Bull. Pharm. Sci., Assiut University,
Vol. 16, Part 1, PP 12-24

SOLID STABILITY TESTING OF IBUPROFEN - EUDRAGIT RESPM SUSTAINED RELEASE TABLETS

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ABSTRACT

Preformulated ibuprofen-Eudragit RSPM sustained release tablets were subjected to accelerated stability testing at 25, 37 and 45°C for 6 months. The stored tablets were evaluated for the intact drug in the formula, drug-polymer interaction and compatibility of the drug with the formulated excipients using infra red spectroscopy (I.R.) and differential scanning calorimetry (DSC).

The IR spectrum of ibuprofen in the tablets prepared by 15% w/v Eudragit RSPM as a granulating agent and containing 23% w/w Avicel pH 102 as an excipient was similar to the IR of standard ibuprofen. There was no change in the IR spectra of the tablet components before and after storage of those tablets at the different investigated temperatures for 1, 3 and 6 months.

The DSC thermograms of ibuprofen stored tablets showed that the drug was still in the highly pure (>98%) crystalline form and there was no significant degradation after storage indicating the stability of the drug on storage.

In detecting ibuprofen purity in the stored tablets, plotting of the sample temeprature versus the reciprocal of the fraction of ibuprofen melted showed deviation from Van't Hoff linear plot.

INTRODUCTION

It has been shown that the degradation of certain drugs[1] may be monitored by thermal analytical techniques. The methodology employed was DSC and thermal gravimetric analysis (TGA).

DSC and IR techniques were used to check the solid state stability and the physico-chemical stability of amorphous frusemide-polyvinylpyrrolidone solid dispersions[2] stored for 12 months at 6, 20, 30, 37 and 45°C. DSC was used to investigate the interaction between drug formulation and a number of commonly used polymers[3]. This technique allowed fast evaluation of the possible complexation and incompatibilities between the formulation components and represents a valuable tool in the first step of formulation. Some researchers[3] recommended the use of DSC in short time stress conditions for investigating durg stability.

An optimized[5] ibuprofen-Eudragit RSPM sustained release tablet formula was prepared. The persent work represents the investigation of the solid state stability of ibuprofen in the formulated tablets stored at 25, 37 and 45°C for 1, 3 and 6 months using IR and DSC techniques. In addition, the purity of ibuprofen in the stored tablets was also evaluated in the test formulations.

The determination of the absolute purity of the organic materials by the DSC had been accepted in pharmaceutical and chemical industries. The thermodynamic theory for the determination of the purity of

compounds by DSC was described[6,7]. Since then, other researchers have critically evaluated this technique for accuracy, reproducibility, and ease of use, as well as sample variables and instrument parameters which are associated with this technique[8,9]. DSC is used in this work for the evaluation of ibuprofen purity in the formulated tablets stored for 6 months at the investigated temperatures.

The DSC purity method is based upon the fact that the presence of even minute amounts of impurities in a material broadens its melting range and lowers the final melting point of the material from To, the melting temperature of an infinitely pure material, to the less temperature, Tm. The dynamic DSC purity technique[6,7] for the quantitative assessment of the purity of the organic materials requires three important sample parameters; melting point, heat of fusion, H_f and analysis of the DSC melting peak shape. From Van't Hoff equation, which describes the rate of melting of a compound as a function of sample temperature, the relationships describing the heat flow to or from a sample and the melting point depression of a sample due to the presence of an impurity could be drawn. Thus the determination of the purity can be derived. This results in an expression which describes the fraction of the material reacted (method in the case of purity) at any sample temperature on the melting curve.

$$F = \frac{TO - Tm}{TO - Ts}$$

as TO = melting point of a 100% pure material

Tm = melting point of the sample system.

(TO - Tm) = melting point depression due to impurity

Ts = sample temperature and F = fraction melted.

$$Ts = TO - \frac{TO - Tm}{F} \quad \ldots\ldots\ldots\ldots (1)$$

$$(TO - Tm) = \frac{R.TO^2\ X2}{H_f} \quad \ldots\ldots\ldots (2)$$

H_f = molar heat of fusion, Joule/mole (cal/mole).

R = molar gas constant, 8.375 J/$mole^{-k}$

X2 = mole fraction of the impurity

$$Ts = TO - \frac{R.TO^2\ X2}{F_f} \cdot \frac{1}{F} \quad \ldots\ldots(3)$$

Since equation (3) is a linear equation, a plot of the sample temperature (Ts) versus the reciprocal of the fraction of the material melted at that temperature (1/F) should give a straight line with a slope equal to the melting point depression, $R.TO^2.X2/\ H_f$, and Y intercept of To. The fraction of the material melted at any sample temperature is determined directly from the dynamic DSC scan, and is proportional to the peak area under the curve up to that temperature.

EXPERIMENTAL

The materials used for the formulation of ibuprofen-Eudragit RSPM sustained release tablets were mentioned before[5,10].

Equipment:

Infra-red spectrophotometer (Beckman 4230 IR spectrophotometer).

Perkin-Elmer differential scanning calorimetric 4-apparatus.

Nuclear magnetic resonance apparatus (NMR Burcker AC 200).

Vacuum rotary evaporator (Buchi Laboratory Techniques Ltd CH-9230 Switzerland).

Methods:

Tablet batches of ibuprofen granulated with 15% w/v Eudragit RSPM and containing 23% w/w Avicel pH 102 and 1% magnesium stearate were packaged (just after compression) in firmly closed colourless glass bottles and kept at the investigated temperatures, 25, 37 and 45°C for 1, 3 and 6 months. The drug-polymer interaction, compatibility of ibuprofen with excipients and ibuprofen purity were checked by IR and DSC techniques as follows:

1-IR spectroscopic analysis: This was adopted using potassium bromide disc method for the following, (a) pure ibuprofen powder alone, (b) ibuprofen granulated by 15% w/v Eudragit RSPM and (c) 500 mg of ibuprofen powder was placed in a watch glass followed by the addition of 1N HCl and kept in an oven at 100°C. Decomposition of ibuprofen was shown to be completed with 60 minutes, whence it turned to yellow-brownish liquid which was subjected to extractive work up after drying.

2-Differential scanning calorimetric analysis: DSC standard procedure was carried out in these studies. Each of the materials used was analysed in the pure form by the stnadard procedure. Mixtures of the ingredients, ibuprofen, Eudragit RSPM, Avicel pH 102 and magnesium stearate as described in the optimum formula[5] were prepared by, (a) mixing the ingredients in the predetermined ratio, (b) mixing the constituents in the predetermined ratio and then compressing them into tablets and (c) mixing the constituents in the predetermined ratio and adding chloroform (25 ml/5 g mix.) followed by chloroform evaporation under reduced pressure at 0° to a constant weight and NMR analysis showed no chloroform remained. Also, ibuprofen hydrolyzed with HCl 1N or NaOH 1N in an oven at 100°C was investigated by DSC.

Recovery from degraded samples was 90% confirming the analytical data. The instrument was calibrated with an indium standard. Thermograms were obtained by running the samples at a temperature range between 30-200°C, with constant rate of 10°C/min.

RESULTS AND DISCUSSION

The solid state stability of sustained release ibuprofen-Eudragit RSPM tablets was performed in order to assess the stability and purity of the drug phase in the solid state as well as the drug-polymer interaction.

The IR spectrum of ibuprofen alone shows absorption peaks at 3400-2600 cm^{-1} for te hydroxyl group and at 1750 cm^{-1} for the carbonyl group, Fig. (1). The IR spectrum of the hydrolyzed products of te drug with HCl (1N) is completely different from that of ibuprofen, Fig.(1).

The IR spectrum of ibuprofen tablets granulated with 15% w/v Eudragit RSPM and containing 23% w/w Avicil pH 102 initially prepared is similar to the IR of standard ibuprofen, Figs. (1) and (2). Comparing the IR spectra of the formulated tablets before and after storage for 6 months at 25, 37 and 45°C, Figs. (2) and (3) shows that no change is observed. These results

confirm that ibuprofen molecule is still intact in the formulated tablets after 6 months storage at 45°C and neither shift of the IR of the function groups nor degradation happened to the drug molecule.

The stability and purity of ibuprofen in the formulated tablets were checked by DSC analysis of: (1) the drug alone, (2) the drug-Eudragit RSPM, (3) the drug hydrolyzed with HCl (1N) and with NaOH (1N), (4) the mixed tablet constituents in the predetermined ratio, (5) the mixed compressed tablet consitutents in the predetermined ratio stored in the different temperatures for 1, 3 and 6 months and (6) the ground tablet constituents in the predetermined ratio after adding chloroform followed by complete solvent evaporation to a constant weight.

Thermograms of ibuprofen alone, Eudragit alone, and ibuprofen granulated with 15% w/v Eudragit RSPM are shown in Fig. (4), illustrating the different thermal reactions relevant to each product. Ibuprofen showed one main endothermic reaction started at 71.77°C and ended at 79.14°C with a maximum peak of transition at 76.51°C. Eudragit RSPM exhibited a shallow broad endotherm that was completed at 190°C. If no interaction occurred between ibuprofen and Eudragit, the DSC thermogram reflected the combined characteristic features of the drug and the polymer, and this was actually the case, Fig. (5), illustrating the thermograms of ibuprofen granulated with 15% w/v Eudragit RSPM combined with Avicel pH 102 and magnesium stearate (with the same ratio in the formulated tablets). As expected, some changes in the peak shape and height-to-width ratios were found, because of the possible difference in the sample geometry[11].

The sharp endotherm at the melting point of ibuprofen is considered to be a useful tool for the investigation of its degradation in a solid mixture. As the decomposition of ibuprofen may be catalyzed by an acid or a bse, decomposition was detected in the acidic and basic hydrolysis of the drug. DSC of the acid hydrolyzed ibuprofen showed a sharp endotherm corresponding to melting at 75.0°C which is related to intact ibuprofen. It can, however, be clearly seen, Fig. (6), that the DSC showed extra endotherm at 55 and 168.2°C, which was attributed to ibuprofen degradation. DSC thermogram of the basic ibuprofen decomposition is shown in Fig. (7). A notable shift in ibuprofen melting point appears at 101.76°C signifying that strong interaction has occurred. Degradation was also confirmed by more than one endothermic peaks at 76, 85 and 160°C and one exothermic peak at 70°C. The latter may be related to a certain crystalline product.

Figs. (8-11) illustrate the thermograms of the stored tablets for 3 and 6 months at 37 and 45°C. There is no change in the characters of the peak shape of ibuprofen and the excipients. The DSC method for the determination of ibuprofen purity in its formulated tablets showed its presence in the highly pure (> 98%) crystalline form, and the absence of other peaks in the thermograms indicates no degradation on storage for 6 months at the investigated temperatures. An exception from the last finding is in ibuprofen tablets stored for 6 months at 45°C, Fig. (10), showing a very small exothermic peak at 38°C which may indicate a minute crystalline degradation product of ibuprofen.

DSC thermograms of the chloroformic extracts of the powdered tablets at 37 and 45°C after 3 and 6 months, Figs. (8), (9), (11), indicate the purity of ibuprofen (99%)

as well as its stability. In many cases when the temperature is plotted versus 1/F it has been found that the Van't Hoff plot obtained from the melting curve is not the straight line as predicted in equation (3)[7], Figs. (8-11). In most cases the concavity of the line results from the underestimation of the amount of melting which occurred at lower temperatures which is not observable on the DSC melting trace. The higher the degree of impurity, the greater the departure from linearity of the Van't Hoff plot. Since the amount of peak area which is underdetectable at the lower temperature (commonly referred to as X) is constant, the Van't Hoff plot can be linearized by adjusting the value of X until a linear plot is obtained. This procedure[7] is not at all arbitrary, in fact, if one calculates theoretical DSC peak shapes, this "X-correction" will be shown to be necessary.

Table (1) shows the X-correction values % needed for the linearization of Van't Hoff plot for the fresh tablets as well as the stored ones at the different storage conditions. These values were calculated by the instrumented Perkin Elmer DSC computer program. The purity of ibuprofen in the fresh tablets and the stored ones was more than 98%. The X-correction values % needed for linearization of Van't Hoff plot were as small as 5% in the fresh tablets as well as the chloroformic extract of the aged ones. Very minute difference was observed between the X-correction needed for the fresh tablets compared to the stored ones, which correlates this X-correction not to the minute degradation of ibuprofen in the stored tablets rather than to the presence of other additives in the tablet formulation as Eudragit RSPM, Avicel and magnesium stearate, resulted in the observed lowering of the melting point of the drug consequently, the observed deviation, which needs the X-correction. On comparing the X-correction values for the chloroformic extract of the drug in tablets with that determined directly (10.72%), it is observed that the values of the former are smaller than the latter which may be attributed to the separation of some chloroformic insoluble materials in the tablet extract responsible for lowering the melting point of ibuprofen, consequently the X-correction value needed.

CONCLUSION

1-No change in the IR spectrum was observed either for ibuprofen in the fresh and stored formulated tablets containing the different additives indicating the compatibility and stability of the drug by ageing in the tested conditions.

2-DSC analysis revealed that no interactions happened between ibuprofen and the tablet components.

3-On storage of the formulated tablets for 6 months at 45°C, ibuprofen tablets showed insignificant degradation.

4-DSC investigations indicated that the drug was still in the highly pure form in the stored tablets, and the deparature from linearity in Van't Hoff plot may be related to the presence of other tablet ingredients, the X-correction values for such deviation were calculated.

Table (1): Effect of storage on the purity of Ibuprofen in the stored sustained release tablets determined by DSC and the values of X-correction needed for Van't Hoff linearization.

Tablet sample	Storage period (months)	Storage Temp. °C	Ibuprofen Purity %	X-correction %
Fresh Tablets	-	-	99.30	5.03
Stored Tablets (chloroformic Ext.)	3	45	99.09	5.54
Stored Tablets (chloroformic Ext.)	6	37	99.13	5.37
Stored Tablets (chloroformic Ext.)	6	45	99.07	5.17
Stored Tablets	6	37	99.30	10.72

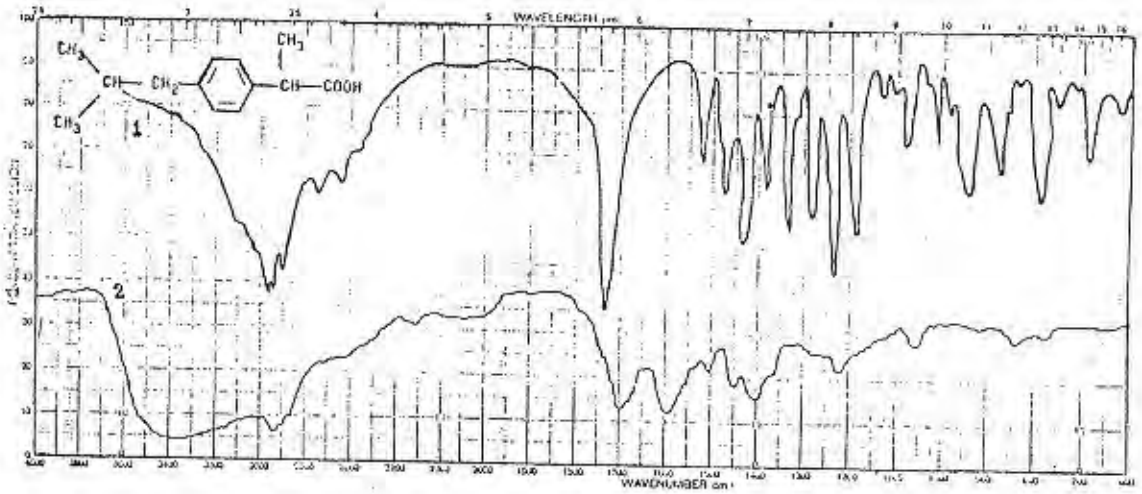

Fig.(1): IR Spectra of Ibuprofen (1) and Ibuprofen Hydrolysed by (1 N HCL) (2).

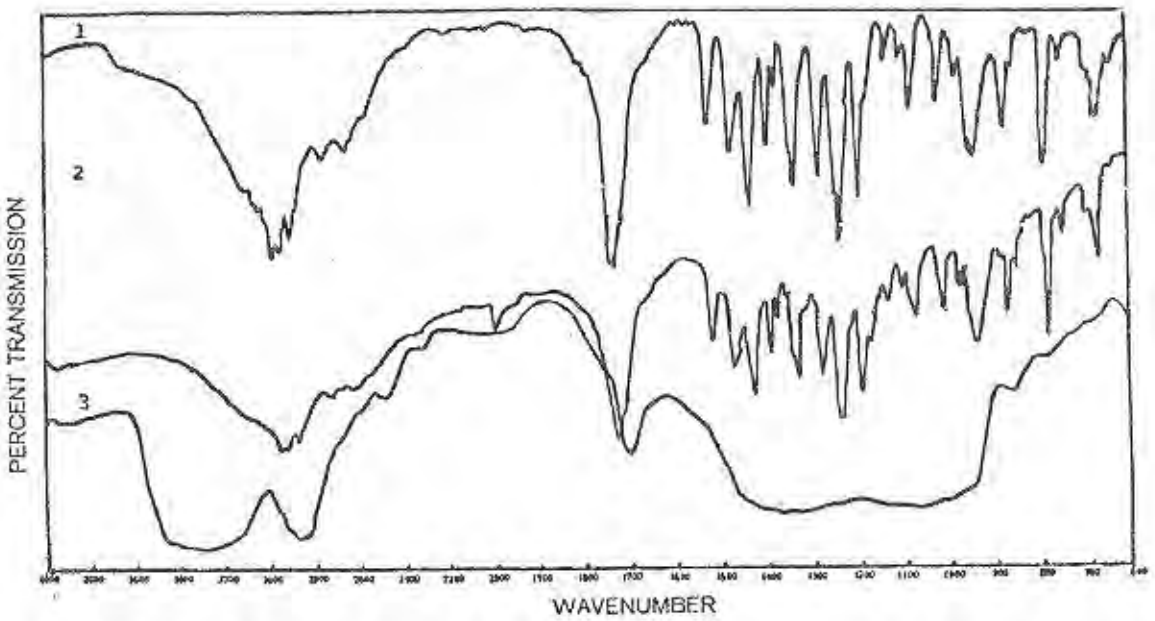

Fig.(2): Effect of Eudragit RSPM Polymer on the IR Spectrum of Ibuprofen
Key : (1) Drug Alone
(2) Ibuprofen Granulated with 15% W/V EudragitRSPM
(3) Eudragit RSPM Alone.

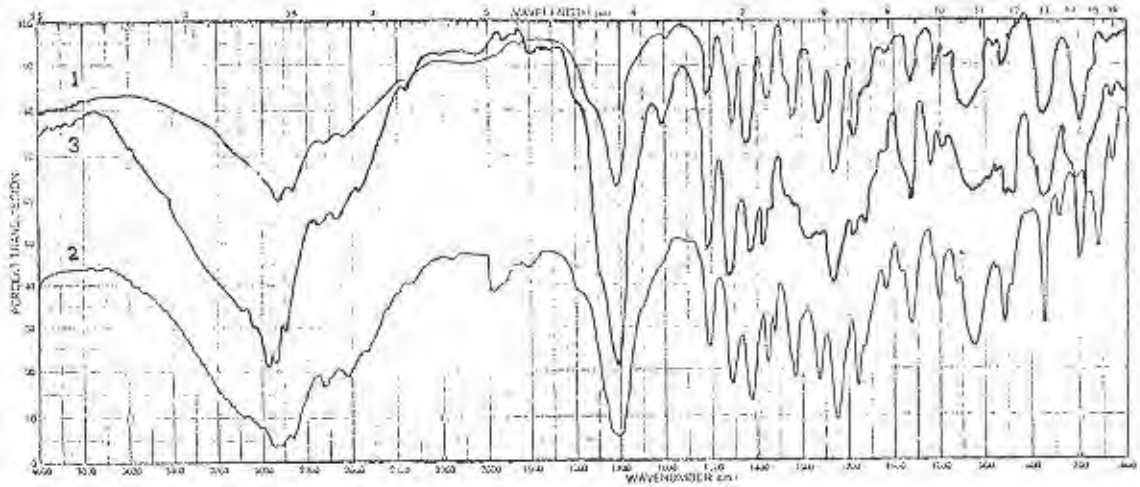

Fig.(3): IR Spectra for Ibuprofen-Eudragit Matrix Tablets.
Key : (1) Intially Prepared.
(2) After Ageing for 6 Months at 37°C.
(3) After Ageing for 6 Months at 45°C.

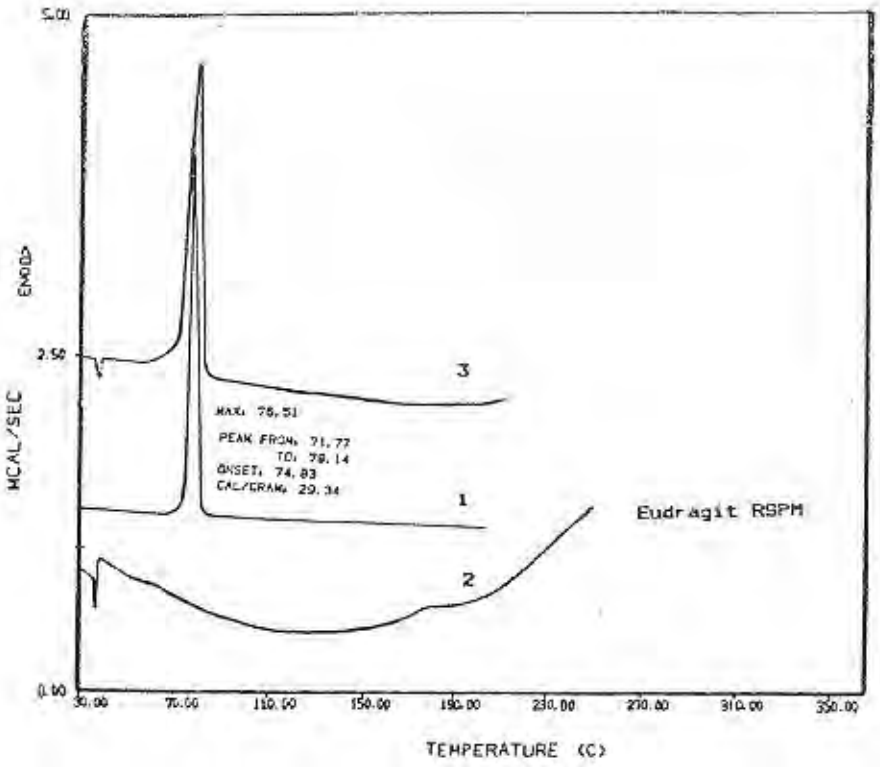

Fig.(4): DSC. Thermograms of Ibuprofen (1), Eudragit RSPM (2),and Ibuprofen Granulated with 15% W/V Eudragit RSPM (3).

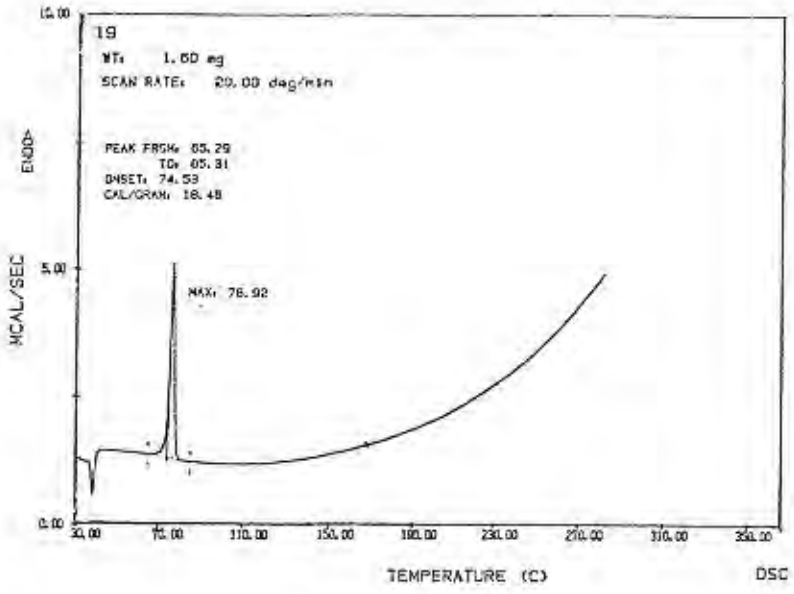

Fig.(5): DSC Thermogram of Predeterming Ratios of Ibuprofen Tablets [Physical Mixture of Ibuprofen Granulated with Eudragit RSPM and Added After that Avicel PH 102, and Mg. Stearate].

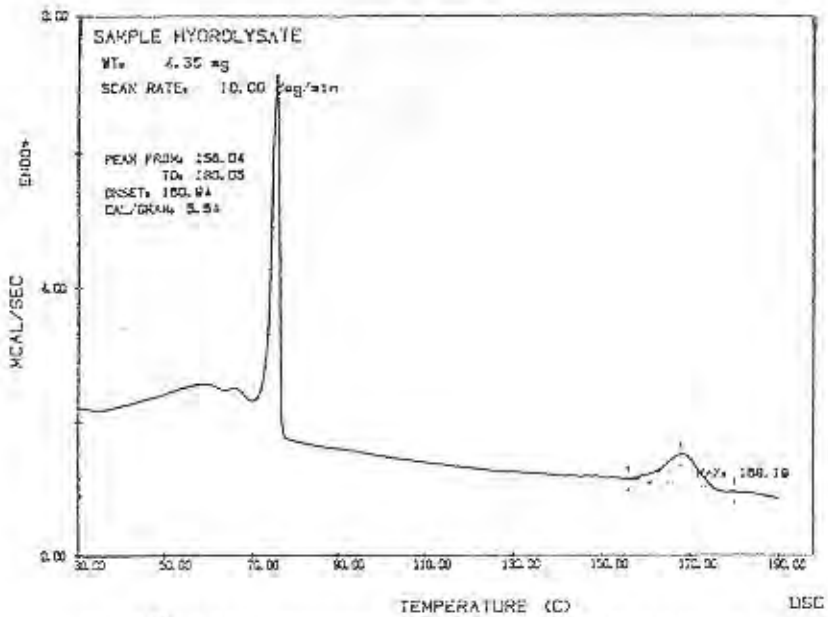

Fig.(6): DSC Thermogram of Ibuprofen Hydrolysed with (1 N HCL).

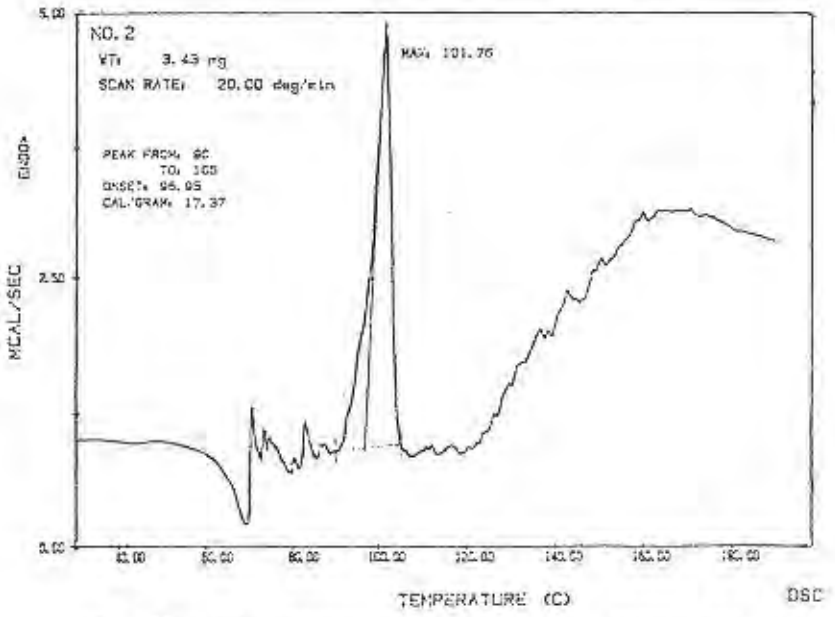

Fig.(7): DSC Thermogram of Ibuprofen Hydrolysed with (1N NaOH).

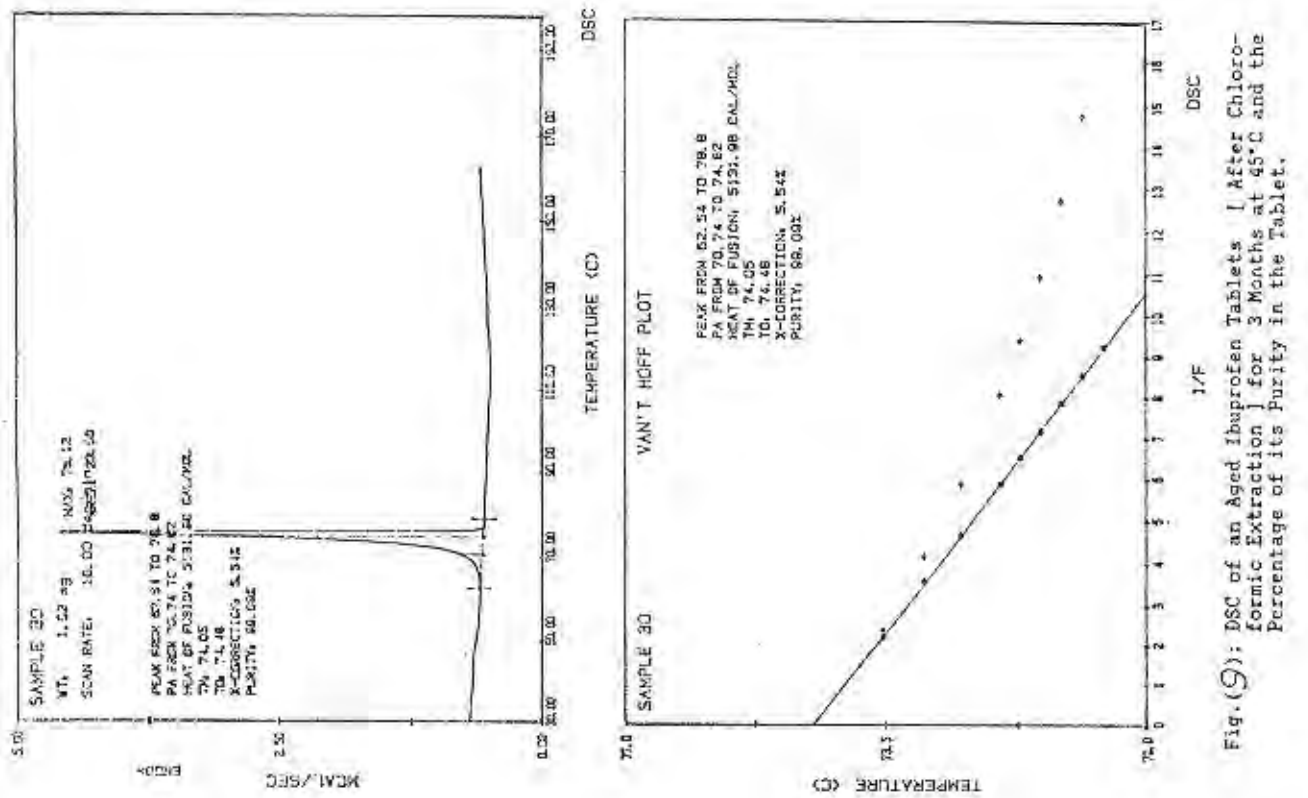

Fig.(9): DSC of an Aged Ibuprofen Tablets [After Chloroformic Extraction] for 3 Months at 45°C and the Percentage of its Purity in the Tablet.

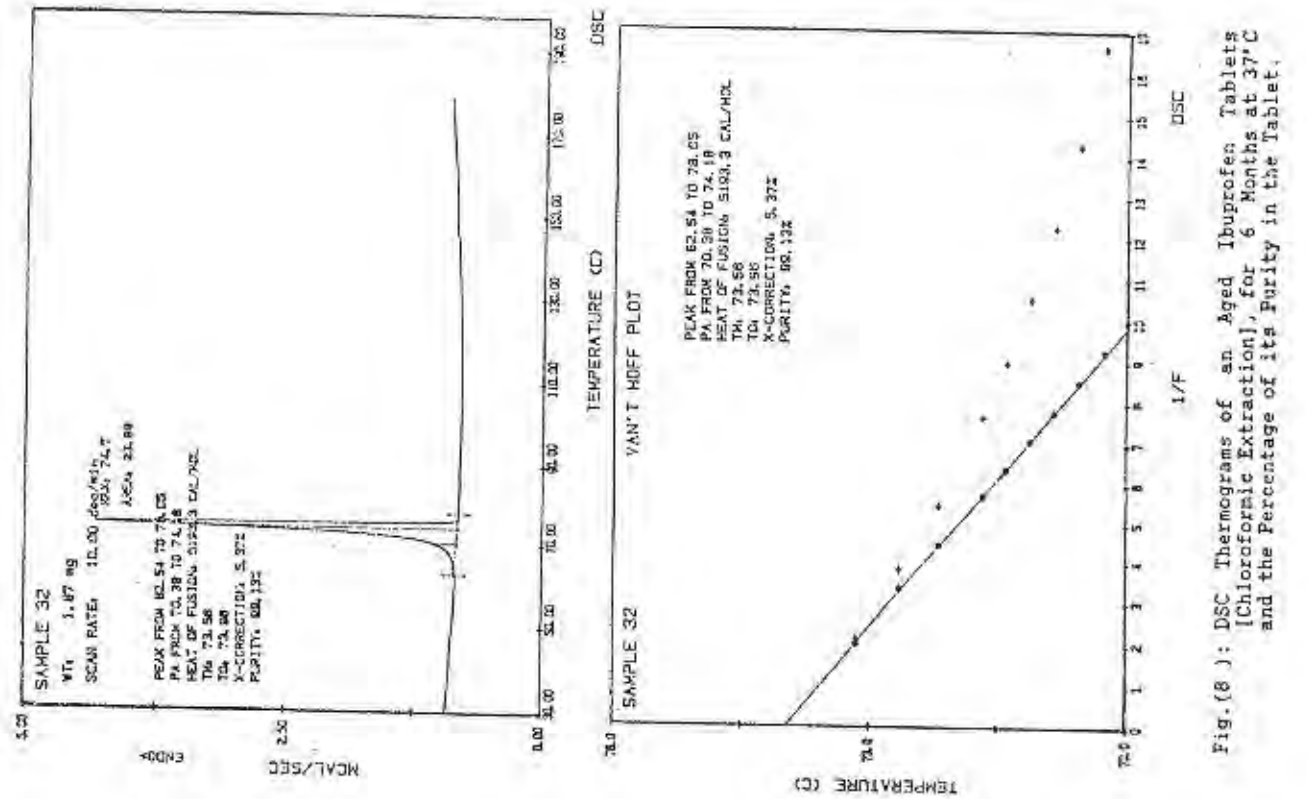

Fig.(8): DSC Thermograms of an Aged Ibuprofen Tablets [Chloroformic Extraction], for 6 Months at 37°C and the Percentage of its Purity in the Tablet.

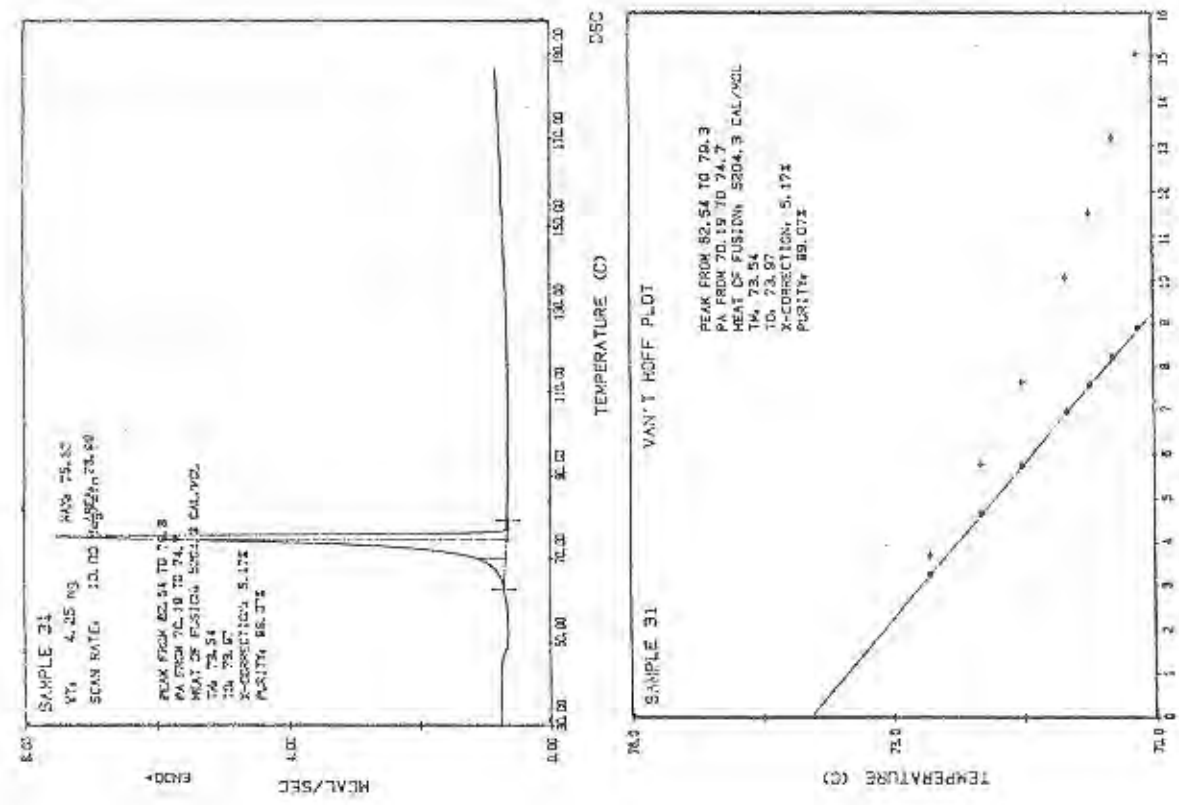

Fig.(///): DSC Thermogram of an Aged Ibuprofen Tablets (After Chloroformic Extraction) for 6 Months at 45°C and the Percentage of its Purity in the Tablet.

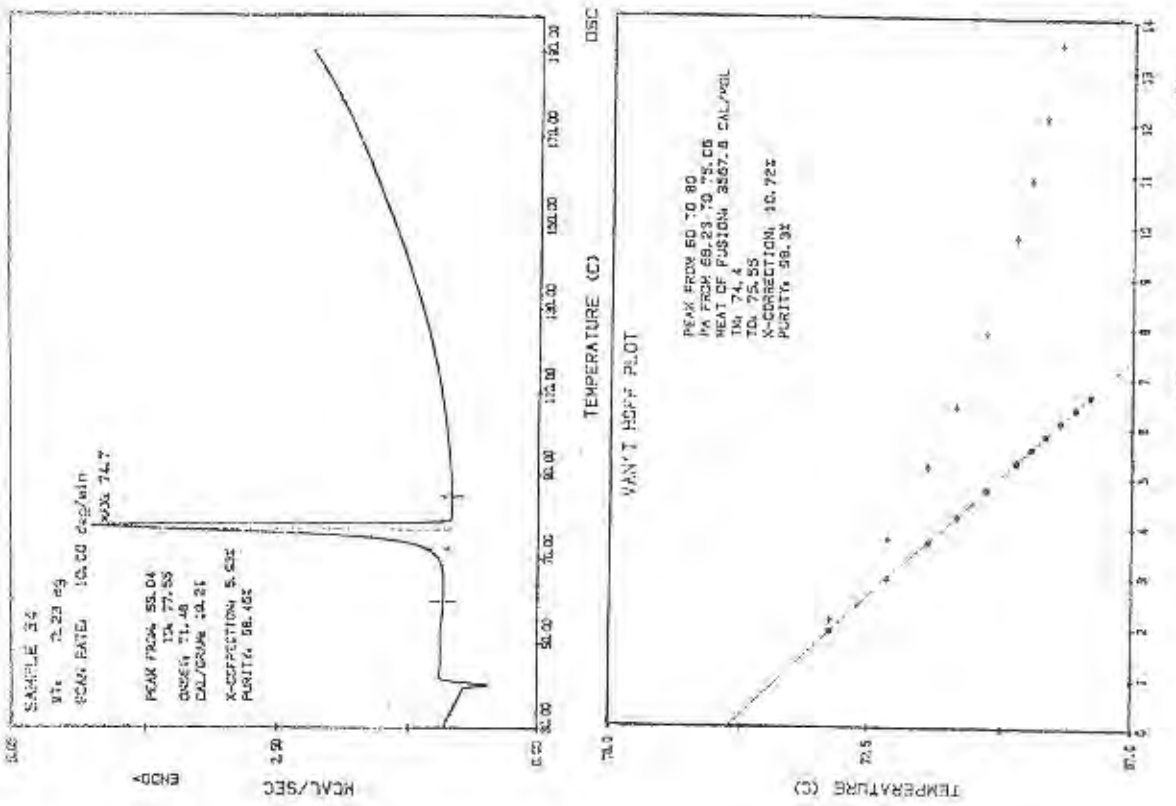

Fig.(IV): DSC Thermogram of an Aged Ibuprofen Tablets for 6 Months at 45°C and the Pecentage of its Purity in the Tablet.

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اختبار ثبات الحالة الصلبة لاقراص ابوبروفين – ايدرجيت RSPM المحضرة الممتدة المفعول

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أقراص ابوبروفين - ايدرجيت RSPM الممتدة المفعول والمحضرة سلفا عرضت لاختبار الثبات السريع عند درجات حرارة ٢٥ ، ٣٧ ، ٤٥ درجة مئوية لمدة ستة أشهر. ولقد قيمت الاقراص المحضرة بالنسبة للمحتوى الدوائى فى الصياغة وكذلك تفاعل العقار مع البوليمر وكذلك توافق العقار مع الاضافات المصاغة باستعمال الاشعة تحت الحمراء والتفاضل السعرى الحرارى.

ولقد وجد أن طيف العقار بالاشعة تحت الحمراء فى أقراصه المحضرة باستعمال ١٥٪ وزنا/حجم أيدرجيت RSPM كعامل محبب وتحتوى على ٢٣٪ وزنا/وزن أفسيل ب هـ ١٠٢ كصواغ مماثل لطيف العقار المعيار. ولا توجد إختلافات فى طيف الاشعة تحت الحمراء قبل وبعد إختبار الثبات لمدة ستة أشهر فى درجات الحرارة المختلفة.

ولقد أظهر التفاضل السعرى الحرارى لاقراص العقار المخزن لمدة ستة أشهر أن العقار مازال فى الحالة البلورية النقية الثابتة.

وفى إختبار درجة النقاء للعقار فى الاقراص المحضرة وجد أن رسم درجة حرارة العينة مع مقلوب الجزء المنصهر من العقار أظهر حيودا عن علاقة فان هوف الخطية.

Received in 1/7/1992 & Accepted in 3/11/1992