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Compatibility Studies of Montelukast with Pharmaceutical Excipients used in Tablet Formulations using Thermal and Chromatographic Techniques

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Abstract

Differential Scanning Calorimetry (DSC) and Isothermal Stress Testing (IST) were carried out to screen compatibility of montelukast (MNLT) with some currently employed pharmaceutical excipients. Initially, DSC thermogram was used to screen MNLT-excipients compatibility. Thermal Gravimetry analysis (TGA) thermogram and Fourier Transform Infra Red (FTIR) spectrum of binary mixture of MNLT-excipients were also compared with that of pure MNLT and excipients. Isothermal stress testing was carried out by storing MNLT-excipient binary mixture (1:1 w/w) for 3 weeks under 500 C. Based on the results of DSC, IR, TGA and HPLC, commenly used excipients were found to be compatible with MNLT excluding citric acid which exhibited interaction with montelukast.

Keywords: Montelukast • Excipients • Incompatibility • Differential scanning calorimetry • Isothermal stress testing

Introduction

Excipients may be inorganic or organic in composition, synthetic or semi synthetic, or derived from biological or natural sources. It may be possible on occasion to exploit such attributes to stabilize unstable materials, but more usually interactions lead to loss of quality [1]. Excipients may have functional groups that interact directly with active pharmaceutical ingredients. Alternatively, they may contain impurities or residues, or form degradation products that in turn cause decomposition of the drug substance. They can also cause unwanted effects such as irritation of the skin or mucosal surfaces, sensitization reactions or adversely affect appearance or organoleptic properties [1,2].

The present study was undertaken to establish the compatibility of montelukast, or 2-[1-[1(R)-[3-[2(E)-(7-chloroquinolin-2yl)vinyl]phenyl]-3[2-(1-hydroxy1methylethyl) phenyl] propylsulfanylmethyl]cyclopropyl] acetic acid sodium, a Leukotriene Receptor Antagonist (LTRA), with a number of commonly used tablet excipients, used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies [3]. Thermo Gravimetry (TG) and Differential Scanning Calorimetry (DSC) were used extensively to evaluate the physical properties of drugs, including melting and vaporization temperatures and with the corresponding enthalpies, glass transitions, vapor pressures, as well as to study the compatibility and stability of the components of pharmaceutical preparations [4-6]. DSC allows a rapid evaluation of possible incompatibilities by revealing changes in the appearance, shift or disappearance of melting or other exothermic processes and variations in the corresponding enthalpies of reaction [7-9]. The DSC curves of the pure drug and of each of the investigated excipients were compared with those obtained from their 1:1 w/w mixtures. The 1:1 w/w ratio was selected to maximize the likelihood of observing any interaction [10,11]. Isothermal Stress Testing (IST), Fourier Transformation-Infrared Spectroscopy (FTIR) and Thermo Gravimetry Analysis (TGA) were used as complementary techniques to assist in the interpretation of DSC results.

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Experimental Section

Materials

Montelukast (MNLT), a gift sample was obtained from Ranbaxy Laboratories, India. Chemicals and excipients selected for studies were purchased from commercial sources and used as such. Hydroxy Propyl Cellulose (Loba Chemie, India), Carnauba wax (Loba Chemie, India), Lactose monohydrate (Loba Chemie, India), Mannitol D (Sigma essar, USA), Microcrystalline cellulose (Avicel PH-112, FMC, USA), Talc (Loba Chemie, India), Starch 1500 (CDH India), HPMC (CDH, India), Magnesium stearate(CDH, India). Carboxy methyl cellulose (CDH India). Methanol and Acetonitrile used were of HPLC grade (Merk, India) and water of HPLC grade was used throughout the experimentation, generated by in-house technique (Younglin Aqua MaxTM water purification system).

Differential scanning calorimetry (DSC)

Samples weighing 3 mg to 4 mg were placed in open aluminum pans and heated from 30°C to 300°C at a rate of 10°C min^{-1} using a temperature modulated jade DSC calorimeter (Perkin Elmer, USA). Nitrogen was used as purge gas at a flux rate of 30 $MLmin^{-1}$. The calibration of temperature and heat flow was performed with standard indium.

Isothermal stress testing (IST)

The method involves storing of the MNLT excipient blends with and without moisture at high temperature and determining the drug content.

Preparation for IST involves accurate weighing of drug and excipients individually. MNLT and different excipients were weighed in replicate (n=2) for control and stress testing. Since MNLT is a photosensitive agent, amber colored vials of 5 ml capacity were used for storage in order to avoid any photo degradation of drug during storage. All vials then further wrapped with black color tapes and aluminum foils to achieve accurate results [11,12].

In each of the vials, 10% w/w water was added and the MNLT excipient blend was further mixed with a glass capillary. Each vial was sealed using a teflon-lined screw cap and stored at 50°C. (Hot Air Oven universal Memmert

Type TIC-4000 N). After 3 weeks of storage at the reported conditions Samples were quantitatively analyzed using HPLC. Drug Excipient blends without water stored in refrigerator, served as control. After 3 weeks storage period, all samples were taken out. 2 ml of methanol was added to each vial and transferred to 10 ml volumetric flask. Vials were rinsed twice with methanol and volume was made up. All volumetric flasks were then kept for sonication (Frontline Ultra Sonic Cleaner FS-10) for 15 min. All samples were then centrifuged (Eppendorf Centrifuge 5810 R) at 8000 rpm for 10 min under 25°C. Supernatants were collected and filtered through 0.45 μ filters. Dilutions of appropriate concentration were prepared [10,11].

High performance liquid chromatography (HPLC)

The LC system consisted of a Simadzu ATvp pump, equipped with a 20 μl sample loop, and a Photodiode array detector (SPD-M10 AVP). A C_{18}250 mm x 4.60 mm, 5 μm, analytical column (phenomenex make) was used for separation. The output signal was monitored and integrated using LC Solutions software (Simadzu). The mobile phase consisted of a mixture of aqueous 20 mM Ammonium acetate (buffer pH adjusted to 3.5 using glacial acetic acid) and Acetonitrile in the ratio of 15:85 (v/v). The mobile phase was filtered through a 0.45μ nylon membrane filter and degassed prior to use. The mobile phase was delivered through the column at a flow rate of 1.2 ml/min. Column was operated at ambient temperature (~ 25°C).The sample injection volume was 20μl. The photodiode array detector was set at a wavelength of 254 nm.

Fourier transformation infrared spectroscopy (FTIR)

Infrared spectra were obtained using a Jasco 700 spectrometer (Bruker Daltonics Inc., Germany). Samples were ground, mixed thoroughly with potassium bromide. All scans were obtained at a resolution 4 cm^{-1}. Results were compared with reference excipient spectra.

Thermogravimetry analysis (TGA)

TGA thermograms of montelukast and of its binary mixture (1:1) with different excipients have also been scanned using Thermo GravimetricAnalyzer (Leco TGA701) to obtain the thermal influence on its weight, which exhibited weight loss or weight gain of the mixture depending upon the reactions occurring between drug-excipient compositions.

Result and Discussion

Drug-excipient compatibility testing by DSC

In the first phase of the study, compatibility of MNLT with different excipients were tested using DSC. Selected DSC scans of MNLT and MNLT-excipient mixtures are shown in Figure 1. Thermo analytical data of Montelukast and Selected Excipients were discussed in Table 1. DSC of MNLT with individual excipients are shown in (Figures 2a-2k).Ratio of MNLT with excipients were taken in equal quantity (3 mg to 4 mg each). The DSC thermogram of amorphous form of MNLT exhibited melting within the range from about 60°C to 100°C (Figure 3).

The DSC scan of Microcrystalline Cellulose (MCC) showed a broad endotherm at 63.29°C (starting from 28.98°C and ending at 104.76°C), which may be attributed to the loss of adsorbed water (Figure 1). The thermogram of MNLT-MCC mixture (Figure 2a) showed same appearance of endothermic peak of drug as in MNLT alone, indicating that there was no interaction. Characteristic bands of montelukast were well retained in the IR spectrum of MNLT-MCC mixture without any new bands, indicating that there was no change in the structure of drug. Based on above results, it was concluded that montelukast is compatible with MCC.

The DSC scan of lactose showed endothermic peaks at 145.50°C (corresponding to dehydration of bound water) [13], 172.10°C (crystalline transition), 217.53°C (melting point) represents the fusion followed by immediate thermal decomposition (Figure 1) [10]. Crystalline transition peak of lactose was present in MNLT–lactose mixture (Figure 2b), but lack of melting point peak of lactose suggesting further interpretation with other technique such as FTIR, TGA, and HPLC. A sharp melting endotherm was observed at 166.45°C in the DSC trace of mannitol D (Figure 1). In case of MNLT- mannitol D mixture, there was broadening of melting endotherm of mannitol D (at 168.78°C) (Figure 2c) [10]. The drug endotherm peak appeared at same range. It was concluded that there is no chemical incompatibility between MNLT and mannitol D.

In DSC trace of magnesium stearate, an endothermic peak was observed at 83°C (Figure 4). A small peak was also present at 120°C, which might be due to palmitate impurity [14].The DSC scans of MNLT-magnesium stearate showed several endothermic peaks that could not be correlated directly either with magnesium stearate or MNLT. The DSC trace of MNLT-magnesium stearate mixture suggests that there is no incompatibility (Figure 2d).

In case of HPMC, no peak was observed in the range of 25°C to 300°C (Figure 1). The superposition of DSC curves of pure MNLT and HPMC evidencing the absence of incompatibility with MNLT. In the DSC trace of MNLT-HPMC mixture, the melting endotherm of the drug was well retained at 55°C to 70°C (Figure 2e), indicating that the drug is compatible with HPMC.

In case of HEC, no peak was observed in the range of 25°C to 320°C (Figure 2). The superposition of DSC curves of pure MNLT and HEC

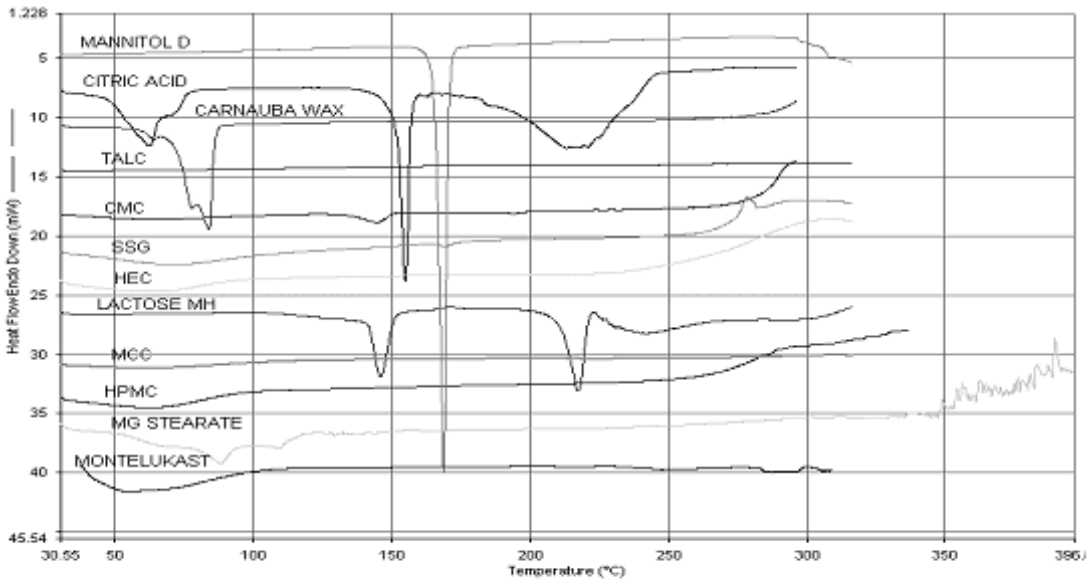

Figure 1. DSC thermogram of Montelukast and Individual Excipient.

Table 1. Chromatographic results from Control Samples by HPLC.

Sr. No.	Samples	RT (min)	Area	Height	Plate Counts	Tailing Factor
1	Montelukast	5.1	2903841	412038	64546	1.06
2	MNLST+CMC	5.13	2993749	421849	55093	1.37
3	MNLST+SSG	5.15	3002781	409672	51729	1.13
4	MNLST+Starch 1500	5.09	2938713	412749	54611	1.13
5	MNLST+Citric Acid	5.11	2809837	390764	52672	1.13
6	MNLST+Lactose MH	5.06	2896732	399356	51708	1.13
7	MNLST+Mg Stearate	5.13	2930918	389847	51729	1.12
8	MNLST+Carnauba Wax	5.09	2997831	409893	58932	1.1
9	MNLST+MCC	5.1	3038948	415490	54581	1.13
10	MNLST+HEC	5.12	3098290	419803	52016	1.12
11	MNLST+HPMC	5.04	2909389	398793	52475	1.08
12	MNLST+Mannitol D	5.12	3098373	409878	53307	1.09
13	MNLST+Talc	5.11	2909827	401898	54367	1.09

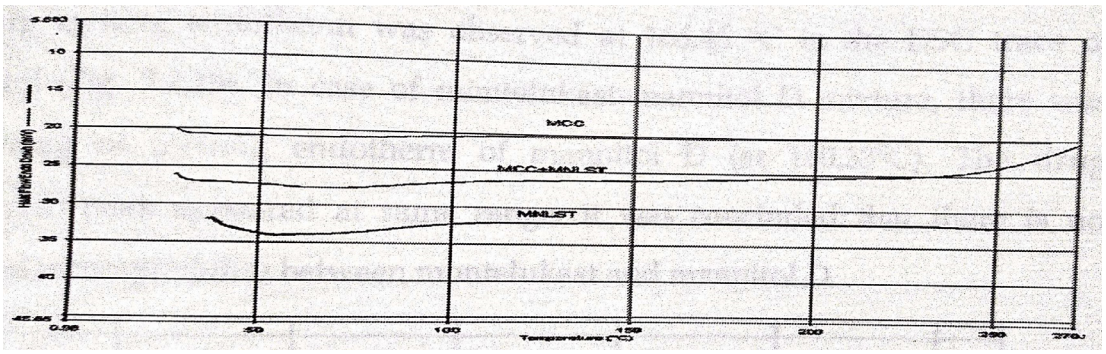

Figure 2a. DSC Thermogram of Montelukast mixed with MCC.

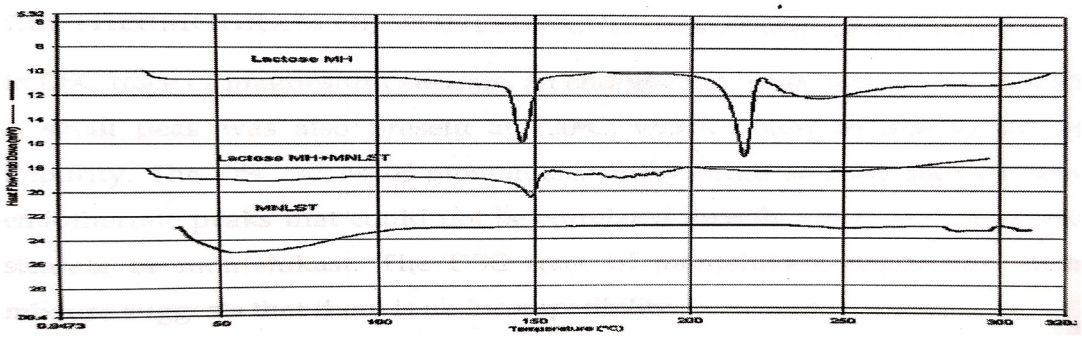

Figure 2b. DSC Thermogram of Montelukast mixed with Lactose.

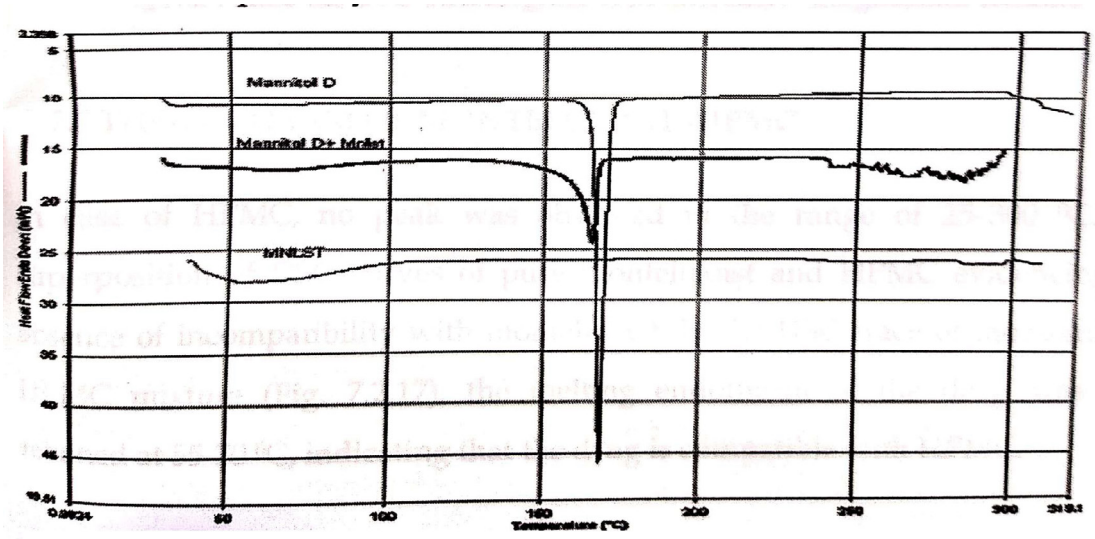

Figure 2c. DSC Thermogram of Montelukast mixed with Mannitol.

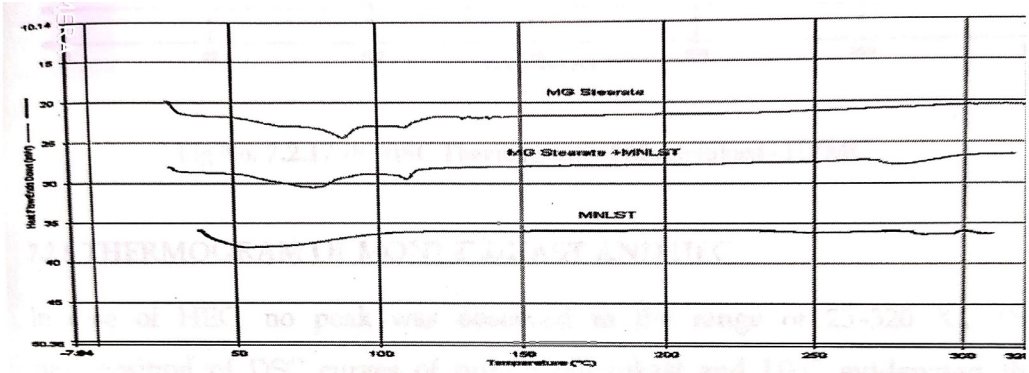

Figure 2d. DSC Thermogram of Montelukast mixed with Mg Stearate.

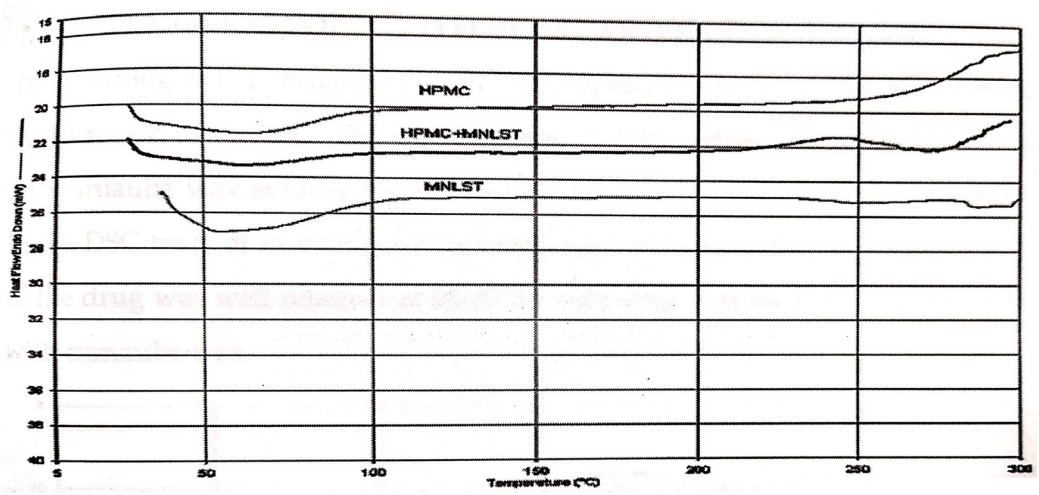

Figure 2e. DSC Thermogram of Montelukast mixed with MPMC.

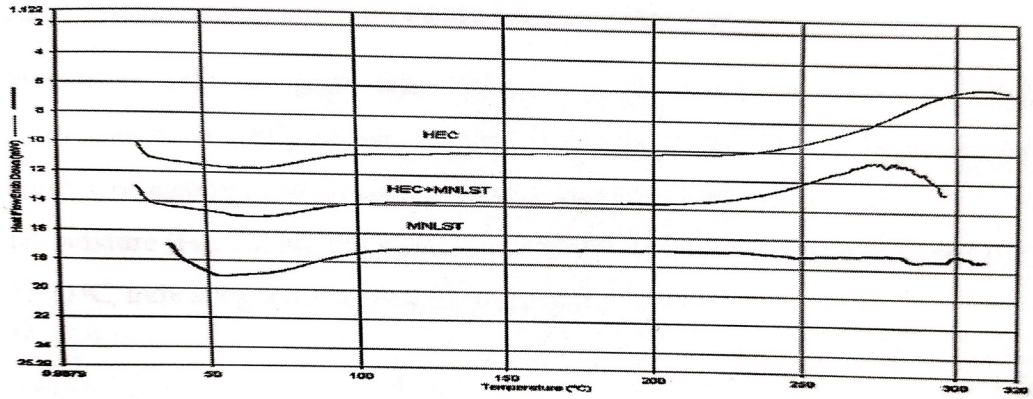

Figure 2f. DSC Thermogram of Montelukast mixed with HEC.

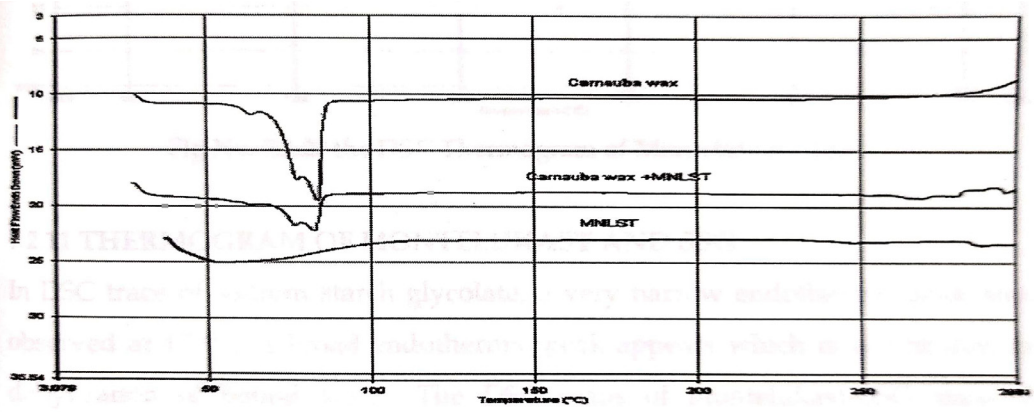

Figure 2g. DSC Thermogram of Montelukast mixed with Carnauba wax.

evidencing the absence of incompatibility with MNLT. In the DSC trace of MNLT-HEC mixture, melting endotherm of the drug was well retained at 55°C to 70°C (Figure 2f), indicating that the drug is compatible with HEC.

DSC thermogram of carnauba wax reveals appearance of broad endotherm peak in the region of 75°C to 85°C (Figure 1). The superposition of DSC curves of pure montelukast and carnauba wax evidencing the absence of incompatibility with MNLT. In the DSC trace of montelukast-carnauba wax mixture, the melting endotherm of the drug was well retained at 55°C to 70°C, indicating that the drug is compatible with carnauba wax (Figure 2g).

In case of Talc, no peak was observed in the range of 25°C to 320°C (Figure 1). The superposition of DSC curves of pure montelukast and talc

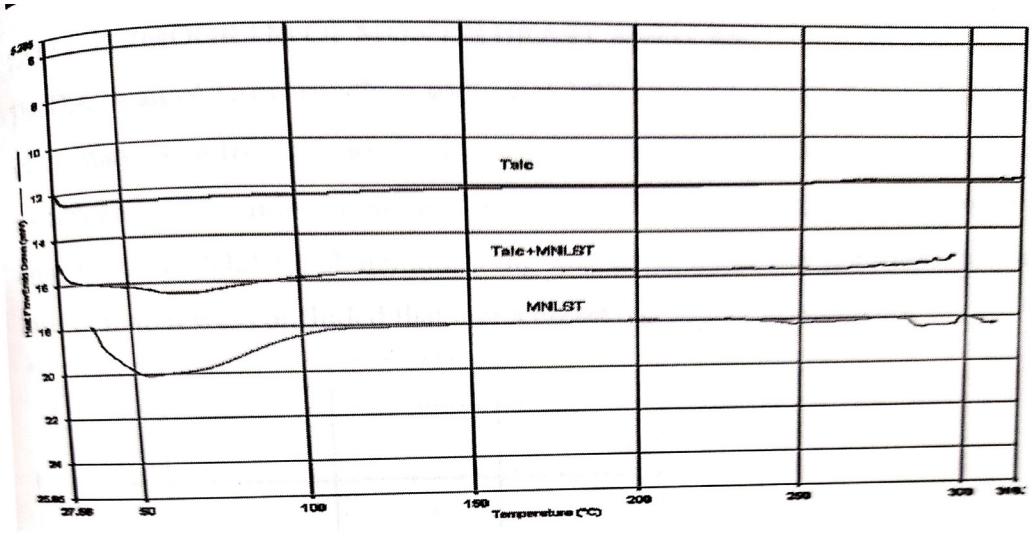

Figure 2h. DSC Thermogram of Montelukast mixed with Talc.

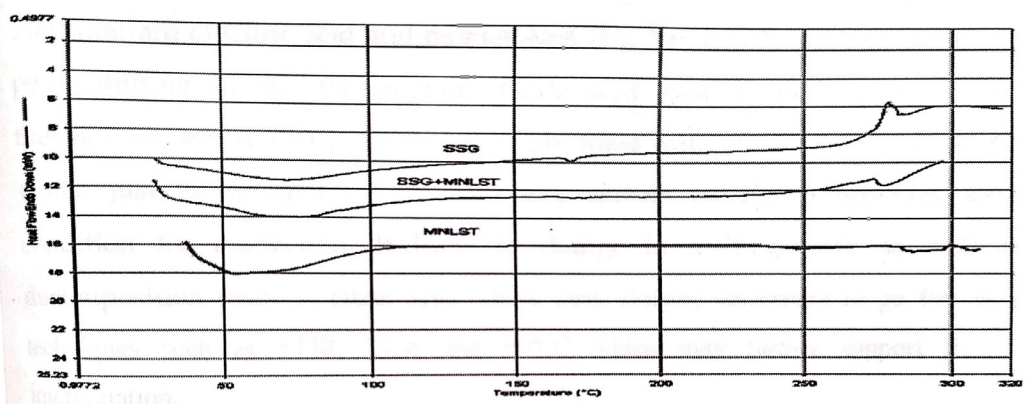

Figure 2i. DSC Thermogram of Montelukast mixed with SSG.

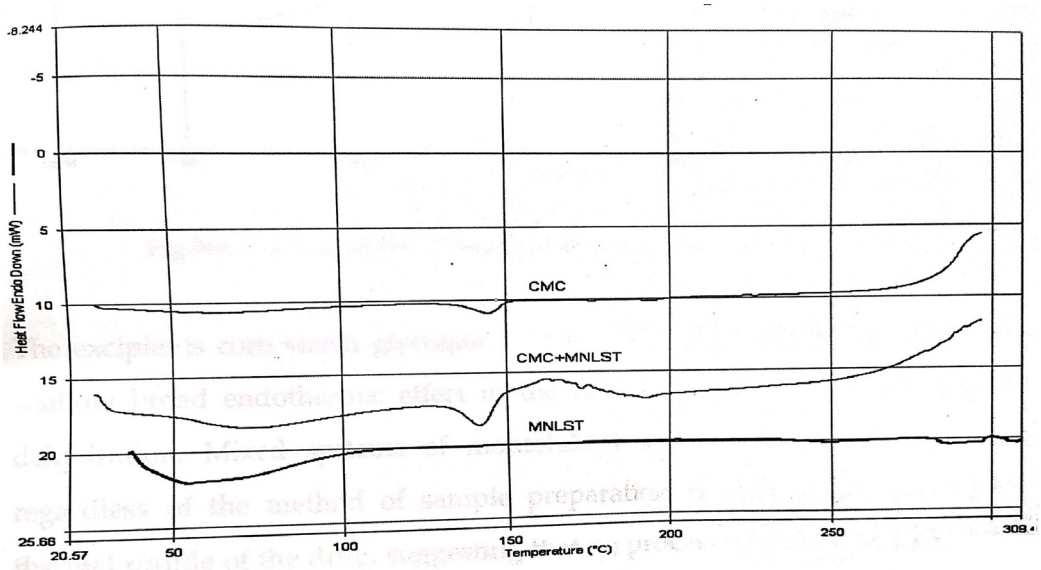

Figure 2j. DSC Thermogram of Montelukast mixed with CMC.

evidencing the absence of incompatibility with MNLT. In the DSC trace of MNLT-talc mixture, the melting endotherm of the drug was well retained at 55°C to 70°C (Figure 2h) [10] indicating that the drug is compatible with talc.

In DSC trace of sodium starch glycolate, a very narrow endothermic peak was observed at 170°C (Figure 1). A broad endothermic peak appeared, which might be due to dehydration of bound water. The DSC scans of MNLT-SSG showed exothermic peaks that could not be correlated directly either with SSG or MNLT (Figure 2i). The DSC trace of MNLT-SSG mixture suggests that there is no incompatibility.

The DSC scan of Croscarmellose Sodium (CMC) shown an endotherm at 140°C (Figure 1), which may be attributed to the loss of adsorbed water. The thermogram of CMC mixture showed same appearance of endothermic peak of drug as in MNLT alone, indicating that there was no interaction (Figure 2j). Based on that, it was concluded that MNLT is compatible with CMC.

Thermogram of Citric acid and MNLT exhibits significant peak shifting in the thermogram. Citric acid exhibits three peaks in its thermogram (Figures 1-6) where first is due to loss of absorbed water in the region of 50°C to 80°C which just in the melting range of MNLT (60°C to 100°C) provides ideal condition for interaction (Figure 2k). It led to change in melting peak as well as decomposition peak of citric acid. These peak shifting encouraged to go for other techniques such as FTIR, TGA and HPLC which may further support for its interpretation.

Drug-excipient compatibility testing by HPLC

Chromatograms of IST samples of MNLT and its binary mixtures with excipients were taken on HPLC and data were collected for qualitative and

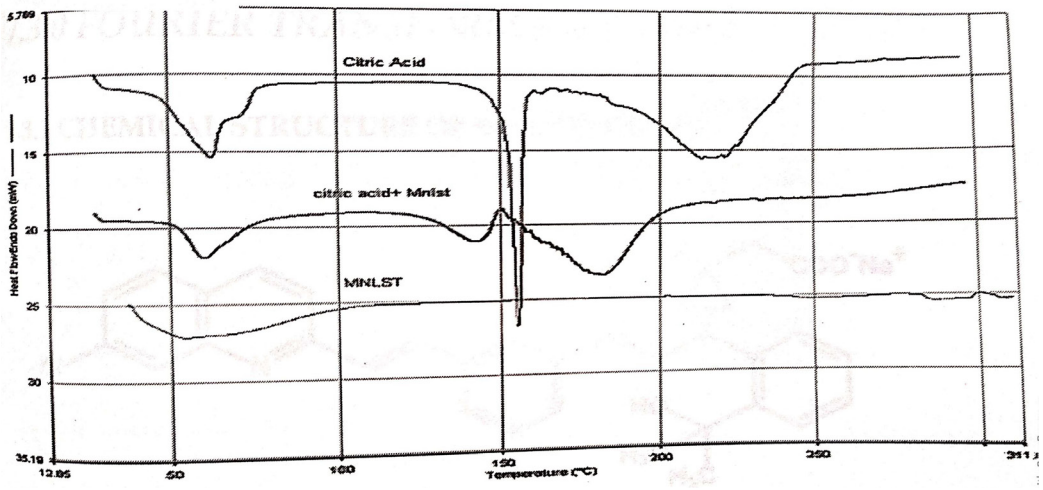

Figure 2k. DSC Thermogram of Montelukast mixed with citric acid MH.

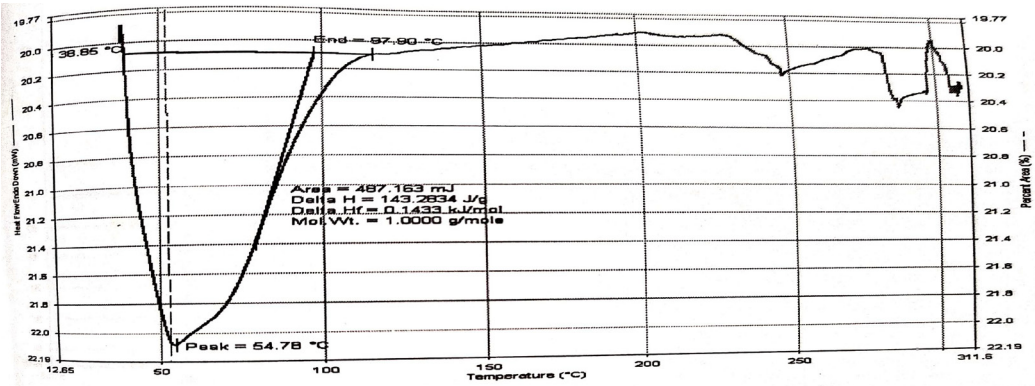

Figure 3. DSC Thermogram of Montelukast.

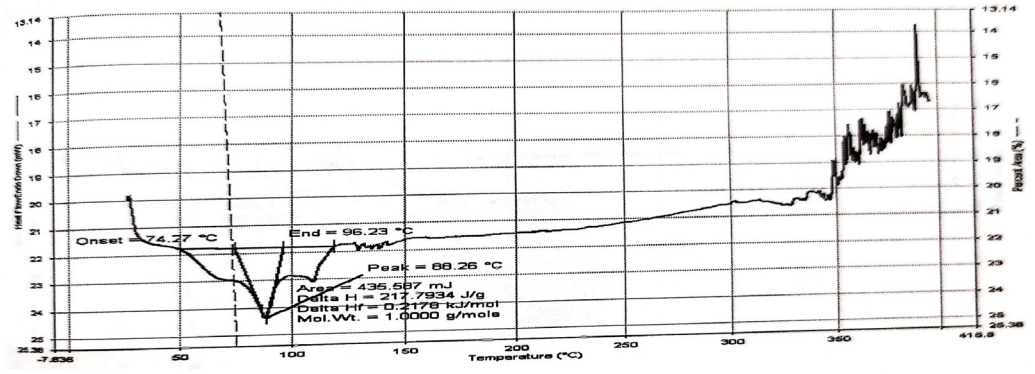

Figure 4. DSC Thermogram of Magnesium Stearate.

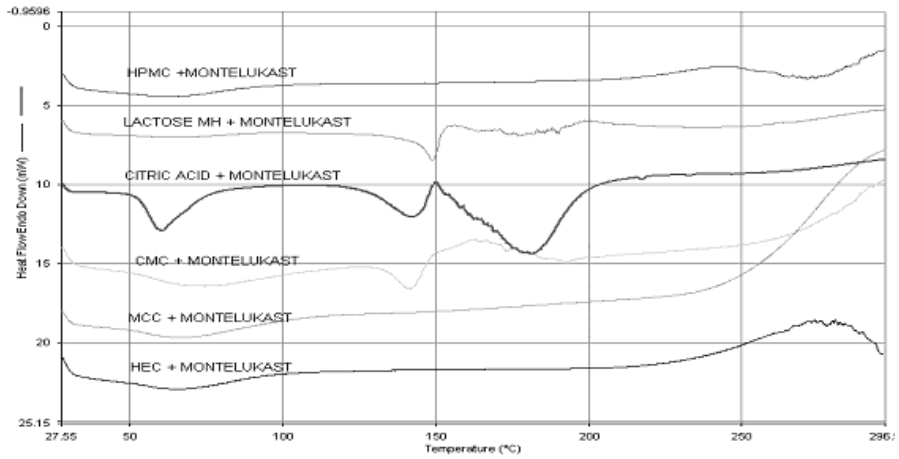

Figure 5. DSC Thermogram of Montelukast mixed with individual excipient.

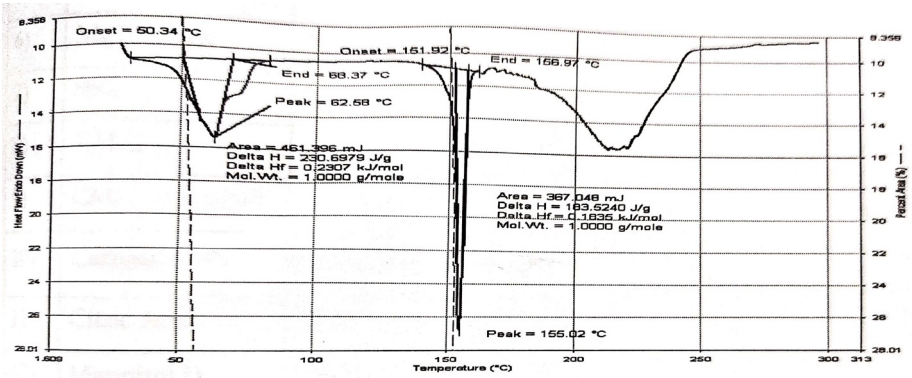

Figure 6. DSC Thermogram of Citric Acid.

Table 2. Thermo analytical data of Montelukast and Selected Excipients.

Sr No	Samples	DSC		Enthalpy/jg1
		tonset (fusion)/°c	tpeak (fusion)/°c	
1	Montelukast	3885	54.78	143.283
2	MCC	27.98	59.15	147.419
3	HPMC	28.17	60.65	151.438
4	HEC	32.65	63.8	76.173
5	Lactose MHI	211.31	217.53	260.617
6	Mg Stearate	74.27	88.26	217.793
7	SSG	28.22	71.47	217.902
8	TALC	-		
9	CMC	135.41	144.34	19.587
10	Carnauba Wax	72.26	84	239.289
11	Citric Acid	50.34	62.58	230.698
12	Mannitol D	165.69	168.78	337.11

Table 3. Chromatographic results from IST Samples by HPLC.

Sr. No.	Samples	RT (min)	Area	Height	Plate Counts	Tailing Factor
1	Montelukast	5.11	2874852	367910	64546	1.06
2	MNLT+CMC	5.1	2897831	370928	57839	1.37
3	MNLT+SSG	5.19	2790832	357801	51937	1.13
4	MNLT+Starch 1500	5.05	2869308	380938	54611	1.12
5	MNLT+Citric Acid	5.09	2184578	250983	56252	1.13
6	MNLT+Lactose MH	5.12	2498742	323784	56780	1.13
7	MNLT+Mg Stearate	5.08	2789189	368909	51729	1.06
8	MNLT+Carnauba Wax	5.13	2903783	378092	58098	1.1
9	MNLT+MCC	5.08	2898038	369098	56765	1.09
10	MNLT+HEC	5.16	2791909	357890	52016	1.12
11	MNLT+HPMC	5.04	2718901	367891	52879	1.08
12	MNLT+Mannitol D	5.1	2893892	390891	53307	1.09
13	MNLT+Talc	5.09	2903462	409872	56783	1.11

Table 4. Summary of montelukast content found in Control and IST condition by HPLC.

Sr. No.	Samples	Ratio (Drug-Excipient)	% Drug Content (Control)	% Drug Content (IST)
1	Montelukast (MNLT)	1:01	100.75	97.03
2	MNLT+CMC	1:01	103.05	96.81
3	MNLT+SSG	1:01	102.07	98.2
4	MNLT+Starch 1500	1:01	98.19	95.85
5	MNLT+Citric Acid	1:01	98.87	82.74
6	MNLT+Lactose MH	1:01	101.77	96.34
7	MNLT+Mg Stearate	1:01	99.93	96.14
8	MNLT+Carnauba Wax	1:01	100.18	97.01
9	MNLT+MCC	1:01	101.57	96.82
10	MNLT+HEC	1:01	102.57	98.24
11	MNLT+HPMC	1:01	100.2	97.77
12	MNLT+Mannitol D	1:01	103.58	96.68
13	MNLT+Talc	1:01	101.35	98.3

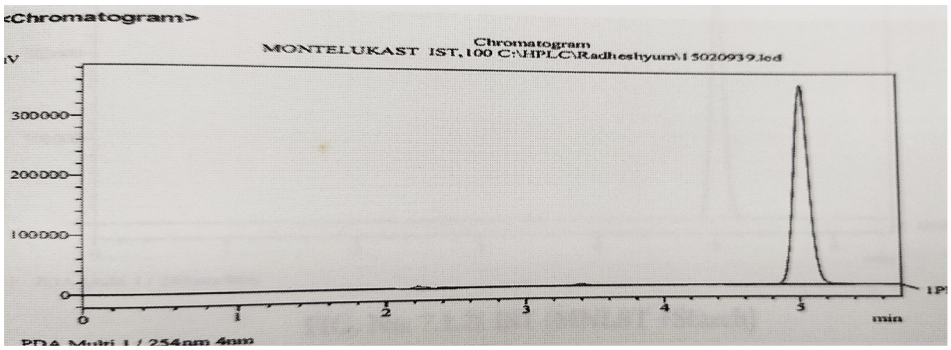

Figure 7. Chromatogram of Montelukast IST sample.

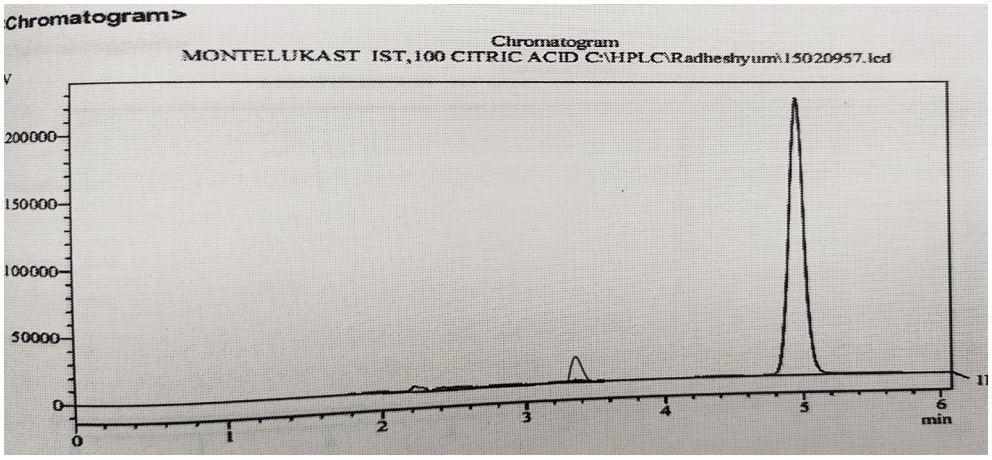

Figure 8. Chromatogram of Montelukast – Citric acid IST sample.

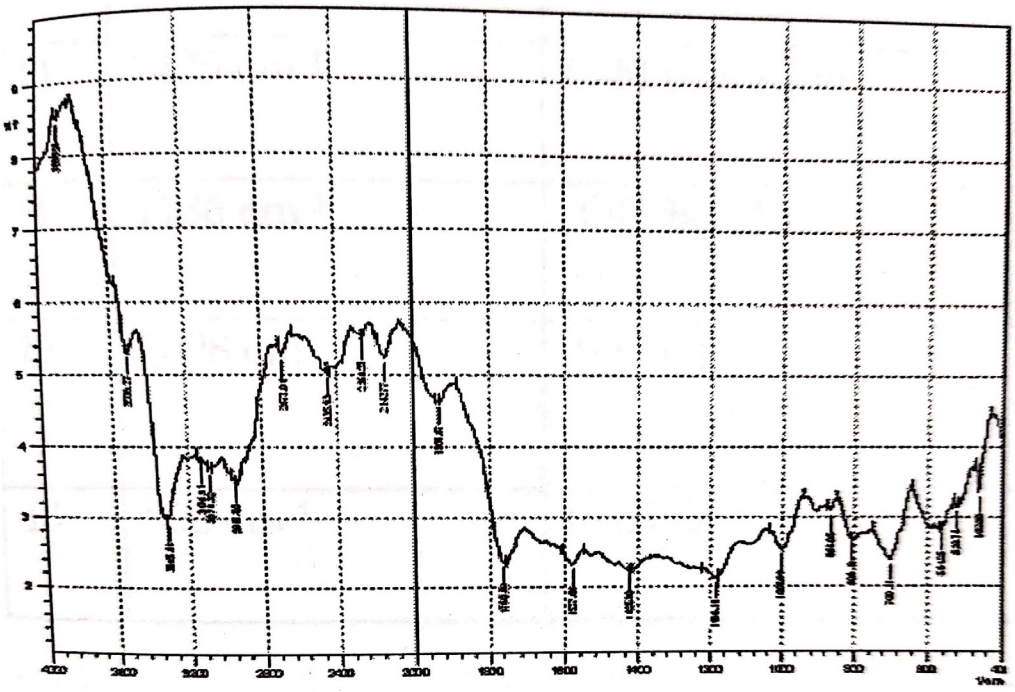

Figure 9. FTIR Spectra of Montelukast.

quantitative measurements (Table 2). Chromatographic data for control and IST samples were depicted in Tables 3 and 4 respectively. Stressed sample of citric acid exhibited an extra peak in chromatographic run eluted at about 3.5 min when compared to chromatogram of control sample of citric acid with MNLT (Figures 7 and 8) suggesting interaction between them. Chromatographic area for MNLT-Citric acid in IST sample had lower response of MNLT when compared to data from Control suggested an interaction of MNLT with citric acid.

Drug-excipient compatibility testing by FTIR and TGA

FTIR and TGA spectra were also then scanned for further interpretation of data obtained from DSC and HPLC. FTIR spectra of binary mixture of MNLT-citric acid exhibited appearance of an extra sharp peak at 2400 cm^{-1} to 2300 cm^{-1} wave number (Figures 9 and 10) indicates formation of new

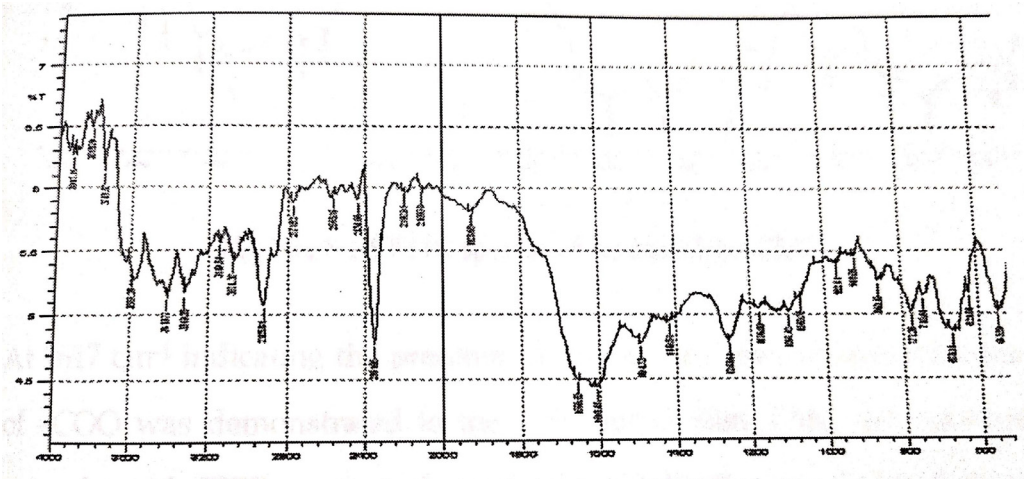

Figure 10. FTIR Spectra of Montelukast – Citric acid.

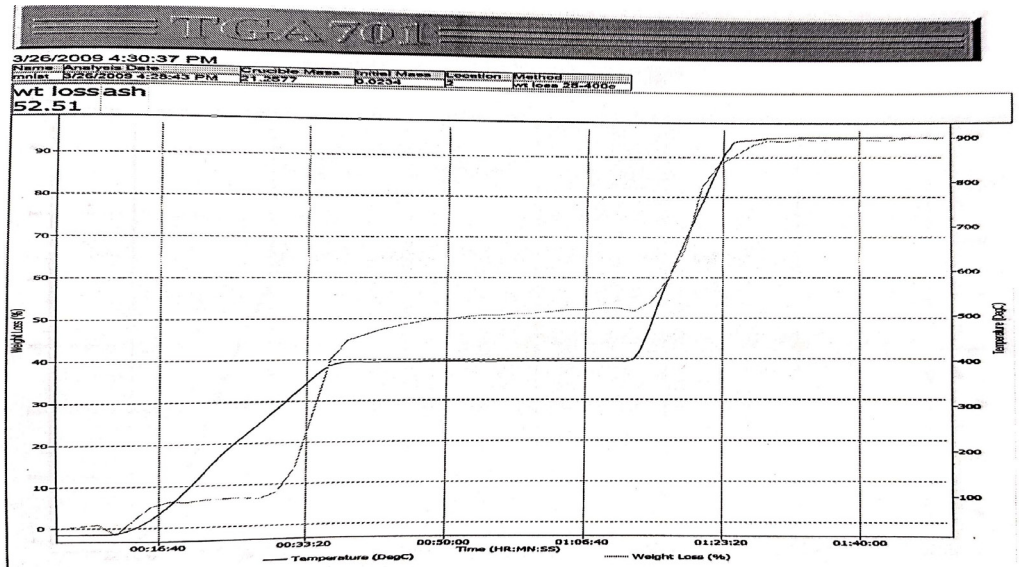

Figure 11. TGA Thermogram of Montelukast.

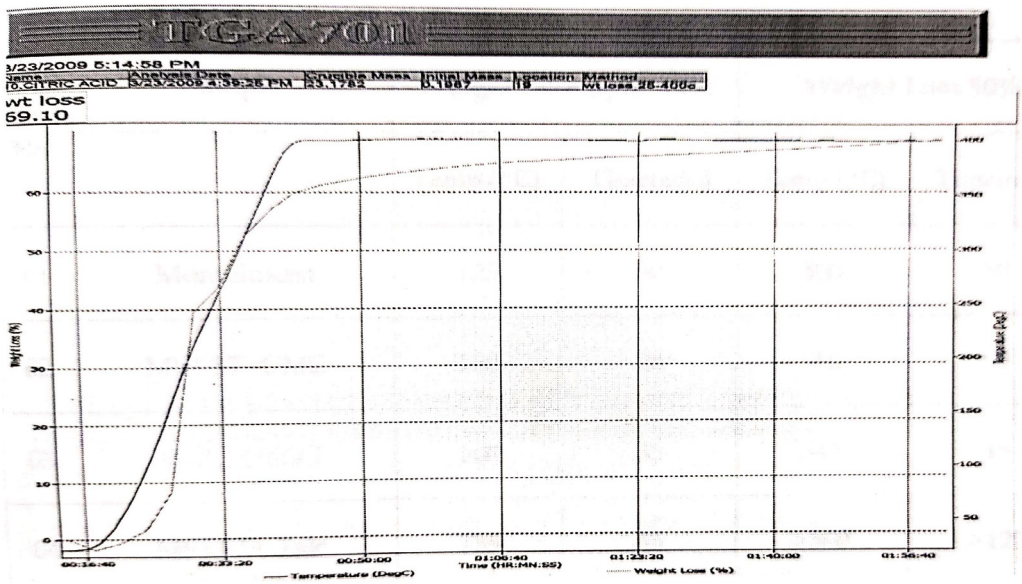

Figure 12. TGA Thermogram of Montelukast – Citric acid.

chemical bond due to interaction while TGA study of montelukast and citric acid exhibited weight gain due to formation of new chemical bond (Figures 11 and 12).

Conclusion

Twelve excipients were tested for their compatibilities with MNLT.

Present study has demonstrated the successful utilization of techniques of DSC and IST (By HPLC) to assess the compatibility of MNLT with the excipients used in the development of tablet formulations. Based on the results of DSC alone, majority of the excipients were found to be compatible with MNLT. However, results showed that there is sign of interaction between MNLT and citric acid. Results of IST and FTIR confirmed that there is chemical interaction between MNLT and citric acid. In conclusion, DSC and IST were successfully used with further interpretation by TGA and FTIR for compatibility studies of MNLT with excipients for tablet formulations.

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