

Characterization of solid-state degradation behaviour of Acebrophylline under accelerated thermal and non-thermal conditions

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Abstract

Proper formulation is an important aspect of any dosage form design. A drug-excipient compatibility screening model was developed by which potential stability problems due to interactions of drug substances with excipients in solid dosage forms can be predicted. The techniques of thermal and isothermal stress testing (IST) were used to assess the compatibility of Acebrophylline with selected excipients. Initially, differential scanning calorimeter (DSC) was used to evaluate the compatibility. IR spectrum of drug-excipient mixture was also compared with that of pure drug and excipient. Compatibility of excipients defined in the prototype formula was tested using IST. Based on the DSC and FT-IR results, lactose monohydrate, Mannitol, croscarmellose sodium, talc, sod benzoate, silicon dioxide, calcium hydrogen phosphate, eudragit, polyvinylpyrrolidone, sodium alginate and starch when added alone or in combination were found to be compatible with Acebrophylline.

Keywords: Acebrophylline, Solid-State degradation, DSC, FT-IR.

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1. Introduction

The formulation of a stable and effective dosage form requires careful selection of excipients used to facilitate administration, promote consistent release and bioavailability of the drug and to protect the active moiety from the environment [1]. Although often regarded as 'inert', excipients can in fact readily interact with drugs. The evaluation of drug-excipient compatibility is therefore an essential aspect of any Preformulation study. The two commonly employed compatibility screening techniques are isothermal stress testing of binary drug-excipient mixtures and thermal analysis using either DSC or differential thermal analysis (DTA) [2].

Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy [3]. Study of drug-excipient

compatibility is an important process in the development of a stable solid dosage form. Drug-excipient compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form[4]. A number of techniques can be used to indicate the drug/ excipient interaction. Differential scanning calorimetry (DSC) is one of the well-developed techniques used in detection of incompatibilities in drug/ drug and drug/excipient interactions. Differential thermal analysis (DTA) is similar to DSC in many respects and analogous information about the same range of thermal events can be observed. ² Other non-thermal methods that have been used to indicate the drug/excipient interactions include infrared spectroscopy, optical microscopy and HPLC studies [5].

In the present study, drug/excipient interaction studies were undertaken to establish the compatibility of

Acebrophylline (ACEBRO). Acebrophylline, 1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo-7H-Purine-7-acetic acid compound with trans -4-[(2-amino-3, 5-dibromophenyl) methyl] amino] cyclohexanol [6]. It is a potent mucoregulator and anti-inflammatory drug, with a number of commonly used tablet excipients [7]. According to the literature survey it was found that few analytical methods such as HPLC method, Solid-State Chemistry, TLC - Densitometry method and UV spectrophotometric method were reported for Acebrophylline. [8-11]

The techniques chosen for evaluation were DSC /TG-DTA along with infrared (IR) spectroscopy and HPLC studies [12].

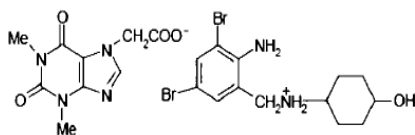


Figure 1: Chemical Structure of Acebrophylline

2. Materials and Methods

Acebrophylline was obtained as a gift sample from Akums Drugs & Pharmaceuticals Ltd. (Haridwar, India). Lactose Monohydrate (LM), Calcium Hydrogen Phosphate (CaHPO₄), Croscarmellose sodium (CCS), Microcrystalline Cellulose (MCC), Mannitol (Mant), Magnesium Stearate (Mg St), Talc (Talc), Sodium Benzoate (Sod Bz), Colloidal Silicon Di- Oxide (SiO₂), Ethyl cellulose (EC), Eudragit L-100 (Edt), Polyvinylpyrrolidone (PVP), Sodium Alginate (SA), Sodium Starch Glycolate (SSG), Modified Starch (Starch) were purchased from Loba Chemie (Mumbai, India) and used.

2.1 Preparation of Samples:

The basic model used in the present study consists of multicomponent blends of drug substances with excipients, which were mixed with 20% added water and stored in closed vials at 50 °C for specific periods of time. Samples were analyzed for chemical and physical stability after 1 and 3 weeks of storage. Accurately weighed amounts of drug substances were placed in 10-mL glass vials, each vial was labelled and weighed amounts of excipients were then added to the vials. The total weight of

drug excipient blend in a vial was usually kept at about 200 mg. The amount of drug substance in a blend was determined on the basis of the expected drug-to-excipient ratio in the final formulation. The highest expected drug-to-excipient ratio was usually used. Both the highest and the lowest drug-to-excipient ratios were occasionally used to bracket drug concentrations in a formulation. The powder in each vial was mixed with the tip of capillary or a thin glass rod and 20% water (40 µL per 200 mg blend) was then added using a micropipette. The blend was further mixed, and to prevent any loss of material, the tip of the stirrer was usually broken and left inside the vial. Each vial was sealed tightly using a Teflon-lined screw cap. The total number of drug-excipient blends for each study may be selected by statistical design. However, because it might be necessary to screen many diluents, lubricants, binders, disintegrants, coloring agents, coating agents, and so forth for a particular formulation, the number of blends selected this way becomes very high. To limit the number of samples, the drug-excipient compatibility testing may be conducted in two phases. In the first phase, the compatibility of drug with diluents and lubricants is tested, and on the basis of the results, one primary diluent and one primary lubricant are selected. Table 1 provides the design of such a study for ACEBRO tested in the present investigation. Using one drug-diluent-lubricant mixture selected in the first phase, the compatibility of other excipients, such as binders and disintegrants, may then be tested in the second phase.

2.2 Storage and Analysis of Samples:

The closed vials containing drug-excipient blends with added water were stored in oven at 50°C served as Exposed group (Exposed). For comparison with Exposed group, samples were stored as unwetted powder in closed vials at 50°C served as Comparison group (Comp group). While, Drug-excipient blends without added water stored at room temperature which served as control group for Comp. group. Samples were analyzed for chemical and physical stability after 45 days using HPLC, DSC/TG-DTA and FT-IR.

Table No. 1: Statistical Design of Compatibility Study (Phase – I)

NAME Group *Ingredients ↓	Composition of Drug-Excipient Blends												
	1	2	3	4	5	6	7	8	9	10	11	12	13
ACEBRO	200	100	100	100	100	100	100	100	100	100	100	100	100
LM		100				95				95			
MCC			100				95				95		
MANT				100				95				95	
CCS					100				95				95
MG ST						5	5	5	5				
TALC										5	5	5	5

2.3 Experimental

2.3.1 HPLC Method:

PHASE – I: (Selection of Diluent and Lubricant)

The drug-excipient blends which were subjected to various conditions such as Exposed, Comparative and Control samples were analyzed by HPLC after 3 week exposure and % undegraded drug was calculated using equation 1.1 and 1.2. Calculation of percent area was performed online by a computer programme connected to UV detector. The results of HPLC analysis were given in table 2. The HPLC assays were carried out using a Shimadzu binary gradient system consisted of Phenomenex ODS 5 μ C₁₈ column (250 X 4.6 mm), Rheodyne injector, SPD – 10 UV detector and LC 10 ADVP Pumps. The mobile phase consisted of Ammonium Phosphate buffer: Methanol, pH 5 (70:30) at a constant flow rate of 1 mL/min. The injecting volume was 20 μ L and the peak was obtained by UV detection at 273 nm which was used for quantitative determination using pure drug as an external standard. In this condition the retention time of

ACEBRO was 4.55 min. the method was validate: accuracy was expressed as percent recovery of ACEBRO and it was found to be 100.005%. Precision was expressed as coefficient of variation of the method and it was found to be CV=0.256 ($n= 5$). Linearity was tested at five concentrations level (80, 90, 100, 110 and 120 % of label claim) and it was found to be 0.9993. No interfering peaks were pointed out.

$$Cu = \frac{Au}{As} \times Cs \times dF \quad (1.1)$$

Where,

Cu = conc. of unknown
 Au = Area of unknown
 Cs = conc. of std.
 As = Area of Std.
 dF = Dilution factor of Sample
 Weight in mg

$$\% \text{ Undegraded} = \frac{\text{Weight in mg}}{\text{Weight taken in mg}} \times 10 \quad (1.2)$$

Table 2: Observations and Results of HPLC study of Phase – I

Sr. No.	NAME	% AREA (45 days)			% UNDEGRADED DRUG
		CONT	COMP	EXPO	
1	ACEBRO ALONE	99.696	96.452	99.260	74.81
2	ACEBRO + LM	99.249	97.002	39.00	37.71
3	ACEBRO + MANT	99.683	99.250	81.049	67.46
4	ACEBRO + MCC	99.563	99.072	41.96	41.80
5	ACEBRO + CCS	99.336	99.257	98.096	27.77
6	ACEBRO+ CaHPO ₄	99.123	98.965	97.874	26.21
7	ACEBRO+LM + MGST	98.980	97.628	38.77	38.52
8	ACEBRO+MANT+MG ST	99.359	99.353	97.25	20.81
9	ACEBRO+MCC +MG ST	99.570	99.434	99.422	67.60
10	ACEBRO+CCS+MG ST	99.442	92.30	60.98	60.98
11	ACEBRO + LM+ TALC	99.501	97.706	73.20	38.54
12	ACEBRO + MANT + TALC	99.958	98.767	98.763	53.90
13	ACEBRO + MCC+ TALC	99.455	99.367	99.352	76.13
14	ACEBRO + CCS+TALC	99.824	99.323	93.76	87.36
15	ACEBRO + LM + SOD BZ	99.007	97.904	97.709	18.44
16	ACEBRO+MANT+SOD BZ	99.958	98.767	98.763	31.30
17	ACEBRO+ MCC+ SOD BZ	99.464	99.151	98.589	55.70
18	ACEBRO +CCS+ SOD BZ	99.473	99.111	98.976	71.22
19	ACEBRO + LM+ SiO ₂	99.380	98.633	95.382	9.85
20	ACEBRO + MANT + SiO ₂	99.803	98.581	71.75	73.92
21	ACEBRO +MCC+ SiO ₂	99.499	99.396	98.954	60.29
22	ACEBRO+ CCS+ SiO ₂	98.879	85.44	54.13	80.69
23	ACEBRO+CaHPO ₄ +MG ST	99.133	98.830	98.440	36.04
24	ACEBRO+CaHPO ₄ + TALC	99.512	98.174	97.775	29.13
25	ACEBRO+CaHPO ₄ +SOD BZ	99.167	98.615	95.256	43.58
26	ACEBRO+CaHPO ₄ +SiO ₂	99.254	98.798	98.315	35.56

From the HPLC study, microcrystalline cellulose and Magnesium Stearate was selected for Phase – II as primary diluent and primary lubricant as they show less than 30% of degradation.

Phase-II: Using diluent-lubricant mixture (i.e. Microcrystalline cellulose and Magnesium Stearate) selected in the First Phase, the compatibility of other excipients such as binder and disintegrant were tested in

second phase and the results of HPLC analysis were given in table 3.

2.3.2 FT-IR Study: IR spectra of drug and drug-excipient blends were recorded on IR spectrophotometer (Shimadzu Fourier Transform Infrared Spectroscopy Shimadzu 8400S) in the range of 4000-400 cm⁻¹ using potassium bromide discs. The IR spectra of ACEBRO and drug-excipient blends of Phase – I were shown in fig. 1

Table 3: Observations and Results of HPLC study of Phase – II

Sr. No.	NAME	% AREA (45 days)			% UNDEGRADED DRUG
		CONT	EXPO	EXPO	
27	ACEBRO- MCC-MG ST (DRUG BLEND)	99.570	99.434	99.422	67.60
28	DRUG BLEND - ETHYL CELLULOSE	90.15	55.66	45.45	88.36
29	DRUG BLEND - EUDRAGIT	62.41	51.56	42.73	57.75
30	DR BLEND- PVP	55.14	49.38	38.11	35.60
31	DRUG BLEND- SOD ALGINATE	60.95	53.35	44.22	58.58
32	DRUG BLEND- ETHYL CELLULOSE- SSG	55.42	45.66	43.10	46.58
33	DRUG BLEND- EUDRAGIT- SSG	90.98	55.42	53.61	85.88
34	DRUG BLEND- PVP- SSG	87.30	60.18	56.65	83.18
35	DRUG BLEND- SOD ALGINATE- SSG	78.11	63.62	52.24	76.59
36	DRUG BLEND- ETHYLCELLULOSE- STARCH	76.70	67.19	56.99	77.11
37	DRUG BLEND - EUDRAGIT- STARCH	75.78	71.78	46.58	69.05
38	DRUG BLEND- PVP- STARCH	66.11	50.30	42.84	41.21
39	DRUG BLEND - SOD ALGINATE- STARCH	53.93	49.07	42.17	53.40

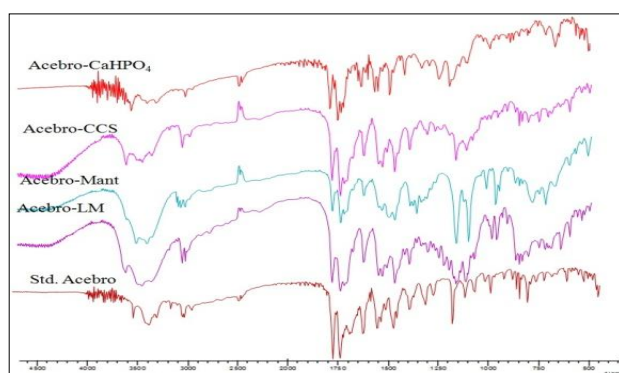


Fig.2. FT-IR spectra of Acebro and drug-diluent blends kept at 50°C for 45 days.

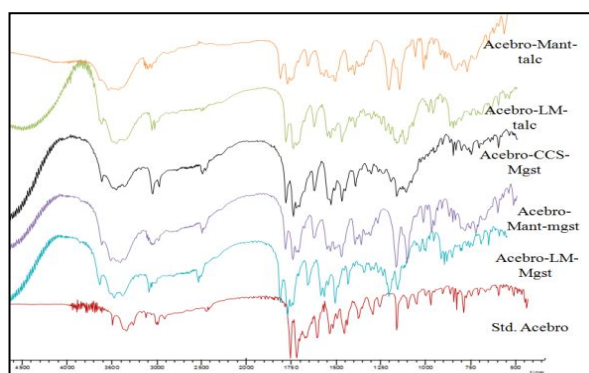


Fig.3. FT-IR spectra of Acebro and drug-diluent-lubricant blends kept at 50°C for 45 days.

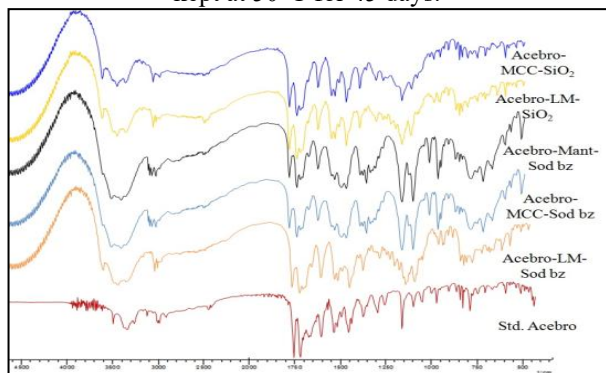


Fig.4. FT-IR spectra of Acebro and drug-diluent-lubricant blends kept at 50°C for 45 days.

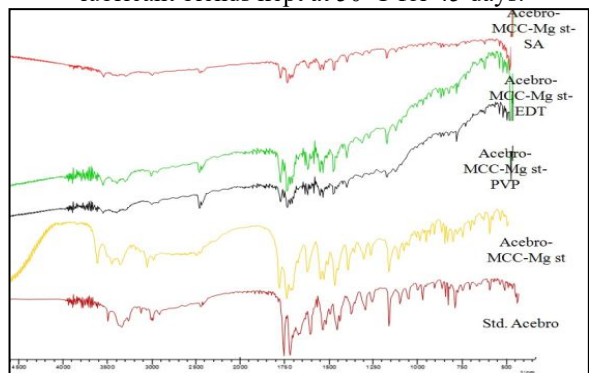


Fig.5. FT-IR spectra of Acebro and drug-excipient blends kept at 50°C for 45 days.

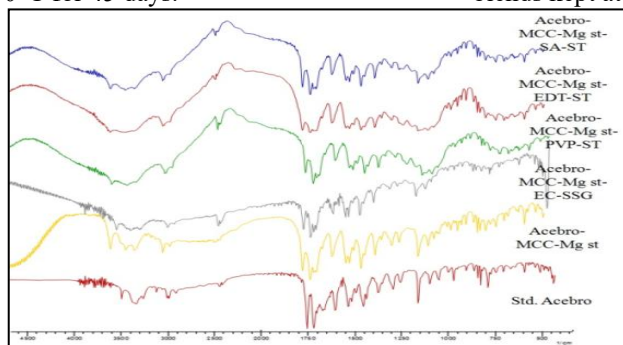


Fig.6. FT-IR spectra of Acebro and drug-excipient blends kept at 50°C for 45 days.

2.3.3 Simultaneous Thermogravimetry (TG) and Differential Thermal Analysis (DTA):

The drug blends of Exposed group in phase – I that showed more than 30% of degradation by HPLC analysis.

Only those samples subjected to TG-DTA Analysis. The heating rate was 5 °C/min and the samples were scanned in the temperature range of 200°C - 400 °C. Thermograms obtained were observed for interaction.

2.3.4 Differential Scanning Calorimetry (DSC): The drug blends that showed a significant degradation results through HPLC analysis in phase – II only those samples subjected to DSC Analysis. The heating rate was 5 °C/min and the samples were scanned in the temperature range of 150°C – 300 °C.

3.Results and Discussion

3.1 Drug – Excipient compatibility testing: Selected TG-DTA scans of drug and drug-excipient blends of phase- I are shown in fig. 6A to 6N

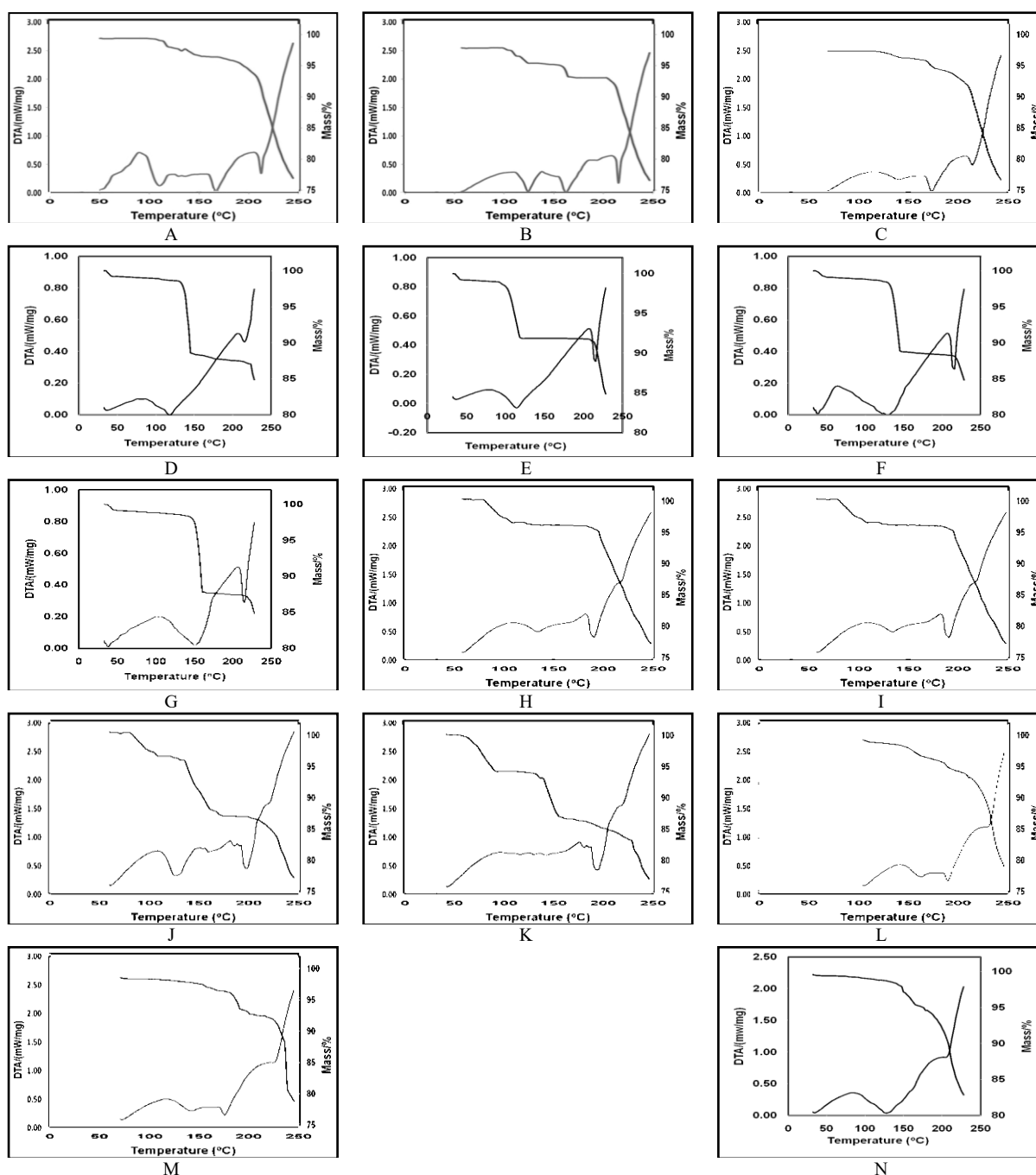


Fig. 7: TG and DTA curves of drug –excipient blends subjected to 50°C for 45 days. A. Std. ACEBRO, B. ACEBRO (Exposed), C. ACEBRO–LM (Exposed), D. ACEBRO–Mant (Exposed), E. ACEBRO–CCS (Exposed), F. ACEBRO–LM –Mg st(Exposed), G. ACEBRO–Mant Mg st(Exposed), H. ACEBRO–CCS –Mg st (Exposed), I. ACEBRO–LM –Talc (Exposed), J. ACEBRO–Mant –Talc (Exposed), K. ACEBRO–Mant –Sod bz (Exposed), L. ACEBRO–MCC –Sod bz (Exposed), M. ACEBRO–LM –SiO₂ (Exposed), N. ACEBRO–MCC –SiO₂ (Exposed)

Table 4: Mass % values of Acebro in various drug-excipient blends

Sr.No.	Name	Temp	Mass %
1.	ACEBRO Standard	217.83914	91.91935
2.	ACEBRO alone	217.83914	91.91935
3.	ACEBRO – LM	215.83914	91.91935
4.	ACEBRO – Mant	215.72373	90.8
5.	ACEBRO – CCS	215.72373	90.8
6.	ACEBRO – LM – Mg St	208.23424	88.27
7.	ACEBRO – Mant – Mg St	215.72373	87.23
8.	ACEBRO– CCS – Mg St	189.65445	96.30109
9.	ACEBRO– LM – Talc	198.77194	89.53
10.	ACEBRO–MCC–SiO ₂	205.73703	93.8
11.	ACEBRO–Mant–Talc	198.77194	88.5
12.	ACEBRO–Mant–Sod bz	189.65445	96.30109
13.	ACEBRO–MCC–Sod bz	169.87996	96.9
14.	ACEBRO–LM–SiO ₂	169.87996	97.7

The thermal behaviour of pure drug, respective excipient, and the combination of drug and excipient is compared in the TG-DTA thermograms. % mass loss of Acebro in various excipient mixtures is summarized in Table 4.

The TG trace of Std. Acebro showed a sharp melting endothermic peak at 217.84 °C with a weight loss of 8.09%. The IR spectra of std. Acebro is shown in fig.1 exhibited the following characteristic bands viz. 1703.03 and 1666.38 cm⁻¹ (C=O ketone), 1089.71 cm⁻¹ (C–N stretch, primary amine), 1309.58 cm⁻¹ (C –N stretch, aromatic tertiary amine), 1550.66 and 1394.44 cm⁻¹ (carboxylate ion), 1645 cm⁻¹ (N–H bend, primary amine), 3292.26 cm⁻¹ (N–H stretch, aromatic primary amine), 1614.31 and 1465.80 cm⁻¹ (Aromatic ring stretching), 3064.68 cm⁻¹ (Ar–CH stretching) and 3448.49 cm⁻¹ (O–H stretching).

TG – DTA trace of Acebro alone (exposed) showed a well-preserved endothermic peak at 217.83 °C with a weight loss of 8.09%. Characteristic bands of Acebro were well retained in the IR spectrum of Acebro alone (exposed) without any new bands, indicating that there was no change in the structure of drug. On the basis of above results, it was concluded that Acebro is thermostable at 50 °C.

TG – DTA trace of Acebro-LM (exposed) showed a well-preserved endothermic peak at 217.83 °C with a weight loss of 8.09 %. But, the IR spectrum of Acebro-LM (exposed) showed the shifting of O–H stretching band from 3448.49 cm⁻¹ to 3500.56 cm⁻¹ as compared to Acebro-LM (control and comparison), std. excipient and std. Acebro. In HPLC assay, area percent was found to be decreased by 61% in Acebro-LM (exposed) as compared to

Standard Acebro which suggested incompatibility with lactose monohydrate.

In case of Acebro–Mant (exposed), the melting endotherm at 217.84 °C of Acebron was missing and a new endothermic peak at 208.23 °C with weight loss of 8.3% was observed. The IR spectrum showed appearance of extra band at 1691.46 cm⁻¹ (w), the shifting of O–H stretching band from 3448.49 cm⁻¹ to 3496.70 cm⁻¹ as compared to Acebro- Mant (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 18.95% in Acebro- Mant (exposed) as compared to Standard Acebro indicating drug–excipient interaction.

In case of Acebro–CCS (exposed), the melting endotherm at 217.84 °C of Acebro was missing and a new endothermic peak at 208.23 °C with a weight loss of 8.3% was observed. While, IR spectrum of Acebro-CCS (exposed) showed appearance of extra bands at 1691.46 cm⁻¹ (w), the shifting of O–H stretching band from 3448.49 cm⁻¹ to 3456.20 cm⁻¹ as compared to Acebro-CCS (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 1.90% in Acebro- CCS (exposed) as compared to Standard Acebro indicating drug–excipient interaction.

In case of Acebro–LM–Mg st (exposed), melting endotherm at 217.84 °C of Acebro disappeared and a new endothermic peak at 208.23 °C was observed with a weight loss of 11.73%. IR spectrum of Acebro- LM-Mg St (exposed) showed shifting of O–H stretching band from 3448.49 cm⁻¹ to 3471.63 cm⁻¹ and shifting of carboxylate ion asymmetric band from 1550.66 cm⁻¹ to 1581.52 cm⁻¹ and the appearance of extra weak bands at 1456.16 cm⁻¹, 1633.59 cm⁻¹ as compared to Acebro-LM-Mg st (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 61.38% in Acebro-LM-Mg st (exposed) as compared to Standard Acebro.

TG – DTA trace Acebro–Mant–Mg st (exposed), the melting endotherm of Acebro was slightly shifted to 215.72 °C with a weight loss of 12.6%. IR spectrum of Acebro-Mant-Mg St (exposed) showed the appearance of extra weak band at 1417.58 cm⁻¹ and shifting of O–H stretching band from 3448.49 cm⁻¹ to 3500.56 cm⁻¹ as compared to Acebro-LM-Mg st (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 2.75% in Acebro-Mant-Mg st (exposed) as compared to Standard Acebro. Thus, it was concluded that Acebro is incompatible with Mannitol and magnesium Stearate when added together.

In TG – DTA trace of Acebro–CCS–Mg st (exposed), the melting endotherm at 217.84°C of Acebro was missing and a new endothermic peak at 189.65 °C with a weight loss of 3.7%. IR spectrum of Acebro–CCS–Mg St (exposed) showed the decreased in intensity of the bands as compared to Acebro–CCS–Mg st (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 39.02% in Acebro–CCS–Mg st (exposed) as compared to Standard Acebro.

In TG – DTA trace of Acebro–LM–Talc (exposed), the melting endotherm at 217.84°C of Acebro was missing and a new endothermic peak at 198.77 °C with a weight loss of 10.47%. IR spectrum of Acebro–LM–Talc (exposed) showed the decreased in intensity of the bands and the shifting of N–H stretching band from 3292.26 to 3334.69 cm^{-1} and shifting of O–H stretching band from 3448.49 cm^{-1} to 3469.70 cm^{-1} as compared to Acebro–LM–Talc (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 26.80% in Acebro–LM–Talc (exposed as compared to Standard Acebro.

In TG – DTA trace of Acebro–Mant–Talc (exposed), the melting endotherm at 217.84°C of Acebro was missing and a new endothermic peak at 198.77 °C withal weight loss of 10.99%. IR spectrum of Acebro–Mant–Talc (exposed) showed the decreased in intensity of the bands and the shifting of N–H stretching band from 3292.26 cm^{-1} to 3334.69 cm^{-1} and appearance of extra band at 3498.63 cm^{-1} (w), and at 1691.46 cm^{-1} (w) and shifting of O–H stretching band from 3448.49 cm^{-1} to 3498.63 cm^{-1} as compared to Acebro–Mant–Talc (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 12.37% in Acebro–Mant–Talc (exposed) as compared to std. Acebro.

In TG – DTA scan of Acebro–Mant–Sod bz (exposed), the melting endotherm at 217.84°C of Acebro was missing and a new endothermic peak at 189.65 °C with a weight loss of 3.7% was observed. IR spectrum of Acebro–Mant–Sod bz (exposed) showed the decreased in intensity of the bands and shifting of O–H stretching band from 3448.49 cm^{-1} to 3494.77 cm^{-1} as compared to Acebro–Mant–Sod bz (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 1.23% in Acebro–Mant–Sod bz (exposed) as compared to std. Acebro. Thus, it can be concluded that Acebro is incompatible with Mannitol and Sodium Benzoate, when added together.

In TG – DTA trace of Acebro–MCC–Sod bz (exposed) showed a weight loss of 3.1% while the characteristic peak pattern (melting endotherm at 217.84°C) of Acebro disappeared and a new endothermic peak at 169.87 °C was observed. IR spectrum of Acebro–MCC–Sod bz (exposed) showed the decreased in intensity of the bands as compared to Acebro–MCC–Sod bz (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 1.411% in Acebro–MCC–Sod bz (exposed) as compared to std. Acebro. From the above data, it can be concluded that Acebro is incompatible with microcrystalline cellulose and Sodium Benzoate, when added together.

In TG – DTA trace of Acebro–LM–SiO₂ (exposed) showed a weight loss of 2.3% while the characteristic peak pattern (melting endotherm at 217.84°C) of Acebro disappeared and a new endothermic peak at 169.87 °C was observed. IR spectrum of Acebro–LM–SiO₂ (exposed) showed the decreased in intensity of the bands and appearance of extra band at 1633.59 cm^{-1} (w) as compared to Acebro–LM–SiO₂ (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 4.62% in Acebro–LM–SiO₂ (exposed) as compared to Std. Acebro. From the above data, it can be concluded that Acebro is incompatible with lactose monohydrate and colloidal silicon dioxide, when added together.

In TG – DTA trace of Acebro–MCC–SiO₂ (exposed), the melting endotherm at 217.84°C of Acebro was shifted to 205.73 °C with a weight loss of 8.55%. IR spectrum of Acebro–MCC–SiO₂ (exposed) showed the decreased in intensity of the bands, shifting of O–H stretching band from 3448.49 cm^{-1} to 3496.70 cm^{-1} as compared to Acebro–MCC–SiO₂ (control and comparison), std excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 1.046% in Acebro–MCC–SiO₂ (exposed) as compared to std. Acebro indicating drug–excipient interaction. From the above data, it can be concluded that Acebro is incompatible with lactose monohydrate and colloidal silicon dioxide, when added together.

Phase – II:

Selected DSC scan of drug and drug-excipient blends are shown in figs. 3. The thermal behaviour of pure drug and the combination of drug and excipient is compared in the DSC thermograms. Heat of fusion or enthalpy (ΔH_f) of Acebro in various excipient mixtures is summarized in Table 5.

Table 5:DSC results of drug and drug-excipient blends

Sr. No	NAME	ONSET TEMP. (°C)	PEAK TEMP.(°C)	ENDSET TEMP. (°C)	ENTHALPY (Jg ⁻¹)
1.	STANDARD ACEBRO	216.44	217.80	219.81	- 228.93
2.	ACEBRO –CaHPO ₄	213.29	216.75	218.72	- 143.41
3.	ACEBRO–MCC–MGST	212.48	214.24	216.47	- 3.02
4.	ACEBRO–MCC–MGST– PVP	213.47	214.97	216.33	- 85.05
5.	ACEBRO–MCC–MGST–EC–SSG	216.43	217.61	218.96	- 18.21
6.	ACEBRO–MCC–MGST–PVP–STARCH	212.06	215.08	217.61	- 115.83
7.	ACEBRO–MCC–MGST–EUDRAGIT	217.38	219.83	221.76	- 128.44
8.	ACEBRO–MCC–MGST–SA–STARCH	217.13	219.08	219.88	- 7.99
9.	ACEBRO–MCC–MGST–SA	214.74	215.24	216.09	- 3.66
10.	ACEBRO–MCC–MGSTEDT–STARCH	213.65	216.04	218.51	- 23.41

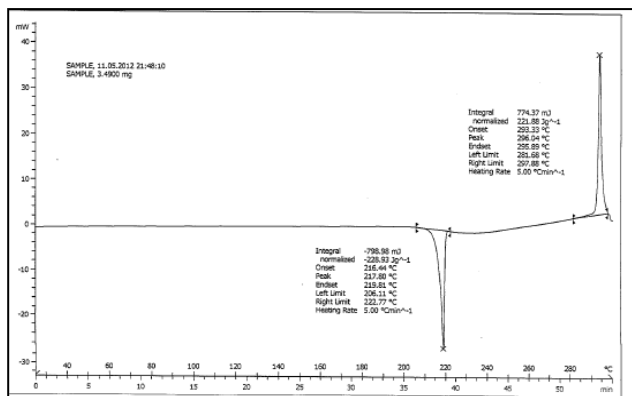
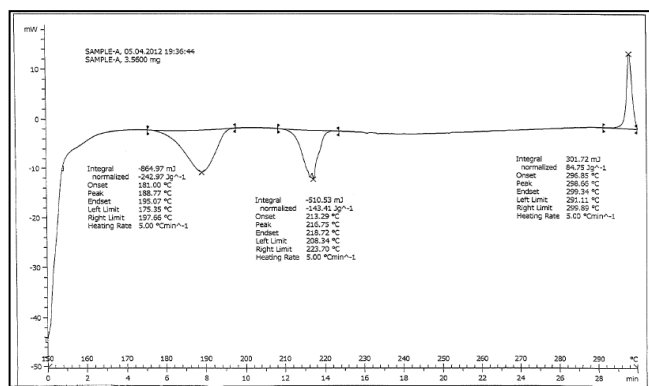


Fig.8. DSC thermogram of Acebro

The DSC trace of Acebro Std (exposed) showed the presence of a sharp melting endothermic peak at 217.80°C and enthalpy value (ΔH_f) of -228.93J/g. An exothermic peak was observed at 296.04°C and enthalpy value of 221.88J/g may be due to decomposition of std. Acebro.

Fig. 9. DSC thermogram of ACEBRO–CaHPO₄

DSC scan of Acebro–CaHPO₄ (exposed) showed the presence of broad endothermic peak at 188.77°C (corresponding to dehydration of bound water). The melting endothermic peak of the drug was resulted into broadening and shifting of peak to 216.75°C with decreased in ΔH_f of -143.41J/g. IR spectrum of Acebro–CaHPO₄ (exposed) showed the disappearance of carboxylate ion band of

1550.66 cm⁻¹ and the appearance of extra band at 1340 cm⁻¹(m) as compared to Acebro–CaHPO₄ (control and comparison), std. excipient and with std. Acebro. In HPLC assay, area percent was found to be decreased by 2.12% Acebro–CaHPO₄ (exposed) as compared to std. Acebro. From the above data, it can be concluded that Acebro is incompatible with calcium hydrogen phosphate, when added together.

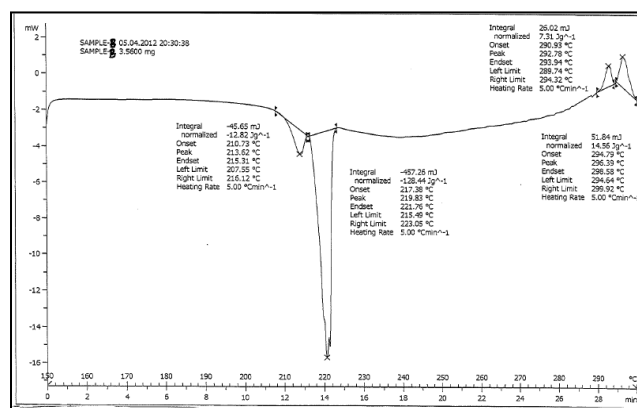


Fig. 10. Thermogram of ACEBRO–MCC–Mg St– EDT

In DSC trace of Acebro–MCC–Mg St (drug blend)–Edt (exposed) showed a small peak present at 213.62 °C may be due to presence of palmitate impurity of magnesium Stearate confirmed from the literature reported by Grag et al. Endothermic peak of Acebro was shifted to higher temperature at 219.83°C with enthalpy change to -128.44J/g. The IR spectrum of Acebro–MCC–Mg St (Drug blend)–Edt (exposed) mixture showed shifting of O–H stretching band from 3448.49 cm⁻¹ to 3456.20 cm⁻¹ and the shifting of carboxylate ion band from 1550.66 cm⁻¹ to 1602.74 cm⁻¹ along with decreased in intensity of the spectrum as compared to Acebro–MCC–Mg St (Drug blend) –Edt mixture (control and comparison) and with std. drug. In HPLC assay, area percent was found to be decreased by 60% in Acebro–MCC–Mg St (Drug blend) –Edt (exposed) mixture as compared to std. Acebro.

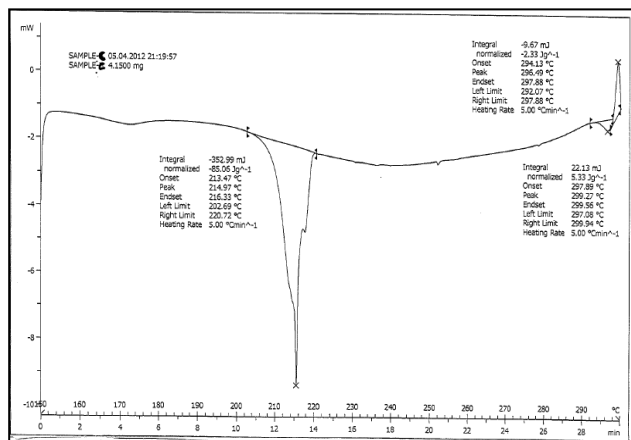


Fig.11. Thermogram of ACEBRO-MCC- Mg St- PVP

In DSC trace of Acebro-MCC-Mg St (drug blend)-PVP (exposed), showed the characteristic peak pattern (endotherm at 217.80 °C) of Acebro disappeared and a new endothermic peak at 214.97 °C with increased in ΔH_f of -85.06 J/g. This could be attributed to the dissolution of Acebro in the excipient blend due to PVP. In addition to DSC, IR spectrum of Acebro-MCC-Mg St (drug blend)-PVP mixture (exposed) showed appearance of extra band at 1240 cm^{-1} , disappearance of C=O band of 1703.03 cm^{-1} and the shifting of O-H band from 3448.49 cm^{-1} to 3475.79 cm^{-1} as compared to Acebro-MCC-Mg St (drug blend)-PVP (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 62% in Acebro-MCC-Mg St (drug blend)-PVP (exposed) mixture as compared to std. Acebro. From the above data, it can be concluded that Acebro is incompatible with polyvinylpyrrolidone (PVP), when added together.

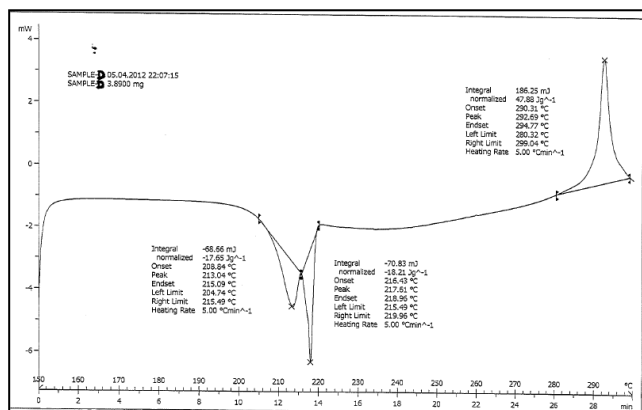


Fig.12. Thermogram of ACEBRO-MCC- Mg St- EC-SSG

In DSC trace of Acebro-MCC-Mg St (drug blend)-EC-SSG (exposed) showed two endothermic peaks. A small peak present at 213.04 °C with enthalpy change to ΔH_f of -17.65 J/g probably due to presence of palmitate

impurity of magnesium Stearate confirmed from the literature reported by Grag et al. Endothermic peak of Acebro was slightly shifted at 217.61 °C with much difference in enthalpy value to -18.21 J/g. The IR spectrum of Acebro-MCC-Mg St (drug blend)-EC-SSG (exposed) mixture showed shifting of N-H stretching to 3305.76 cm^{-1} , shifting of N-H bending to 1635.52 cm^{-1} along with decreased in intensity of the spectrum was observed as compared to Acebro-MCC-Mg St (drug blend)-EC-SSG (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 57% in Acebro-MCC-Mg St (drug blend)-EC-SSG (exposed) mixture as compared to std. Acebro indicating drug-excipient interaction. From the above data, it can be concluded that Acebro is incompatible with ethyl cellulose and sodium starch glycolate, when added together.

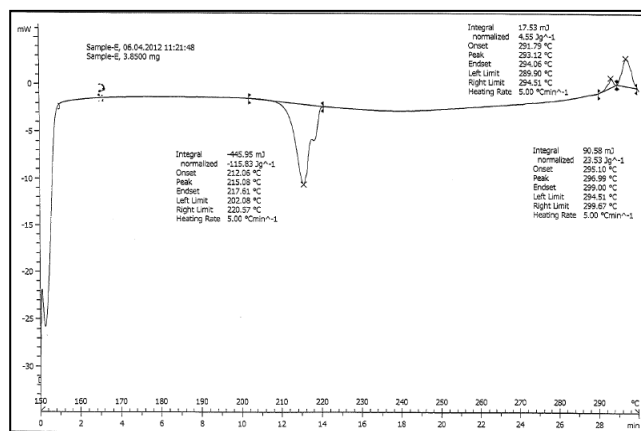


Fig.13. Thermogram of ACEBRO-MCC- Mg St- PVP-STARCH

Two endothermic peaks were observed in the DSC trace of Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed). A small peak present at 211.01 °C with enthalpy change to ΔH_f of -37.39 J/g may be due to presence of palmitate impurity of magnesium stearate confirmed from the literature reported by Grag et al. Endothermic peak of Acebro was shifted to lower temperature at 216.04 °C with large difference in enthalpy value to -23.41 J/g. The IR spectrum of Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed) mixture showed shifting of N-H stretching from 3292.19 cm^{-1} to 3305.76 cm^{-1} along with decreased in intensity of the spectrum as compared to Acebro-MCC-Mg St (drug blend)-EDT-Starch (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 53% in Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed) mixture as compared to std. Acebro indicating drug-excipient interaction. Hence, it can be concluded that, Acebro is incompatible with eudragit and starch when added together.

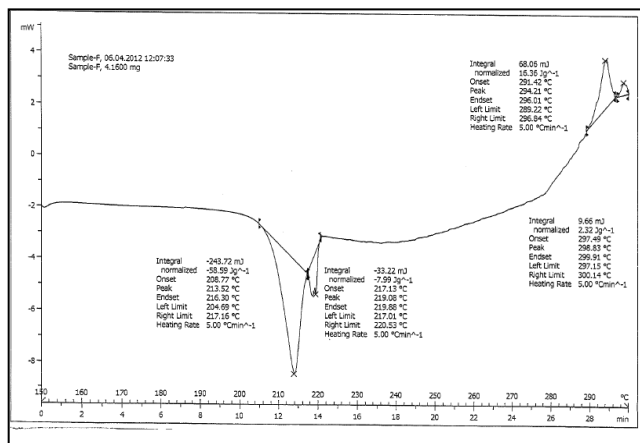


Fig.14. Thermogram of ACEBRO-MCC- Mg St- SA- STARCH

The characteristic peak pattern (endotherm at 217.80°C) of Acebro was shifted to higher temperature at 219.08°C, which was broadened and enthalpy value change to -7.99 J/g. Another endothermic peak was observed at 213.52°C which was more intense and having enthalpy value of -58.59J/g in DSC trace of Acebro-MCC-Mg St(drug blend)-SA-Starch (exposed). IR spectrum of Acebro-MCC-Mg St(drug blend)-SA-Starch (exposed) showed the shifting of all bands as compared to Acebro-MCC-Mg St(drug blend)-SA-Starch (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 58% in Acebro-MCC-Mg St (drug blend)-SA-Starch (exposed) as compared to std. Acebro indicating drug-excipient interaction. Hence, it can be concluded that Acebro is incompatible with sodium alginate and starch, when added together.

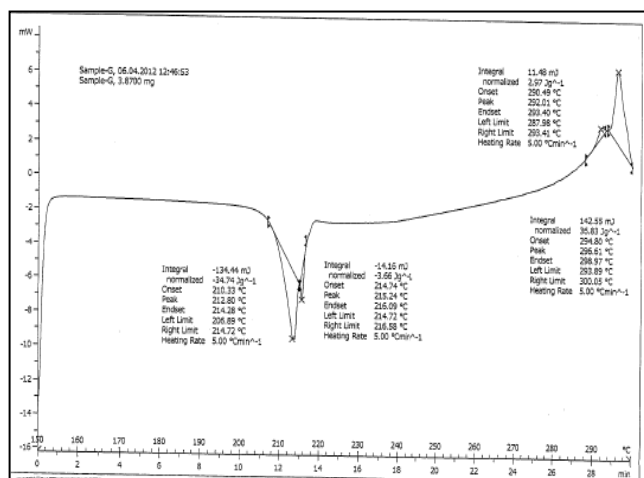


Fig.15. Thermogram of ACEBRO-MCC- Mg St- SA

Endothermic peaks at 212.80 °C having ΔH_f of -34.74 J/g and 215.24°C with enthalpy change to ΔH_f of -

3.66 J/g. The melting endothermic peak (at 217.80°C) of the drug was disappeared in DSC trace of Acebro-MCC-Mg St(drug blend)-SA (exposed). The IR spectrum of Acebro-MCC-Mg St(drug blend)-SA (exposed) showed the disappearance of carboxylate ion band of 1550.66 cm^{-1} and the appearance of extra band at 1340 cm^{-1} (m) as compared to Acebro-MCC-Mg St(drug blend)-SA (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 56 % in Acebro-MCC-Mg St(drug blend)-SA mixture (exposed) as compared to std. Acebro indicating drug-excipient interaction. Hence, it can be concluded that Acebro is incompatible with sodium alginate, when added together.

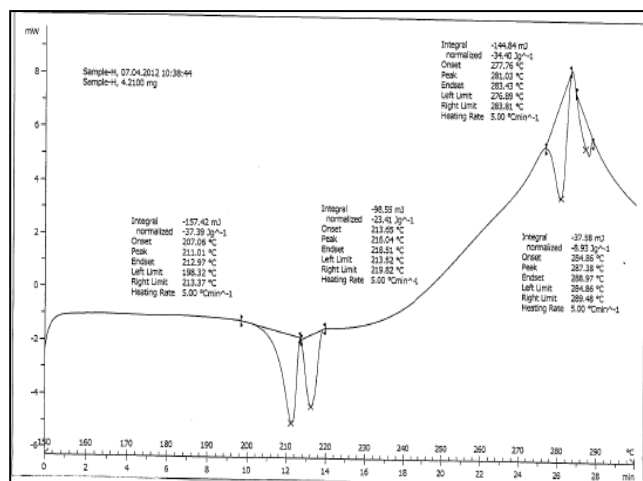


Fig.16. Thermogram of ACEBRO-MCC- Mg St- EDT- STARCH

Two endothermic peaks were observed in the DSC trace of Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed). A small peak present at 211.01 °C with enthalpy change to ΔH_f of -37.39 J/g may be due to presence of palmitate impurity of magnesium stearate confirmed from the literature reported by Grag et al. Endothermic peak of Acebro was shifted to lower temperature at 216.04°C with large difference in enthalpy value to -23.41J/g. The IR spectrum of Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed)mixture showed shifting of N-H stretching from 3292.19 cm^{-1} to 3305.76 cm^{-1} along with decreased in intensity of the spectrum as compared to Acebro-MCC-Mg St (drug blend)-EDT-Starch (control and comparison) and with std. Acebro. In HPLC assay, area percent was found to be decreased by 53% in Acebro-MCC-Mg St (drug blend)-EDT-Starch (exposed)mixture as compared to std. Acebro indicating drug-excipient interaction. From the above data, it can be concluded that, Acebro is incompatible with eudragit and starch when added together.

4. Conclusion

The results obtained in this work with DSC/TG-DTA method are comparable and in good agreement with the results obtained with FT-IR study and HPLC analysis. HPLC analysis requires a long time, but it is able to offer qualitative and quantitative indications on the degradation pathway.

In this study, Isothermal stress testing using DSC and FT-IR revealed that the incompatibility of Acebrophylline with lactose monohydrate, Mannitol, croscarmellose sodium, talc, sod benzoate, silicon dioxide, calcium hydrogen phosphate, eudragit, Polyvinylpyrrolidone, sodium alginate and starch when added alone or in combination. Similarly, Microcrystalline Cellulose and Magnesium Stearate were found to be compatible with Acebrophylline.

In conclusion the application of the thermal method in studying solid drug substances and in particular their stability and their predictive shelf life appear of great interest in the Preformulation studies for the screening of the excipients and confirms that this technique is a powerful tool in pharmaceutical technology for its high sensitivity and the rapid response which allows to identify the incompatibilities in a very short time.

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