Thermal Behaviour of Candesartan
Active substance and in pharmaceutical compounds

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Thermal analysis is one of the most frequently used instrumental techniques in the pharmaceutical research, for the thermal characterization of different materials from solids to semi-solids, which are of pharmaceutical relevance. In this paper, simultaneous thermogravimetry/derivative thermogravimetry (TG/DTG) and differential scanning calorimetry (DSC) were used for characterization of the thermal behaviour of candesartan cilexetil – active substance (C-AS) under dynamic nitrogen atmosphere and nonisothermal conditions, in comparison with pharmaceutical product containing the corresponding active substance. It was observed that the commercial samples showed a different thermal profile than the standard sample, caused by the presence of excipients in the pharmaceutical product and to possible interaction of these with the active substance. The Fourier transformed infrared spectroscopy (FT-IR) and X-ray powder diffraction (XRPD) were used as complementary techniques adequately implement and assist in interpretation of the thermal results. The main conclusion of this comparative study was that the TG/DTG and DSC curves, together with the FT-IR spectra, respectively X-ray difractograms constitute believe data for the discrimination between the pure substance and pharmaceutical forms.

Keywords: candesartan, active substance, pharmaceutical product, TG/DTG/DSC, FT-IR, X-ray

Candesartan cilexetil, 1-cyclohexyloxycarbonyloxyethyl 2-ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl] benzimidazole-4-carboxylate (fig. 1), is a nonpeptide antihypertensive drug and used either single or in combination with other drugs, to treat high blood pressure. In the gastrointestinal tract candesartan cilexetil is converted to candesartan, an angiotensin II receptor antagonist which blocks the ability of angiotensin II to raise blood pressure by constricting or squeezing arteries and veins and ultimately leads to a reduction in blood pressure. It also reduced the work of heart by reducing the pressure against which the heart must pump blood, and is useful in patients with heart failure [1–2].

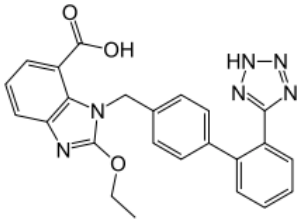

Fig. 1. Chemical structure of Candesartan cilexetil

Essential arterial hypertension (EAHT) is a major cause of morbidity and mortality, which affects approximately 1 billion people worldwide.

Angiotensin receptor blockers (ARBs) are regarded as first line therapy for hypertensive patients with type 2 diabetes mellitus. In addition to their antihypertensive effects, results of a multi-center trial showed that ARBs had a role in preventing the development of type 2 diabetes. Also, ARBs have been shown to protect many organs by controlling inflammation and decreasing oxidant stress in hypertensive patients without arteriosclerosis. But there is little evidence that ARBs have a positive effect in patients with advanced arteriosclerosis, such as those with type 2 diabetes mellitus of long duration accompanied by hypertension as were the patients in the ACCORD BP study. Furthermore, pulse pressure increases during the process of arteriosclerosis. It has been reported that pulse pressure is not only a predictor of cardiovascular events, but also is an independent predictor of new-onset diabetes in high-risk hypertensive patients [3-10].

The thermal analysis is a routine method applied for drugs characterization and it is useful in the preformulation stage in the development of solid dosage forms. Research in thermal decomposition of drugs is of great interest in developing new products since it is often necessary to predict degradation rates at marketing temperatures from collected data on accelerated processes studied at elevated temperatures [11-16].

Thermal analytical techniques, such as thermogravimetry/derivative thermogravimetry (TG/DTG) and differential scanning calorimetry (DSC) technique, provide important information regarding the physical properties of the pharmaceutical compounds (purity, polymorphism, thermal stability, compatibility, kinetic analysis, etc.)

Thermogravimetry is an analytical, quantitative and comparative method, capable of producing fast and reproducible results. It can be used in the quality control of drugs, with a view to the improvement of the final product and for the determination of drug quality via technological parameters [17,18].

Thermogravimetry, during which the change of mass of a sample heated at constant rate is recorded and plotted versus temperature, is an effective method of studying thermal stability and for determining the kinetic parameters of the decomposition of drugs and medicines [19,20].

Differential scaning calorimetry, which is frequently use instead of the DTA, can be used in pharmaceutical researches as an analytical tool of great importance for the identification and purity testing of active drugs and especially to elucidate the miscibility/incompatibility with its effects on thermal stability, yielding results rapidly and efficiently [21,22].

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The thermal stability is a very important factor since the determination of the temperature range in which a certain medicine substance (drug) is stable regarding its structure, as well as its pharmaceutical action is crucial for stocking drugs, for its technological transformations and for the obtaining technology of the right formulas.

The evaluation of the stability of a drug in solid form is realized especially by analysing its decomposition in isothermal and non-isothermal conditions. Usually, this takes place by irreversible weight loss. The drugs decomposition reactions have a theoretical, as well as a practical signification.

In our previous articles we provided the importance and utility of the thermal analysis in estimation of thermal stability and compatibility of different pharmaceuticals by the thermal behaviour, respectively kinetic analysis [23-28].

The purpose of the present paper is to evaluate the thermal behaviour of candesartan cilexetil active substance, in comparison with pharmaceutical products, together with the finding of the melting point through DSC, which is a criterion for the quality control.

As pharmaceutical products were studied four from the main used commercial products (drugs).

Also, the FT-IR spectra and X-ray diffractograms of pure substance and the pharmaceuticals were drawn up in order to establish an easy way for sample identification by means of a simultaneous analysis of TG/DTG and DSC curves, respectively FT-IR spectra and X-ray diffractograms.

Experimental part

Materials and methods

The substances examined by thermal analysis, FT-IR spectroscopy and X-ray analysis were candesartan cilexetil – active substance (C-AS) and four pharmaceutical products (P1, P2, P3, P4)

The active substance was obtained from Antibiotice Iasi, Romania, as pure compound, able to be used for medical purposes.

The pharmaceuticals (drugs) were commercial products, containing different excipients.

Thermal analysis

The TG/DTG and DTA curves were recorded using a Netzsch-STA 449 TG/DTA instrument in the temperature range 20–1000 °C, under a dynamic atmosphere of nitrogen (20 mL·min^{-1}) and at a heating rate (β) 10 °C·min^{-1}, using platinum crucibles and weighed ≈ 20 mg of samples.

Fourier transformed infrared spectroscopy (FT-IR) and X-ray diffraction

FT-IR spectra were recorded on a Shimadzu Prestige-21 apparatus using KBr discs in the range 4000–400 cm^{-1}.

X-ray diffraction patterns (XRPD) were obtained with a Rigaku Ultima IV diffractometer ($Cu_{K\alpha}$ radiation).

Results and discussions

Thermal behaviour

The thermoanalytical curves for the studied compounds are presented in figures 2-6 and these are obtained under

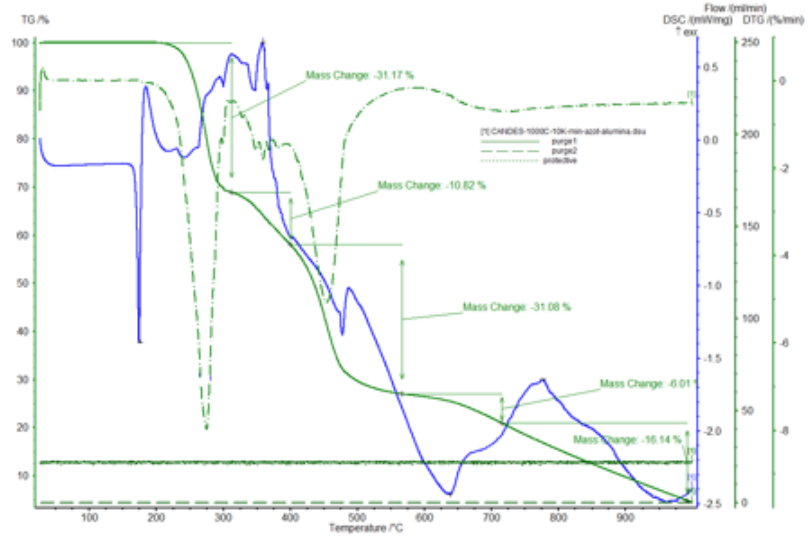

Fig. 2 TG/DTG and DSC curves for C-AS

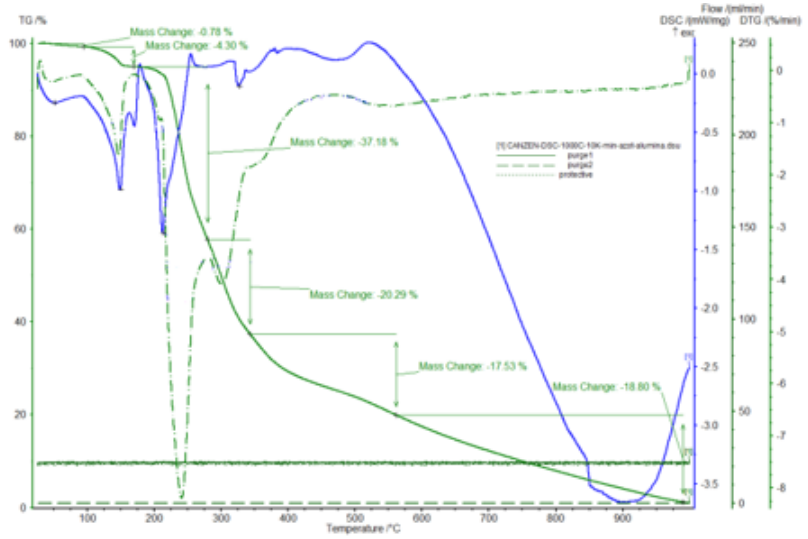

Fig. 3 TG/DTG and DSC curves for P1

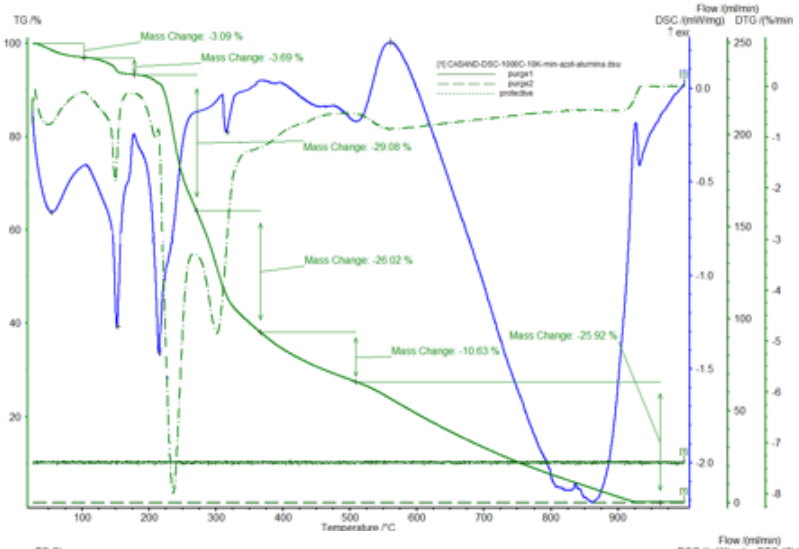

Fig. 4 TG/DTG and DSC curves for P2

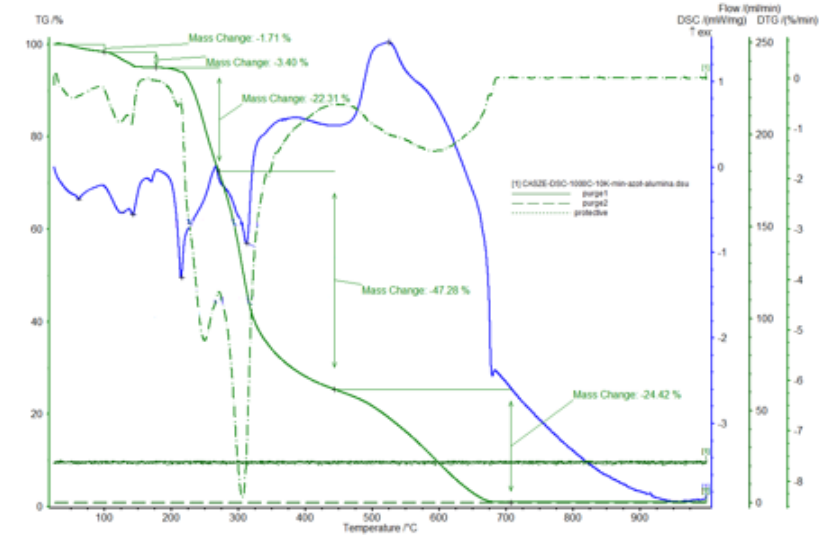

Fig. 5 TG/DTG and DSC curves for P3

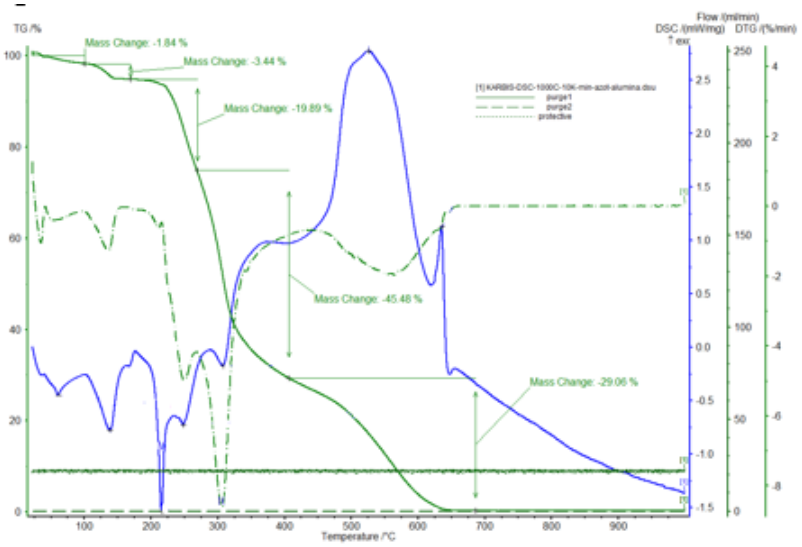

Fig. 6 TG/DTG and DSC curves for P4

dynamic temperature conditions, at heating rate of 10 °C·min^{-1} and a nitrogen atmosphere.

The main observations are summarized in table 1.

Among the main excipients present in the commercial products of Candesartan active substance are: hydroxypropyl cellulose, calcium carmellose, starch, lactose monohydrate, microcrystalline cellulose, magnesium stearate, red iron oxide, crospovidone, etc.

The presence of these excipients leads to a different composition of the pharmaceutical compounds and obviously to the C-AS, so that there are differences between the thermoanalytic curves of the studied compounds.

From the thermal curves (fig. 2) and thermoanalytical data (table 1) it is observed that the C-AS presents a relatively high thermal stability, and, at 183.1 °C, this substance is melting. The melting process, of endothermic nature, is followed immediately by an exothermic process, which corresponds to one polymorphic transformation.

The value of the melting point obtained from the DSC curve is similar to the values mentioned in speciality literature 183 – 183°C [29,30], and together with the accuracy of the melting process indicate a high purity of C-AS.

Table 1
CHARACTERISTICS OF THE THERMAL BEHAVIOUR OF THE STUDIED COMPOUNDS

Sample	Range of mass loss, °C	Maximum of DTG, °C	Maximum of DSC, °C	Mass loss Δm %
C-AS			183.1	fusion
			192.6	polym. trsf.
	209.6 – 313.3	275.2	242.5;300.0	31.2
	313.3 – 400.0	356.8	346.2; 356.2 exo	10.8
	400.0 – 569.2	453.0	476.9	31.1
	569.2 – 1000.0	716.4	638.5;776.2 exo	22.2
P1	25.0 – 96.2	50.0	50.8	0.80
	96.2 – 161.5	149.5	149.5	4.30
			180.1	fusion
	161.5 – 281.5	240.7	186.9	polym. trsf.
			213.2;253.8 exo	37.2
	281.5 – 345.1	303.8	326.4	20.3
	345.1 – 563.1	525.0	473.8	17.5
	563.1 – 1000.0	–	902.3	18.8
P2	25.0 – 106.2	50.0	54.9	3.10
	106.2 – 180.8	152.5	152.5	3.70
	180.8 – 267.7	233.8	215.2	29.1
	267.7 – 507.7	305.4	315.4	36.7
	507.7 – 965.4	569.2;935.4	557.7 exo;861.5	26.0
P3	25.0 – 96.2	62.1	62.1	1.70
	96.2 – 177.0	127.0	127.0	3.40
	177.0 – 271.5	250.0	215.4	22.3
	271.5 – 451.5	305.4	312.6	47.3
	451.5 – 692.3	589.2	525.2 exo	24.4
P4	25.0 – 100.0	58.5	60.9	1.85
	100.0 – 169.2	138.9	138.7	3.45
	169.2 – 268.5	248.5	216.2;248.0	19.9
	268.5 – 406.9	307.6	307.8	45.5
	406.9 – 650.0	561.5	526.3 exo;623.8	29.0

polym. trsf. = polymorphic transformations

After the two processes mentioned without loss of mass in the TG curve, the thermal decomposition of C-AS begins, which takes place in four stages, of which the second and third stages are difficult to delineate on the TG curve. The difficult delimitation is due to a complex decomposition process with successive and/or concomitant reactions, particularly emphasized on the DTG and DSC curves, by the presence of the corresponding peaks.

The complex nature of the decomposition process also results from the presence of endothermic and exothermic peaks on the DSC curve.

At 1000 °C the thermal decomposition is not complete, the residual mass being 5.00%.

The thermal decomposition of commercial products presents additional decomposition steps compared to the active substance. These steps are particularly emphasized on the DTG and DSC curves, with the corresponding peaks, because on the TG curves some of these are difficult to delimit. This is the case:

- stages one and two, respectively three, four and five in the case of P1;
- stages one and two, respectively three, four and five in the case of P2;
- stages one and two, respectively three and four in the case of P3;
- stages one and two, respectively three and four in the case of P4.

These additional steps are due to the presence of the excipients in the molecule, respectively their possible interactions with the active substance.

For exemple:

- the microcrystalline cellulose, as calcium carmelose, lost the absorbed water below 110°C, between 35 and 110 °C, apparently in a single endothermic process ($T_{peak\ DTG}$ = 50.0; 50.8; 54.9 and 57.1 °C);
- the lactose monohydrate (α-lactose) lost the water content between 100 and 170 °C ($T_{peak\ DTG}$ = 149.5; 152.5; 134.3 and 138.9 °C);
- the magnesium stearate loss the surface and structural water in several stages, below 110 °C;
- for crosspovidone, apparently, dehydration is completed at 110 °C in N_2. However, a second loss stage begins past 150 °C and completes around 250 °C.

According to the thermoanalytical curves, the active substance, as well as the pharmaceutical products acts in the same manner thermally, but still showing some differences regarding the nature and the number of the processes taking place, which was expected.

The influence of the different composition on the thermal behavior of the studied compounds results from the following relatively simple aspects:

- the temperature range corresponding to thermal decomposition is ≈25 – 1000 °C for C-AS, P1, P2 (935 °C) ; ≈700 °C for P3 and ≈ 650 °C for P4 ;
- the nature of the thermal effect in the temperature range 500 - 1000 °C: 638.5 °C endo and 776.2 °C exo for C-AS; 902.3 °C endo for P1; 557.7 °C exo and 861.5 °C endo for P2; 525.2 °C exo for P3; 526.3 °C exo and 623.8 °C endo for P4.

By comparison of thermal curves, it is found that C-AS has a better thermal stability than pharmaceutical correspondant: P1, P2, P3 and P4, because of reasons already mentioned.

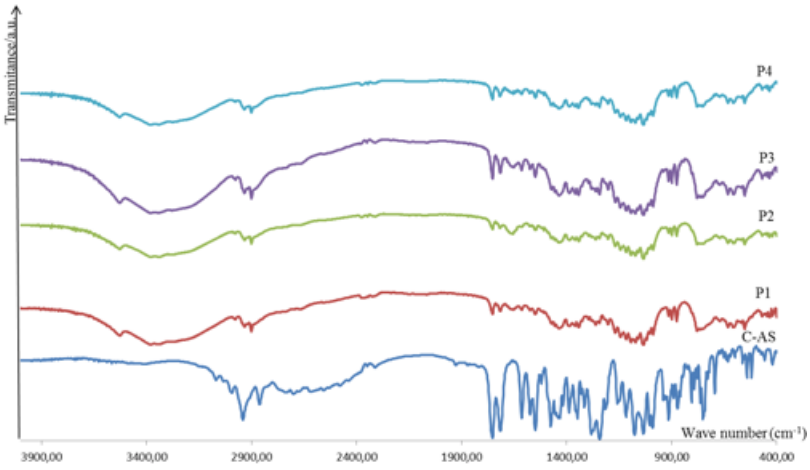

Fig. 7. FT-IR spectra for the studied compounds

Table 2

THE MAIN ABSORPTION BANDS (CM^{-1}) FOR THE STUDIED COMPOUNDS

C-AS	P1	P2	P3	P4	Assignement
3700 – 3300 3446 w	3800 – 3000 3381 i	3800 – 3000 3528m;3379m;3339m	3800 – 3000 3526 i ; 3381 vi	3800 – 3000 3528 m ; 3381 i	ν_{OH}(COOH) ; ν_{NH}(N-H)
3300 – 2200 2941 i ; 2862 m	2934 m ; 2899 m	2934 m ; 2899 m	2934 m ; 2899 m	2934 m ; 2899 m	$\nu_{asymC-H}$(CH_3;CH_2) ν_{symC-H}(CH_3;CH_2)
1751 vi ; 1715 vi	1751 w-m ; 1715 w-m	1751 w ; 1715 w-m	1751 m ; 1715 w-m	1751 m ; 1717 m	ν_{C-O}
1614 vi ; 1549 vi	1549 m	1549 w	1614 w ; 1549 w-m	1612 w ; 1549 w-m	ν_{C-N} ; ν_{C-O} ; ν_{N-H}
1476 vi ; 1439 i ; 1348 i	1435 m ; 1387 m ; 1341 m	1437 m ; 1341 m	1435 m ; 1387 m ; 1342 m	1431 m ; 1387 m ; 1342 m	$\nu_{N=N}$; ν_{C-C} ring ; $\nu_{asymCOO}$; ν_{symCOO}
1242 vi	1261 m	1261 m	1242 m	1242 m	ν_{C-N}; $\delta_{asym}CH_3$;CH_2;CH $\delta_{sym}CH_3$;CH_2;CH
1157 m ; 1117 m 1074 vi ; 1034 vi 989 i	1201 m ; 1169 m 1144 m ; 1117 m 1094 m ; 1072 m 1034 i ; 988 i	1169 m ; 1144 m 1117 m ; 1094 m 1072 m ; 1034 m 988 m	1201 m ; 1167 m 1146 i ; 1116 i 1094 vi ; 1072 vi 1034 vi ; 988 i	1201 m ; 1167 m 1146 m ; 1117 m 1094 m ; 1072 m 1034 i ; 988 m	$\delta_{asym}CH_3$;CH_2;CH $\delta_{sym}CH_3$;CH_2;CH ν_{C-O} ; ν_{C-C-O} ; $\nu_{C-C/-O)-O}$ in p. C-H band
914 i ; 872 m	909 m ; 873 m	899 w ; 875 w	914 m ; 899 m ; 876 m	914 w ; 899 w ; 876 w	o.p. C-H (ring) ; o.p. C-H band
804 m ; 750 i	777 m	777 m	764 i	777 m ; 750 m	ν_{Fe-O}; o.p. C-H band
694 m	633 m ; 605 m	633 m ; 606 m	633 m ; 606 m	633 m ; 606 m	o.p. (ring) C=C bend o.p. N-H bend
540 m ; 519 m	552 m	552 m	552 m	552 m	o.p. C-H benzene substituted

Spectroscopy FT-IR

The FT-IR spectroscopy was used as a supplementary technique in order to investigate the possible chemical interaction between drug – excipient and to confirm the results obtained by the thermal analysis. It is the most suitable technique of the non-destructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid-state transformations. The appearances of new absorption band(s), broadening of band(s), and alteration in intensity are the main characteristics to obtain the resultats recherche.

The FT-IR spectra are presented in figure 7 and the main absorption bands are summarized in table 2.

The main differences resulting from comparing the spectrum of C-AS with the spectra of P1, P2, P3 and P4 are presented below, as follow:

– the considerable broadening of the region of absorption from 3700 – 3300 cm^{-1} at 3800 – 3000 cm^{-1} and the significant increase, (≈ 45% for P1; ≈40% for P2; ≈ 70% for P3 and ≈ 40% for P4) of the bands attributed to the NH group present in the all compounds, but especially to the OH group present in the carboxylic group, respectively in the excipients as: starch, lactose monohydrate, calcium carmellose, hydroxypropyl cellulose;

– the two bands of absorbtion from the region 3300 – 2200 cm^{-1} that correspond to the methyl, respectively methylene group from C-AS as well as the excipients: hydroxypropyl cellulose, starch, lactose monohydrate, calcium carmellose, magnesium stearate, crospovidone, it changes its ratio of the magnitude of the absorption intensity thus:

a) for the band of absorption from 2941 cm^{-1} the intensity from ≈70% for C-AS, decreases at ≈ 23% for P1, ≈ 20% for P2, ≈ 45% for P3 and ≈ 20% for P4;

b) for the band of absorption from 2862 cm^{-1} the intensity from ≈ 50% for C-AS, decreases at ≈ 30% for P1, ≈25% for P2 and ≈ 25% for P4, respectively increases at ≈55% for P3;

– for the two bands of absorption from 1751, respectively 1715 cm^{-1}, which represent the carbonyl vibration bands from C-AS as well as the excipients: crospovidone and magnesium stearate, the intensity decreases in the same manner, from ≈ 95%, respectively ≈80% at: 28 and 22% for P1, 15 and 10% for P2, 38 and 32% for P3 and 30 and 25% for P4;

– the intensity of the bands from 1614 cm^{-1}, respectively 1549 cm^{-1},that correspond to the vibrations bands of the groups C=N and C=C from C-AS as well as the excipients: crospovidone, decreases form ≈65%, respectively ≈ 85% at: ≈ 30 and 20% for P3 and P4, respectively at ≈ 25% for P1, ≈ 10% for P2, ≈ 35% for P3 and 25% for P4. For P1 and P2 the band from 1614 cm^{-1} disappears;

– for the bands of absorbtion from the region 1480 – 1340 cm^{-1} that correspond to asym and sym COO vibrations, respectively the C-C ring stretching and N=N vibrations from C-AS, as well as the excipient magnesium stearate, the intensity decreases in the same manner: from 70-80% at: ≈ 45% for P1, ≈ 30% for P2, ≈ 65% for P3 and ≈ 40% for P4;

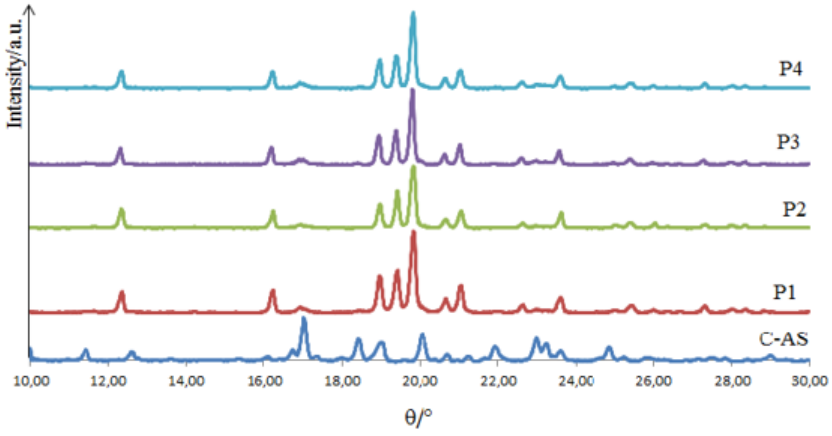

Fig. 8. X-ray diffractogram for the studied compounds

C-AS		P1		P2	
2teta	I%	2teta	I%	2teta	I%
10.00	27.64				
11.44	25.42				
12.60	18.91	12.37	25.63	12.35	30.42
		16.24	27.07	16.25	27.19
16.75	24.13				
17.03	100				
18.42	48.85				
18.95	38.48	18.97	45.01	18.97	39.01
18.98	40.81				
19.01	42.32				
		19.42	51.33	19.41	59.22
		19.82	100	19.82	100
20.07	63.36				
		20.69	16.93	20.67	13.23
		21.07	33.45	21.07	26.53
21.93	32.61				
22.99	51.30				
23.25	38.88				
23.60	22.51	23.59	17.61	23.62	24.34
24.87	31.15				

P3		P4	
2teta	I%	2teta	I%
12.32	20.92	12.37	22.36
16..20	21.95	16.23	22.78
18.93	38.19	18.96	37.42
19.38	43.48	19.39	42.77
19.80	100	19.81	100
20.65	13.53	20.65	13.26
21.04	25.23	21.06	23.61
23.57	17.47	23.59	16.42

Table 3
THE X-RAY DIFFRACTION DATA FOR THE STUDIED COMPOUNDS Co

– the band from 1242 cm^{-1} with one shoulder, which correspond to the C-N, respectively to asym. and sym. CH_3, CH_2, CH vibrations on displaces at 1261 cm^{-1} in P1 and P2, while the intensity decreases from ≈ 95% for C-AS at ≈40% for P1, ≈25% for P2, ≈60% for P3 and ≈35% for P4;

– for the bands of absorbtion from 1200 – 980 cm^{-1} present in C-AS, which correspond to the C-O (C-C-O) vibrations, respectively in p. band and o.p. C-H band it comes out the appearance of new bands, while the intensity decreases from ≈ 50-90% at 35-50%;

– the decrease of the intensity of the bands from the region 920 – 870 cm^{-1} that correspond to the o. p. C-H (ring) o.p. C-H band from ≈ 55-70% at 20-30%;

– in the place of the two bands from 804 and 750 cm^{-1} that correspond to o.p. C-H band and Fe-O vibrations appears one broad band while the intensity decreases from

≈60% at: ≈ 40% for P1, ≈30% for P2, ≈45% for P3 and ≈35% for P4;

- the band from 694 cm^{-1}that corresponds to the vibrations of: o.p. (ring) C=C band and o.p. N-H band appears as one duplicate with the intensity decreased from ≈ 63% for C-AS at: ≈ 35% for P1, ≈25% for P2, ≈ 30% for P3 and ≈ 25% for P4;

– the two bands from 540 and 519 cm^{-1} which correspond to the vibrations of o.p. C-H benzene substituted appear as one band displaced at 552 cm^{-1} and with the intensity decreased from ≈ 40% in C-AS at: ≈27% for P1, ≈ 25% for P2, ≈23% for P3 and ≈ 20% for P4.

On the basis of mentioned differences it may be considered that the composition of the studied compounds is different.

From the FT-IR spectra and wave number where characteristic bands appear, the active substance and its pharmaceutical forms can be easily differentiated.

X-ray analysis

To investigate the thermal behaviour of C-AS and correspondent pharmaceuticals: P1, P2, P3 and P4, besides the FT-IR spectroscopy which is a qualitative analysis technique, the X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity.

By the comparison of diffractogram of C-AS with the diffractograms of pharmaceutical compounds correspondents (fig. 8), the appearance of new lines or the disappearance of some of the diffraction lines of higher, moderate and lower intensities from C-AS, respectively the modification of the intensity for certain lines presented in C-AS, indicates the differences of the studied compounds.

The X-ray diffraction data for the studied compounds are presented in table 3.

By the comparing the data from table 2 on constants great differences between these, by:

- the disappearance of certain important lines from C-AS diffractogram;

- the appearance of the new significant lines in diffractograms of P1, P2, P3 and P4;

- the modification (by increase or decrease) of intensity for certains lines present in the C-AS diffractogram.

These differences indicate a different composition between C-AS respectively, pharmaceuticals correspondent: P1, P2, P3 and P4, due to the presence of excipients, in fact to their possible interactions with the active substance.

Conclusions

Candesartan, 1-cyclohexyloxycarbonyloxyethyl 2-ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl] methyl]benzimidazole-4-carboxylate, is a drug used in therapy for hypertension. Excipients are very important components in drug formulation, they can influence positive or negative the characteristics of commercially drugs. Based on that, it is really important to study all the possible interactions between active substance and all the excipients used in drug formulation.

The candesartan active substance (C-AS) and four of pharmaceutical products correspondents: P1, P2, P3 and P4 were simultaneously characterised by thermal analysis, FT-IR spectroscopy and X-ray diffraction patterns.

The thermal behaviour of the five compounds has been investigated by the TG/DTG and DSC techniques. There have been observed differences between thermal curves of the pure compound and those of the pharmaceutical products, due to the presence of the excipients in drug and due to the possible interactions with the active substance.

Also, between the FT-IR spectra and X-ray diffractograms of the two compounds categories there are significant differences, due to the same causes as those mentioned above.

The study of thermal behaviour of the five candesartan samples evidenced that the presence of excipients decrease the thermal stability of this drug.

The melting point is commonly used as a preliminary identification parameter for crystalline organic compounds. In comparison with the melting point determined by using the classical methods, the determination under a dynamic flow of dry nitrogen can provide a reliable value for the fusion temperature.

This justifies the usage of DSC as a routine technique for the identification and quality control of the active substance created for pharmaceutical usage, by melting point.

The simultaneous analysis of the TG-DTG-DSC, FT-IR and X-ray data constitutes a credible and secure method of control and just evaluation in the practice of the pure and pharmaceutical compounds.

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