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Compatibility study between antiparkinsonian drug Levodopa and excipients by FTIR spectroscopy, X-ray diffraction and thermal analysis

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Abstract Levodopa (L-Dopa or LD) is nowadays considered one of the essential medicines in the World Health Organization list, being a main treatment component for Parkinson's disease. This paper deals with the investigation of solid-state stability and compatibility of binary mixtures of Levodopa with various pharmaceutical excipients, by employment of several instrumental techniques, such as attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy, powder X-ray diffraction (PXRD) data and thermal analysis (TG/DTG/HF). Along L-Dopa, eleven pharmaceutical excipients were investigated, namely calcium lactate (CaL), mannitol (Man), magnesium stearate (MgSt), anhydrous lactose (LAnh), talc (T), magnesium citrate (MgC), sorbitol (Sb), silica (SiO_2), polyvinylpyrrolidone K30 (PVP), sodium carboxymethylcellulose (NaCMC) and starch (St). FTIR analysis suggested possible interactions with calcium lactate, mannitol, magnesium stearate, anhydrous lactose, talc and SiO_2, which were confirmed by PXRD patterns, except for talc. When the samples were subjected to thermal stress, solely magnesium citrate did not present interactions in binary mixture, while all other excipients were incompatible with L-Dopa.

Keywords L-Dopa · Levodopa · Compatibility study · Excipient · FTIR · PXRD · Thermal analysis

Introduction

One of the most frequent neurodegenerative conditions in the third age patients, Parkinson's disease presents a series of symptoms that have high impact on the quality of life. These are the consequence of a correlation between dysfunctions in the locomotor system and degeneration of the central nervous system [1]. The main encountered problems relate to tremors, rigidity and postural instability [2] correlated with depression, anxiety, hallucinations and cognitive loss [3].

Ever since researchers have discovered the correlation between low dopamine levels in the *substantia nigra* from the central nervous system (CNS) and Parkinson's disease, levodopa has become the main treatment component in almost every patients' therapy pattern [4]. It has been proven that dopamine in itself cannot cross the blood–brain barrier in order to reach its desired target, but, with the help of a carrier protein, levodopa is able to enter the CNS [5]. The L-Dopa conversion to dopamine, the actual pharmaceutical active substance, takes place under the catalytic action of dopa-decarboxylase, an enzyme that is not specific for the CNS. Because of this, L-Dopa is often associated with a series of inhibitors that constrain the transformation in the peripheral areas, allowing for most of

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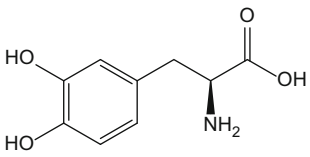

Fig. 1 Structure of L-Dopa

the active substance to arrive at its active situs [6]. The structure of L-Dopa is presented in Fig. 1.

As a result, researchers have been focused on the study of different formulations that can offer alternatives not only in the types of dosage forms, but also in the components of the final pharmaceutical drug [7–9].

In regard to its physico-chemical properties, it has been shown that levodopa presents as a white, odorless,

Table 1 ATR-FTIR characteristic peaks for pure L-Dopa and in binary mixtures with excipients

Sample	Characteristic ATR-FTIR bands/cm^{-1}										
	H–O			H–X (X = C, N)							C=O
L-Dopa	3500–2400	1404	1248	3357	3192	3038	2981	2929	2834	1560	1649
L-Dopa + CaL	3500–2400	1404	1249	–	3192	3038	2983	2929	–	1562	1655
L-Dopa + Man	3500–2400	1405	1250	3397	3227	–	2984	2948	–	1563	1657
L-Dopa + MgSt	3500–2400	1409	1249	3359	–	3038	2981	–	–	1570	1656
L-Dopa + LAnh	3500–2400	1407	1253	–	3200	3039	2983	2930	2834	1562	1655
L-Dopa + T	–	1404	1253	–	–	–	–	–	–	–	1653
L-Dopa + MgC	3500–2400	1405	1249	–	3192	–	2985	–	2835	1560	1649
L-Dopa + Sb	3500–2400	1404	1248	–	3222	3038	2984	2930	–	1560	1650
L-Dopa + SiO_2	–	1405	–	–	–	–	2981	2923	2855	1563	1657
L-Dopa + PVP	3500–2400	1404	1250	3368	3202	3038	2980	2929	–	1562	1650
L-Dopa + NaCMC	3500–2400	1405	1248	3370	3198	3038	2982	2930	2850	1562	1650
L-Dopa + St	3500–2400	1404	1248	3357	3192	3040	2981	2929	–	1560	1650

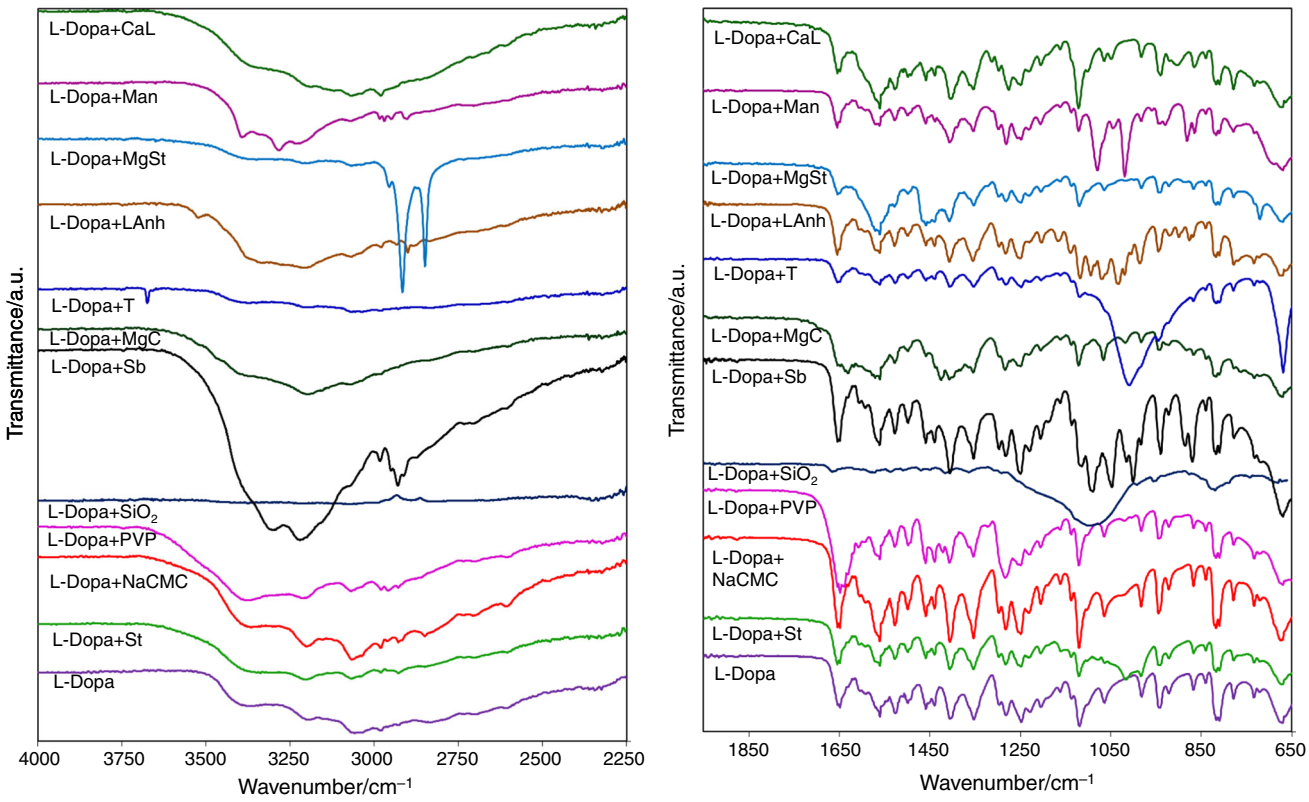

Fig. 2 ATR-FTIR spectra of LD and binary mixtures with excipients: **a** 4000–2250 cm^{-1} and **b** 1875–650 cm^{-1} spectral regions

crystalline powder that has poor water solubility, but is fairly soluble in various acids [10, 11]. An improvement in the solubility properties translates itself in an increase in the drug's bioavailability; thus, in order to achieve a good dosage form that meets the desired characteristics, a series of excipients are required in all pharmaceutical formulations. The main conditions that these substances have to satisfy are related to the compatibility between the active pharmaceutical substance and the added compounds and, respectively, the stability of the final product [12]. Basically, excipients are used in relatively high quantities in comparison with the active substance, and as such, a low cost is important. Because of this, in the pharmaceutical industry there is a permanent struggle between cost and quality and, thus, an increasing interest from researchers is only to be expected [12, 13].

Considering the fact that there are several generic products that contain Levodopa as an active substance and taking into consideration that the basic difference between these is represented by the variability in the excipients list, an analysis regarding compatibility is highly significant not only for future dosage forms, but for those already present on the pharmaceutical market.

Up to the date, an extended study regarding the compatibility of L-Dopa was not published, according to our knowledge. The selected excipients were calcium lactate (CaL), mannitol (Man), magnesium stearate (MgSt), anhydrous lactose (LAnh), talc (T), magnesium citrate (MgC), sorbitol (Sb), silica (SiO_2), polyvinylpyrrolidone K30 (PVP), sodium carboxymethylcellulose (NaCMC) and starch (St). The selection of excipients was carried out taking into consideration the fact that they belong to different classes, with various roles in the final solid formulation.

The compatibility was evaluated under ambient temperature employing ATR-FTIR spectroscopy and PXRD pattern and then completed with thermal treatment of the samples, according to well-established protocols [14–24].

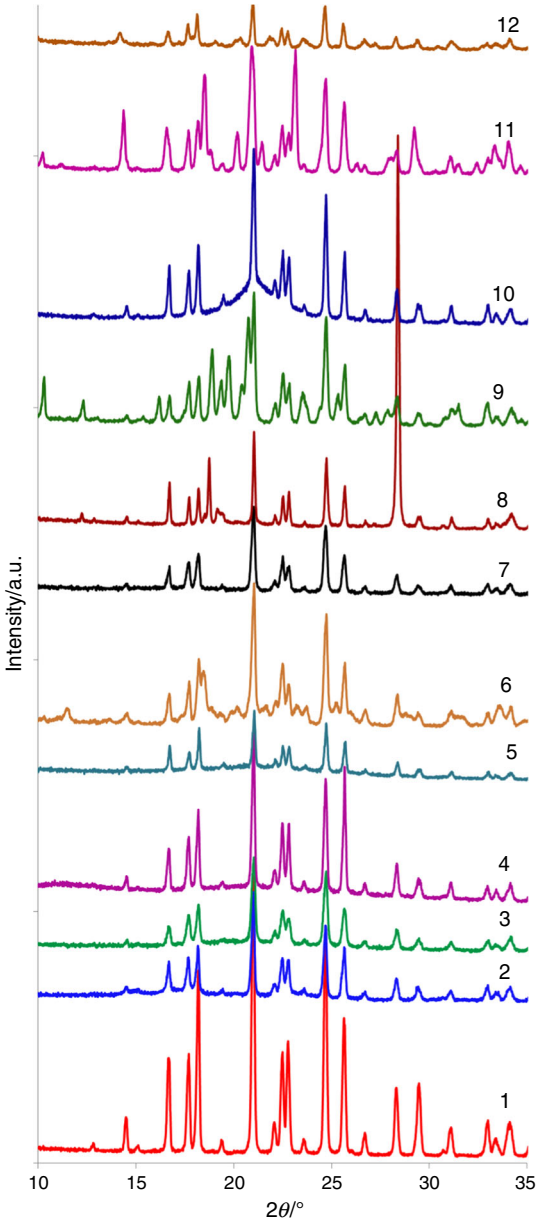

Fig. 3 PXRD patterns obtained for: *1* L-Dopa and binary mixtures; *2* L-Dopa + St; *3* L-Dopa + NaCMC; *4* L-Dopa + PVP; *5* L-Dopa + SiO_2; *6* L-Dopa + Sb; *7* L-Dopa + MgC; *8* L-Dopa + T; *9* L-Dopa + LAnh; *10* L-Dopa + MgSt; *11* L-Dopa + Man and *12* L-Dopa + CaL

Materials and methods

Materials and sample preparation

Levodopa (L-Dopa, LD) was provided by Fluka Analytical through Sigma-Aldrich (lot LRAA0007, pharmaceutical secondary standard; traceability to United States Pharmacopeia, European Pharmacopoeia and British Pharmacopoeia), and it was used as received. The compound was stored according to the supplier requirements, at low temperatures (4 °C) and away from light.

As excipients, calcium lactate (Aldrich, Germany), mannitol (Merck, Germany), magnesium stearate (Union Derivan, Spain), anhydrous lactose (Friesland Foods Domo, Holland), talc (Luzenac Pharma, Italy), magnesium citrate (Fluka, Germany), sorbitol (Sigma, Germany), colloidal silica (Aerosil 200 Evonik Degussa, Germany), polyvinylpyrrolidone K30 (BASF, Germany), sodium carboxymethyl cellulose (Aldrich, Germany) and starch (Grain Processing Corporation, USA) were used. All excipients were of pharmaceutical grade.

Binary mixtures were prepared at room temperature by homogenization of equal masses of excipient and LD in

Table 2 Diffraction peaks of L-Dopa as pure ingredient and in binary mixtures with investigated excipients

2θ diffraction angle for L-Dopa+											
Pure	St	NaCMC	PVP	SiO_2	Sb	MgC	T	Lanh	MgSt	Man	CaL
12.72	–	–	–	–	–	–	–	–	–	–	–
14.44	14.22	14.27	14.50	14.22	14.22	14.26	14.22	14.26	14.40	14.33	–
14.76	–	–	–	–	–	–	–	–	–	–	–
16.62	16.64	16.58	16.60	16.68	16.61	16.65	16.68	16.65	16.70	16.51	16.54
17.66	17.64	17.63	17.70	17.64	17.67	17.58	17.67	17.66	17.66	17.62	17.61
18.14	18.15	18.13	18.17	18.20	18.18	18.11	18.16	18.13	18.15	18.14	18.10
19.23	19.23	–	–	–	–	–	–	19.30	–	–	–
21.21	20.86	20.90	20.68	21.01	20.98	20.93	21.01	20.99	20.79	21.35	20.92
22.01	21.96	22.00	22.01	21.91	22.04	21.88	21.99	22.02	22.03	–	–
22.45	22.42	22.42	22.45	22.47	22.43	22.44	22.46	22.44	22.46	22.40	22.36
22.75	22.54	22.55	22.78	22.76	22.57	22.56	22.78	22.58	22.78	–	22.52
23.47	23.34	–	23.34	–	23.52	–	–	23.43	–	–	–
24.41	24.49	24.50	24.64	24.68	24.71	24.63	24.70	24.68	24.60	24.63	24.54
25.60	25.60	25.60	25.64	25.66	25.63	25.58	25.64	25.63	25.71	25.70	25.55
26.61	26.45	26.40	26.60	–	26.60	26.41	–	–	26.62	–	26.63
28.25	28.24	28.30	28.25	28.27	28.28	28.23	28.26	28.23	28.27	–	28.01
29.41	29.33	29.30	29.35	29.29	29.17	29.29	29.20	29.31	29.34	29.17	29.12
32.90	32.80	32.70	32.89	32.74	32.83	32.78	32.90	32.86	32.90	–	–
33.10	33.20	33.10	33.06	–	33.41	33.19	33.15	33.30	33.25	–	–
34.00	33.90	33.90	33.91	33.88	34.90	33.93	33.97	34.02	33.98	34.01	33.94

agate mortars. After grinding for approximately 5 min, the solid samples were transferred into sealed tubes. After preparation, the samples were kept under ambient conditions.

ATR-FTIR analysis

Attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) spectra were collected on a PerkinElmer SPECTRUM 100 spectrometer. Spectra were collected in the 4000–650 cm^{-1} spectral range, with a resolution of 1 cm^{-1} and with 16 co-added scans.

PXRD analysis

PXRD analysis was carried out on a Rigaku Ultima IV instrument operating at 40 kV and 40 mA, using the CuK_α monochromatic radiation ($\lambda = 0.15418$ nm) under ambient condition and the 2θ scan range was 10.00°–35.00°.

Thermal investigations

Thermoanalytical profile of all samples consists in TG, DTG and HF curves recorded simultaneously. The experiments were carried out in oxidative medium (air atmosphere), under non-isothermal conditions at a heating rate $\beta = 10$ °C min^{-1} from room temperature to 500 °C on a PerkinElmer DIAMOND thermobalance, in aluminum crucibles. The samples were weighted in the same mass range, approx. 5 mg. The DTA data (μV) were converted in heat flow (HF) data (mW).

All the measurements were taken in duplicate, and the results were practically identical.

Results and discussions

ATR-FTIR spectroscopy

Previously, we reported the ATR-FTIR spectrum of pure L-Dopa and the attribution of characteristic bands, especially for important functional moieties.

L-Dopa is an amino acid, containing as reactive functional groups the carboxyl moiety, amino moiety and two vicinal aromatic hydroxyls. Since the interactions with functional groups of excipients are more probable to take place at this groups, in Table 1 are comparatively presented the wavenumbers where the FTIR peaks were observed for pure LD versus LD in binary mixtures.

The ATR-FTIR spectra are presented in Fig. 2, while the main peaks are presented in Table 1.

Analyzing the FTIR results, several conclusions can be drawn. The broad band in the spectral region

3500–2400 cm^{-1} is present in most binary mixtures, and it is even more intense in the case of excipients with O–H groups in the molecule. In the case of binary mixtures L-Dopa + T and L-Dopa + SiO_2, the broad band is no longer present in the spectrum. The attenuation of these bands could be explained due to the presence of the intense band of talc, at ~1000 cm^{-1}, respectively, by the intense and large band at ~1100 cm^{-1}, characteristic to Si–O bonds. The other bands of L-Dopa in the 1875–650 cm^{-1} range are still visible, mainly those that are not overlapped by the large band of the excipient.

Other clear modifications are observed in the case of binary mixture L-Dopa + MgSt, where the H–X signals are completely attenuated in comparison with the intense bands of the excipient from 2917 to 2850 cm^{-1}. The H–X bands are also drastically attenuated in the case of L-Dopa + T and L-Dopa + SiO_2.

Some important modifications over C=O and H–O bands are observed in the case of L-Dopa + CaL, L-Dopa + Man, L-Dopa + MgSt, L-Dopa + LAnh, L-Dopa + SiO_2, where the shifting of the peak position is considerable high, up to 8 cm^{-1}, clearly suggesting structural modifications. However, the preliminary results revealed by FTIR analysis will be further investigated by PXRD and thermal analysis.

PXRD profile

L-Dopa presents a high crystallinity degree, showing diffraction peaks at following 2θ angles: 12.72; 14.44; 14.76; 16.62; 17.66; 18.14; 19.23; 21.21; 22.01; 22.45; 22.75; 23.47; 24.41; 25.6; 26.61; 28.25; 29.41. In order to search modification of crystalline phases, amorphization or pseudomorphic/polymorphic transitions, binary mixtures were investigated in identical experimental conditions as L-Dopa (Fig. 3). In Table 2, the main diffraction peaks observed for L-Dopa are presented, and in comparison, the existence of same bands in binary mixtures.

The attenuation of diffraction peaks of L-Dopa was expected, since the proportion of L-Dopa in the analyzed powders decreased from 100% in the pure L-Dopa to 50% in the mixtures. This led to the disappearance of weaker peaks. The XRD patterns of some mixtures show new peaks that can be assigned to the excipients.

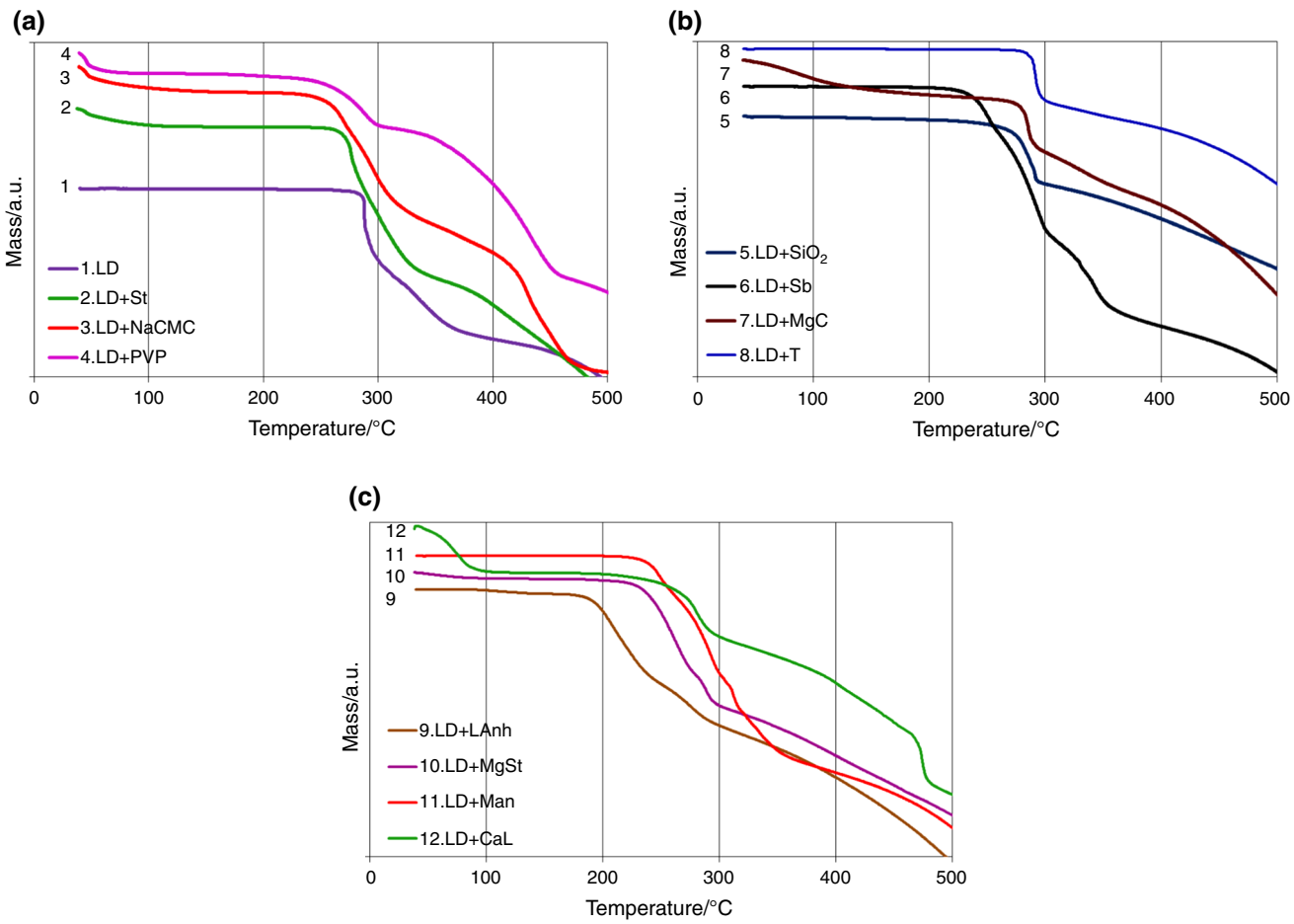

Fig. 4 Thermoanalytical curves (mass versus temperature) obtained for levodopa (LD) and binary mixtures

By the analysis of the diffraction patterns, it can be stated that no modification of crystallinity occurs in most of binary mixtures. The most important changes are observed in the case of L-Dopa + MgSt, where several peaks of the active substance are no longer visible. Also, modifications are observed in the cases of binary mixtures L-Dopa + CaL, L-Dopa + Man, L-Dopa + LAnh, L-Dopa + SiO_2 and L-Dopa + T.

Since FTIR and PXRD analyses indicated interactions between the components of several binary mixtures, an evaluation of the thermal behavior was further investigated.

Thermal treatment investigations

Mass, mass derivative and heat flow curves are presented in Figs. 4–6a–c, and the important thermal events in Table 3.

The thermal profile of pure L-Dopa reveals a single-step decomposition process. The degradation occurs in the 271–500 °C temperature range and corresponds to a total mass loss $\Delta m = 60\%$. HF curve shows two adjacent thermal events, an exothermic decomposition followed by an endothermal process with peak at 289 °C. The endothermic event is generally attributed to the melting-decomposition process, in correspondence with TG/DTG curves and literature [25].

Following the analysis of pure L-Dopa, the differences between the thermoanalytical parameters (temperature range, temperature of maximum, according to Table 3) were checked for the eleven binary mixtures in comparison with the main degradation step of the pure sample.

The binary mixture L-Dopa + St shows a similar HF profile with pure active pharmaceutical ingredient, with the difference in the shifting of peak's maximum for HF and DTG at lower temperature values. The mass loss presents a different value due to the decomposition of the used excipient. The shifting of the peak by 12 °C is a clear indication of the interaction between the components.

NaCMC used in binary mixture with L-Dopa leads to a thermal behavior which differs by the initial temperature of decomposition, by the events on HF curve (nature and maximum of peaks, respectively) and DTG event. In this case, it can be said that the difference of 15 °C between melting of pure compound versus binary mixture is due to thermal-induced interaction between the components.

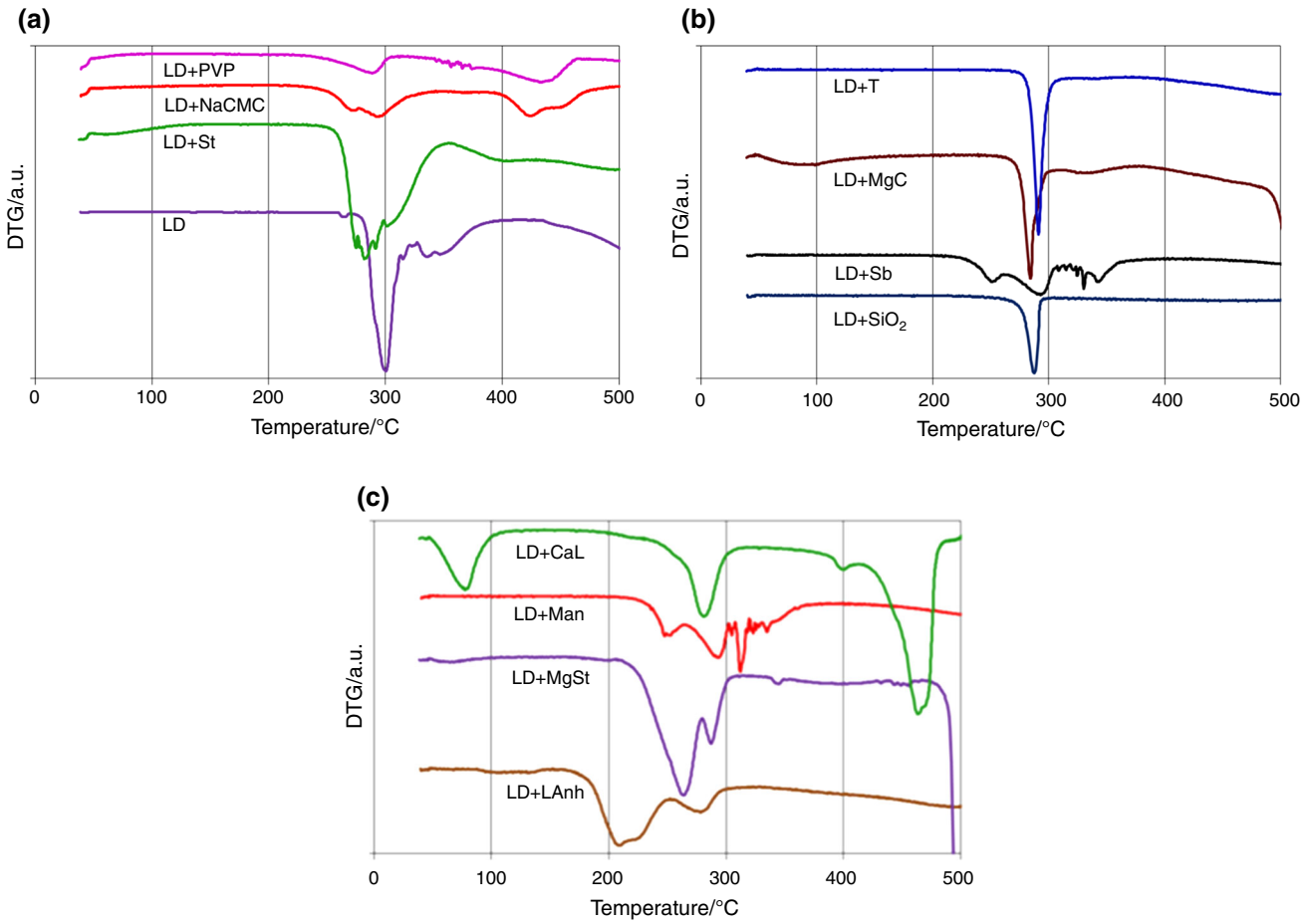

Fig. 5 Thermoanalytical curves (mass derivative versus temperature) obtained for levodopa (LD) and binary mixtures

The mixture with PVP has the thermoanalytical curves without prominent thermal events on DTG and HF curves, the characteristic peaks of L-Dopa are still visible as a much-attenuated peak in a larger temperature range (the mass loss is visible on TG), is also in this case a clear suggestion of interaction.

For the mixture with SiO_2 which is considered a totally inert excipient, the HF curve contains a process characterized by an exothermic peak and the percent of mass loss is bigger than the calculated value due to the fact that the mixture is 1:1 in mass percent ($\Delta m_{\text{experimental}} = 42\%$ comparative with $\Delta m_{\text{calculated}} = 30\%$). The thermal-induced incompatibility was also suggested by other two instrumental techniques, carried out under ambient conditions.

Another interaction is observed in the case of binary mixture with sorbitol (Sb). For this mixture, thermoanalytical curves contain three large and weak endothermic events due to the presence of sorbitol and L-Dopa, the one in the middle could be assigned to the active substance.

The thermogravimetric curve of the mixture with MgC presents a dehydration step. The next region is characterized by the same processes with the same thermoanalytical

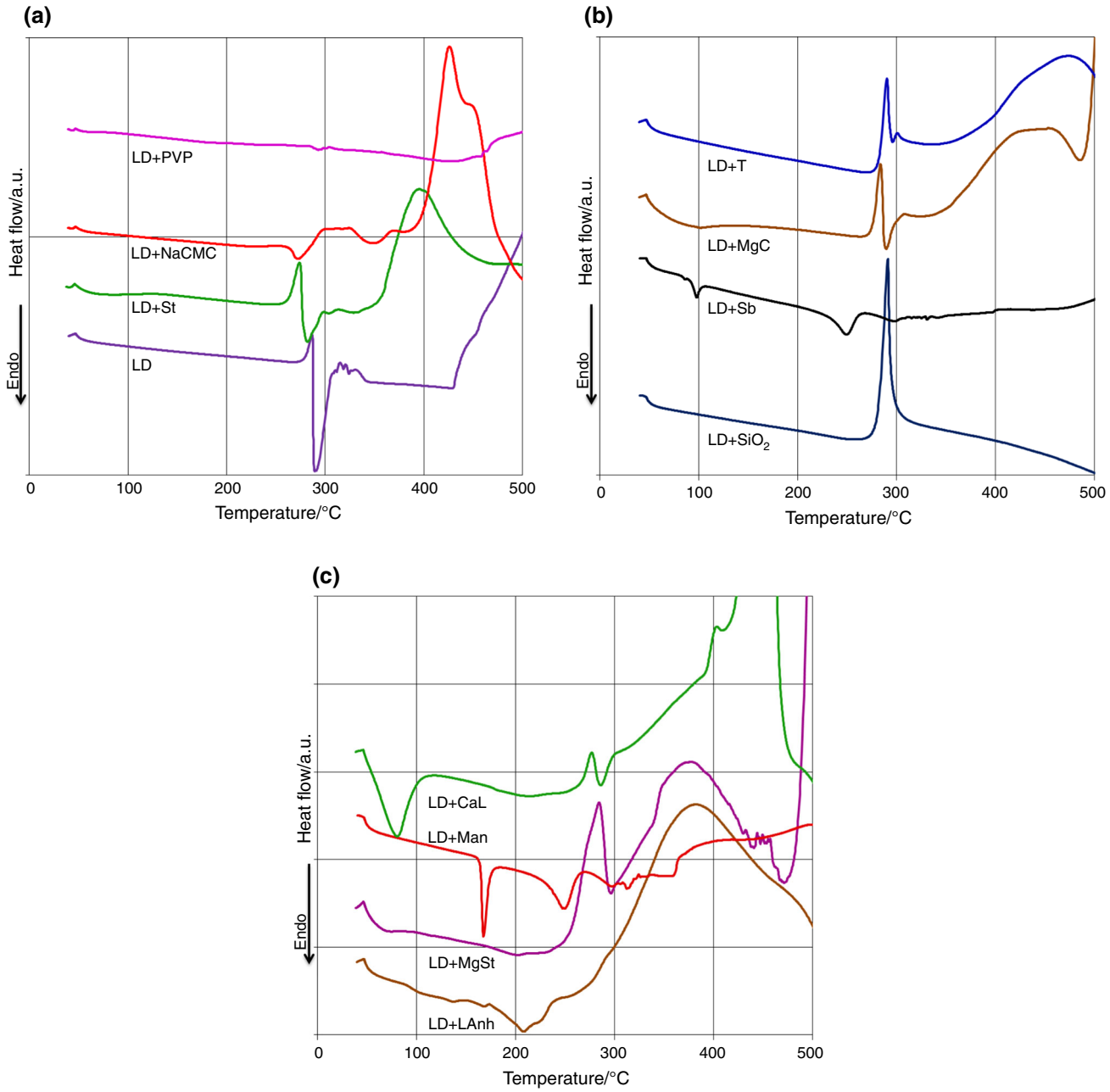

Fig. 6 Heat flow (HF) data obtained for levodopa (LD) and binary mixtures

Table 3 Thermoanalytical data recorded for analyzed samples

Sample	HF		DTG		TG	Δm
	Onset/°C	Peak/°C	Onset/°C	Peak/°C	Onset/°C	%
L-Dopa	266	281	266	297	271	60
	288	289				
L-Dopa + St	252	269	247	274	263	85.3
	276	279				
L-Dopa + NaCMC	254	266	229	265; 288	223	88
	316	342				
L-Dopa + PVP	–	–	232	279	242	70.4
L-Dopa + SiO_2	268	288	264	284	260	42
L-Dopa + Sb	83	94	224	243	207	78.8
	226	244	257	287		
L-Dopa + MgC	265	278	50	84	40	10.6
	286	288	254	282	260	74.4
L-Dopa + T	276	283	278	290	266	38.7
	293	284				
L-Dopa + Lanh	173	200	167	205	166	85
	285	379				
L-Dopa + MgSt	245	280	205	257	207	94
	292	378	276	281		
L-Dopa + Man	154	166	219	244	220	84.2
	223	243	258	286		
			305	310		
L-Dopa + CaL	40	74	40	72	40	14.6
	257	273	228	276	204	66
	274	280	409	460		

parameters as was the case of the pure substance, showing that no interaction took place and the thermal events associated with the presence of excipient occur independently from the ones which determine the thermolysis of the active pharmaceutical ingredient.

In the case of mixture with talc, the curves are similar with the curves for LD, the difference being that the first event on the curve HF has a strong exothermic nature and the decomposition of L-Dopa is no longer visible, suggesting that the degradation of the active compound occurs in the earlier stages of thermolysis.

All three curves recorded for the mixture with anhydrous lactose have thermal parameters which differ totally from the parameters presented in the table for the active substance. The interaction with this excipient was also suspected to occur even under ambient conditions.

When the investigated excipient was MgSt, the incompatibility was sustained by the shifting of the HF peak and by the exothermic nature of the event.

The thermal profile of the binary mixture with mannitol is totally dissimilar with the thermal profile of L-Dopa. The degradations occur at comparable lower temperatures, so in the characteristic temperature range where L-Dopa is decomposed, no thermal events are observed: two peaks appear on HF curve, but these are due to the transformation of mannitol.

Thermolysis of the binary mixture with calcium lactate reveals a three-step degradative process, with some resemblance to the degradation of L-Dopa. However, in this case thermal-induced interactions are also observed, which were likewise visible under room-temperature conditions, by spectroscopic and difractometric techniques.

Conclusions

In this study, the investigations regarding the thermal stability of L-Dopa in binary mixtures with solid excipient were discussed. The investigations were realized in solid state, using FTIR spectroscopy and PXRD diffraction for thermally untreated samples, and later completed with the thermal stress analysis.

FTIR analysis and PXRD results were in agreement, revealing possible interactions between Levodopa and calcium lactate, mannitol, magnesium stearate, anhydrous

lactose, talc and SiO_2. Thermal stress determined the interactions in all samples, an exception being the mixture with magnesium citrate.

This preformulation study can be a starting tool for the selection of adequate excipients in new solid dosage forms that contain Levodopa as active pharmaceutical ingredient.

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