LABORATORY-SCALE DEVELOPMENT OF AN OVER-THE-COUNTER FAMOTIDINE FORMULATION

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LABORATORIUMSKAAL ONTWIKKELING VAN 'N OOR-DIE-TOONBANK FAMOTIDIENFORMULERING

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ABSTRACT

The laboratory-scale development of an over-the-counter (O.T.C.) 10mg famotidine tablet is described. A literature review and drug-excipient compatibilty studies conducted at Potchefstroom University for Christian Higher Education (P.U. for C.H.E.) represented the initial preformulation development stage. Physicochemical properties of famotidine pertinent to the formulation of a stable and bioavailable dosage form were elucidated : poor aqueous solubility (Budavari, 1989:617); poor lipophylicity (Islam & Narurkar, 1993:686); photosensitivity (McEvoy, 1995:2029); susceptibility to gastric degradation (Güvener & Ates (1988:142); and interactions between famotidine and Kollidon, Primojel, Crospovidone, Emdex, Emcompress, lactose, sorbitol or stearic acid as reported by Indrayanto *et al.* (1994:911) and/or determined by P.U. for C.H.E.

The performance of five direct compression excipients viz. Zeparox spray-dried lactose, Sorbitol Instant FG, Avicel pH 102 (microcrystalline cellulose), Emdex (dextrates, NF hydrate) and Emcompress (dibasic calcium phosphate dihydrate), in a tablet containing 10mg of famotidine and 1% of magnesium stearate , as lubricant, was subsequently evaluated. The influence of the diluents on selected physical properties of the powder blend and of the tablets was assessed.

The direct compression excipients which performed most favourably were then selected and three model formulations were derived, with the addition of Explotab (sodium starch glycolate), as disintegrant, to enhance bioavailability. The first formulation comprised 10mg of famotidine, 8mg of Explotab, 180mg of Zeparox spray-dried lactose and 2mg of magnesium stearate per tablet. The second formulation contained 10mg of famotidine, 4mg of Explotab, 40mg of Avicel, 144mg of Emcompress and 2mg of magnesium stearate per tablet; while, the third included 10mg of famotidine, 2mg of Explotab, 166mg of Avicel and 2mg of magnesium stearate. These formulations were produced

on a laboratory scale, using a Manesty F3 single punch tablet press, and were subjected to three months preliminary accelerated stability testing in polypropylene securitainers. Conditions of 40°C ±2°C and 75% ±5% relative humidity were maintained in a Gallenkamp environmental chamber. The second formulation failed accelerated stability testing; while, the first and third were found to be acceptable. The first formulation; however, demonstrated a reduction in famotidine assay and slight brown discolouration over the three months test period. The third formulation is therefore recommended.

Further investigations suggested in the development of alternative O.T.C. formulations include enteric coating to eliminate gastric degradation (Güvener & Ates, 1988:142) and the use of melt extrusion technology (Grünhagen & Müller, 1995:167) to improve biovailability and/or reduce production costs.

UITTREKSEL

Die laboratoriumskaal ontwikkeling van 'n oor-die-toonbank (O.T.C.) famotidientablet (10mg) word beskryf. 'n Literatuurondersoek en geneesmiddel-hulpstofverenigbaarheidstudie, deur die Potchefstroomse Universiteit vir Christelike Hoër Onderwys (PU vir CHO), is as eerste fase van die preformuleringsondersoek gedoen. Die fisies-chemiese eienskappe van famotidien, wat noodsaaklik is vir die formulering van 'n stabiele en biologies beskikbare doseervorm, is bespreek naamlik swak wateroplosbaarheid (Budavari, 1989:617); lae vetoplosbaarheid (Islam & Narurkar, 1993:686); fotosensitiwiteit (McEvoy, 1995:2029); afbraak in die maag (Güvener & Ates, 1988:142) en interaksies tussen die geneesmiddel en bepaalde tablethulpstowwe (Kollidon®, Primojel®, Crospovidone®, Emdex®, Emcompress®, laktose, sorbitol, of stariensuur) soos aangetoon deur Indrayanto *et al.* (1994:911) en/of aangetoon deur die PU vir CHO.

Die gedrag van vyf direksaampersbare tabletvulstowwe, naamlik Zeparox® (gesproeidroogte laktose), Sorbitol Instant FG, Avicel® pH 102 (mikrokristallyne sellulose), Emdex® (dextran) en Emcompress® (dibasiese kalsiumfosfaatdihidraat) is ge-evalueer deur hul invloed in die teenwoordigheid van 10mg famotidien en 1% magnesiumstearaat (as smeermiddel) op bepaalde fisiese eienskappe van die poeiermengsels en tablette te bepaal.

Die direksaampersbare vulstowwe wat die gunstigste resultate gelewer het, naamlik Avicel® pH 102, Zeparox® en Emcompress® is vervolgens gebruik en drie proefformules is saamgestel. Explotab®, as disintegreermiddel, is bygevoeg om geneesmiddelvrystelling en biologiese beskikbaarheid te verbeter.

Formule 1 het 10mg famotidien, 8mg Explotab®, 180mg Zeparox® en 2mg magnesiumstearaat bevat; formule 2 is saamgestel uit 10mg famotidien, 4mg Explotab®, 40mg Avicel®, 144mg Emcompress® en 2mg magnesiumstearaat, terwyl formule 3 bestaan het uit 10mg

famotidien, 2mg Explotab®, 166mg Avicel® en 2mg magnesiumstearaat.

Die tablette is op laboratoriumskaal berei en op 'n Manesty F3 enkeltabletpers getabletteer. Tablette van elke formule, verpak in polipropileen houers, is vir 3 maande aan 'n versnelde stabiliteitstudie onderwerp. Toestande van 40° +2°C en 75% +5% relatiewe humiditeit in 'n Gallenkamp-beheerkamer is tydens bewaring gehandhaaf. Na bewaring is die formules aan 'n reeks fisiese en chemiese toetse onderwerp. Formule 2 het die vereistes van die toetse gefaal, terwyl formules 1 en 3 se resultate aanvaarbaar was. Formule 1 het egter 'n afname in geneesmiddelinhoud en ook verkleuring (ligbruin) oor die drie maande toetstydperk getoon. Die derde formule (formule 3) is dus aanbeveel.

Verdere ondersoeke is voorgestel vir die ontwikkeling van alternatiewe O.T.C. famotidienformules om biobeskikbaarheid te verbeter en/of om produksiekoste te verlaag. Die toetse behels onder andere enteriese bedekking om afbraak in die maag te voorkom (Güvener & Ates, 1988:142) en die gebruik van smeltingsekstrusietegnologie (Grünhagen & Müller, 1995:167).

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I should also like to thank my supervisor, Mr A.F. Marais, and those colleagues who provided advice and assistance.

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1. INTRODUCTION

In January 1994 famotidine was reclassified in the United Kingdom (U.K.) from prescription-only to pharmacy status rendering it available over the counter for specified indications. Centra Healthcare subsequently launched Pepcid AC in the U.K. (Anon., 1994:20). More recently, the Food and Drug Administration (F.D.A.) in the United States (U.S.) granted approval for Pepcid AC to Merck & Co. in the U.S. (Anon., 1995:20). In addition, the Medicines Control Council (M.C.C.) in South Africa indicated, in January 1995, that it had resolved to recommend the rescheduling of famotidine to Schedule 2, "when intended for the symptomatic relief of heartburn caused by excess acid, where the maximum dose is 10mg and the maximum daily dose (per 24 hours) is 20mg, for a maximum treatment period of two weeks" (M.C.C., 1995:2). An opportunity to develop a generic version of this over-the-counter (O.T.C.) histamine H_2-receptor antagonist locally thus presented itself.

1.1 Objectives

In developing an O.T.C. famotidine formulation for the local market, the following objectives were identified:

A. To investigate the physical and chemical properties of famotidine alone and in combination with excipients.

B. To evaluate the use of direct compression excipients in a 10mg famotidine tablet.

C. To develop one or more model formulation/s for a direct compression tablet containing 10mg of famotidine, on a laboratory scale, and to confirm the acceptability of such formulation/s through preliminary accelerated stability analysis.

1.2 Structure

This study is reported in four sections, as indicated below:

Section 1, **INTRODUCTION**, provides a brief background to the research and outlines the objectives of the study.

Section 2, **PREFORMULATION RESEARCH**, presents physicochemical data relevant to the development of a 10mg famotidine tablet. This data was derived from a literature review, and from drug-excipient compatibility studies conducted at Potchefstroom University for Christian Higher Education (P.U. for C.H.E.).

Section 3, **FORMULATION DEVELOPMENT**, describes the development of a 10mg famotidine tablet on a laboratory scale at Adcock Ingram (Pty) Ltd., Consumer Health Care Division, Durban. In view of the trend to direct compression, where possible, as the preferred method of tablet manufacture (Banker & Anderson, 1986:336), an investigation of the performance of five direct compression diluents in a tablet containing 10mg of famotidine and 1% magnesium stearate, as lubricant, was conducted. The influence of the diluents on selected physical properties of the powder blend and of the tablets was assessed. Model formulations were then derived and were subjected to preliminary accelerated stability testing. Experimental design and equipment, results and conclusions are detailed.

Section 4, **CONCLUSION**, summarises the development process and the outcome of this study, and puts forward suggestions for further investigations in the development of alternative O.T.C. formulations.

2. PREFORMULATION RESEARCH

The first step in the rational development of dosage forms of a drug substance is preformulation testing (Wadke *et al.*, 1989:1). Initial research, therefore, focussed on generating information that would assist in the development of a stable and bioavailable tablet dosage form, capable of being consistently produced on a large scale. Investigations included a review of the available literature, as well as drug-excipient compatibility studies, conducted at P.U. for C.H.E. The physicochemical properties of famotidine thus established are presented in this chapter.

2.1 Literature review

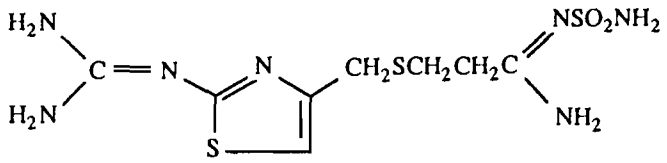
Reference to the indicated information sources revealed the following known particulars pertaining to the compound, famotidine:

2.1.1 Chemical name

The following chemical name is recognised for famotidine : 3-[[[2-[(Aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(amino sulfonyl)propanimidamide (Budavari, 1989:617).

2.1.2 Chemical structure

Chemical formula:



Empirical formula : $C_8H_{15}N_7O_2S_3$ Molecular weight : 337.43 (Budavari, 1989:617)

2.1.3 Purity

The raw material utilised in this study and manufactured by Uquifa, Spain, met the U.S.P. 23 (1995:651) requirements for chromatographic purity and organic volatile impurities.

2.1.4 Therapeutic category

Budavari (1989:617) classifies famotidine as an anti-ulcerative. A 10mg dose is, however, intended for the symptomatic relief of heartburn caused by excess acid (M.C.C., 1995:2).

2.1.5 O.T.C. dose

An O.T.C. formulation for famotidine is required to deliver a maximum single dose of 10mg (M.C.C., 1995:2).

2.1.6 Organoleptic properties

"Famotidine occurs as a white to pale yellow, odorless, crystalline powder having a moderately bitter taste." (McEvoy, 1995:2029.)

2.1.7 Particle size

The material manufactured by Uquifa, Spain complied with the following particle size specifications:
Maximum diameter at 90% of the population: 100µm
Maximum diameter at 50% of the population: 50µm
Maximum diameter at 10% of the population: 15µm

2.1.8 Solution properties

2.1.8.1 Solubility
Famotidine has approximate solubilities at 20°C of 80%m/v in dimethylformamide; 50%m/v in acetic acid; 0,3%m/v in methanol; 0,1%m/v in water; and 0,01%m/v in ethanol, ethyl acetate and chloroform (Budavari, 1989:617).

2.1.8.2 pKa

Islam & Narurkar (1993:682-686), using spectrophotometric, solubility, and partitioning methods, found the pKa of famotidine at 23°C and an ionic strength (μ) of 0,03 to be 6,76; 6,98; and 6,89; respectively. The spectrophotometric method is considered accurate and reliable in view of the limited aqueous solubility of famotidine at 23°C.

2.1.8.3 Partition coefficient

Studies conducted by Islam & Narurkar (1993:686) indicate an octanol/water partition coefficient of 0,23 for free drug at 23°C. This low value they attribute to the four terminal primary amino groups in the molecular structure of famotidine, which, in the nonprotonated state, can readily form hydrogen bonds with water molecules and hinder partitioning in the non-polar phase.

2.1.9 Stability

2.1.9.1 Solution stability

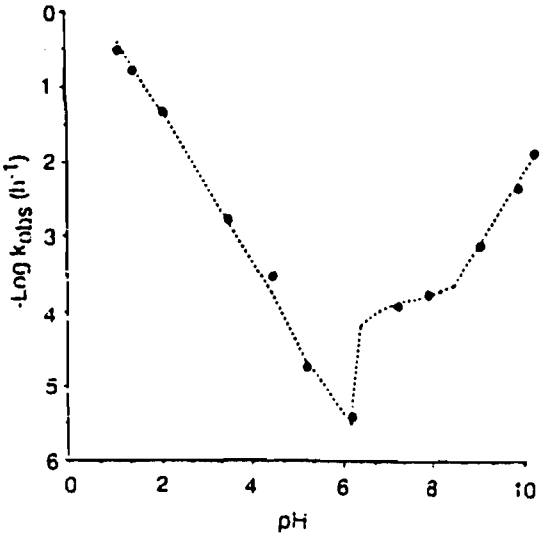
Islam & Narurkar (1993:683-685) report that at pH 1-11, drug degradation follows pseudo-first-order kinetics at 37°C (μ=0,5). The pH-rate profile (refer to Graph 1) is explained in terms of specific acid and base catalyzed decomposition of protonated and free drug with maximum stability occurring at pH 6.3.

Güvener & Ates (1988:142) showed famotidine to be unstable in simulated gastric medium using liquid chromatographic and thin layer chromatographic methods.

2.1.9.2 Solid state stability

Famotidine should be stored in well-closed, light-resistant containers at a temperature of 40°C or less. Commercially available famotidine tablets (Pepcid, MSD 20mg & 40mg) "have an expiration date of 30 months following the date of manufacture when stored under these conditions" (McEvoy, 1995:2029).

Graph 1. pH-rate profile for famotidine degradation in aqueous solution at 37±0,2°C (μ=0,5). (Adapted from Islam & Narurkar, 1993:684.)



2.1.9.3 Drug-excipient compatibility

Indrayanto *et al.* (1994:911) report indications of interactions between famotidine and Kollidon, Primojel, Crospovidone, Emcompress or lactose, based on differential scanning calorimeter (D.S.C.) thermograms obtained over a temperature range of 26°C to 200°C. No interactions are evident with talc, magnesium stearate or Avicel pH 101. High pressure liquid chromatographic (H.P.L.C.) analysis confirmed interactions with Emcompress or Crospovidone.

2.2 Drug-excipient compatibility studies

In addition to the compatibility data derived from the literature review, further information was obtained from D.S.C. studies conducted by Dr M.M. De Villiers of the Institute for Industrial Pharmacy, P.U. for C.H.E.

2.2.1 Study design

The compatibility between famotidine and the following commonly used tablet excipients was evaluated : Zeparox spray-dried lactose, Sorbitol Instant FG, Avicel pH 102 (microcrystalline

cellulose), Emdex (dextrates), Emcompress (dibasic calcium phosphate), magnesium stearate, stearic acid and Explotab (sodium starch glycolate).

2.2.1.1 Preparation of samples

Mixed samples consisting of famotidine in a 1:1 ratio with each of the excipients were prepared. The mixtures were then divided into two parts, one being kept at room temperature and the other at 37°C with 75% relative humidity for three weeks.

2.2.1.2 Differential scanning calorimetry

D.S.C. thermograms were obtained with a Schimadzu DSC-50 differential scanning calorimeter, at a heating rate of 10°C/min. under nitrogen purge with a flow rate of 35ml/min. The instrument was calibrated using ultrapure indium as a standard (melting point 156,4°C). Samples (1-8mg) were weighed to the nearest 0,001mg and sealed in aluminium pans.

2.2.2 Results

D.S.C. thermograms (included in Appendix A) indicated the presence of interactions between famotidine and Zeparox spray-dried lactose, Sorbitol Instant FG, Emdex (dextrates), Emcompress (dibasic calcium phosphate) and stearic acid; while, no significant interactions were apparent between famotidine and Avicel pH 102 (microcrystalline cellulose), magnesium stearate and Explotab (sodium starch glycolate).

2.3 Recommendations

The poor aqueous solubility of famotidine and consequent slow dissolution was recognised as a concern, since this could result in incomplete and retarded absorption of the active into the systemic circulation. The poor lipophilicity of famotidine and susceptibility to gastric degradation could further compromise oral bioavailability. McEvoy (1995:2030) indicates a value of only 40% to 50%. Means of improving bioavailability from the

dosage form thus needed to be devised. The use of rapidly disintegrating excipients was one such option. The possibility of enteric coating to eliminate gastric degradation was also considered; however, the latter alternative was not explored in this study. Laboratory analysis of Pepcid AC tablets manufactured by Centra Healthcare, U.K., (refer to Appendix B) indicated that this registered pharmaceutical product containing 10mg of famotidine is not enteric coated.

The stability prognosis for famotidine tablets on the shelf was good; however, due to the photolytic instability of famotidine, protection from light was considered to be necessary. Opaque packaging was indicated for the tablets.

The previously identified drug-excipient interactions were noted and the significance of such apparent incompatibilities in a tablet dosage form was to be assessed through preliminary accelerated stability testing.

Having considered the implications of the known physicochemical properties of famotidine, the study progressed to the next stage: formulation development.

3. FORMULATION DEVELOPMENT

The laboratory-scale development of a 10mg famotidine tablet was accomplished in two main phases. Firstly, the performance of five direct compression excipients was assessed. This was achieved through an evaluation of the influence of the excipients on selected physical parameters of the powder blend and of the compressed tablets. Secondly, three model formulations for a direct compression tablet were generated and subjected to preliminary accelerated stability testing. Both these phases are detailed in this section.

3.1 Evaluation of direct compression excipients

3.1.1 Direct compression excipient details

The direct compression excipients assessed in this study are identified in Table 1, and their sources are indicated. Important characteristics of the five excipients are also outlined. Refer to Table 2.

Table 1. Direct compression excipients evaluated in a 10mg famotidine tablet with 1% magnesium stearate.

Chemical Name	Proprietary Name	Manufacturer
A. Spray-dried lactose	Zeparox spray-dried lactose	Borculo Whey Products, UK
B. Sorbitol	Sorbitol Instant FG	E.Merck, Darmstadt
C. Microcrystalline cellulose	Avicel pH 102	Wei Ming Pharmaceutical Mfg. Co.,Ltd.
D. Dextrates, NF hydrate	Emdex	Mendell, UK
E. Dibasic calcium phosphate, dihydrate	Emcompress	Mendell, UK

3.1.2 Experimental design and equipment

Of the three generally recognised tabletting techniques, viz. wet granulation, slugging and direct compression, the latter

Table 2. Characteristics of five direct compression excipients: A.Spray-dried lactose B.Sorbitol C.Microcrystalline cellulose D.Dextrates E.Dibasic calcium phosphate dihydrate (Adapted from Wade & Weller, 1994).

Excipient	A	B	C	D	E
Pharmaceutical Applications	Filler/Diluent May be combined with microcrystalline cellulose Usually require a lubricant eg. 0,5% magnesium stearate	Sweetner/Diluent	Diluent/Lubricant/ Disintegrant	Sweetner/Diluent Lubrication with 0,5%-1,0% magnesium stearate is recommended	Diluent Abrasive, thus a lubricant is essential eg. 1% magnesium stearate Disintegration poor, need a disintegrant
Aqueous Solubility at 25°C	1 in 4,63	1 in 0,5	Practically insoluble	1 in 1	Practically insoluble
Hygroscopicity	Amorphous form may convert to monohydrate	Very hygroscopic Avoid humidities above 50% at 25°C	Hygroscopic	-	Nonhygroscopic
Stability	Mould growth possible under humid conditions Brown discolouration accelerated by warm, damp conditions	Relatively inert chemically and compatible with most excipients Stable in air in the absence of catalysts Does not darken or decompose at high temperatures or in the presence of amines	Stable, though hygroscopic	May be heated at 50°C without appreciable darkening in colour	Relatively stable, nonhygroscopic
Incompatibilities	Maillard-type condensation reaction with a primary amine to form brown-coloured products is possible	Forms water soluble chelates with many di- and trivalent metal ions in strongly acidic and alkaline conditions	Incompatible with strong oxidising agents	At high temperatures and humidities, may react with a primary amine group Incompatible with strong oxidising agents	Incompatible with tetracyclines and indomethacin Alkali, thus incompatible with actives sensitive to a pH equal to or above 7,3

involves the fewest processing steps and is thus the preferred method of tablet manufacture (Banker & Anderson, 1986:318). Direct compression entails weighing the raw materials, milling or screening, mixing and compressing. In this study, all raw materials were initially passed through a 14 mesh screen in an attempt to produce particles of approximately the same size, promote more uniform blending and, thereby, achieve greater uniformity of dose. A 20g quantity of famotidine was then geometrically diluted with 376g of each of the direct compression excipients. A 4g quantity (1%) of magnesium stearate was finally added to each of the blends. Standardised hand-mixing times of two minutes prior to the addition of the lubricant and one minute thereafter, were employed. The blending time with magnesium stearate was carefully controlled since tablet dissolution rate and crushing strength have been noted to decrease with increased blending time and magnesium stearate may also increase tablet friability (Allen & Luner, 1994:281-282). Compression was accomplished on a Manesty F3 single punch machine using a biconcave punch with a diameter of 7,1mm. A tablet mass of 200mg was targetted.

The physical tests specified in Table 3 were conducted to compare the performance of the five direct compression excipients listed in Table 1 in a 10mg famotidine tablet with 1% magnesium stearate. These tests were performed using the apparatus specified in Table 4.

Table 3. Physical parameters monitored in the evaluation of five direct compression excipients in a 10mg famotidine tablet with 1% magnesium stearate.

Parameter	Unit
Powder flow rate	s
Angle of repose	°
Moisture content of powder	%
(Uniformity of) tablet mass	mg
Tablet diameter	mm
Tablet thickness	mm
Tablet hardness	N
Tablet friability	%
Disintegration time	minutes

Table 4. Test apparatus used in the evaluation of five direct compression excipients in a 10mg famotidine tablet with 1% magnesium stearate.

Test	Apparatus
Powder flow rate	Pharma Test, type PTG
Angle of repose	Pharma Test, type PTG
Moisture content of powder	Sartorius moisture analyser
(Uniformity of) tablet mass	Mettler PM400 balance
Tablet diameter	Mitutyo digimatic vernier
Tablet thickness	Mitutyo digimatic vernier
Tablet hardness	Pharma Test hardness tester, type PTB 301
Tablet friability	Erweka TAR friabilator
Disintegration time	Erweka ZT3 apparatus

3.1.3 Results and conclusions

In-process and post-compression results for each of the five trials, P19-2 A to E, containing excipients A to E, respectively, as listed in Table 1, are included in Appendix C. The results are summarised in Table 5.

3.1.3.1 Moisture determinations

Banker and Anderson (1986:299) note that "a low but acceptable moisture level frequently acts as a binder", producing less friable tablets than very dry powders. Batches P19-2 A and P19-2 E possessed a powder moisture level of 0% and tended to exhibit greater friability than the remainder of the batches; however, all friabilities were below 1% which is generally considered to be acceptable (Banker & Anderson, 1986:299).

3.1.3.2 Powder flow and angle of repose

An evaluation of flow properties is important to ensure proper die filling and uniform tablet weight. According to Banker & Anderson (1986:317), hopper tests and angles of repose are commonly used methods for studying powder flow, although these methods do not necessarily correlate well. The absence of exact correlation was seen to a limited extent in this study : the

Table 5. Summary of in-process and post-compression results for 10mg famotidine tablet trials, P19-2 A to E.

POWDER					
	P19-2 A	P19-2 B	P19-2 C	P19-2 D	P19-2 E
MOISTURE (%)	**0,00**	0,30	1,60	0,20	**0,00**
FLOW (s)	12,7	13,6	15,7	10,1	11,1
ANGLE OF REPOSE (°)	27,9	34,3	37,5	28,6	30,5

TABLETS					
IN-PROCESS RESULTS					
	19-2 A	19-2 B	19-2 C	19-2 D	19-2 E
APPEARANCE					
Colour	slightly off-white	white	off-white	off-white	white
Shape	biconvex, circular	biconvex, circular	biconvex, circular	biconvex, circular	biconvex, circular
Surface	shiny, smooth	matt, **sticking**	matt, smooth	shiny, **sticking**	shiny, smooth
DIAMETER					
Average (mm)	7,20	7,12	7,19	7,18	7,20
s (mm)	0,01	0,01	0,01	0,02	0,02
RSD (%)	0,14	0,18	0,16	0,26	0,34
THICKNESS					
Average (mm)	4,54	**5,41**	**4,86**	4,54	3,56
Range (<±5% / >±5%)	<±5%	<±5%	<±5%	**>±5%**	<±5%
s (mm)	0,05	0,02	0,02	**0,14**	0,02
RSD (%)	1,07	0,28	0,43	**3,19**	0,68
MASS					
Average (mg)	193,3	206,9	198,2	198,3	205,4
Uniformity	1/20; 0/20	0/20; 0/20	0/20; 0/20	**10/20; 2/20**	0/20; 0/20
s (mg)	8,9	2,3	3,4	**21,6**	1,7
RSD (%)	4,62	1,11	1,72	**10,90**	0,81
HARDNESS					
Average (N)	59,5	59,2	58,3	88,8	31,6
s (N)	19,2	9,4	7,8	**64,7**	1,8
RSD (%)	32,27	15,80	13,36	**72,83**	5,62
FRIABILITY					
(%)	0,34	0,07	0,28	0,40	0,90
DISINTEGRATION					
(min.)	**19**	5,5	5	13	**>30**

TABLETS					
POST-COMPRESSION RESULTS					
	19-2 A	19-2 B	19-2 C	19-2 D	19-2 E
DIAMETER					
Average (mm)	7,25	7,16	7,23	7,22	7,23
s (mm)	0,03	0,02	0,04	0,03	0,03
RSD (%)	0,47	0,32	0,54	0,47	0,46
THICKNESS					
Average (mm)	4,62	**5,46**	**4,93**	4,56	3,60
Range (<±5% / >±5%)	<±5%	<±5%	<±5%	**>±5%**	<±5%
s (mm)	0,05	0,02	0,04	**0,16**	0,02
RSD (%)	1,19	0,43	0,82	**3,60**	0,65
MASS					
Average (mg)	197,2	195,7	197,4	183,4	204,9
Uniformity	0/20; 0/20	2/20; 0/20	0/20; 0/20	**5/20; 2/20**	1/20; 0/20
s (mg)	6,0	10,8	3,0	**17,1**	6,3
RSD (%)	3,06	5,54	1,52	**9,29**	3,08
HARDNESS					
Average (N)	40,1	67,1	56,4	50,3	35,1
s (N)	8,2	18,7	11,1	**48,9**	6,1
RSD (%)	20,34	27,85	19,73	**97,30**	17,50
FRIABILITY					
(%)	0,47	0,30	0,33	0,16	0,76
DISINTEGRATION					
(min.)	**20' 52"**	3' 52"	9' 11"	12' 0"	**>30'**

flow time for P19-2 D was the shortest, while the smallest angle of repose was noted with P19-2 A. Banker & Anderson (1986:317) also state that values for angles of repose less than or equal to 30° indicate free-flowing materials and angles of repose greater than or equal to 40° suggest a poorly flowing material. Excipient C thus appeared to be the least free-flowing of the five direct compression excipients. None of the excipients, however, could be classed as poorly flowing.

3.1.3.3 Tablet appearance

The visual appearance of a tablet must be acceptable to the consumer and should be free from deformities such as those caused by sticking. Sticking refers to tablet material adhering to die walls or building up on punches. Serious sticking may

result in chipped tablets or tablets with rough edges and may also damage cam tracks and punch heads. For these reasons, P19-2 B and P19-2 D were considered to be unsuitable.

3.1.3.4 Diameter and thickness

Tablet size can be monitored and controlled through dimensions such as diameter and thickness. Diameters generally show slight variation; however, thickness is related to the compression process. Variation in thickness may indicate a powder blend which is inconsistent in particle size or size distribution, poor powder flow, or a press which is not in good working order. Banker and Anderson (1986:296) maintain that tablet thickness should be controlled to within 5% variation of a standard value. P19-2 D exhibited significantly greater variation in thickness than the other batches and failed this requirement. P19-2 B and P19-2 C possessed the two highest average thickness values and were displeasing aesthetically.

3.1.3.5 Mass uniformity

For a 200mg tablet, the B.P. (1993:153) requires that not more than 2 out of 20 tablets deviate by more than 7,5% from the average tablet mass and that no tablet deviates by more than 15%. All of the trial batches complied with this criterion, with the exception of P19-2 D.

3.1.3.6 Hardness, friability and disintegration

"Adequate tablet hardness and resistance to ... friability are necessary requisites for consumer acceptance." (Banker & Anderson, 1986:297.) Once again P19-2 D showed the largest degree of variation in hardness, however, all five batches complied with the generally accepted friability limit of 1.0% (as mentioned previously). The relationship of tablet hardness to tablet disintegration, as well as to drug dissolution release rate has also become apparent (Banker %& Anderson, 1986:297) so that monitoring of tablet hardness is especially important for

drug products such as famotidine with potential bioavailability problems. Although the average hardness value of P19-2 E was reduced to 31,6N, no disintegration was apparent after thirty minutes. P19-2 A also required approximately twenty minutes to disintegrate. P19-2 A and P19-2 E thus failed the B.P. (1993:753) requirement for disintegration within fifteen minutes. Of the five trial batches, P19-2 B and P19-2 C exhibited the most rapid disintegration.

3.1.3.7 Price considerations

Table 6 outlines approximate prices for the direct compression excipients evaluated in this study and reveals that spray-dried lactose is the most cost effective excipient, while microcrystalline cellulose pH 102 is the most expensive.

Table 6. Comparative prices of the five direct compression excipients evaluated in a 10mg famotidine tablet with 1% magnesium stearate.

Chemical Name	Proprietary Name	Price (R/kg)
A. Spray-dried lactose	Zeparox spray-dried lactose	11,50
B. Sorbitol	Sorbitol Instant FG	15,00
C. Microcrystalline cellulose	Avicel pH 102	27,00
D. Dextrates, NF hydrate	Emdex	23,00
E. Dibasic calcium phosphate, dihydrate	Emcompress	17,00

Based on the foregoing discussions, a decision was made to proceed by including a disintegrant with excipient A; by investigating a combination of excipients C and E together with a disintegrant; and by including a disintegrant with excipient C. The significance of the interactions between famotidine and lactose (excipient A) or Emcompress (excipient E), as indicated previously, was to be assessed in a tablet dosage form through preliminary accelerated stability testing.

3.2 Derivation of model formulations

3.2.1 Experimental design and equipment

Three trial batches comprising the formulations given in Table 7 were prepared similarly to the direct compression excipient trials. A 10g quantity of famotidine was geometrically diluted with the disintegrant, sodium starch glycolate, and with the direct compression excipient(s). Magnesium stearate (1%) was then added and blended, as lubricant. Once again standardised hand-mixing times of 2 minutes before the addition of the lubricant and 1 minute thereafter, were employed and materials were passed through a 14 mesh screen, where necessary, to eliminate lumps. Finally, tablets were compressed on a Manesty F3 single punch press.

Table 7. Three model formulations for a direct compression tablet containing 10mg of famotidine.

Formulation 1		
Item	**Quantity per tablet (mg)**	**Trial batch, P19-4, quantity (g)**
Famotidine	10	10
Explotab (sodium starch glycolate)	8	8
Zeparox spray-dried lactose	180	180
Magnesium stearate	2	2
Formulation 2		
Item	**Quantity per tablet (mg)**	**Trial batch, P19-5, quantity (g)**
Famotidine	10	10
Explotab (sodium starch glycolate)	4	4
Avicel (microcrystalline cellulose)	40	40
Emcompress (dibasic calcium phosphate, dihydrate)	144	144
Magnesium stearate	2	2
Formulation 3		
Item	**Quantity per tablet (mg)**	**Trial batch, P19-7, quantity (g)**
Famotidine	10	10
Explotab (sodium starch glycolate)	2	2
Avicel (microcrystalline cellulose)	166	166
Magnesium stearate	2	2

The tests detailed in Table 8 were performed on the tablets initially and after three months storage in polypropylene securitainers in a Gallenkamp environmental chamber maintained at 40°C ±2°C and 75% ±5% Relative Humidity (R.H.). The test apparatus specified in Table 9 were utilised.

Table 8. Stability parameters assessed for three model tablet formulations containing 10mg of famotidine.

Parameter	Unit
(Uniformity of) tablet mass	mg
Tablet diameter	mm
Tablet thickness	mm
Tablet hardness	N
Tablet friability	%
Disintegration time	minutes
Famotidine assay	mg
Famotidine dissolution rate	minutes

Table 9. Test apparatus used to evaluate three model tablet formulations containing 10mg of famotidine.

Test	Apparatus
(Uniformity of) tablet mass	Mettler PM400 balance
Tablet diameter	Mitutyo digimatic vernier
Tablet thickness	Mitutyo digimatic vernier
Tablet hardness	Pharma Test hardness tester, type PTB 301
Tablet friability	Erweka TAR friabilator
Disintegration time	Erweka ZT3 apparatus
Famotidine assay	Water's High Pressure Liquid Chromatograph
Famotidine dissolution rate	Hanson SR8 dissolution bath with Dissoette II

3.2.2 Results and conclusions

Initial and accelerated stability results for the three trial batches, P19-4, P19-5 and P19-7, are included in Appendix D.

Batch P19-4 complied with the listed specifications on initial testing and at the three month accelerated stability take-off. A

reduction in the famotidine assay and slight brown discolouration of the tablet was, however, noted with time. This may be explained by the recognised incompatibility between lactose and primary amines, leading to a Maillard-type condensation reaction to form brown-coloured products (refer to Table 2).

Batch P19-5 failed assay and dissolution requirements. The stated incompatibility between alkaline Emcompress (dibasic calcium phosphate) and actives sensitive to a pH equal to or above 7,3 (refer to Table 2) may be pertinent in this instance. The pH-rate degradation profile of an aqueous solution of famotidine (refer to Graph 1) indicates maximum stability at a pH of 6,3 with an increase in the degradation rate as the pH is raised.

Batch P19-7 passed the specified tests at both the initial and the three month testing stations. This formulation is thus recommended for an O.T.C. famotidine tablet.

4. CONCLUSION

This study has reviewed the known physicochemical properties of famotidine; evaluated direct compression excipients in an O.T.C. famotidine tablet formulation; and assessed three proposed model formulations, two of which (formulation 1 & formulation 3) appear to meet the requirements of the South African M.C.C. in terms of physical, chemical and stability characteristics of the final product. The formulation containing 10mg of famotidine, 8mg of Explotab (sodium starch glycolate), 180mg of Zeparox spray-dried lactose and 2mg of magnesium stearate per tablet (formulation 1); however, demonstrates a reduction in famotidine assay and a slight brown discolouration over three months accelerated stability testing. A direct compression formulation comprising 10mg of famotidine, 2mg of Explotab (sodium starch glycolate), 166mg of Avicel pH 102 (microcrystalline cellulose) and 2mg of magnesium stearate per tablet (formulation 3) is thus recommended.

In view of the noted susceptibility of famotidine to gastric degradation, it is suggested that further investigations in the development of an O.T.C. famotidine formulation include an assessment of the influence of enteric coating on the bioavailability of the active, with a potential reduction in active content and a resultant cost saving. Opaque coating materials would also afford protection against photolytic degradation.

New formulation technologies may offer additional development opportunities. Knoll AG and the plastics research laboratory at BASF, for example, have jointly developed a melt extrusion process (Grünhagen & Müller, 1995:167) which has been shown to improve the bioavailability of some poorly soluble compounds. The melt extrusion process is claimed to provide an economical alternative to conventional manufacturing methods used by the pharmaceutical industry, "enabling tablets to be produced in a

single facility on a continuous basis" (Grünhagen & Müller, 1995:167).

BIBLIOGRAPHY

ACTS
See
SOUTH AFRICA (Republic)

ALLEN, L.V. & LUNER, P.E. 1994. Magnesium stearate. (*In* Wade, A. & Weller, P.J. *eds.* Handbook of pharmaceutical excipients. 2nd ed. London : The Pharmaceutical Press & Washington : American Pharmaceutical Association. p280-282.)

ANON. 1994. OTC famotidine launched in the UK. *Scrip world pharmaceutical news,* 1994 (1900) : 20, Feb.

ANON. 1995. Approvable letter for OTC Pepcid in US. *Scrip world pharmaceutical news,* 1995 (2021) : 20, May.

BANKER, G.S. & ANDERSON, N.R. 1986. Tablets. (*In* Lachman, L., Lieberman, H.A. & Kanig, J.L. *eds.* The theory and practice of industrial pharmacy. 3rd ed. Philadelphia : Lea & Febiger. Chapter 11 : 293-345.)

B.P.
See
THE BRITISH PHARMACOPOEIA.

BUDAVARI, S., *ed.* 1989. The merck index : an encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway, N.J. : Merck. 1606p.

BIBLIOGRAPHY (CONTINUED)

GRÜNHAGEN, H.H. & MÜLLER, O. 1995. Melt extrusion technology. *Pharmaceutical manufacturing international*, 1995:167-170.

GÜVENER, B. & ATES, S. 1988. The stability study on famotidine in simulated gastric medium by high-performance liquid chromatography. *Acta Pharmaceutica Turcica*, 30(3) : 139-142.

INDRAYANTO, G., MUGIHARDJO & HANDAYANI, R. 1994. Compatibility study between famotidine and some excipients using differential scanning calorimetry. *Drug development and industrial pharmacy*, 20(5) : 911-920.

ISLAM, M.S. & NARURKAR, M.M. 1993. Solubility, stability and ionization behaviour of famotidine. *Journal of pharmacy and pharmacology*, 45 : 682-686, Aug.

M.C.C.
See
THE MEDICINES CONTROL COUNCIL.

MCEVOY, G.K., *ed.* 1995. American Hospital Formulary Service (AHFS) : Drug information. Bethesda, Md. : AHFS.

BIBLIOGRAPHY (CONTINUED)

SOUTH AFRICA (Republic). 1965. Medicines and Related Substances Control Act, no. 101 of 1965. Pretoria : State Press.

THE BRITISH PHARMACOPOEIA. 1993. London : HMSO. 1281p.

THE MEDICINES CONTROL COUNCIL. 1995. Scheduling matters. Proposed circular A95. Pretoria. 6p.

THE UNITED STATES PHARMACOPEIA. 1995. 23rd revision. Rockville, Md. : United States Pharmacopeial Convention, Inc. 2391p.

U.S.P. 23
See
THE UNITED STATES PHARMACOPEIA.

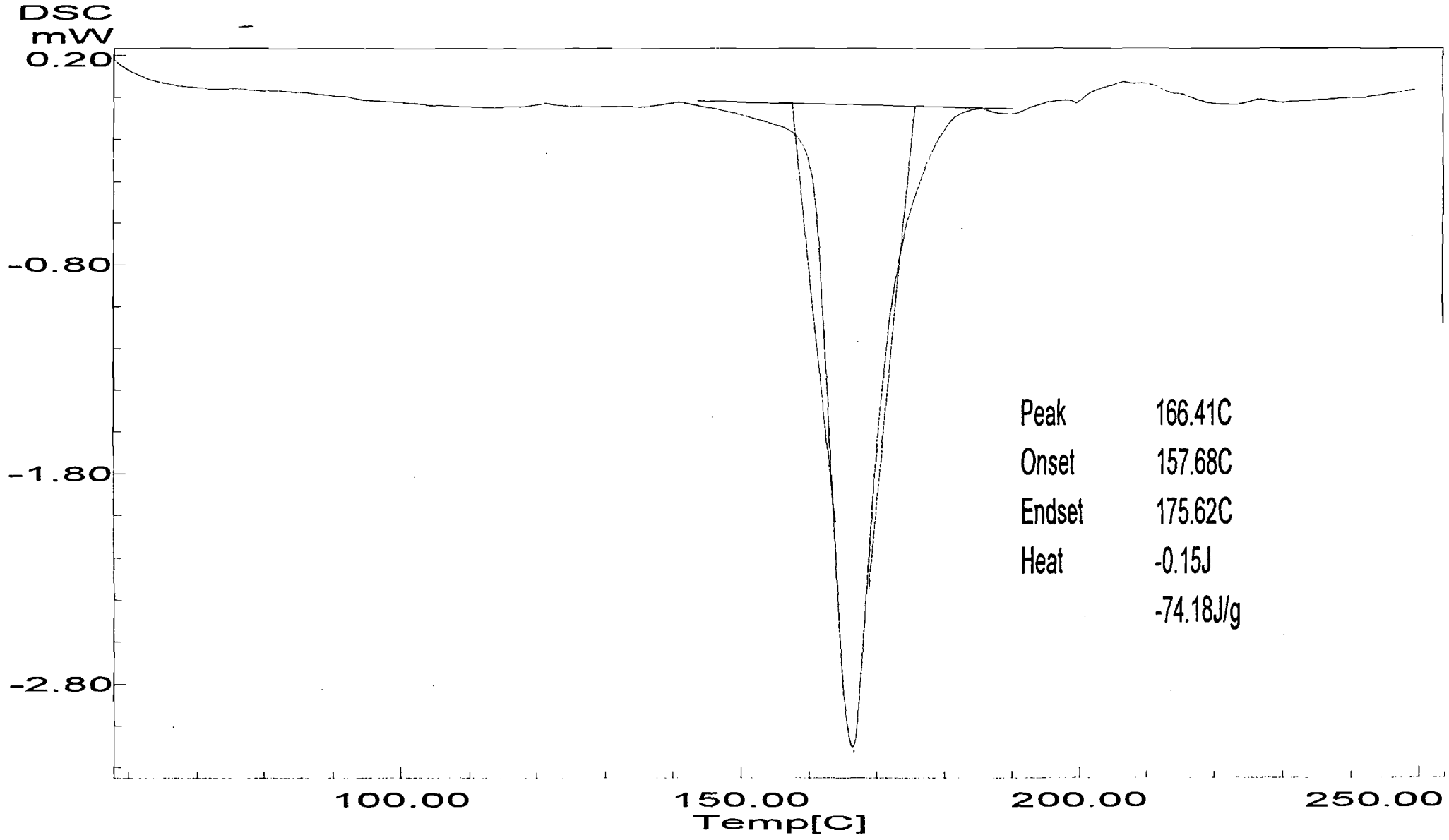
WADE, A. & WELLER, P.J. *eds.* 1994. Handbook of pharmaceutical excipients. 2nd ed. London : The Pharmaceutical Press & Washington : American Pharmaceutical Association. 375p.

WADKE, D.A., SERAJUDDIN, A.T.M. & JACOBSON, H. 1989. Preformulation testing. (*In* Lieberman, H.A., Lachman, L. & SCHWARTZ, J.B. *eds.* Pharmaceutical dosage forms : tablets. 2nd ed. New York : Marcel Dekker. Chapter 1 : 1-73.)

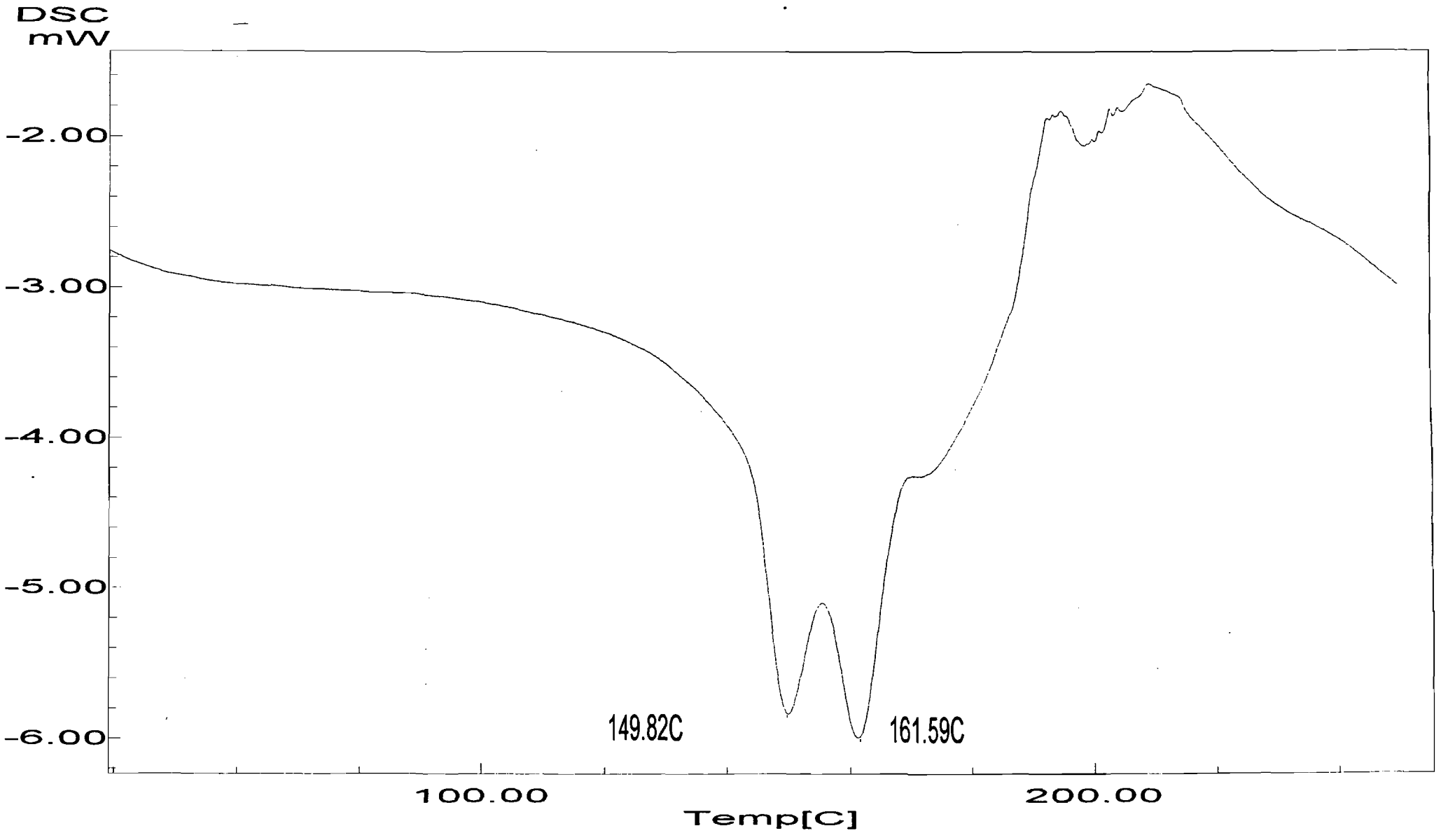
APPENDIX A

D.S.C. thermograms : famotidine-excipient mixtures

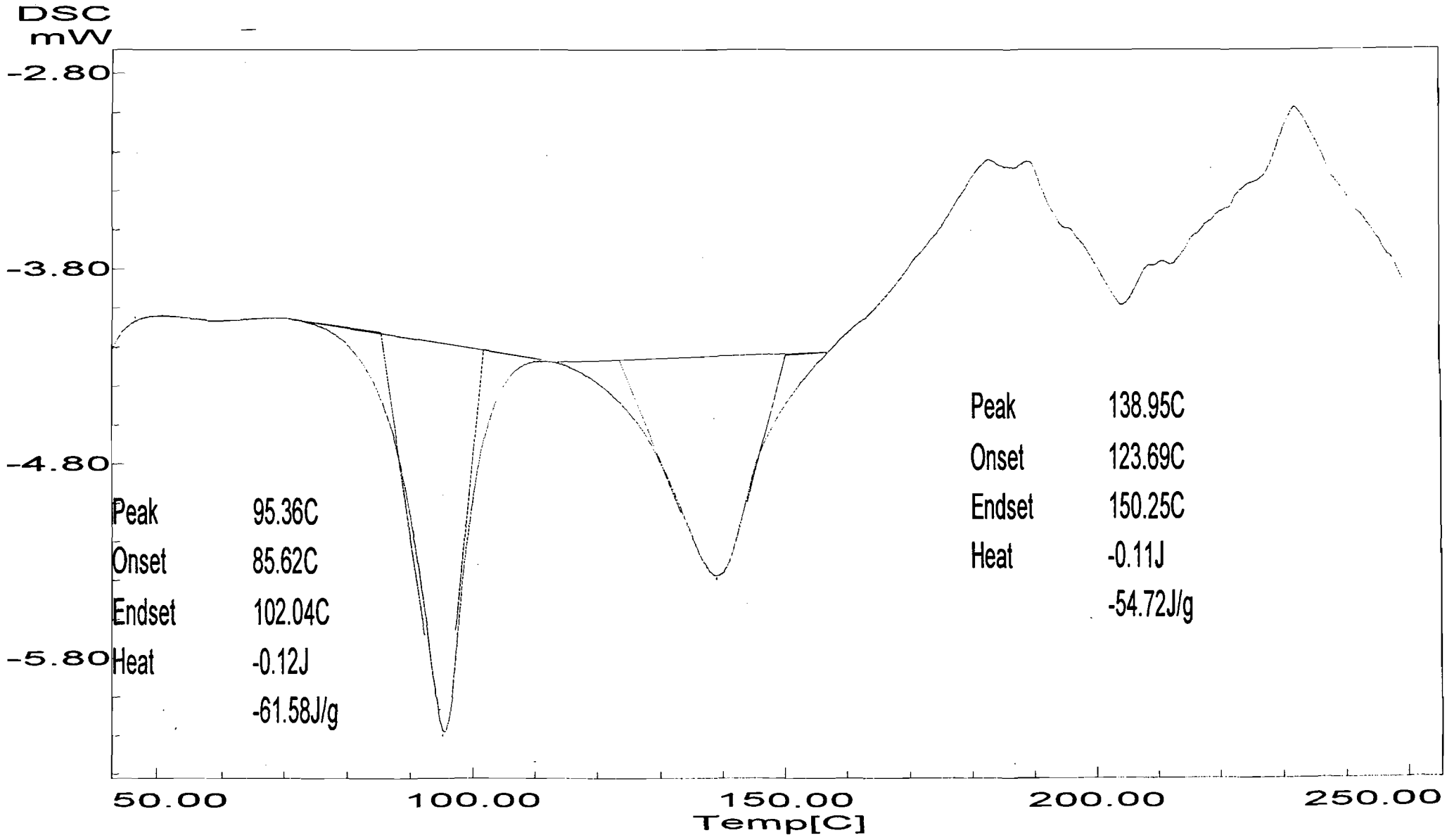
Famotidine


DSC
mW
0.20
-0.80
-1.80
-2.80
100.00
150.00
200.00
250.00
Temp[C]
Peak 166.41C
Onset 157.68C
Endset 175.62C
Heat -0.15J
-74.18J/g

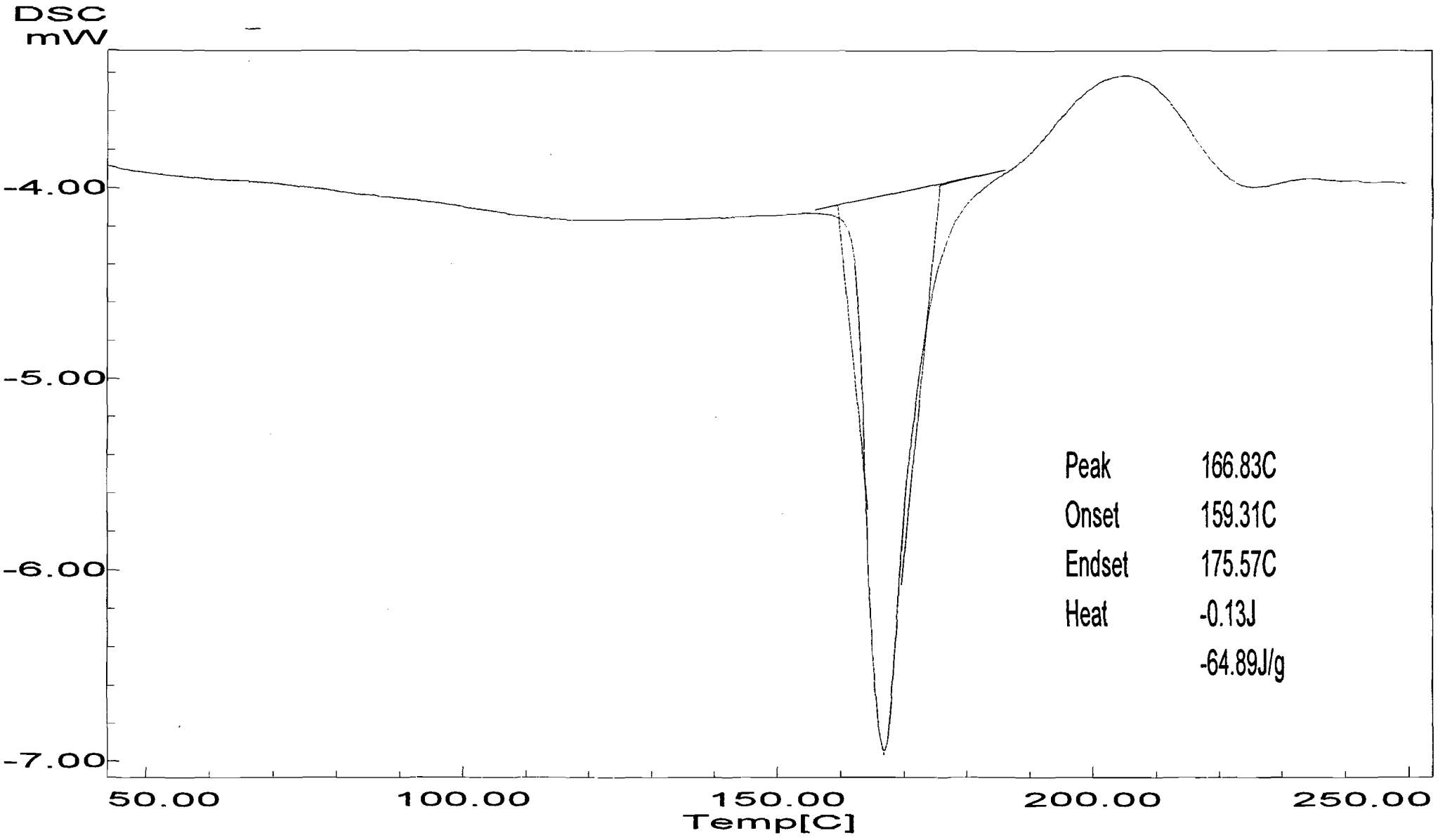
Physical Mixture (Famotidine + Lactose)



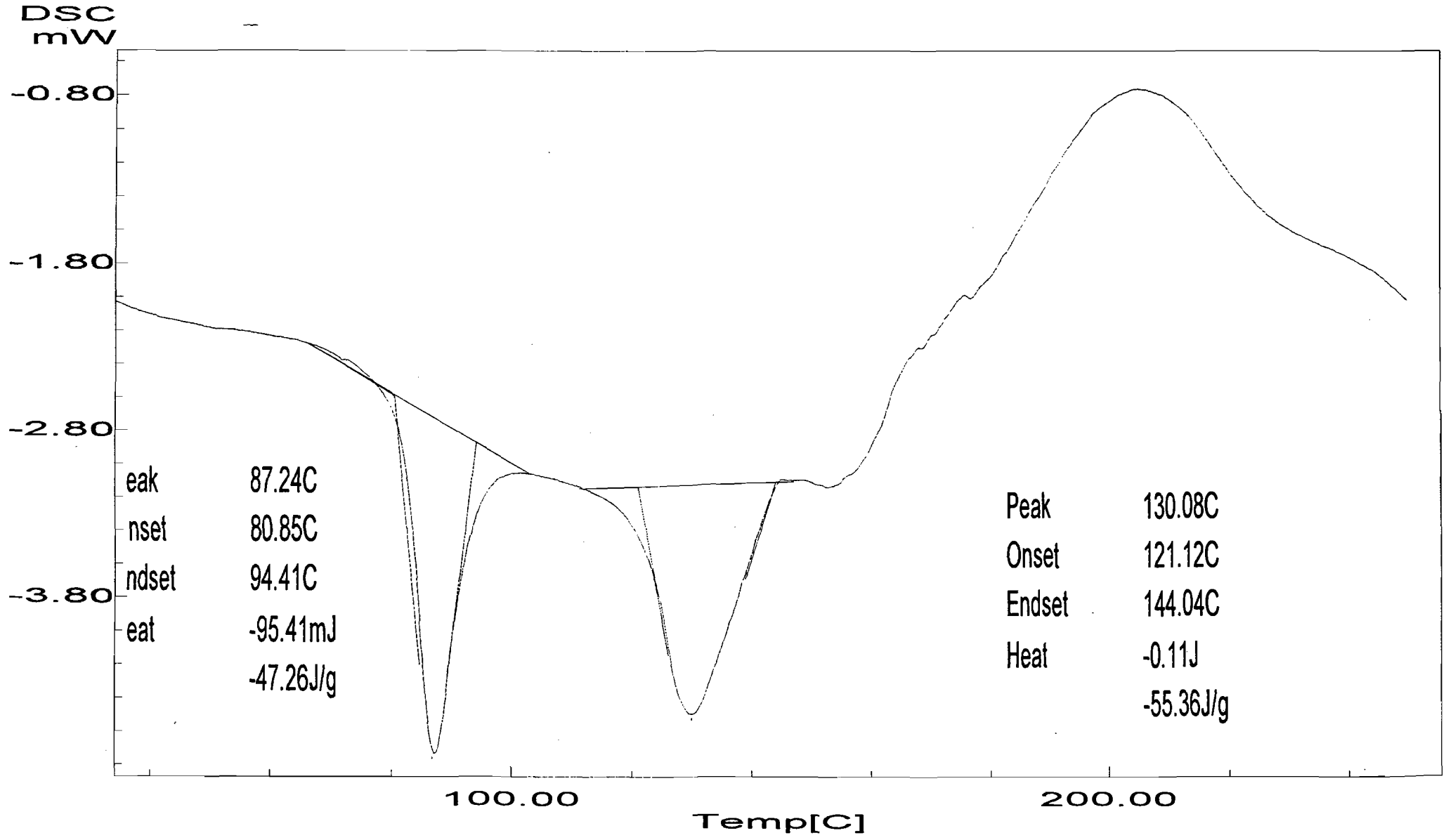
Physical Mixture (Famotidine + Sorbitol)



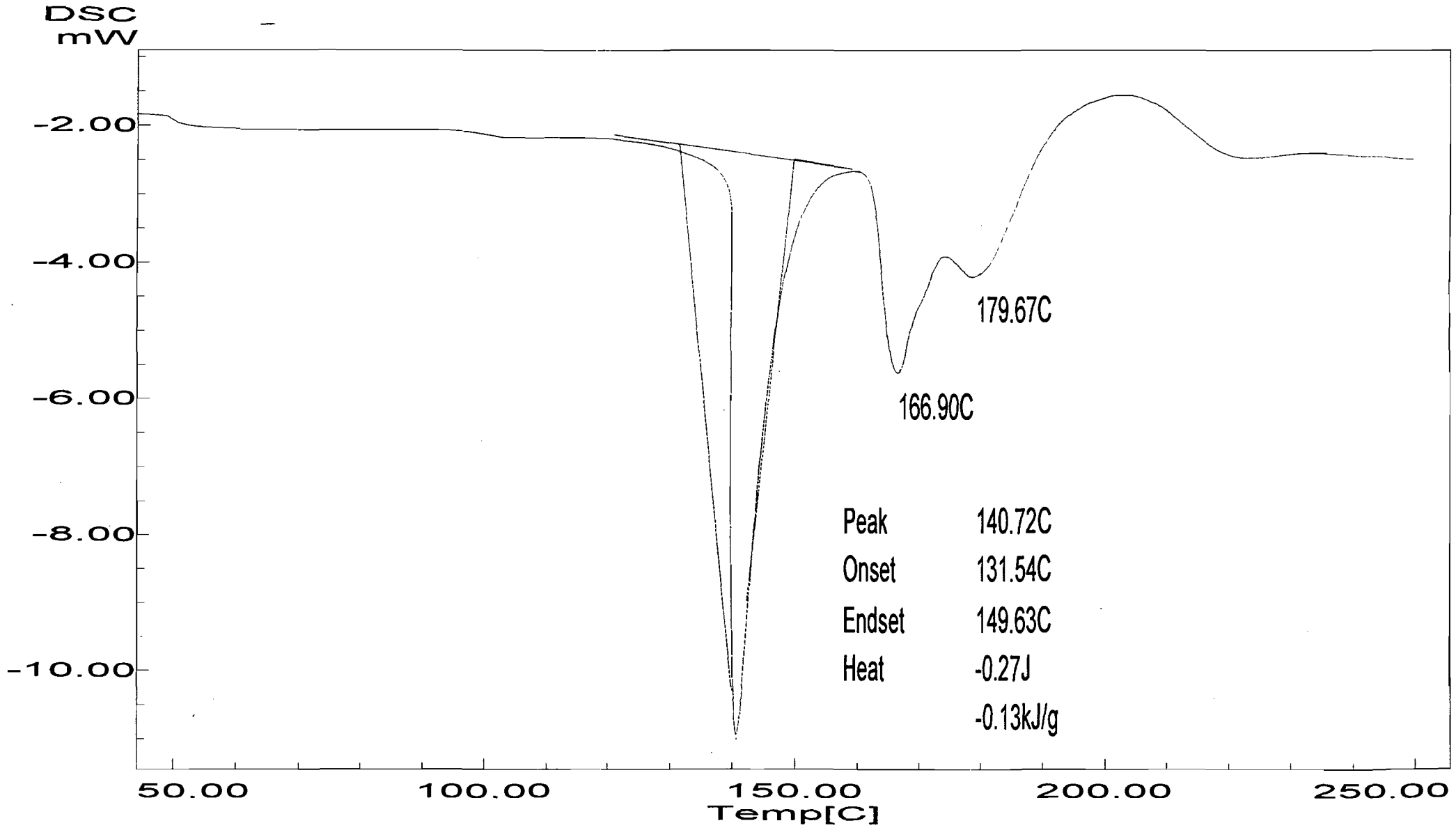
Physical Mixture (Famotidine + Microcrystalline cellulose)



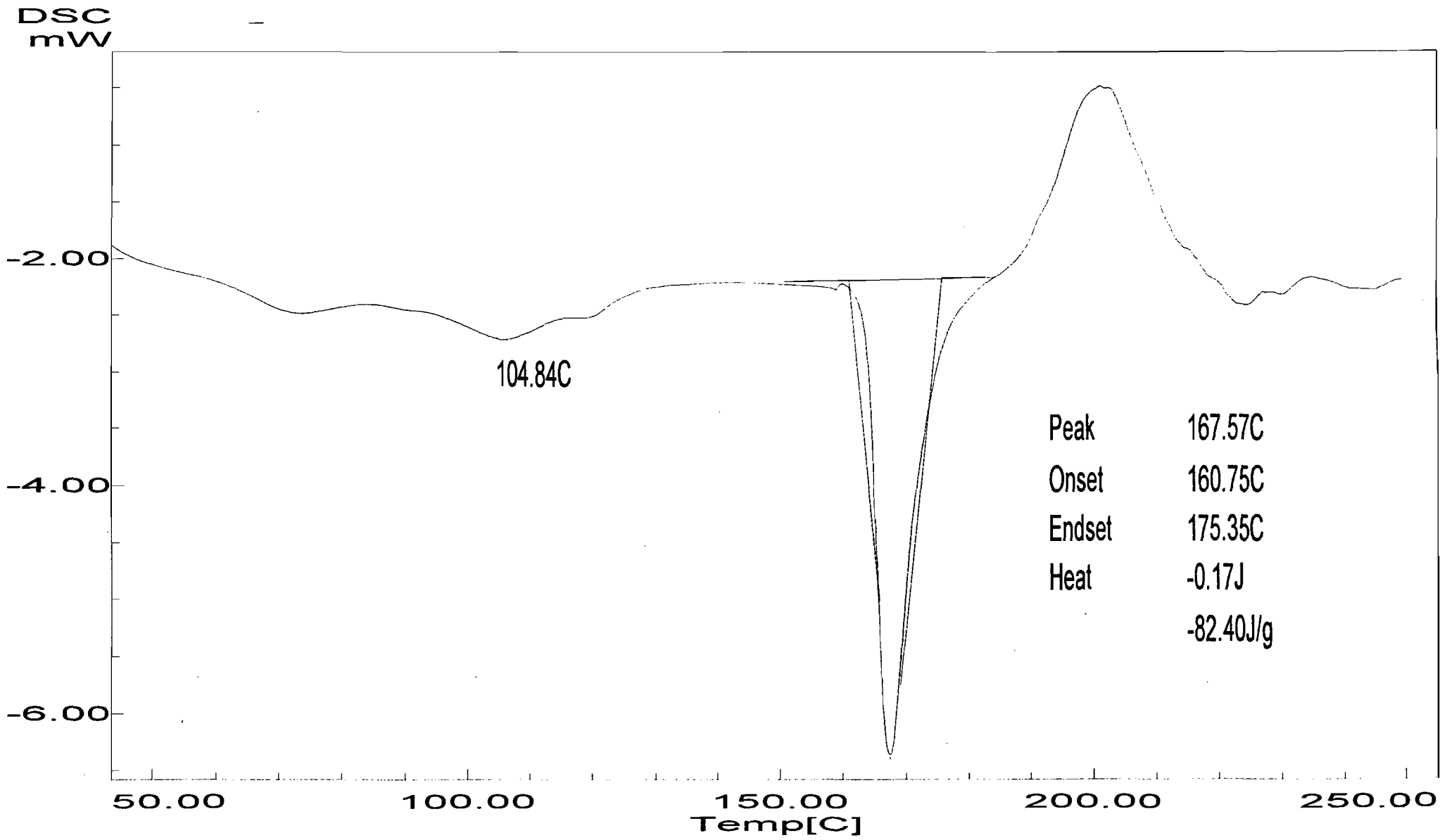
Physical Mixture (Famotidine + Emdex)



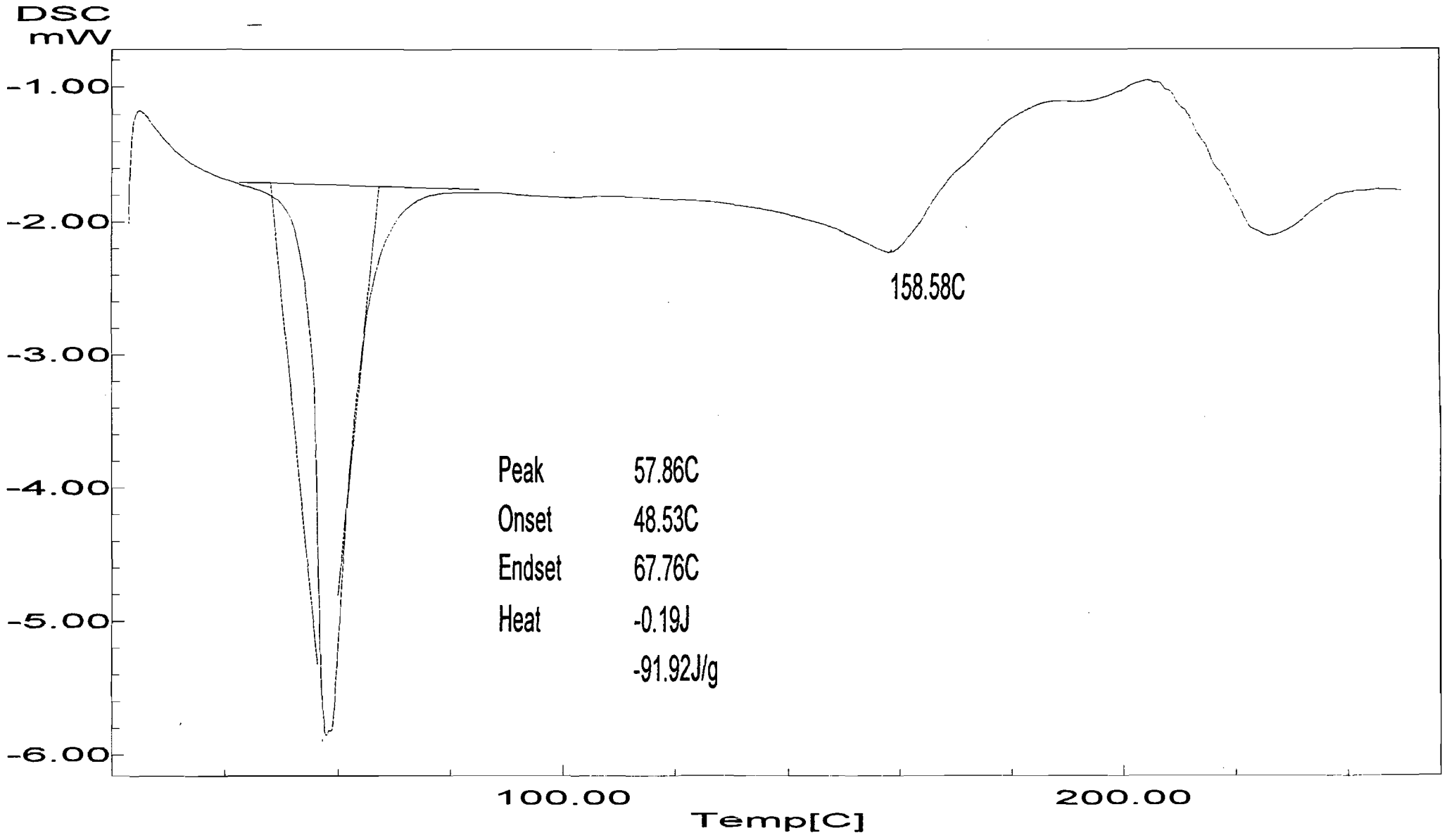
Physical Mixture (Famotidine + Dicalcum Phosphate)



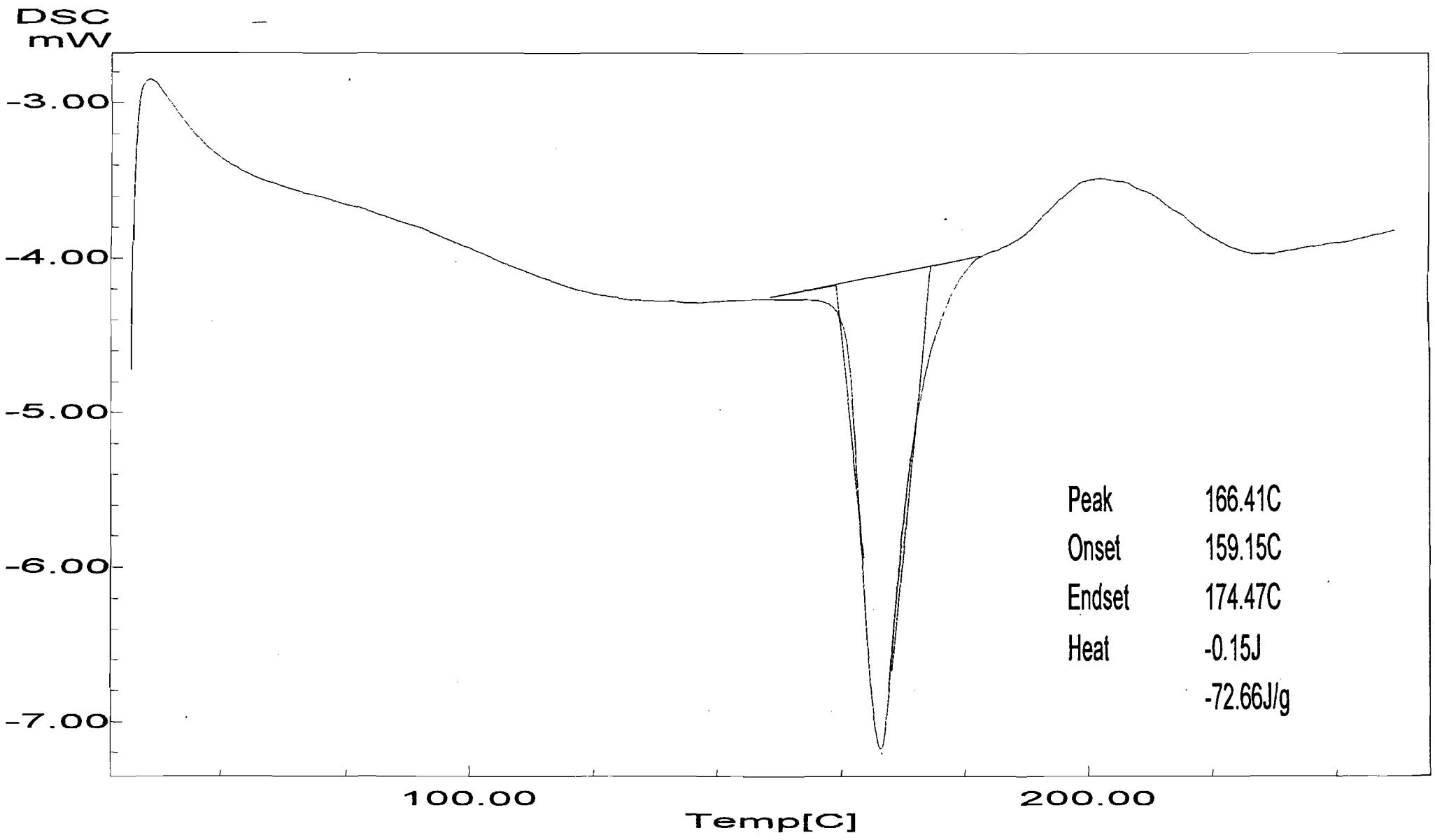
Physical Mixture (Famotidine + Magnesium Stearate)



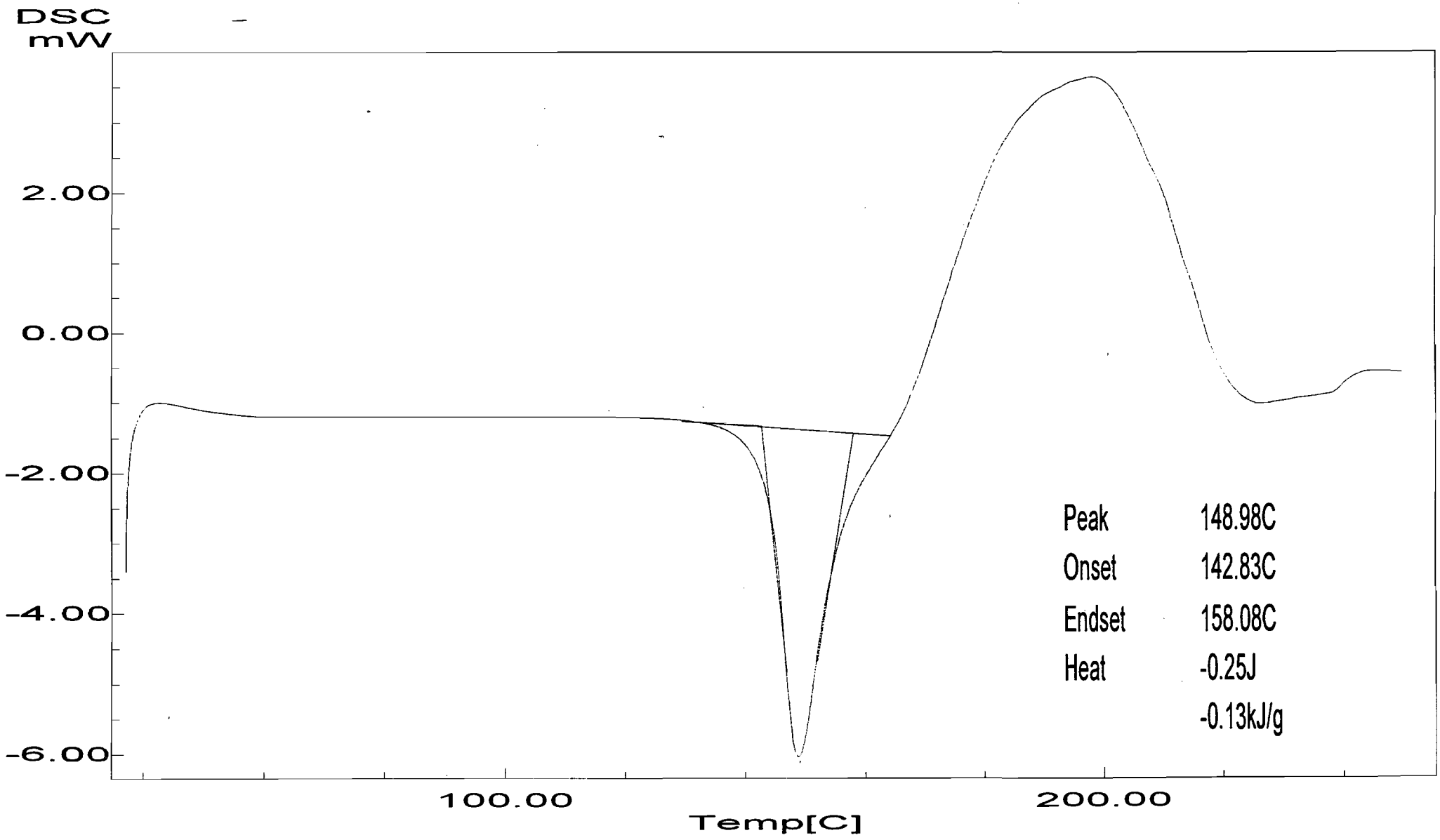
Physical Mixture (Famotidine + Stearic Acid)



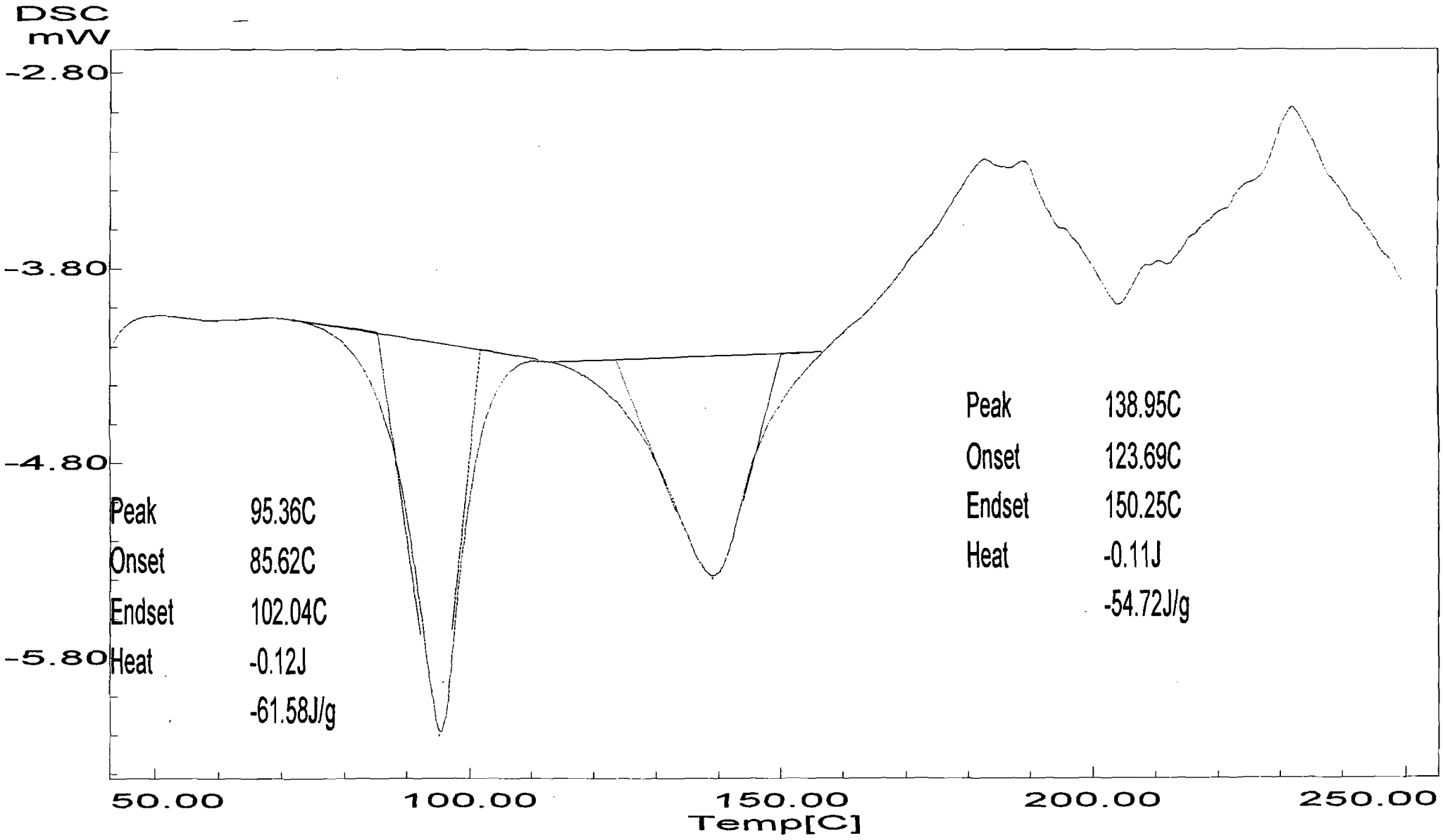
Physical Mixture (Famotidine + Explotab)



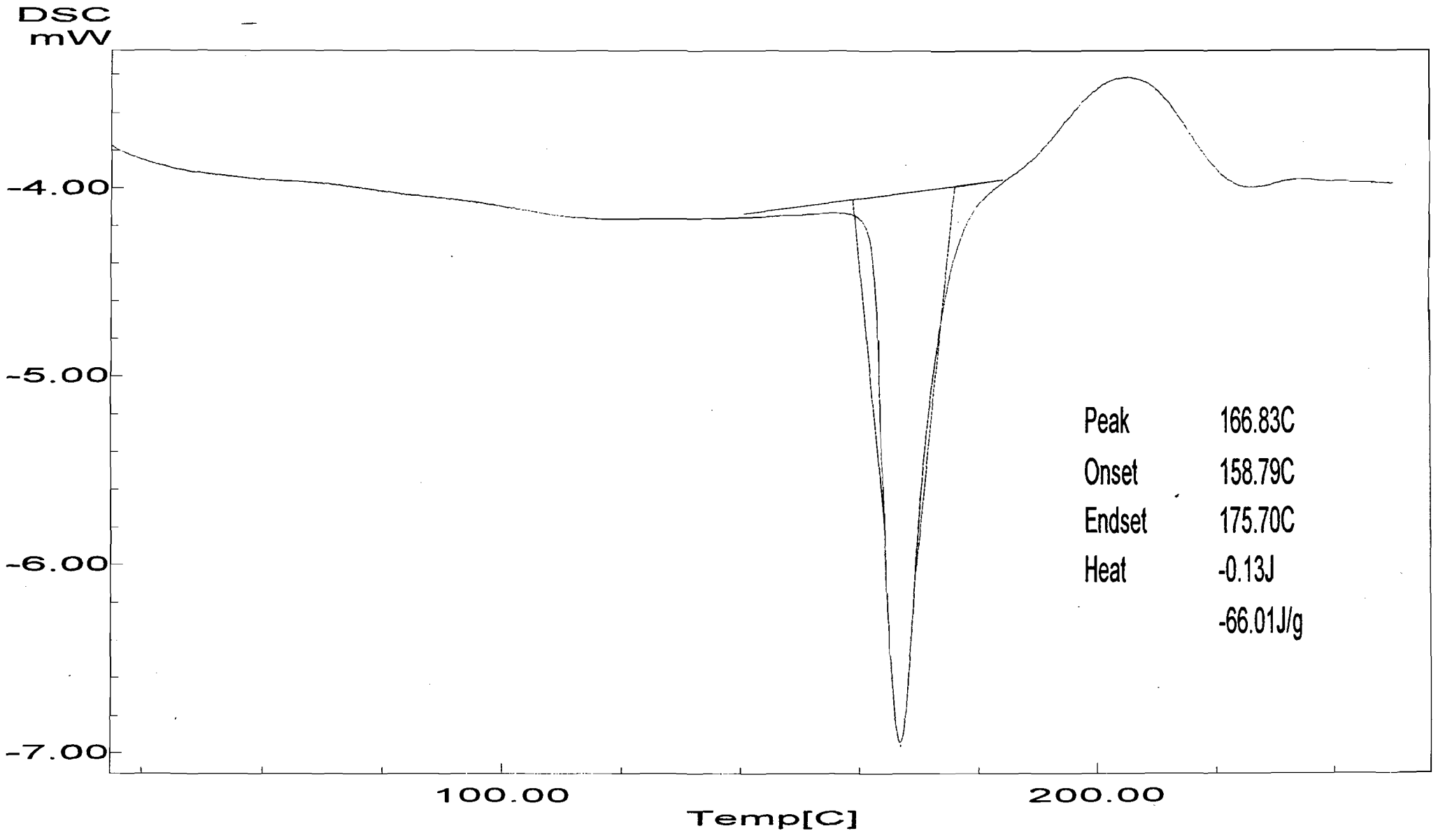
3 weeks at 40 deg. C + 75 RH (Famotidine + Lactose)



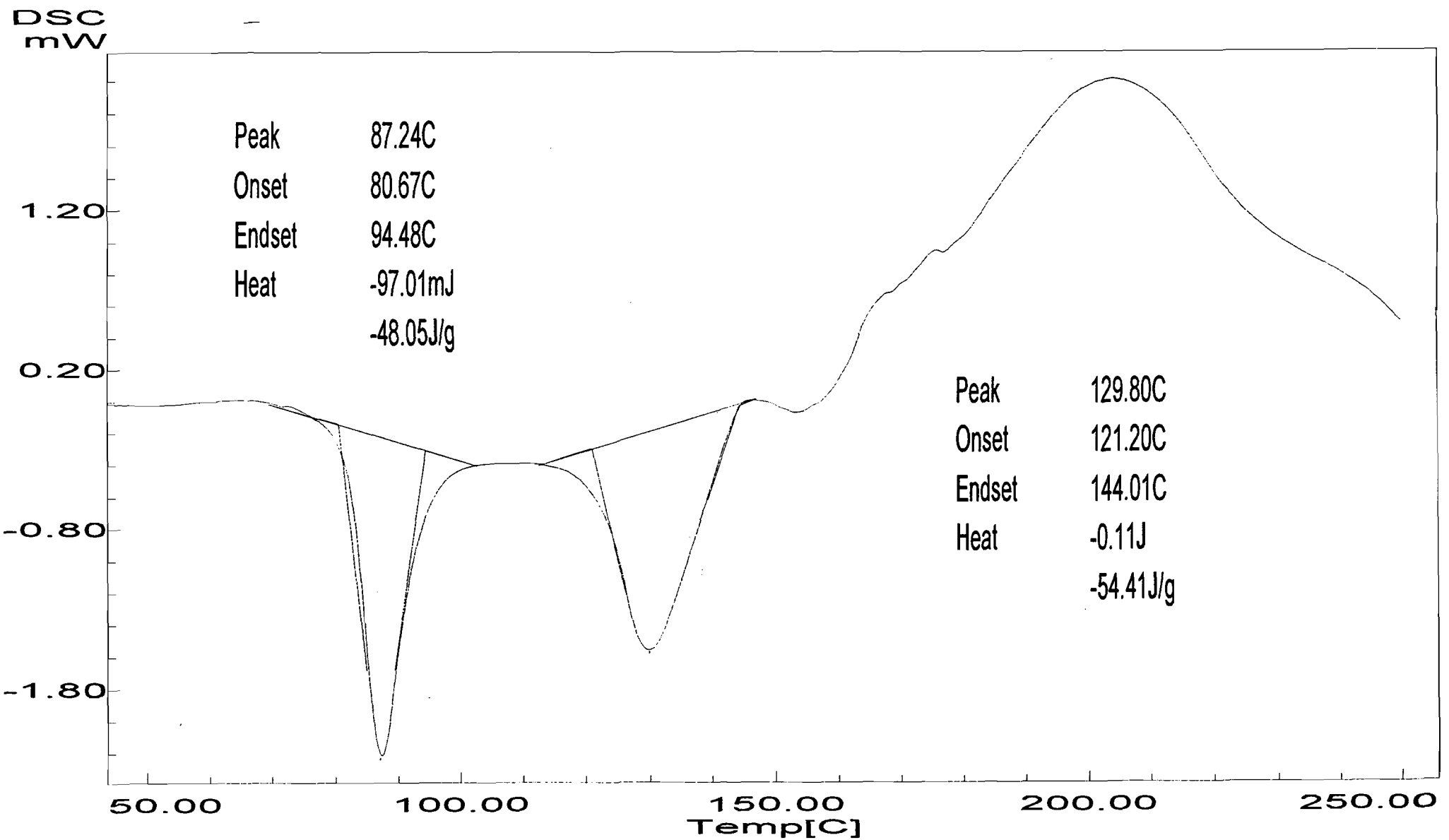
3 weeks at 40 deg. C + 75 RH (Famotidine + Sorbitol)



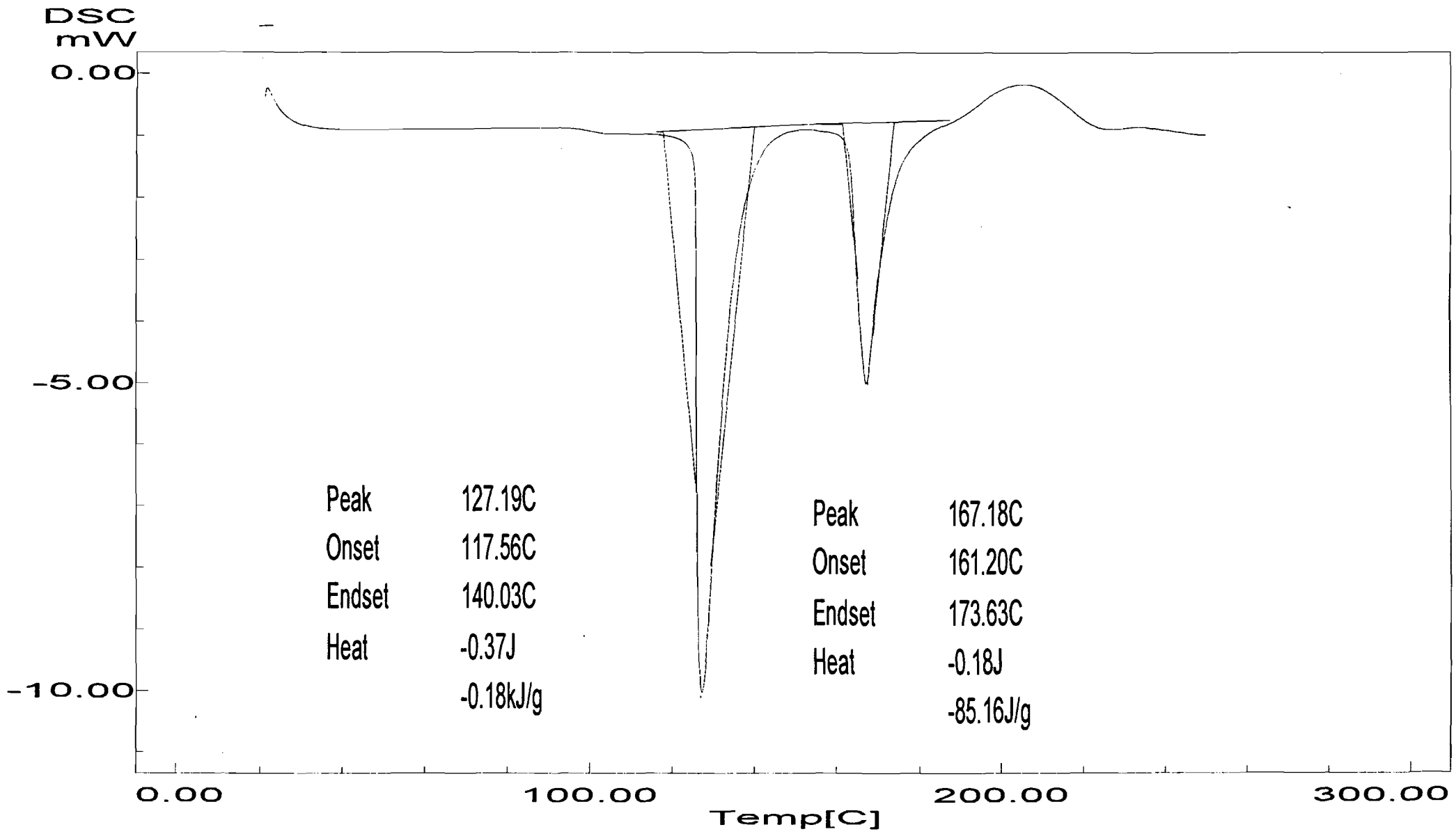
3 weeks at 40 deg. C + 75 RH (Famotidine + Microcrystalline Cellulose)



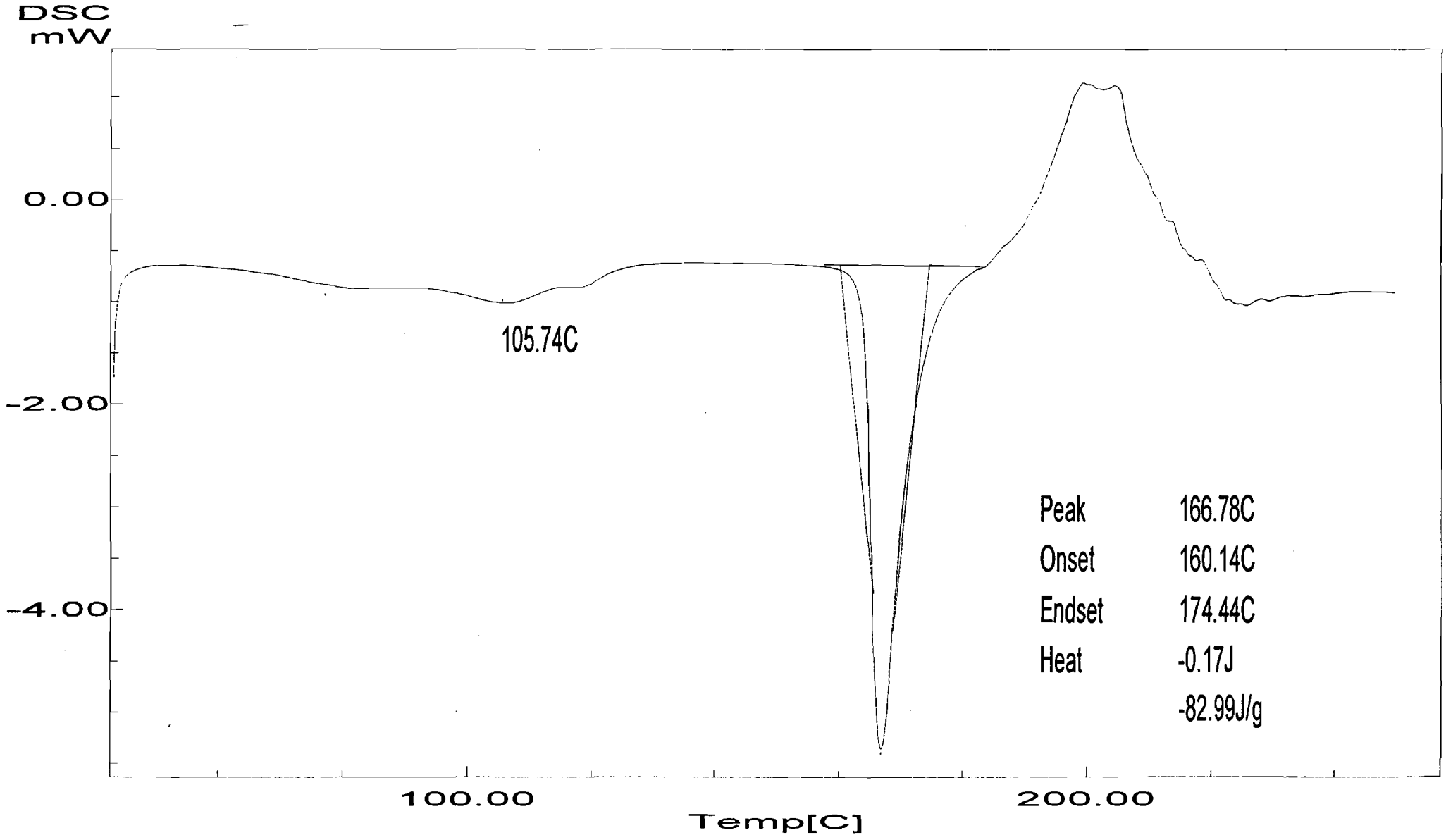
3 weeks at 40 deg. C + 75 RH (Famotidine + Emdex)



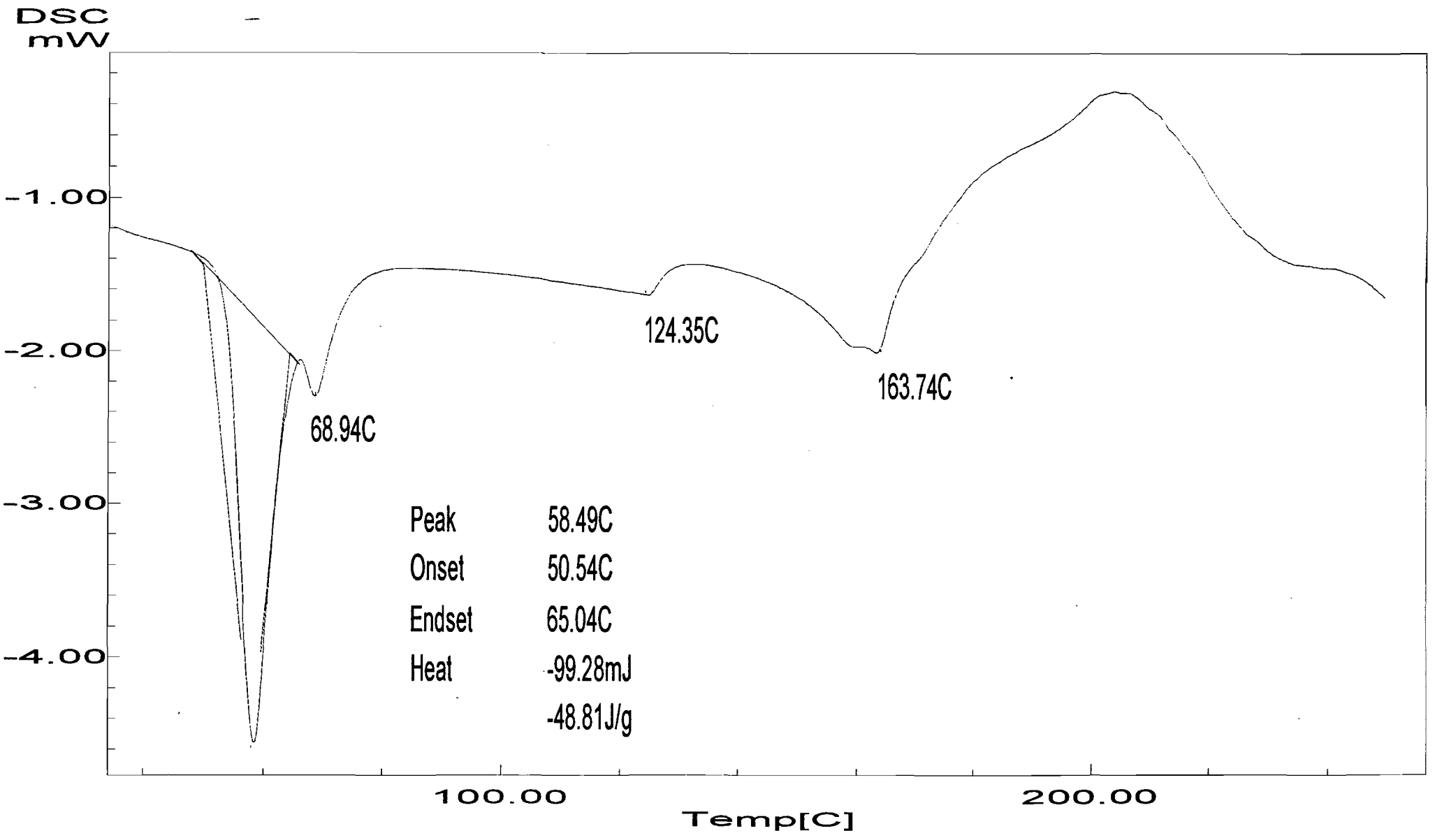
3 weeks at 40 deg. C + 75 RH (Famotidine + Dicalcium Phosphate)



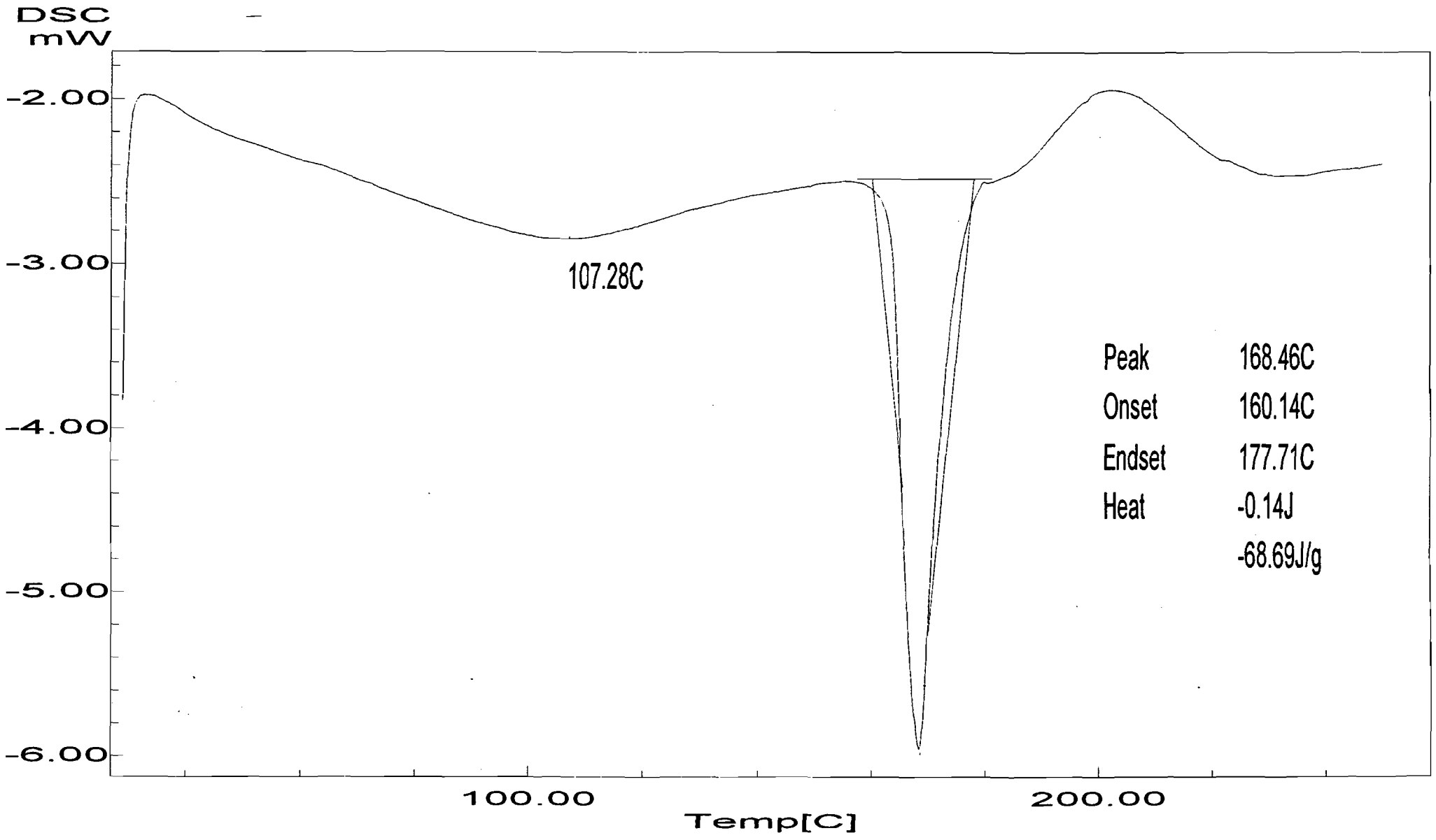
3 weeks at 40 deg. C + 75 RH (Famotidine + Magnesium Stearate)



3 weeks at 40 deg. C + 75 RH (Famotidine + Searic Acid)



3 weeks at 40 deg. C + 75 RH (Famotidine + Explotab)



APPENDIX B

Pepcid AC dissolution results

Pepcid AC tablets : Batch No. 940059

Dissolution results

Sample in 0,1 N HCl for 2 hours		
Sample No.	**Absorbance of sample (Au)**	**% Dissolution**
1	0,397	95,99
2	0,400	96,72

Potency of Standard : 99,8%

Mass of Standard : 10,2mg

Absorbance of Standard (As) : 0,421

Calculation :

$$\% \text{ Dissolution} = \frac{Au}{As} \times \frac{\text{Mass of Standard} \times \text{Potency}}{10}$$

Note : The standard was prepared at the start of the 2 hour test period, so that any effects due to acid degradation were negated.

APPENDIX C

Direct compression excipient results for 10mg famotidine tablets

Famotidine 10mg tablets

In-process results

BATCH No. : P19-2 A			
POWDER			
Moisture (%)	**Flow (s)**	**Angle of repose (°)**	
0,00	$\frac{12,5 + 12,9}{2} = 12,7$	$\frac{27,9 + 27,8}{2} = 27,9$	
TABLETS			
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Appearance**
7,22	4,55	195	Clour:slightly off-
7,21	4,60	202	white
7,20	4,55	200	Shape:biconvex,circular
7,19	4,45	188	Surface:shiny,smooth
7,19	4,56	**173**	**Hardness (N)**
7,20	4,55	200	25
7,19	4,54	195	61
7,19	4,45	203	78
7,20	4,47	191	68
7,20	4,48	198	75
7,19	4,53	199	28
7,22	4,59	200	78
7,19	4,57	191	70
7,19	4,56	181	57
7,20	4,57	180	55
7,20	4,60	189	Average:59,5
7,18	4,56	180	Range:25-78
7,20	4,46	204	s:19,2
7,19	4,56	201	RSD:32,27%
7,20	4,54	195	**Friability (%)**
Average:7,20	Average:4,54	Average:193,3	$\frac{(3,851g - 3,838g) \times 100}{3,851g} = 0,34\%$
Range:7,18-7,22	±5%:4,31-4,77	±7,5%:178,8-207,8	
s:0,01	Range:4,45-4,60	±15%:164,3-222,2	
RSD:0,14%	s:0,05	Range:173-204	
	RSD:1,07%	s:8,9	**Disintegration (min.)**
		RSD:4,62%	**19**

Famotidine 10mg tablets`

Post-compression results

BATCH No. : P19-2 A			
Diameter (mm)	**Thickness (mm)**	**Mass Uniformity (mg)**	**Hardness (N)**
7,23	4,55	201	40
7,28	4,62	200	33
7,22	4,64	203	44
7,32	4,65	200	42
7,23	4,62	191	26
7,22	4,62	201	38
7,26	4,72	196	48
7,21	4,65	177	31
7,27	4,61	200	51
7,25	4,52	195	48
Average:7,25	Average:4,62	200	Average:40,1
Range:7,21-7,32	±5%:4,39-4,85	193	Range:26-51
s:0,03	Range:4,52-4,72	197	s:8,2
RSD:0,47%	s:0,05	194	RSD:20,34%
	RSD:1,19%	192	
		203	**Friability (%)**
		198	$\frac{(3,888g - 3,870g) \times 100\%}{3,888g}$
		197	
		203	
		202	= 0,47%
		Average:197,2	
		±7,5%:182,4-212,0	**Disintegration (min.)**
		±15%:167,6-226,8	**19min. 43s - 20min. 52s**
		Range:177-203	
		s:6,0	
		RSD:3,06%	

Famotodine 10mg tablets

In-process results

BATCH No. : P19-2 B			
POWDER			
Moisture (%)	**Flow (s)**	**Angle of repose (°)**	
0,30	$\frac{13,8 + 13,3}{2} = 13,6$	$\frac{34,0 + 34,5}{2} = 34,3$	
TABLETS			
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Appearance**
7,13	5,43	209	Colour:white
7,12	5,39	208	Shape:biconvex,circular
7,13	5,40	209	Surface:matt,**sticking**
7,12	5,41	205	
7,12	5,40	206	**Hardness (N)**
7,12	5,42	208	60
7,12	5,43	209	58
7,14	5,45	209	62
7,11	5,41	207	59
7,10	5,41	208	60
7,11	5,43	208	38
7,12	5,41	201	56
7,13	5,41	207	70
7,12	5,41	204	73
7,11	5,43	205	56
7,12	5,42	204	Average:59,2
7,12	5,43	210	Range:38-73
7,13	5,40	205	s:9,4
7,12	5,41	207	RSD:15,80%
7,16	5,39	209	**Friability (%)**
Average:7,12	Average:**5,41**	Average:206,9	$\frac{(4,147g - 4,144g) \times 100}{4,147g} = 0,07\%$
Range:7,10-7,16	±5%:5,14-5,68	±7,5%:191,4-222,4	
s:0,01	Range:5,39-5,45	±15%:175,9-237,9	
RSD:0,18%	s:0,02	Range:201-210	
	RSD:0,28%	s:2,3	**Disintegration (min.)**
		RSD:1,11	5,5

Famotidine 10mg tablets

Post-compression results

BATCH No. : P19-2 B			
Diameter (mm)	**Thickness (mm)**	**Mass Uniformity (mg)**	**Hardness (N)**
7,11	5,46	190	87
7,17	5,49	**178**	80
7,17	5,45	207	48
7,13	5,46	187	81
7,16	5,49	208	72
7,18	5,48	205	34
7,17	5,43	203	86
7,13	5,43	202	64
7,17	5,46	207	74
7,16	5,43	**176**	45
Average:7,16	Average:**5,46**	208	Average:67,1
Range:7,11-7,18	±5%:5,19-5,73	190	Range:34-87
s:0,02	Range:5,43-5,49	201	s:18,7
RSD:0,32%	s:0,02	186	RSD:27,85%
	RSD:0,43%	202	
		204	**Friability (%)**
		182	$\frac{(3,962g - 3,950g) \times 100\%}{3,962g}$
		200	
		181	
		196	= 0,30%
		Average:195,7	
		±7,5%:181,0-210,4	**Disintegration (min.)**
		±15%:166,3-225,1	2min. 27s - 3min. 52s
		Range:176-208	
		s:10,8	
		RSD:5,54%	

Famotidine 10mg tablets

In-process results

BATCH No. : P19-2 C			
POWDER			
Moisture (%)	**Flow (s)**	**Angle of repose (°)**	
1,60	15,7	37,5	
TABLETS			
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Appearance**
7,21	4,87	196	Colour:off-white
7,20	4,87	194	Shape:biconvex,circular
7,19	4,88	200	Surface:matt,smooth
7,19	4,89	194	
7,19	4,90	199	**Hardness (N)**
7,21	4,85	198	55
7,19	4,88	203	74
7,19	4,88	205	47
7,19	4,87	192	61
7,18	4,86	195	60
7,19	4,83	200	67
7,18	4,87	200	58
7,19	4,88	198	55
7,21	4,88	200	51
7,18	4,84	194	55
7,19	4,82	200	Average:58,3
7,19	4,84	199	Range:47-74
7,19	4,86	202	s:7,8
7,21	4,84	200	RSD:13,36%
7,22	4,87	195	**Friability (%)**
Average:7,19	Average:**4,86**	Average:198,2	$\frac{(3,957g - 3,946g) \times 100}{3,957g}$
Range:7,18-7,22	±5%:4,62-5,10	±7,5%:183,3-213,1	
s:0,01	Range:4,82-4,90	±15%:168,5-227,9	
RSD:0,16%	s:0,02	Range:192-205	= 0,28%
	RSD:0,43%	s:3,4	**Disintegration (min.)**
		RSD:1,72%	5

Famotidine 10mg tablets

Post-compression results

BATCH No. : 19-2 C			
Diameter (mm)	**Thickness (mm)**	**Mass Uniformity (mg)**	**Hardness (N)**
7,15	4,90	198	58
7,22	4,86	196	51
7,23	4,91	198	86
7,21	4,97	200	51
7,22	4,89	202	60
7,24	4,90	197	52
7,27	4,95	193	55
7,28	4,97	197	46
7,20	4,98	198	54
7,27	4,92	198	51
Average:7,23	Average:**4,93**	195	Average:56,4
Range:7,15-7,28	±5%:4,68-5,18	198	Range:46-86
s:0,04	Range:4,86-4,98	198	s:11,1
RSD:0,54%	s:0,04	196	RSD:19,73%
	RSD:0,82%	200	
		200	**Friability (%)**
		198	$\frac{(3,949g - 3,936g) \times 100\%}{3,949g}$
		202	
		195	
		189	= 0,33%
		Average:197,4	
		±7,5%:182,6-212,2	**Disintegration (min.)**
		±15%:167,8-227,0	4min. 0s - 9min. 11s
		Range:189-202	
		s:3,0	
		RSD:1,52%	

Famotidine 10mg tablets

In-process results

BATCH No. : P19-2 D

POWDER

Moisture (%)	**Flow (s)**	**Angle of repose (°)**
0,20	$\frac{10,3 + 9,9}{2}$ = 10,1	$\frac{28,6 + 28,5}{2}$ = 28,6

TABLETS

Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Appearance**
7,18	4,56	**173**	Colour:off-white
7,20	4,62	203	Shape:biconvex,circular
7,21	**4,83**	206	Surface:shiny,**sticking**
7,19	4,59	**176**	
7,18	4,71	209	**Hardness (N)**
7,20	4,42	**238**	112
7,20	4,44	185	52
7,19	4,58	**175**	49
7,20	4,48	**223**	41
7,20	4,45	209	132
7,16	4,61	203	238
7,18	4,41	**183**	49
7,17	4,40	184	44
7,16	**4,92**	**176**	131
7,19	4,44	199	40
7,16	4,55	**176**	Average:88,8
7,19	4,45	213	Range:40-238
7,16	4,48	209	s:**64,7**
7,14	4,42	**247**	RSD:**72,83%**
7,18	4,41	**179**	**Friability (%)**
Average:7,18	Average:4,54	Average:198,3	$\frac{(3,687g - 3,669g) \times 100}{3,687}$
Range:7,14-7,21	±5%:4,31-4,77	±7,5%:183,4-213,2	
s:0,02	Range:4,40-**4,92**	±15%:168,6-228,0	
RSD:0,26%	s:**0,14**	Range:**173-247**	= 0,49%
	RSD:**3,19%**	s:**21,6**	**Disintegration (min.)**
		RSD:**10,90%**	13

Famotidine 10mg tablets

Post-compression results

BATCH No. : P19-2 D			
Diameter (mm)	**Thickness (mm)**	**Mass Uniformity (mg)**	**Hardness (N)**
7,23	4,54	**204**	28
7,20	**4,94**	**227**	30
7,18	4,45	173	181
7,19	4,59	180	26
7,24	4,50	**201**	27
7,29	4,76	177	33
7,23	4,48	179	83
7,21	4,45	179	32
7,18	4,43	197	29
7,23	4,48	175	34
Average:7,22	Average:4,56	173	Average:50,3
Range:7,18-7,29	±5%:4,33-4,79	173	Range:**26-181**
s:0,03	Range:4,43-**4,94**	175	s:**48,9**
RSD:0,47%	s:**0,16**	175	RSD:**97,28%**
	RSD:**3,60%**	176	
		172	**Friability (%)**
		222	(3,744g - 3,738g) x 100%
		169	3,744g
		178	
		170	= 0,16%
		Average:183,8	
		±7,5%:170,0-197,6	**Disintegration (min.)**
		±15%:156,2-211,4	4min. 59s - 12min. 0s
		Range:**169-227**	
		s:**17,1**	
		RSD:**9,29%**	

Famotidine 10mg tablets

In-process results

BATCH No. : P19-2 E

POWDER

Moisture (%)	Flow (s)	Angle of repose (°)
0,00%	$\frac{11,2 + 11,0}{2}$ = 11,1	$\frac{30,3 + 30,6}{2}$ = 30,5

TABLETS

Diameter (mm)	Thickness (mm)	Mass (mg)	Appearance
7,20	3,54	204	Colour:white
7,20	3,51	203	Shape:biconvex,circular
7,21	3,53	207	Surface:shiny,smooth
7,21	3,55	208	
7,20	3,54	206	**Hardness (N)**
7,19	3,54	203	31
7,21	3,55	207	33
7,20	3,59	205	30
7,19	3,57	206	30
7,19	3,57	203	33
7,20	3,58	208	29
7,20	3,59	205	33
7,19	3,56	207	30
7,21	3,56	206	34
7,22	3,58	204	33
7,21	3,59	207	Average:31,6
7,21	3,57	205	Range:29-34
7,19	3,61	206	s:1,8
7,21	3,57	203	RSD:5,62%
7,21	3,57	205	**Friability (%)**
Average:7,20	Average:3,56	Average:205,4	$\frac{(4,110g - 4,073g) \times 100}{4,110g}$ = 0,90%
Range:7,19-7,21	±5%:3,38-3,74	±7,5%:190,0-220,8	
s:0,02	Range:3,51-3,61	±15%:174,6-236,2	
RSD:0,34%	s:0,02	Range:203-208	**Disintegration (min.)**
	RSD:0,68%	s:1,7	**> 30**
		RSD:0,81	

Famotodine 10mg tablets

Post-compression results

BATCH No. : P19-2 E			
Diameter (mm)	**Thickness (mm)**	**Mass Uniformity (mg)**	**Hardness (N)**
7,22	3,60	203	39
7,29	3,58	206	25
7,23	3,61	213	36
7,21	3,62	206	47
7,19	3,60	199	30
7,26	3,57	204	29
7,19	3,57	206	39
7,22	3,62	203	35
7,27	3,62	216	36
7,23	3,56	205	35
Average:7,23	Average:3,60	205	Average:35,1
Range:7,19-7,29	±5%:3,42-3,78	211	Range:25-47
s:0,03	Range:3,56-3,62	**185**	s:6,1
RSD:0,46%	s:0,02	206	RSD:17,48%
	RSD:0,65%	212	
		200	**Friability (%)**
		204	$\frac{(4,096g - 4,065g) \times 100\%}{4,096g}$
		207	
		203	
		203	= 0,76%
		Average:204,9	
		±7,5%:189,5-220,3	**Disintegration (min.)**
		±15%:174,2-235,6	**> 30min.**
		Range:185-216	
		s:6,3	
		RSD:3,08%	

APPENDIX D

Stability results for 10mg famotidine tablets

Famotidine 10mg tablets

Stability results

BATCH No. : P19-4		TEST STAGE : Initial	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 185-215**	**Spec. : 40-120**
7,20	4,42	202	57
7,19	4,44	208	64
7,19	4,43	200	65
7,19	4,43	201	68
7,20	4,43	202	61
7,19	4,41	201	77
7,19	4,43	205	66
7,19	4,42	200	66
7,19	4,43	202	63
7,19	4,45	203	61
Average : 7,19	Average : 4,43	204	Average : 64,8
Range : 7,19-7,20	Range : 4,41-4,45	206	Range : 57-77
s : 0,01	s : 0,01	202	s : 5,3
RSD : 0,06%	RSD : 0,25%	202	RSD : 8,22%
Appearance		203	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		199	**Spec. : < 1**
		201	$\frac{(4,039g - 4,027g) \times 100}{4,039g}$
		201	
		203	= 0,30 %
Complies		202	**Disintegration (min.)**
		Average : 202,4	**Spec. : < 15**
Assay (mg/tablet)		Range : 199-208	0min. 31s - 0min. 35s
Spec. : 9-11		s : 2,1	**Dissolution (%)**
10,2		RSD : 1,05%	**Spec. : NLT 75%/30 min.**
			103,99%

Famotidine 10mg tablets

Stability results

BATCH No. : P19-4		**TEST STAGE : 3 Months Humidity**	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 185-215**	**Spec. : 40-120**
7,17	4,45	204	57
7,18	4,47	204	55
7,17	4,42	202	52
7,18	4,50	204	52
7,18	4,41	202	56
7,20	4,47	202	56
7,18	4,45	205	61
7,18	4,39	204	61
7,17	4,42	204	62
7,18	4,44	194	63
Average : 7,18	Average : 4,44	206	Average : 57,5
Range : 7,17-7,20	Range : 4,39-4,50	205	Range : 52-63
s : 0,01	s : 0,03	201	s : 4,03
RSD : 0,12%	RSD : 0,74%	202	RSD : 7,02%
Appearance		200	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		202	**Spec. : < 1**
		203	$\frac{(4,059-4,046) \times 100}{4,059}$
		203	
		203	= 0,32%
Complies*		205	**Disintegration (min.)**
		Average :202,8	**Spec. : < 15**
Assay (mg/tablet)		Range : 194-206	1min. 21s - 2 min. 5s
Spec. : 9-11		s : 2,6	**Dissolution (%)**
9,78		RSD : 1,26%	**Spec. : NLT 75%/30 min.**
			88,04%

* Slight brown discolouration is evident when compared with a room temperature sample

Famotidine 10mg tablets

Stability results

BATCH No. : P19-5		TEST STAGE : Initial	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 185-215**	**Spec. : 40-120**
7,19	3,60	198	85
7,19	3,59	201	72
7,20	3,60	201	94
7,20	3,60	208	70
7,20	3,59	197	71
7,20	3,60	202	59
7,22	3,59	202	69
7,19	3,60	200	70
7,23	3,59	204	69
7,20	3,60	201	87
Average : 7,20	Average : 3,60	202	Average : 74,6
Range : 7,19-7,23	Range : 3,59-3,60	202	Range : 59-94
s : 0,01	s : 0,01	201	s : 10,6
RSD : 0,18%	RSD : 0,14%	201	RSD : 14,18
Appearance		200	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		201	**Spec. : < 1**
		202	$\frac{(4,029g - 4,004g) \times 100}{4,029g}$
		203	
		203	= 0,62%
Complies		200	**Disintegration (min.)**
		Average : 201,5	**Spec. : < 15**
Assay (mg/tablet)		Range : 197-208	0min. 28s - 0min. 34s
Spec. : 9-11		s : 2,2	**Dissolution (%)**
8,1		RSD : 1,11%	**Spec. : NLT 75%/30 min.**
			82,35%

Famotidine 10mg tablets

Stability results

BATCH No. : P19-5		**TEST STAGE : 3 Months Humidity**	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 185-215**	**Spec. : 40-120**
7,21	3,62	202	86
7,23	3,63	204	83
7,21	3,61	200	101
7,21	3,62	203	84
7,21	3,61	204	88
7,22	3,62	202	79
7,22	3,62	201	54
7,24	3,60	206	75
7,21	3,60	199	88
7,23	3,65	204	83
Average : 7,22	Average : 3,62	201	Average : 82,1
Range : 7,21-7,24	Range : 3,60-3,65	202	Range : 54-101
s : 0,01	s : 0,01	201	s : 12,0
RSD : 0,15%	RSD : 0,41%	203	RSD : 14,62%
Appearance		203	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		201	**Spec. : < 1**
		204	$\frac{(4,034-4,002) \times 100}{4,034} = 0,79\%$
		201	
		202	
Complies		202	**Disintegration (min.)**
		Average : 202,3	**Spec. : < 15**
Assay (mg/tablet)		Range : 199-206	25s - 38s
Spec. : 9-11		s : 1,7	**Dissolution (%)**
7,99		RSD : 0,82%	**Spec. : NLT 75%/30 min.**
			72,60%

Famotidine 10mg tablets

Stability results

BATCH No. : P19-7		TEST STAGE : Initial	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 167-193**	**Spec. : 40-120**
7,25	4,95	182	66
7,21	4,82	183	55
7,19	4,89	185	64
7,17	4,84	180	67
7,19	4,92	184	63
7,20	4,88	181	62
7,19	4,91	185	58
7,16	4,89	183	66
7,24	4,89	182	67
7,23	4,88	184	74
Average : 7,20	Average : 4,89	184	Average : 64,2
Range : 7,16-7,25	Range : 4,82-4,95	181	Range : 55-74
s : 0,03	s : 0,04	183	s : 5,2
RSD : 0,41%	RSD : 0,76%	183	RSD : 8,17%
Appearance		181	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		186	**Spec. : < 1**
		181	$\frac{(3,6771-3,6714) \times 100}{3,6771} = 0,16\%$
		188	
		184	
Complies		186	**Disintegration (min.)**
		Average : 183,3	**Spec. : < 15**
Assay (mg/tablet)		Range : 180-188	11s - 15s
Spec. : 9-11		s : 2,1	**Dissolution (%)**
9,78		RSD : 1,12%	**Spec. : NLT 75%/30 min.**
			96,71%

Famotidine 10mg tablets

Stability results

BATCH No. : P19-7		TEST STAGE : 3 Months Humidity	
Diameter (mm)	**Thickness (mm)**	**Mass (mg)**	**Hardness (N)**
Spec. : To be established	**Spec. : To be established**	**Spec.: 167-193**	**Spec. : 40-120**
7,26	5,00	181	52
7,22	4,99	189	48
7,23	5,03	182	53
7,24	5,00	184	52
7,29	5,02	189	49
7,22	5,01	184	54
7,26	5,03	185	55
7,25	5,01	183	53
7,21	5,02	189	46
7,26	5,04	179	52
Average : 7,24	Average : 5,02	183	Average : 51,4
Range : 7,21-7,29	Range : 4,99-5,04	183	Range : 46-55
s : 0,02	s : 0,02	184	s : 2,8
RSD : 0,34%	RSD : 0,32%	190	RSD : 5,52%
Appearance		174	**Friability (%)**
Spec. : White to off-white, biconvex, circular tablet, with no visible defects		184	**Spec. : < 1**
		188	$\frac{(3,688-3,688) \times 100}{3,688}$
		186	
		185	= 0%
Complies		184	**Disintegration (min.)**
		Average :184,3	**Spec. : < 15**
Assay (mg/tablet)		Range : 174-190	8s - 16s
Spec. : 9-11		s : 3,8	**Dissolution (%)**
9,70		RSD :	**Spec. : NLT 75%/30 min.**
		2,05%	98,54%