Annals of West University of Timisoara

Series of Chemistry **20 (1)** (2011) 27-40

SHORT CONSIDERATIONS ABOUT THERMAL ANALYSIS AND FT-IR SPECTROMETRY OF SOME PYRIMIDINE PHARMACEUTICAL COMPOUNDS

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Received: 14 January 2011 Modified 24 February 2011 Accepted 30 March 2011

SUMMARY

Pyrimidine compounds for pharmaceutical use which were analyzed belong to cardiac agents (dipiridamol, moxonidine, piribedilum) and to cholesterol lowering drugs, the statins (rosuvastatin). This paper briefly characterizes two aspects: FT – IR spectra of drugs containing these active substances, before and after thermal transformation in which they were subjected; thermal analysis of these drugs by combining thermogravimetry (TG) with diferential thermal analysis (DTA) and diferantial scanning calorimetry (DSC). The results obtained indicate: drug decomposition accompanied by cleavage of pyrimidine ring and its substitutes, changes in sample with temperature, evidence of endo-and exothermic processes.

Keywords: dipiridamol; moxonidine; piribedilum; rosuvastatin; FT – IR spectra; thermal analysis.

INTRODUCTION

Many drugs can be analyzed by thermal analysis methods, including thermogravimetry (TG), derivative thermogravimetry (DTG), diferential thermal analysis (DTA) and diferantial scanning calorimetry (DSC). These techniques can be combined together: TG with DTA, TG with DSC.

The TG and DTG provides information about mass changes only, and not about the nature of transformations, so TG follows and measures the mass changes as a function of temperature or time.[1]

DSC determines the changes of enthalpy (ΔH); it measures the difference between the energy received by a substance and a blank sample when they are simultaneously subjected to a controlled program of increasing temperature.[1]

DTA is similar to the DSC. In DTA the sample and the blank sample are subjected to identical thermal cycles, meanwhile any difference in temperature between the sample and the blank sample is recorded. This difference is plotted as a function of time or temperature. Endo or exothermic changes are detected in relation to the blank sample.[1]

IR spectrometry is used especially to identify organic substances, including drugs without destroying the integrity of molecules. This method is less used for dosing. Fourier-transform infrared (FTIR) spectroscopy analyzes the entire spectrum simultaneously. The detection is based on the absorption, rather than reflection of radiation, in this area. IR bands are so characteristic for some functional groups, links and structural units, so IR spectrum can be considered as a "fingerprint" of the studied molecule, which facilitates the deduction of structural details and their recognition.[2]

The combination of thermal analysis techniques with microscopy is applied to collect information about the sample structure, such couplings were made between a thermal analyzer (TG, DTA, DSC) and an optical microscope - Perkin Elmer equipment.

Studied drugs have in common pyrimidine ring and are discussed briefly.

Dipiridamol is a derivative of pirimido - pyrimidine (4.8-dipiperidino-2 ,6-bis-pirimido dietanolamino-[5,4-d]-pyrimidine) used as a preventive medication in: thrombosis, heart attack, long-term therapy of coronary heart disease.[3]

Moxonidine is 4 – chloro – 5 - (2-imidazolin-2il-amino) – 6 –methoxy – 2 – methyl – pyrimidine. It is indicated in essential hypertension, especially for patients with increased sympathetic tone, asthma, diabetes, dyslipidemia, left ventricular hypertrophy and low tolerance to other antihypertensive.[3]

Piribedilum is a cerebral vasodilator musculotrop which causes significant improvements in ADL (Activity of Daily Living), especially in patients with Parkinson's syndrome.[3]

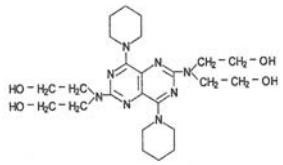
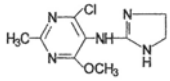
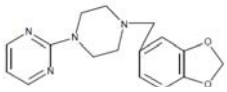
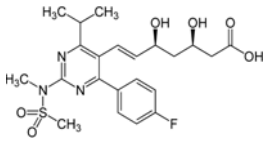
Rosuvastatin is a statin, cholesterol lowering drug, used in patients with: primary hypercholesterolemia and combined hyperlipidemia who did not respond favorably to diet low in fat, dyslipidemia syndrome associated with diabetes, coronary heart disease associated with hypercholesterolemia moderate / severe, for prevention of recurrence of heart attack or stroke.[3]

Thermal analysis and FT - IR spectroscopy of these drugs provide important information which is a foundation in the research of corresponding active substances.

MATERIALS AND METHODS

The study was carried out on drugs. Trade names with corresponding chemical structures are presented in Table I.

Table I. Studied drugs

Nr.	Trade name	Active substance	Chemical structure
1	Dipiridamol coated tablet 25 mg	dipiridamol	
2	Physiotens coated tablet 0,2 mg	moxonidine	
3	Pronoran extended-release tablets 50 mg	piribedilum	
4	Crestor coated tablet 20 mg	rosuvastatin	

Tablets were fine mortar and then subjected to thermal and spectral analysis.

FT - IR spectrum of drugs were made using a 100 FT-IR spectrometer Perkin Elmer, resolution 4 cm^{-1} accesory UATR (Universal atennuated total reflectance) area 4000-650 cm^{-1}. It collects in few seconds MIR spectrum (4000-400 cm^{-1} range), providing a simultaneous analysis of the entire spectrum.[4]

Thermal analysis was performed by Perkin Elmer Diamond equipment, aluminum crucible, synthetic air current Lindegaz 5.0 100ml/min flow, heating rate 10 ^{0} / min, which has a coupling between thermal analyzer (TG, DTA, DSC) and an optical microscope. The sample is subjected to a temperature program and its surface will be examined by highlighting the changes that occur when the sample surface is heat treated. The atmosphere is gas and flow control. Microscopy coupled with a differential scanning calorimeter allows,

on a particular sensor, the measurement of heat flow. Microscopy coupled with thermogravimetric allows the measurement of mass changes, based on association of the samples support of the balance with the support of the heated microscope.[4]

RESULTS

The spectrometric FT – IR analysis of drugs, before and after thermal processing, has the following graphs:

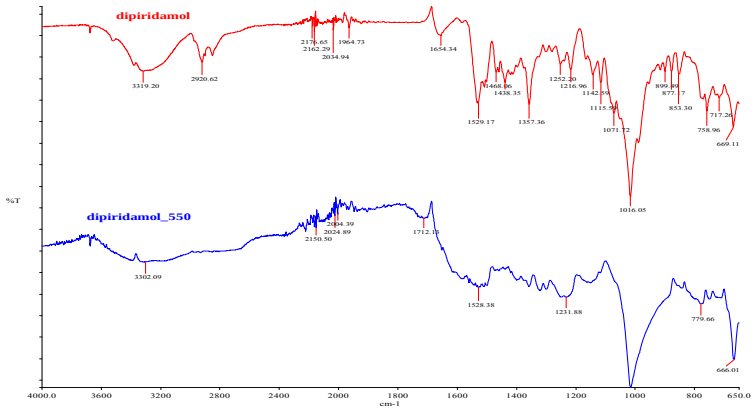


Figure 1. FT – IR spectrum of dipyridamol sp(red) and 550 sp (blue)

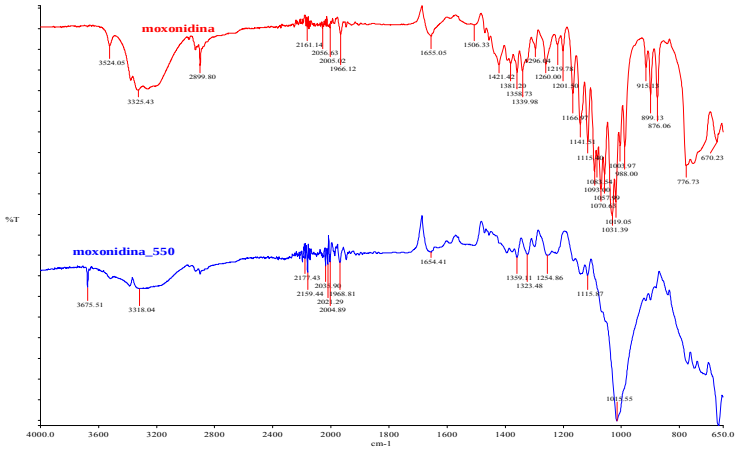


Figure 2. FT – IR spectrum of moxonidine sp(red) and 550 sp (blue)

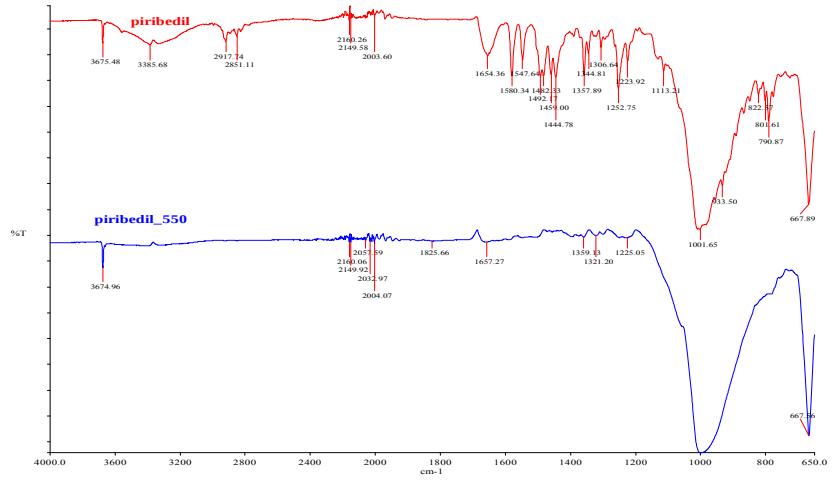


Figure 3. FT – IR spectrum of piribedilum sp(red) and 550 sp (blue)

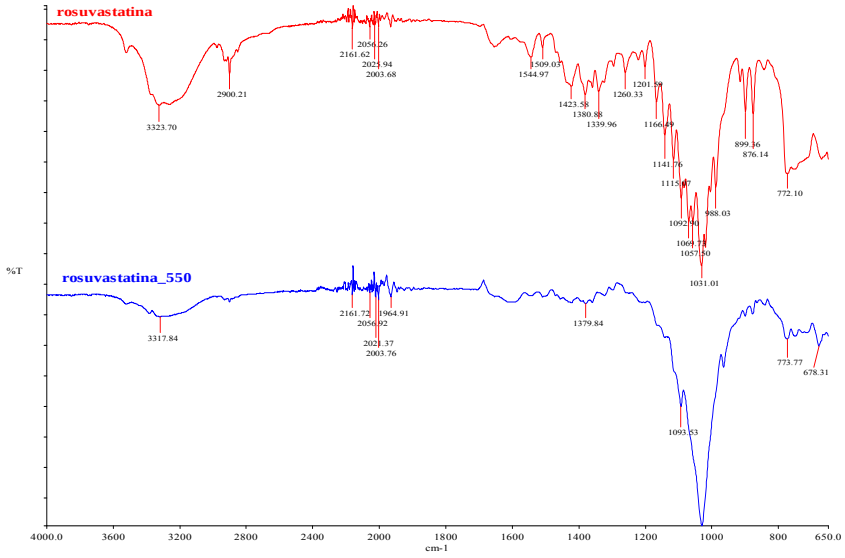


Figure 4. FT – IR spectrum of rosuvastatin sp(red) and 550 sp (blue)

Thermal analysis of drugs have the following curves:

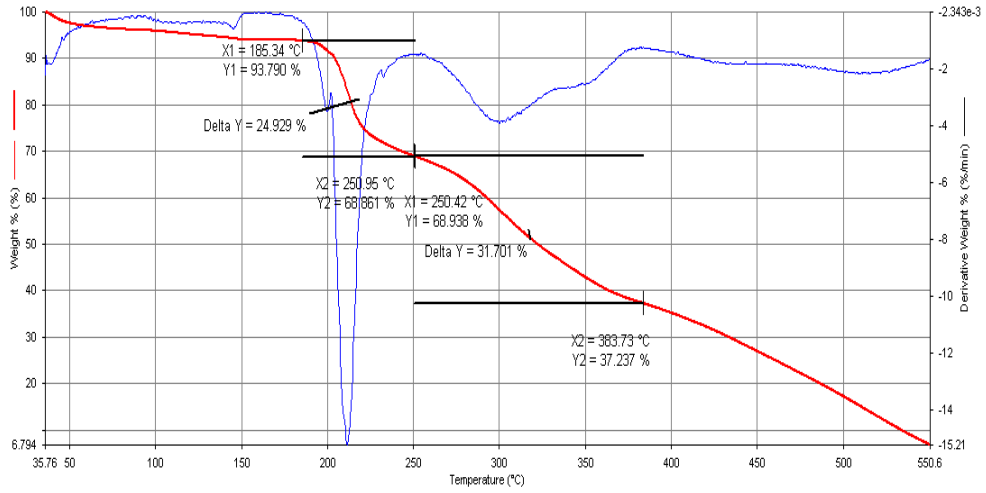


Figure 5. TG and DTG curve of dipyridamol

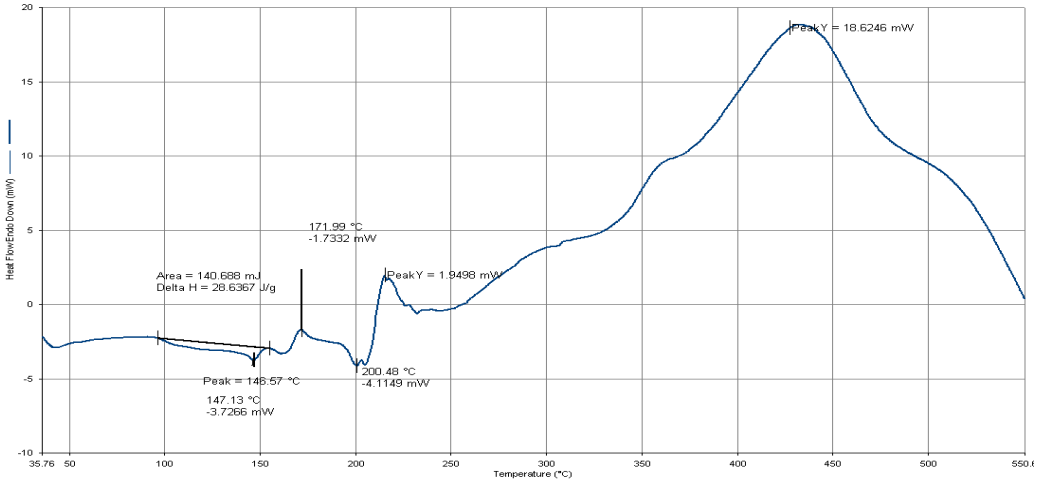


Figure 6. DTA curve of dipyridamol

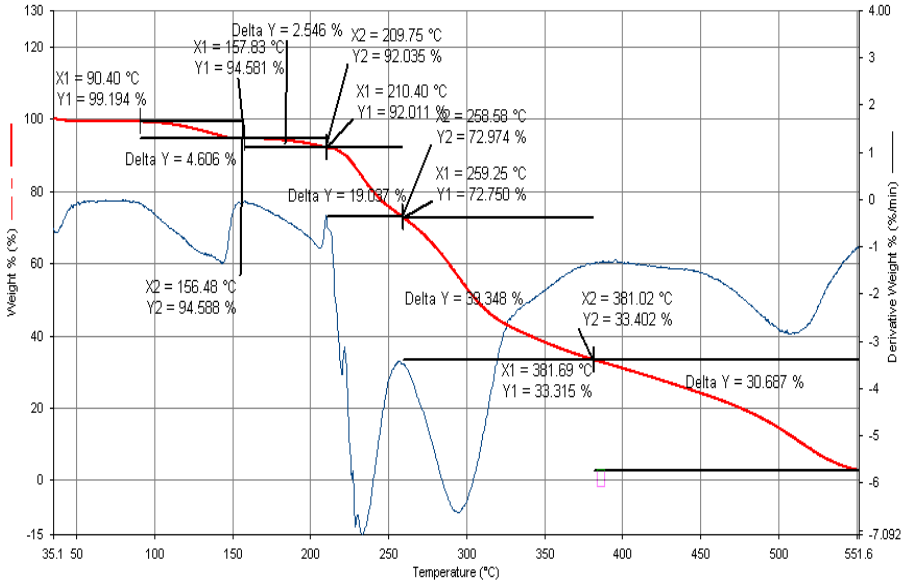


Figure 7. TG and DTG curve of moxonidine

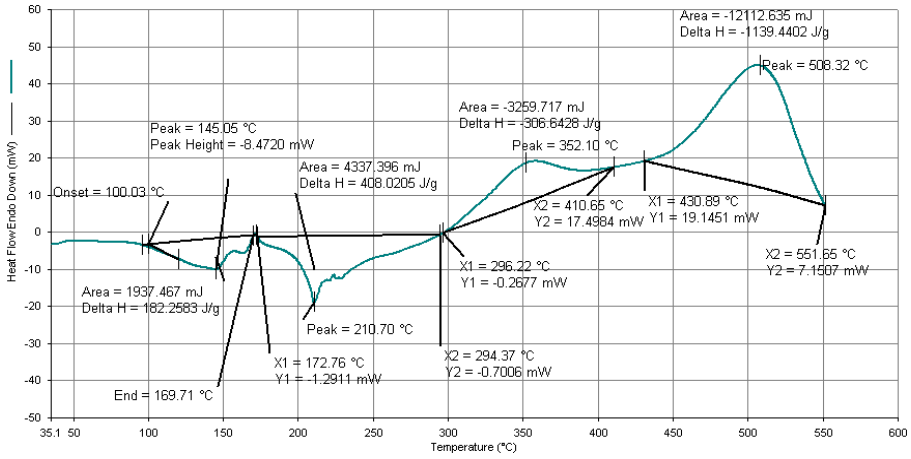


Figure 8. DTA curve of moxonidine

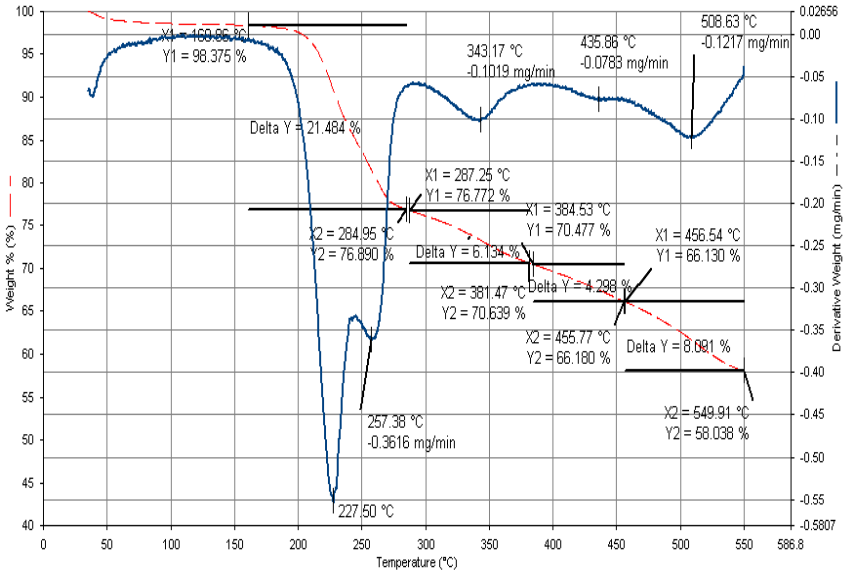


Figure 9. TG and DTG curve of piribedilum

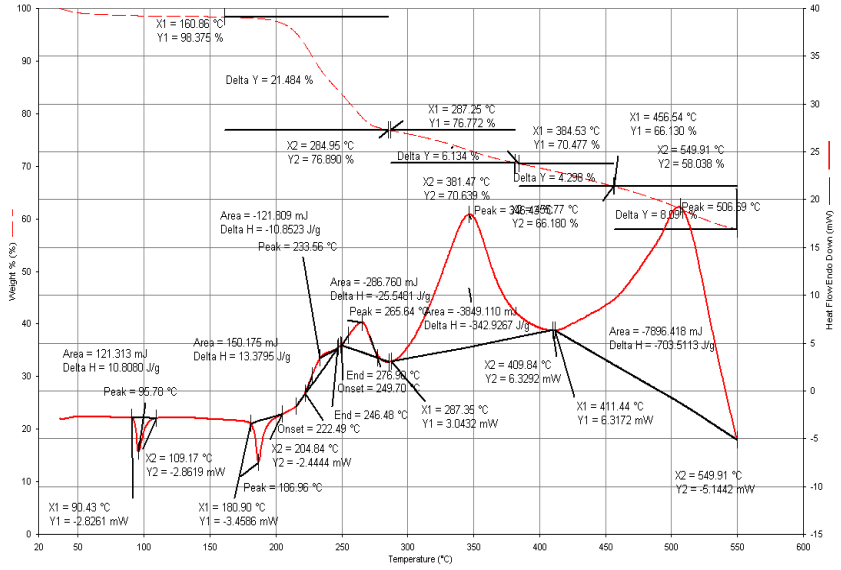


Figure 10. TG and DTA curve of piribedilum

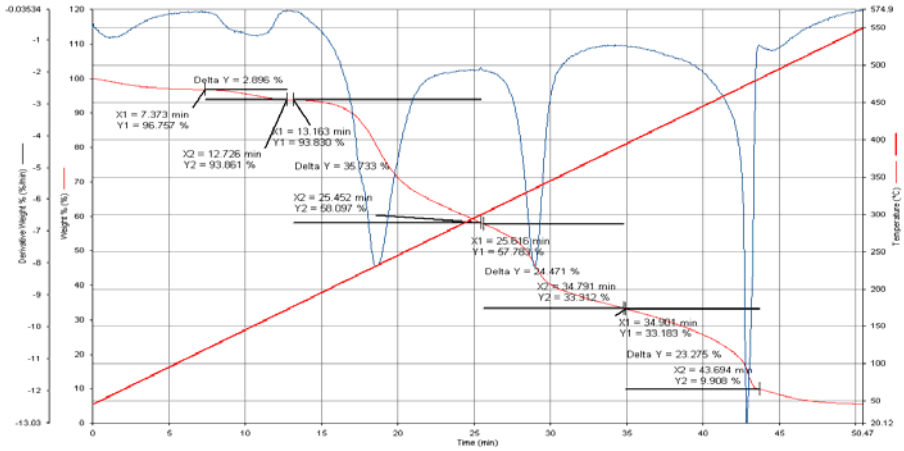


Figure 11. TG and DTG curve of rosuvastatin

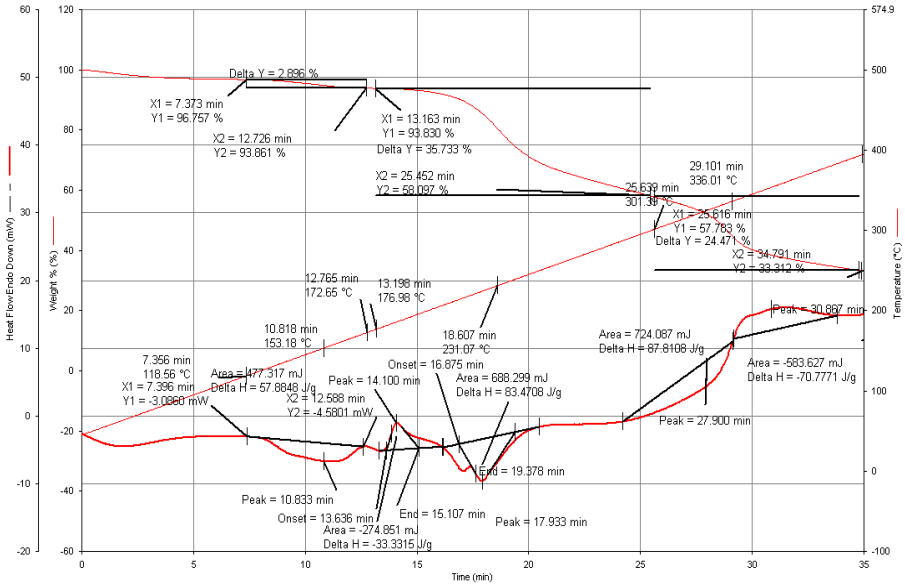


Figure 12. TG and DTA curve of rosuvastatin

DISCUSSION

Based on obtained FT – IR spectras (Figures 1,2,3,4 sp) pyrimidine ring exists in the analyzed drugs, because these present characteristic absorption bands of the ring.[5]

This analysis is outlined in Table II..

Table II. Characteristic infrared bands of pirimidine ring

Nr.	Assignment	Wavenumber (cm^{-1})
1	Substitution of benzene ring	2000-1700
2	1,3 – disubstituted benzene	900-860, 810-750
3	C=C stretching	1650-1430
4	In-plane C– H bending	1275-100
5	Out-of-plane C– H bending	900-690 must submit two peaks

After thermal analysis pyrimidine ring is destroyed because the characteristics bands change or disappear (Figures 1, 2, 3, 4 550 sp).

Besides the presence of pyrimidine ring is also observed various groups attached to it.

FT - IR spectrum of dipyridamol (Figure 1 sp.) indicates in its structure the presence of pyridine, disubstituted nitrogen and condensed aromatic compounds, because the characteristic absorption bands appear.[5] They are presented in Table III.

Table III. Characteristic infrared bands of dipyridamol substitutes

Nr.	Assignment	Wavenumber (cm– 1)	Observations (550sp)
1		1600-1300	peaks change
2	Aril – N – alchil | alchil	1360-1250 vC aromatic – N 1280-1180 vC aliphatic -N	peak disappears peak disappears
3	Condensed aromatic compounds	1650-1600 1525-1450	peak disappears peak changes

Thermal transformations applied to dipyridamol generate IR spectrum (Figure 1 550sp.) showing a destruction of pyrimidine substitutes (Table III).

TG analysis of dipyridamole (Figure 5) shows that tablet mass decreases with

increasing temperature. Values are presented in Table IV.

Table IV. The main mass variations depending on the temperature of dipyridamole

Nr.	TG curve	$T_1{}^0C$	$T_2{}^0C$	Δm%
1	I	185,34	250,95	24,929
2	II	250,42	383,73	31,701

DTG first portion(I) on the TG curve (Figure 5) shows two overlapping processes: first with a maximum at about. 190 ^{0} C, and the second at about. 215 ^{0} C.

On the DTA curve (Figure 6) endothermic process is observed beginning at about 95 ^{0} C and ends at 155 ^{0} C, with a maximum at 146.57 ^{0} C with ΔH = 28.6367 J / g. According to this chart is present another endothermic process with peak at 200.48^0 C and yet three exothermic processes.

The existence of various groups from moxonidine structure apparent from its IR spectrum (Figure 2 sp), which shows their changes after thermal analysis (Figure 2 550sp) applied to the drug.[5] These data are summarized in Table V.

Table V. Characteristic infrared bands of moxonidine substitutes

Nr.	Assignment	Wavenumber (cm^{-1})	Observations (550sp)
1	N – H	3500-3200	peaks change
2	C – Cl	800-400	peaks change
3	C = N -	1690-1580	peaks change

By TG analysis, the coated tablet moxonidine (Figure 7.) presents a number of mass variations depending on the temperature. Mass losses are presented in Table VI and significant from 250 ^{0} C, which means that this tablet is relatively stable until this temperature.

Table VI. The main mass variations depending on the temperature of moxonidine

Nr.	TG curve	$T_1{}^0C$	$T_2{}^0C$	Δm%
1	I	90,40	156,48	4,606
2	II	157,83	209,75	2,546
3	III	210,40	258,58	19,037
4	IV	259,25	381,02	39,349
5	V	381,69	551	30,687

DTA curve of moxonidine (Figure 8) shows two endothermic and two exothermic

processes. They are detailed in Table VII.

Table VII. DTA processes of moxonidine

Nr.	Process Type	Wavenumber (cm^{-1})	Temp. max.(^0C)	Enthalpy variation ΔH (J/g)
1	endothermic	95-169,71	145,05	182,2583
2		172,76-294,37	210,70	408,0205
3	exothermic	296,22-410,65	352,10	-306,6428
4		430,89-551,65	508,32	-1139,4402

IR spectra obtained of piribedilum (Figure 3) indicates the presence of characteristic groups, which are processed from thermal analysis applied (Table VIII).[5]

Table VIII. Characteristic infrared bands of piribedilum substitutes

Nr.	Assignment	Wavenumber (cm^{-1})	Observations (550sp)
1		2910 ν_{CH}	peaks disappears
		1480 δ_{CH2}	peaks disappears
		1250 ν_{C-O-C}	peaks disappears
		925 ν_{C-O}	peaks disappears
2	N – CH_2	2780	peaks disappears

DTG of piribedilum (Figure 9) for the temperature range between 160.86 to 284.95 ^{0} C on TG curve shows two overlapping processes with the following maximum: first at about 155 ^{0} C, and the second at about 260 ^{0} C.

Piribedilum mass variation according to temperature (Figure 9) is presented in Table IX.

Table IX. The main mass variations depending on the temperature of piribedilum

Nr.	TG curve	$T_1{}^0C$	$T_2{}^0C$	Δm%
1	I	160,86	284,95	21,484
2	II	287,25	381,47	6,134
3	III	384,53	455,77	6,134
4	IV	456,54	549,91	8,091

DTA curve of piribedilum (Figure 10) shows two endothermic and four exothermic processes. They are detailed in Table X.

Table X. DTA processes of piribedilum

Nr.	Process Type	Wavenumber (cm^{-1})	Temp. max.(^0C)	Enthalpy variation ΔH (J/g)
1	endothermic	90,43-109,17	95,70	10,8080
2		180,90-204,84	186,96	13,3795
3	exothermic	224,49-246,48	233,56	-10,8523
4		250-276,90	265,64	-25,5481
5		287,35-409,84	346,43	-342,9267
6		411,44-549,91	506,96	-703,5113

IR spectra of rosuvastatin (Figure 4) shows that its structure changes in thermal analysis.[5] These data are presented in Table XI.

Table XI. Characteristic infrared bands of rosuvastatin substitutes

Nr.	Assignment	Wavenumber (cm^{-1})	Observations (550sp)
1		1500	peaks disappears
2	C – F	800-400	peaks disappears
3	R – OH	1075-1010	peaks disappears
4	R – SO_2 – R	1350-1300	peak changes
5	-COOH	3300-2500	peak changes

Tablet mass of rosuvastatin in 12.289 minutes is reduced by 35.733%, after which the decrease is almost constant (Figure 11). Change in mass over time is detailed in Table XII.

Table XII. The main mass changes versus time of rosuvastatin

Nr.	TG curve	t_1 min	t_2 min	Δm%
1	I	7,373	12,726	2,896
2	II	13,163	25,452	35,733
3	III	25,6161	34,791	24,471
4	IV	34,901	43,694	23,275

DTA analysis (Figure 12) shows three endothermic and two exothermic processes presented in Table XIII.

Table XIII. DTA processes of rosuvastatin

Nr.	Process Type	t_{peak} (min)	Enthalpy variation ΔH (J/g)
1	endothermic	10,833	57,8848
2		17,933	83,478
3		27,900	87,8108
4	exothermic	14,100	-33,3315
5		30,817	-70,771

CONCLUSION

This paper proves that the drugs examined by thermal analysis and with the help of FT – IR spectrometry, suffer a split of pyrimidine ring and radicals grafted on it.

Thermal analysis of these compounds provides valuable information about mass and sustained processes of each drug.

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