

SOLID STATE COMPATIBILITY STUDIES BETWEEN MONTELUKAST SODIUM AND LEVOCETIRIZINE

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ABSTRACT

Objective: The aim of this research is to evaluate montelukast (MNT)-levocetirizine (LVZ) incompatibility when they gather in one solid dosage form.

Methods: Both drugs and their binary mixture (2:1) (MNT-LVZ) were subjected to the following condition: 25°C/60% RH and 40°C/75% RH for 14 weeks. Samples were withdrawn and analyzed using stability-indicating high-performance liquid chromatography (HPLC) method at time intervals (0, 1, 4, 14 weeks). Further investigations were carried out using differential scanning calorimeter (DSC), Fourier transform infrared (FTIR), and X-ray powder diffraction (XRPD)

Result: On the basis of HPLC results, the degradation percentage of both drugs in binary mixtures was <10% indicating no chemical interaction; this was confirmed by all FTIR results except new band 668 cm⁻¹ appeared in the spectrum of the mixture after storing 14 weeks at 40°C/75% RH, revealing possible hydrogen bond formed in the mixture. DSC and XRPD revealed possible physical interaction including phase transformation (release the acid form of montelukast and basic form of levocetirizine and sodium chloride in the medium); this may affect dissolution rate and bioavailability.

Conclusion: The results obtained from this research gave an evidence to formulate MNT and LVZ in stable fixed-dose combination for the effective treatment of allergic diseases.

Key words: Montelukast, Levocetirizine, Fixed-dose combination, Solid-state incompatibility, High-performance liquid chromatography, Differential scanning calorimeter, Fourier transform infrared, X-ray powder diffraction.

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INTRODUCTION

Among the chronic illnesses, allergic diseases (ADs) are increasing in prevalence, reducing patients' quality of life. AD is harmful immune-mediated response against harmless environmental substances called allergen [1]. This immune response includes releasing many mediators from mast cells in different stages. One of them is histamine as a preformed mediators releasing in early stage and another one is leukotriene as newly formed lipid-derived mediators in late stage [2], and according to which, tissues are affected with the allergen; the outcome symptoms manifest in one or more of the following ADs: Asthma, allergic rhinitis, food allergy, atopic dermatitis, and anaphylaxis [1]. It is clearly noted that the drugs of choice for management of AD are antihistamine and leukotriene receptor's antagonist. Levocetirizine (LVZ) is a third-generation, non-sedating H₁-antihistamine indicated for treatment of seasonal and perennial allergic rhinitis and skin urticarial [3]; it is used as a Di-hydro chloride form which is known to be white crystal powder and freely soluble in water [3]. Montelukast (MNT) is a selective cystin-leukotriene receptor antagonist indicated for chronic treatment of asthma and relief of symptoms of allergic rhinitis [4], it's used as a Sodium salt which known to be white to off-white, hygroscopic, light-sensitive, amorphous powder and freely soluble in water [4]. In such chronic cases, there is much interest to use fixed-dose combination (FDC) due to its benefits such as safety and efficacy, patient's compliance, and cost reduce [5]. FDC implies many active ingredients incorporated into single dosage form in fixed ratio [6]. However, incompatibilities between ingredients may occur in mixture as physical or chemical interactions during manufacture and storage. Since MNT-LVZ solid-state mixing is happened, a yellow color appears in the mixture. Preliminary studies about combine MNT and LVZ in single dosage form are done utilizing separation method but without studying the physiochemical solid-state interaction. Hence,

the purpose of this study was to predict the type of interaction using thermal and non-thermal methods.

MATERIALS AND METHODS

Materials

LVZ Di-hydro chloride is from Chempifine (India); MNT sodium is from Ranbaxy (India). All of chemicals were of high-performance liquid chromatography (HPLC) or analytical grade and obtained from Merck (Germany).

Isothermal stress testing

MNT: LVZ (2:1, w/w) mixture, MNT alone, and LVZ alone were put in open darkness glassy vials and cotton balls were put on the top to prevent water condensate to go into the vials. Set of vials were kept for 14 weeks in controlled stability cabinets for temperature and relative humidity as follows: 25°C/60% RH and 40°C/75% RH. The active agent contents were determined using stability-indicating HPLC method at time intervals (0, 1, 4, 13 weeks). To determine the physical-chemical drug-drug interaction, Fourier transform infrared (FTIR), differential scanning calorimeter (DSC), and X-ray powder diffraction (XRPD) studies were performed immediately after mix preparation and after 14 weeks of storing in different conditions outlined above.

HPLC analysis of samples

The drug contents were determined using in-house developed validated stability-indicating HPLC method, utilizing instrument VWR-Hitachi, Germany, equipped with a L-2130 pump and a L-2200 thermostatted column compartment and programmable detector module ultraviolet (UV) Photo diode array). The chromatographic separation was performed on ODS-3 L₁ c₁₈ (4.6×250 mm, 5 μm) column and a mobile

phase consisting of mixture of 0.05 M ammonium acetate buffer and methanol (15:85, v/v); the PH was adjusted at 3.5 with glacial acetic acid. The mobile phase was pumped at flow rate of 1.5 ml/min at 25°C. The injection volume was 20 μ L and the UV detector was set at a wavelength of 230 nm. Triplicate samples withdrawn at each time intervals were diluted suitably with methanol, and the recovery percentage is calculated.

DSC

DSC analysis was performed on 821e Mettler Toledo, Switzerland. Approximately 5 mg of the samples were weighed directly in the DSC aluminum pan and scanned in the temperature range of 25°C–300°C at heating rate of 10°C/min under constant purging of dry nitrogen at 100 ml/min.

FTIR spectroscopy

FTIR spectra were obtained by using FTIR spectrophotometer (Vector 22, Buker, Germany). Samples were prepared by KBr disc

method. The spectra were scanned over wavenumber range of 500–4000 cm^{-1} .

XRPD

The physical state of LVZ and MNT in different samples was evaluated using Bruker's D8 Advance diffractometer (Karlsruhe, West Germany). XRPD patterns were recorded using Germanium monochromatic and Cu radiation with nitrogen filter at voltage of 50 keV and a current of 30 mA. The samples were analyzed over 2θ range of 3–70°.

RESULTS

Visual inspection

LVZ is white crystalline powder [7]. Samples of LVZ alone were white powder initially and after 14 weeks in 25°C/60% RH and 40°C/75% RH.

MNT is white to off-white powder [8]. Samples of MNT alone were off-white initially. MNT sample which was stored 14 weeks in 25°C/60%

Table 1: HPLC results of isothermal stress studies on solid samples

| Sample | Initial | 25°C/60% RH, Assay % | | | 40°C/75%RH, Assay % | | |
|------------|-------------|----------------------|-----------|-----------|---------------------|-----------|-----------|
| | Assay % | 1 week | 4 weeks | 14 weeks | 1 week | 4 weeks | 14 weeks |
| LVZ alone | 96.49±1.32* | 96.06±1.3 | 95.2±0.07 | 97.04±0.6 | 95.07±2.8 | 95.38±1.8 | 95.82±0.3 |
| LVZ in mix | 104.67±0.69 | 99.69±2.6 | 96.57±1.6 | 99.11±0.7 | 95.56±0.8 | 95.08±1.1 | 95.76±1.4 |
| MNT | 102.25±0.9 | 95.92±0.5 | 95.25±0.5 | 96.35±0.8 | 91.91±0.1 | 92.37±0.7 | 90.74±1.1 |
| MNT in mix | 100.91±1.6 | 95.94±0.8 | 94.85±0.9 | 96.82±1.1 | 92.43±1.2 | 90.57±0.8 | 91.21±0.9 |

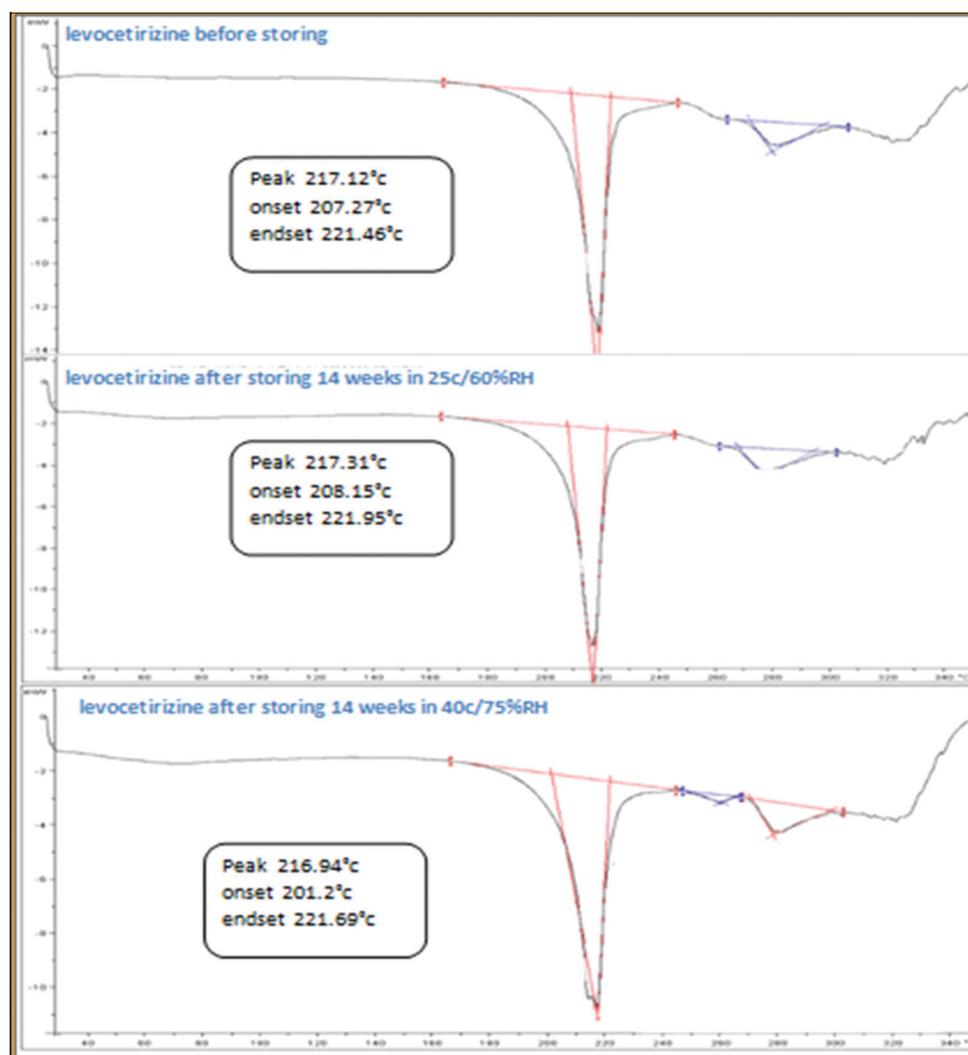


Fig. 1: Differential scanning calorimeter results of levocetirizine before storing, after storing 14 weeks in 25°C/60% RH, after storing 14 weeks in 40°C/75% RH

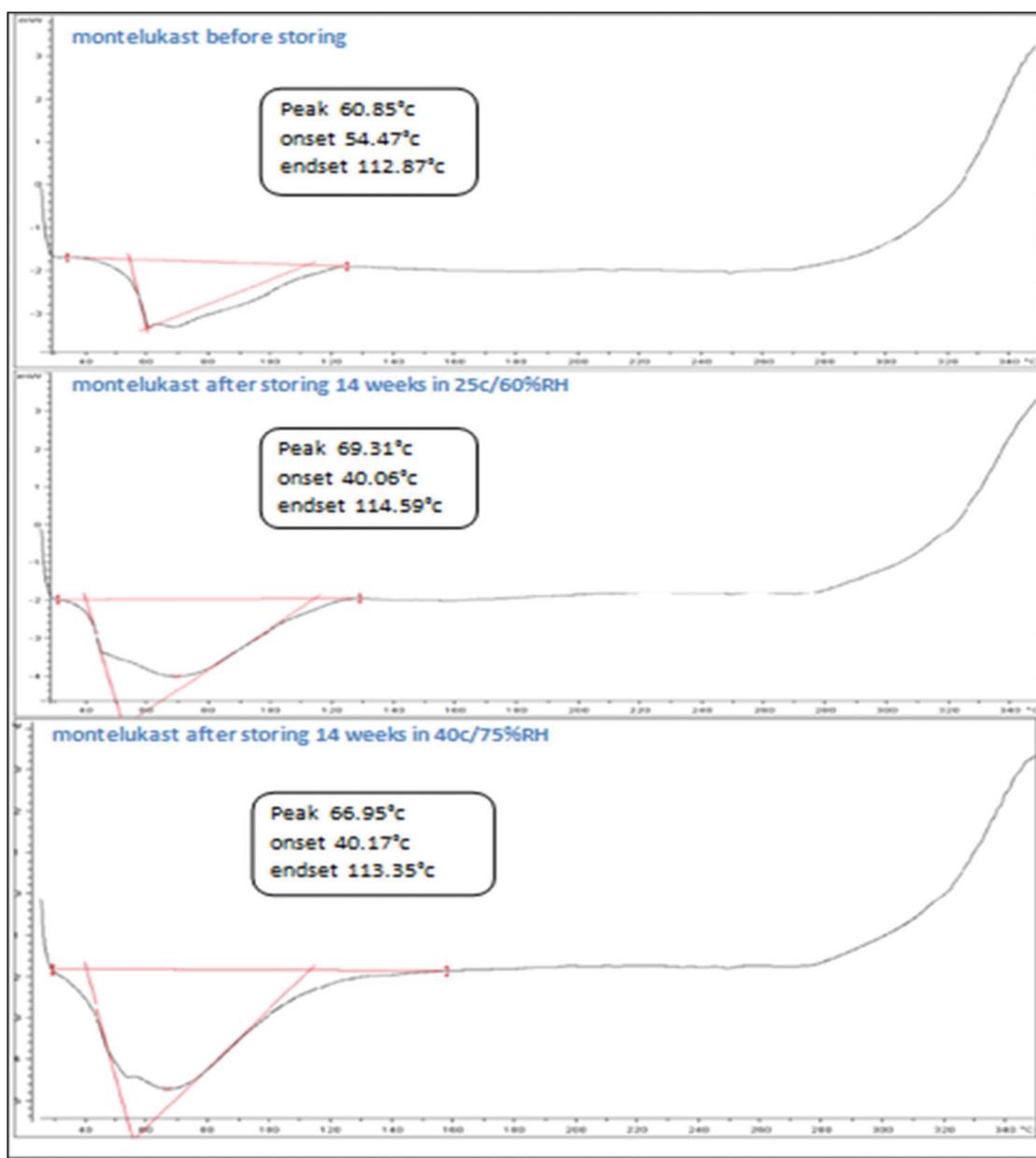


Fig. 2: Differential scanning calorimeter results of montelukast before storing, after storing 14 weeks in 25°C/60% RH, after storing 14 weeks in 40°C/75% RH

RH, formed an off-white agglomerates. MNT sample which was stored 14 weeks 40°C/75% RH, became an one transparent glassy mass; this may be due to the disadvantages of MNT property and its hygroscopicity, it easily absorbs up to 3 equivalent of water [9]. Since MNT and LVZ were mixed in solid state, a yellow color appeared in the mixture, the color intensity increased within time in both conditions (25°C/60% RH and 40°C/75% RH); this yellow color is perhaps due to desalting of sodium salt of MNT and its transformation to MNT acid which is yellow in color [9], or because of that MNT colors yellow after exposure to the light [10]. Sample of MNT-LVZ which was stored in 40°C/75% RH formed agglomerates; this may be due to MNTs' hygroscopicity

HPLC analysis of isothermally stressed samples

The HPLC analysis of samples is shown in Table 1. The degradation of the drugs in the mixture and each drug alone was found in less than 10% in different conditions during 1, 4, and 13 weeks. Retention times (LVZ Rt = 2.7 min, MNT Rt = 13.5 min) and the shape of peaks did not change in all chromatograms. Furthermore, no additional peak appeared. Hence, the chromatographic analysis provided the evidence

that there was no degradation of analytes over storage times. MNT-LVZ mixture was compatible.

DSC results

The thermograms of LVZ alone initials and after storing 14 weeks in conditions 25°C/60% RH and 40°C/75% RH were shown in Fig. 1; it exhibited a sharp endothermic peak with onset at 207°C, peak at 217°C, and enthalpy about 177 J/g corresponding to melting of pure LVZ following by decomposition of the material, which did not change after storage. The sharp endothermic peaks reflect the crystalline nature of LVZ. The thermograms of MNT alone initials and after storing 14 weeks in conditions 25°C/60% RH and 40°C/75% RH were shown in Fig. 2; it exhibited a broad endothermic peak with a slight shoulder at range about 40–114°C corresponding to dehydration of water absorbed by MNT and overlapping with glass transition of amorphous MNT. The enthalpy (J/g) increased from 80.29 initial to 143 (after 14 weeks in 25°C/60% RH) and 216 (after 14 weeks in 40°C/75% RH), resulting from dehydration of addition water amount absorbed by MNT during storing, that was confirmed by Karl Fischer result (data not showed for Karl Fischer).

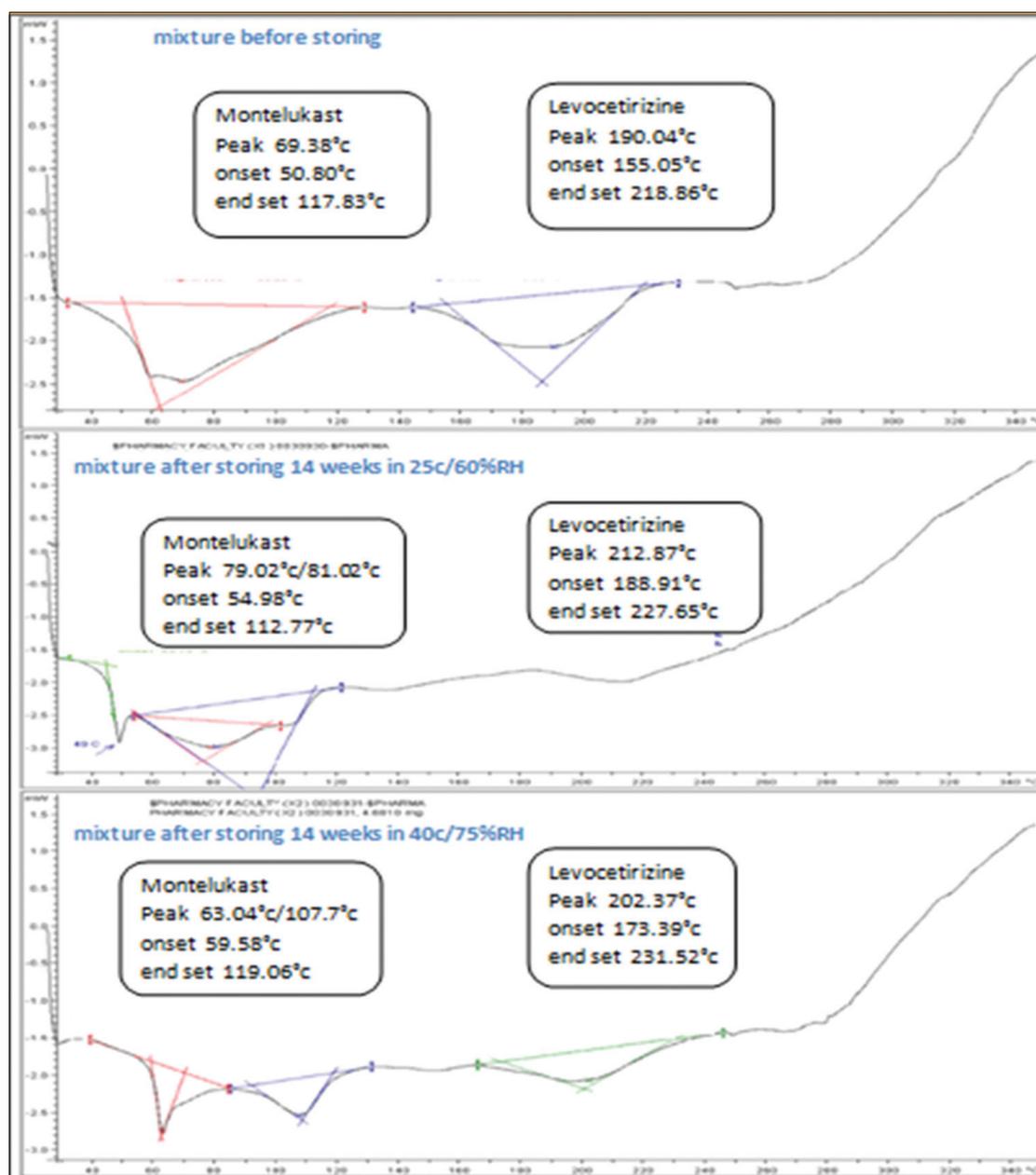


Fig. 3: Differential scanning calorimeter results of mixture before storing, after storing 14 weeks in 25°C/60% RH, after storing 14 weeks in 40°C/75% RH

The thermograms of MNT-LVZ (2:1) mixture initials and after storing 14 weeks in conditions 25°C/60% RH and 40°C/75% RH were shown in Fig. 3. For LVZ endothermic peak, this peak became broaden and the onset of peak shifted toward lower temperature and the enthalpy of the peak decreased, which indicates reducing in crystallinity [11]; this change could be attributed to the mixing process and impurities maybe water [12] which low the purity of LVZ and does not indicate incompatibility [13,14]. For MNT endothermic peak, in the thermograms of mixture, slight changes in temperature ranges and enthalpies were shown initially. After storing for 14 weeks, the peak stayed at the same temperature range but the shoulder began to split to sharp phase in 25°C/60% RH and was more obvious in 40°C/75% RH; this may be due to decreasing the amount of water absorbed by MNT, and the initial fast phase is the direct result of dehydration of water from the surfaces of particles [15].

The less water amount absorbed by MNT maybe because of desalting of MNT sodium and converting to MNT acid which differentiates from the sodium salt with its low hygroscopicity [9].

FTIR spectroscopy results

Pure MNT spectra (Fig. 4a) showed characteristic peaks at 3430 cm^{-1} (O-H, stretching), 3075, 2970, 2949, cm^{-1} (C-H, stretching), 2360 cm^{-1} (S-H, stretching), 1594 cm^{-1} (C=O carboxylate salt, stretching), 1496 cm^{-1} (C=C aromatic stretching), 1407 cm^{-1} (O-H tertiary, bending), 761 cm^{-1} (C-CL, stretching), and 690 cm^{-1} (C-S, stretching). No changes in the peak positions were observed after exposure to 25°C/60% RH and 40°C/75% RH for 14 weeks as demonstrated by spectra of MNT alone (Fig. 4f and i), respectively. Pure LVZ spectra (Fig. 4c) showed characteristic peaks at 3430 cm^{-1} (O-H stretching), 2949 cm^{-1} (C-H, stretching), 2366 cm^{-1} (N-H, stretching), 1745 cm^{-1} (C=O carboxylic acid, stretching), 1434 cm^{-1} (O-H carboxylic acid, bending), 1356, 1320 cm^{-1} (C-H, bending), 1184 cm^{-1} (N-H tertiary, stretching), 1136 cm^{-1} (C-O ether, stretching), and 758 cm^{-1} (C-CL stretching). No changes in the peak positions were observed after exposure to 25°C/60% RH and 40°C/75% RH for 14 weeks as demonstrated by spectra of LVZ alone (Fig. 4d and g), respectively. The FTIR spectra of MNT-LVZ mixture initial (Fig. 4b) can be considered as the superposition of individual ones without absence, shift, or intensity

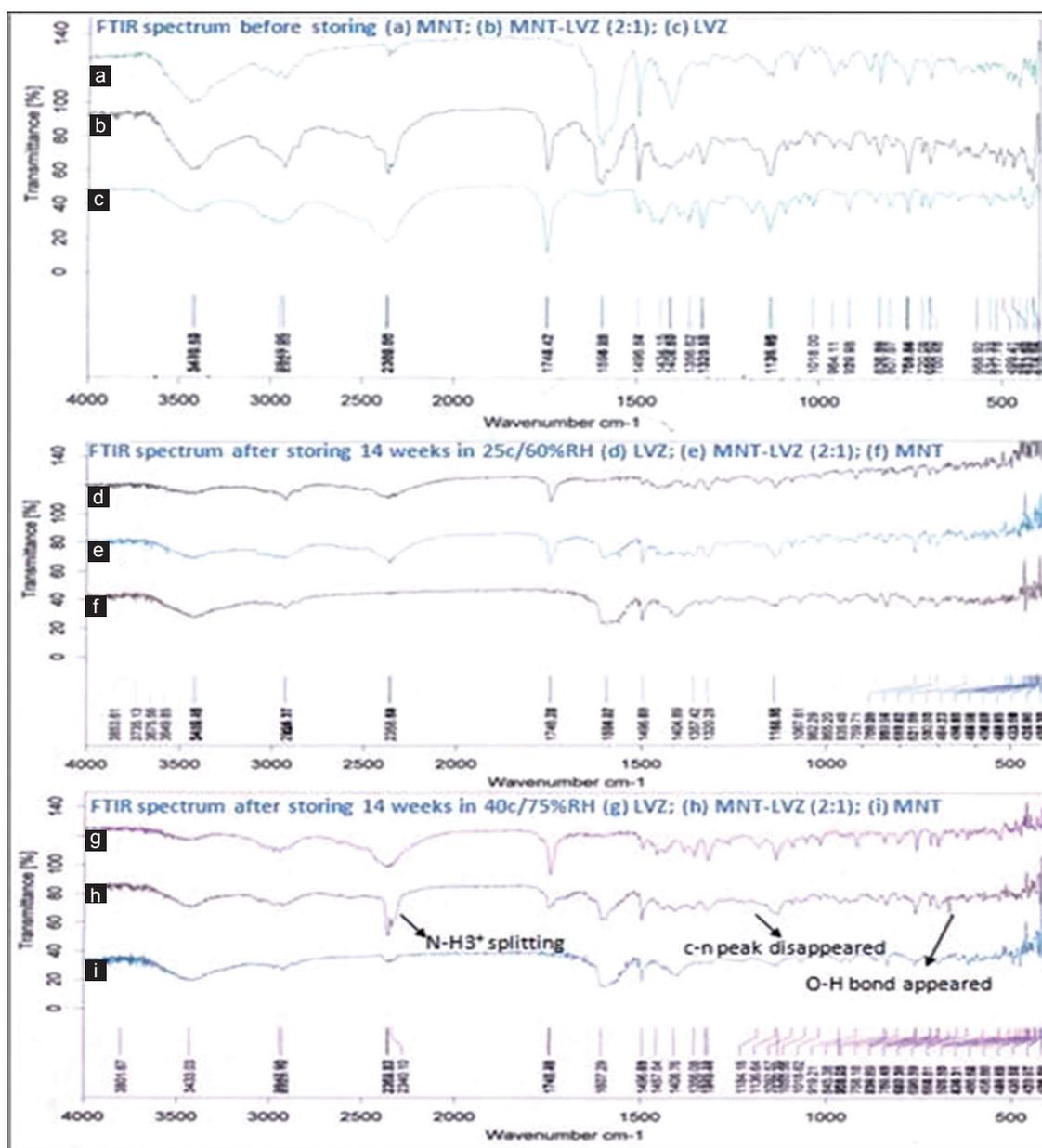


Fig. 4: Fourier transform infrared spectrum of (a) montelukast (MNT), (b) mixture, (c) levocetirizine (LVZ), (d) LVZ after storing 14 weeks in 25°C/65% RH, (e) mixture after storing 14 weeks in 25°C/65% RH, (f) MNT after storing 14 weeks in 25°C/65% RH, (g) LVZ after storing 14 weeks in 40°C/75% RH, (h) mixture after storing 14 weeks in 40°C/75% RH, (i) MNT after storing 14 weeks in 40°C/75% RH

changes in the vibration bands of MNT or LVZ. Similar observations were seen when mixture stored 14 weeks in 25°C/60% RH (Fig. 4e). For the mixture stored 14 weeks in 40°C/75% RH (Fig. 4 h), the FTIR spectra exhibited the characteristic peaks of each one without any shift in frequencies; this indicates no MNT-LVZ interaction [16] but changes in the intensities of 2366 cm^{-1} , 1745 cm^{-1} , 1594 cm^{-1} , and 1408 cm^{-1} were observed, and disappearance of 1184 cm^{-1} (tertiary amine, LVZ) and a new peak at 668 cm^{-1} were appeared; this may be due to intra and/or inter hydrogen bonding which affect intensity of vibrational modes [16,17]; the small shoulder in the stretching of N-H^3+ (2366 cm^{-1}) may be due to the effect of additional water absorbed in the mixture [18].

XRPD results

The X-ray powder diffractogram of LVZ initial and after 14 weeks of storing in 25°C/60% RH and 40°C/75% RH (Fig. 5a-c), respectively, showed characteristic sharp intensity diffraction peaks at 2θ values of 7.12°, 7.97°, 14.44°, 14.82°, 18.262°, 18.59°, 20.38°, 23.45°, 24.22°,

25.15°, 25.322°, and 26.194° which reflected the crystalline nature of LVZ. The X-ray powder diffractogram of MNT initial and after 14 weeks of storing in 25°C/60% RH and 40°C/75% RH (Fig. 5d-f), respectively, reveals no crystallographic peak just halos suggesting that MNT was amorphous. The X-ray powder diffractogram of MNT-LVZ mixture initial and after 14 weeks of storing in 25°C/60% RH and 40°C/75% RH (Fig. 5g-i), respectively, showed characteristic sharp intensity diffraction peaks of LVZ, although their relative intensities were reduced, suggesting reduced degree of crystallinity of LVZ [19] or maybe due to the reducing of LVZ percentage in mixture to half. New sharp diffraction peaks at 2θ values of 31.665°, 45.434°, and 56.426° appeared in mixture stored 14 weeks in different conditions, and their relative intensities were increased in accelerated condition. However, after research, these peaks may belong to sodium chloride salt, as demonstrated in lecture. Sodium chloride salt is produced from desalting of MNT sodium and releasing of sodium ion in media and interacts with hydrochloride ion from LVZ.

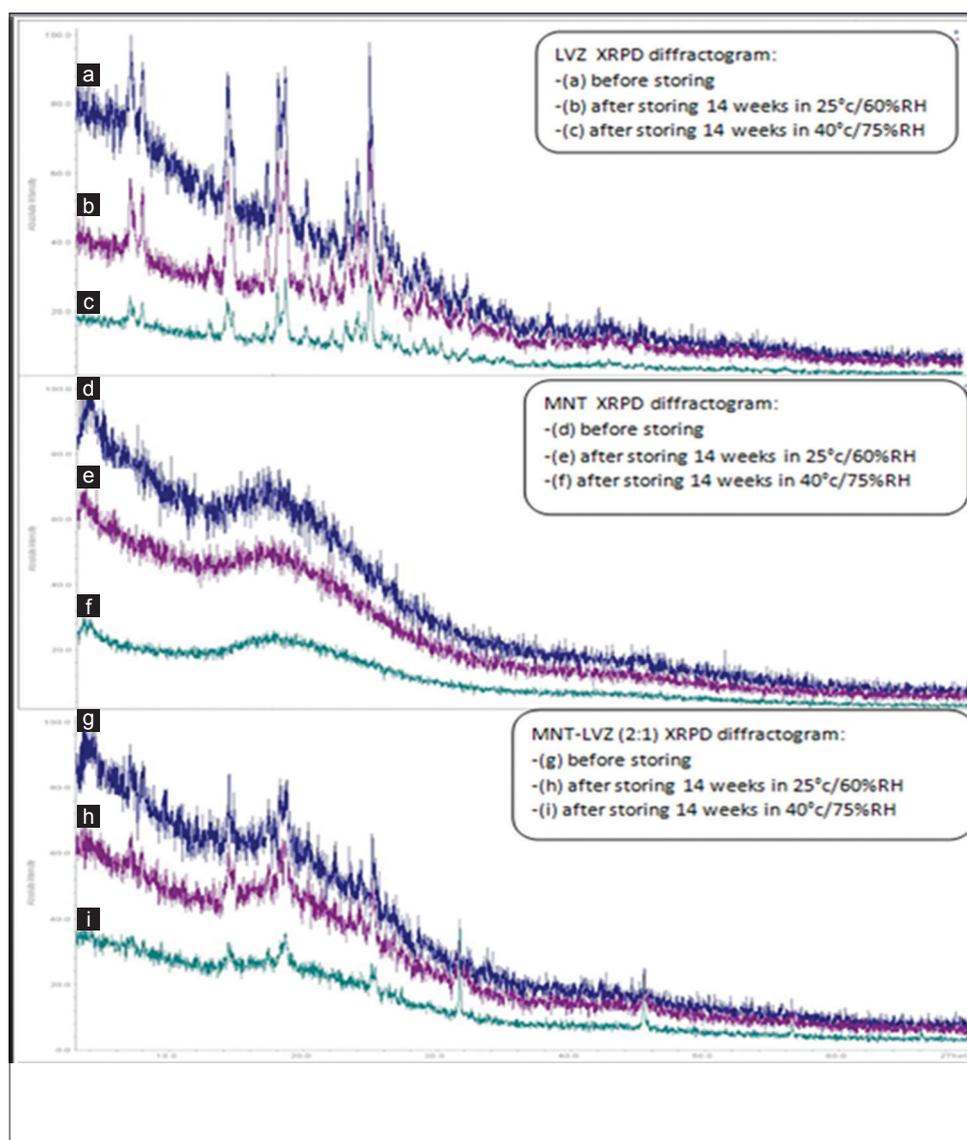


Fig. 5: X-ray powder diffraction of (a) levocetirizine (LVZ), (b) LVZ after storing 14 weeks in 25°C/65% RH, (c) LVZ after storing 14 weeks in 40°C/75% RH, (d) montelukast (MNT), (e) MNT after storing 14 weeks in 25°C/65% RH, (f) MNT after storing 14 weeks in 40°C/75% RH, (g) mixture, (h) mixture after storing 14 weeks in 25°C/65% RH, (i) mixture after storing 14 weeks in 40°C/75% RH

CONCLUSION

MNT-LVZ (2:1, w/w) mixture compatibility was studied to form FDC. HPLC analysis results evidenced the chemical stability during storage at 25°C/60% RH and 40°C/75% RH. FTIR results showed some changes which indicate an interaction related to the formation of hydrogen bonding which is not covalent bonding, and sometimes, it offers the formation of molecular complexes which may improve chemical stability and/or solubility [16]. DSC and XRPD revealed possible physical interaction arises from the phase transformation including salt and parent conversion which involves the releasing: (1) acidic form of MNT, which characterized with yellow color and its low hygroscopicity, (2) sodium chloride in the medium. This could affect pharmaceutical character like the dissolution rate. Finally, development a FDC of MNT and LVZ is possible, as long as HPLC result confirmed a compatibility between MNT and LVZ, but there is a need to control the pharmaceutical aspects.

AUTHOR CONTRIBUTION

D.S.H.A and H.Z designed the stability study strategies. D.S.H.A performed the experiment, collected and analysed the data. D.S.H.A wrote the manuscript. H.Z supervised and edited the manuscript.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest.

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