the crystallinity varies from 60 to 100%, the enthalpy obtained is significantly different from the ideal, as represented by the dotted straight line. In other words, the experimentation shows that the method put forward [4, 5] can only be applied very imperfectly to the case under consideration. For this reason, a different approach to the measurement of the degree of crystallinity was investigated.

#### IV. Description and development of the non-crystallinity control method

##### A. Principle

It was believed that the algebraic sum  $\Delta H_s$  of the enthalpies of recrystallization ( $\Delta H_b$ ) and fusion ( $\Delta H_c$ ) had to be 0 or minimal when the sample was entirely non-crystalline.

After verification of this supposition with a number of preliminary tests, the following hypothesis was advanced: the relationship between  $\Delta H_s$  and the degree of crystallinity,  $X\%$ , had to be linear between  $X\% = 0$  and  $X\% = 100$ , or there had to be a summing interval for which linearity was verifiable.

##### B. Method

The method being envisaged as a quality control technique, the rate  $v = 5 \text{ deg} \cdot \text{min}^{-1}$ , was not chosen, since it was too slow. All tests were therefore effected at  $v = 10 \text{ deg} \cdot \text{min}^{-1}$ . Measurements were performed by single-stage summing, using a computer. A straight line was drawn between the points of the memorized DTA curve corresponding to the two extreme temperatures (beginning-recrystallization and end-melting) chosen for the duration of the experiment. Fluxes were considered positive or negative depending on which side of the straight line they fell on.

Three summing intervals were chosen: 150 to 245°, 150 to 240°, and 160 to 240°.

##### C. Results

Results are tabulated in Figs 6–8. They show that the relationship between  $\Delta H_s$  and  $X\%$  may be considered linear in the three cases. Nonetheless, with the exception of the case shown in Fig. 8, the value of  $\Delta H_s$  for  $X = 100\%$  does not seem in line with the results obtained for  $0 \leq X\% < 100$ . For this reason, each series of measurement was subjected to statistical analysis [6] in which only mean values of  $\Delta H_s$  for  $X\% = 0$  and  $X\% = 100$  were introduced. The results present  $X\%$  as a function of  $\Delta H_s$ . This choice was deliberate. In fact, when the method is applied to product control,  $\Delta H_s$  is the value from which  $X\%$  is deduced.

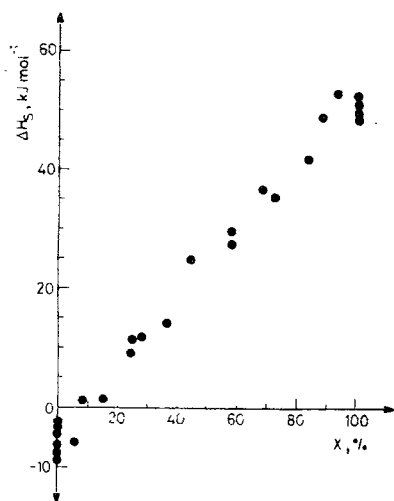


Fig. 6 Enthalpy  $\Delta H_s = \Delta H_b + \Delta H_c$  vs percentage crystallinity  $X\%$ . Summing limits: 150 to 245°

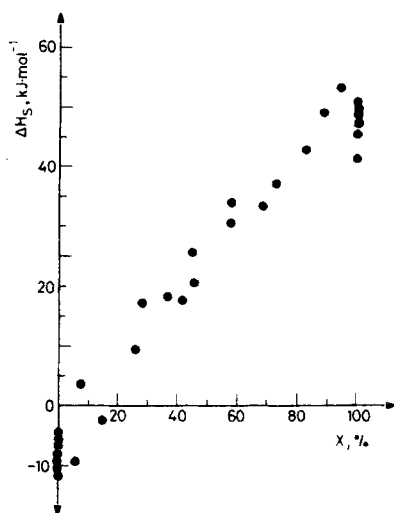


Fig. 7 Enthalpy  $\Delta H_s$  vs percentage crystallinity  $X\%$ . Summing limits: 150 to 240°

Summing between 150 and 245°

With all 17 pairs of experimentally obtained values ( $\Delta H_s$ ,  $X\%$ ) the following values were found for the relationship ( $X\% = A \cdot \Delta H_s + B$ ): coefficients  $A = 1.6625$  and  $B = 9.9409$ , with  $R = 0.991$ . The corresponding straight line is shown in Fig. 9 within an envelope determined for risk  $P = 0.05$ , together with the standard deviations  $\sigma(A) = 0.12$  and  $\sigma(B) = 3.55$ .

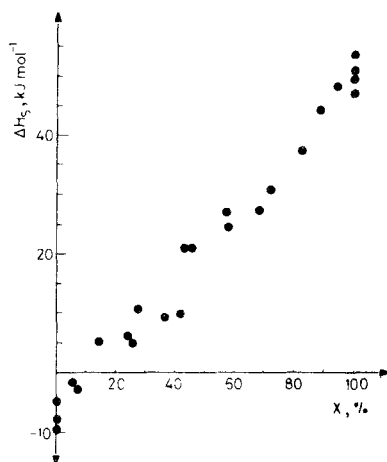


Fig. 8 Enthalpy  $\Delta H_s$  vs percentage crystallinity  $X\%$ . Summing limits: 160 to 240°

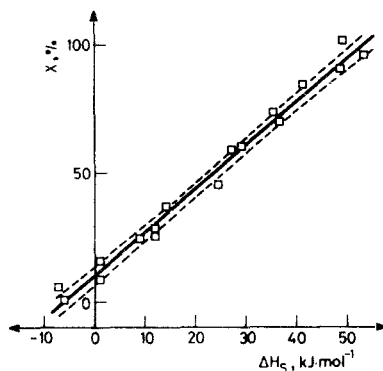
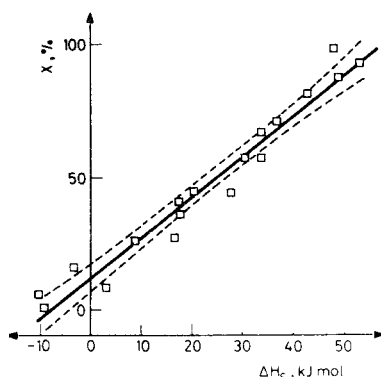


Fig. 9 Percentage crystallinity,  $X\%$ , vs enthalpy  $\Delta H_s$ . The regression straight line is shown in its envelope (dotted curves) defined by risk  $P = 0.05$  (from results in Fig. 6)

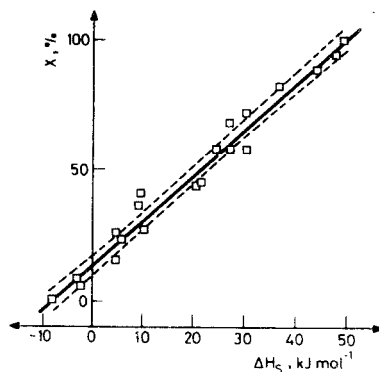
When the mean values of  $\Delta H_s$  for  $X\% = 0$  and  $X\% = 100$  are not included, the following relationship is obtained:  $X\% = 1.6375 \cdot \Delta H_s + 9.9776$ , with  $R = 0.992$ . This is hardly different from the previous result. It ought nonetheless to be verified.

Summing between 150 and 240°

Application of the same procedure to the 18 pairs of experimental values yields  $A = 1.5645$  and  $B = 11.560$ , with  $R = 0.976$ . Figure 10, showing the corresponding straight line in its envelope ( $P = 0.05$ ), reveals that the mean value  $\Delta H_s$  for



**Fig. 10** Percentage crystallinity,  $X\%$ , vs enthalpy  $\Delta H_c$ . The regression straight line is shown in its envelope (dotted curves) defined by risk  $P = 0.05$  (from results in Fig. 7)



**Fig. 11** Percentage crystallinity,  $X\%$ , vs enthalpy  $\Delta H_c$ . The regression straight line is shown in its envelope (dotted curves) defined by risk  $P = 0.05$  (from results shown in Fig. 8)

$X\% = 100$  does not differ significantly from the value given by the regression straight line ( $\sigma(A) = 0.18$  and  $\sigma(B) = 5.5$ ).

Summing between 160 and 240°

With 20 pairs of experimental values,  $A = 1.7368$  and  $B = 13.780$  were obtained with  $R = 0.984$ . Figure 11 shows the corresponding straight line in its envelope ( $P = 0.05$ ). It is to be observed that the mean value of  $\Delta H_c$  for  $X\% = 100$  is correctly situated on the regression straight line.

#### D. Discussion

These results shown that it is possible to establish a relationship between  $X\%$  and  $\Delta H_s$ , providing that a single summing interval is imposed whatever the value of  $X\%$ .

For the three intervals selected, it would seem that the best results are obtained by summing between 150 and 245°. Given the accuracy of the analyzer, as mentioned above, the three intervals studied may be considered as giving equivalent results.

It should be noted that the enthalpy,  $\Delta H_s$ , is not the true algebraic sum of the enthalpies of recrystallization and fusion, since the specific heats of the crystalline solid appearing between these two changes of the state are not taken into account. However, this does not influence the linearity of the results, since the resulting departure from the base line is constant, whatever the degree of crystallinity. Similarly, exotherm "b'", which is only recorded with MOM : EC, must exercise an influence on the DTA curves of the semi-crystalline samples. However, this influence will be constant, since it is only dependent on the ethylcellulose content, which is itself constant.

#### V. Conclusion

In order to have in vivo antibiotic properties, 'miokamycin (9,3'-diacetylmi-decamycin, MOM) must be soluble.

This purpose was achieved [1] by two means: addition of ethylcellulose to pure MOM and presentation of this mixture in a non-crystalline form, which is more soluble than the crystalline one.

This paper first shows that the non-crystalline material obtained is a glass,  $T_g$  being clearly detected by DTA between 99 and 106°. The material is therefore likely to change in time, in other words, to undergo a recrystallization which would render it inactive by solubility lowering. In the context of human therapeutic use, this risk justified the development of a method of determining the degree of crystallinity.

This paper subsequently showed that the method of measuring the area of the recrystallization peak was not applicable to a binary mixture, for two reasons: 1) the recrystallization exotherm is not clearly separated from the endotherm of fusion, 2) the latter is in fact an endotherm of the liquidus type, which in addition may explain the considerable differences between the melting enthalpy values obtained when the sample is crystalline and when the sample is not crystalline.

Lastly, it was shown that DTA could still be applied to the determination of the crystallinity of a semi-crystalline material formed by a binary mixture.

The method put forward is, of course, still based on the existence of a linear relationship between the enthalpy and the degree of crystallinity, but the enthalpy

considered,  $\Delta H_s$ , is that of a thermal balance between two opposite effects: recrystallization and then fusion, measured between their two limiting temperatures.

The statistical analysis of the results obtained with semi-crystalline samples shows that the relationship between  $\Delta H_s$  and the degree of crystallinity is linear.

Thus, in terms of its qualitative and quantitative aspects, the method put forward is more appropriate to the desired objective than radiocrystallographic analysis.

Moreover, this method should allow evaluation of the degree of crystallinity, as a function of time, for non-crystalline samples in contact with water or an excipient, and also improve the definition of the therapeutic shelf-life of a such a material.

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**Zusammenfassung** — Ein Gemisch von 9,3"-Diacetylmidecamycin mit 9,1 Gew.-% Ethylcellulose wird wegen dessen antibiotischen Eigenschaften angewandt, ist aber nur im nicht-kristallinen, glasigen Zustand aktiv. DTA ergibt für  $T_g$   $99 < T^\circ < 106$ . Die DTA wurde zur Entwicklung einer quantitativen Methode zur Kontrolle der Nicht-Kristallinität herangezogen, die auf einer linearen Beziehung zwischen dem in % ausgedrückten Kristallinitätsgrad und der berechneten algebraischen Summe der Rekristallisations- und Schmelzenthalpie beruht. Es wird gezeigt, daß bei binären Mischungen mit Schmelzkurven des Liquidustyps diesem Verfahren gegenüber der Messung der Rekristallisationsenthalpie in Abhängigkeit vom Kristallisationsgrad der Vorzug zu geben ist.

**Резюме** — Смесь 9,3"-диацетилмидекамина с 9,1 весовыми % этилцеллюлозы обладает антибиотическими свойствами только в некристаллическом состоянии и  $T_g$  которого, как показывает ДТА, наблюдается в области  $99 < T^\circ < 106^\circ$ . Метод ДТА был использован для разработки количественного метода контроля некристалличности, исходя из линейного соотношения между процентом кристалличности и вычисленной алгебраической суммой энтальпий рекристаллизации и плавления. Показано, что в случае двойных смесей с кривыми плавления типа ликвидуса, этот метод является предпочтительным по сравнению с измерением зависимости энтальпии рекристаллизации от процента кристалличности.