Comparative Studies of Pentoxifylline - Active Substance and Tablets

TUNDE JURCA[1,*], ELEONORA MARIAN[1], BOGDAN TITA[2], GHEZA BANDUR[3], DUMITRU TITA[2], NARCIS DUTEANU[3,*]
[1]University of Oradea, Faculty of Medicine and Pharmacy, Speciality of Pharmacy, 29 Nicolae Jiga Str.,410028, Oradea, Romania
[2]"Victor Babes" University of Medicine and Pharmacy, Faculty of Pharmacy, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania
[3]Politehnica University Timisoara, Industrial Chemistry and Environmental Engineering Faculty, 2 Victoriei Sq., Timisoara, 300006, Romania

Pentoxifylline, 1-(5-oxohexyl)-3,7-dimethylxanthine, is an active haemorheological drug which is widely used for treatment of intermittent claudication and other circulatory disorders.The scanning electron microscope (SEM) is one of the most versatile instruments available for the nondestructive examination and analysis of the microstructure, morphology and chemical composition characterizations of pharmaceuticals. Scanning electron microscopy provides visual information about the organic and inorganic submicron particles (size, shape, and morphology), and also chemical identification based on the X-ray energy lines. FT-IR spectroscopy, DSC (differential scanning calorimetry) and X-ray powder diffraction (XRPD) were used as complementary techniques to adequately implement and assist in interpretation of the SEM results. Based on all this data we can say that the commercial product was observed to have physical interactions between the active compound and used excipients.

Keywords: pentoxifylline, SEM, FT-IR, XRD, DSC

Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3,7-dimethylxanthine that, unlike theophylline, is a haemorheologic agent, i.e. an agent that can regulate the blood viscosity. Regarding its structure can be observed that pentoxifylline has a similar structure like another xanthine derivates: caffeine, theophilline and theobromine [1]. Based on the chemical structure and in correlation with clinical observation, all mentioned xanthine derivates act as muscular relaxant, in special in case of bronchial muscle. Also, these derivates act as stimulant of central nervous system and also on the kidney level where they promote diuresis. Furthermore, caffeine and teophylline act in a similar manner on blood circulation activities. Additionally, because pentoxifylline act on the red cell by increasing their deformability, decreases the platelet aggregation, and lower the sanguine plasma viscosity is used in order to improve the effectiveness of blood microcirculation. M. Zhang et al. [2] demonstrate in 2004 that pentoxifylline can also modify the immune system. These specific properties of pentoxifylline can be also associated with its good solubility in water. This good solubility in water (and also in ethanol) is a consequence of pentoxifylline chemical structure – presented in figure 1.

In present paper the active compound (pure pentoxifylline) was studied in comparison with commercial product by using SEM, FTIR, DSC and X-ray diffractometry.

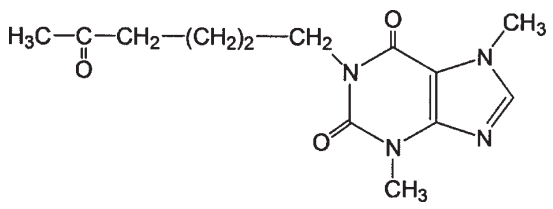

Fig. 1. The chemical structure of pentoxifylline

SEM technique was used in order to compare the morphological structure of pure active compound with structure of commercial product.

Pharmaceutical developers and manufacturers are finding that they need the high resolution provided by a scanning electron microscope (SEM) to characterize, control, and elementally quantify the size and shape of these particles. In pharmaceutical industry is really important to establish an easy way to identify different product samples, by using FTIR and XRD diffractograms.

A very important method in the preformulation of drugs is the differential scanning calorimetry (DSC). This analysis offers information regarding the possible interaction between the compounds of the pharmaceutical forms, the changes or the lack of endothermic or exothermic peaks or the variation of the enthalpy in the difractograms of the mixtures between the medical substance and the excipients [3].

Experimental part

Materials and methods

The substances examined by thermal analysis were: pentoxifylline-active substance or drug (PEX) and pentoxifylline retard-tablets (PEXR).

All materials were of reagent grade and were used without further purification. Pentoxifylline was obtained from Sigma-Aldrich GmbH, Germany. The pharmaceutical was a commercial product, containing different (qualitative and quantitative) excipients like: lactose, talc and magnesium stearate.

Scanning electronic microscopy (SEM)

The examinations were realized using the scanning electronic microscope SEM type FEI Quanta, having mounted an EDX module.

* *email: jurcatunde@yahoo.com, narcis.duteanu@upt.ro*

Fourier transform infrared spectroscopy (FTIR)

FT–IR spectra of drug, excipients and drug-excipients blends were recorded on a Perkin–Elmer Model 1600 apparatus using KBr discs in the range of 4000–400 cm^{-1}.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry curves were obtained in a NETZSCH-STA 449C, cell using platinum crucibles with about ~2mg of samples, under N_2 atmosphere (flow rate: 20 mL/min) and at a heating rate of 10°C/min in the temperature range 25-400°C.

X-ray powder diffraction (XRPD)

X–ray diffraction patterns (XRPD), for the same category of substances, were obtained with a Bruker D8 Advance.

Results and disscutions

SEM characterization

One of the most surprising aspects of scanning electron microscopy is the apparent ease with which SEM images of three-dimensional objects can be interpreted by any observer with no prior knowledge of the instrument [4, 5].

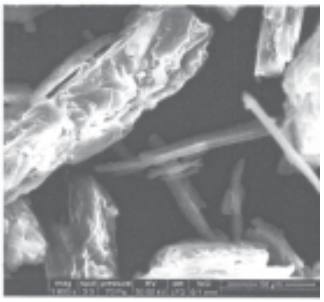

Fig. 2. Pentoxifylline – Magnification: 1600X

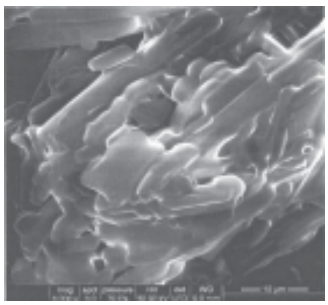

Fig. 3. Pentoxifylline – Magnification: 6000 X

The SEM images of the pentoxifylline –active substance and commercial product are depicted in figure 2, 3, 4 and 5, respectively.

Analyzing the SEM pictures recorded in case of pure compound (fig. 2 and 3) can be observed a high crystallinity degree at booth magnifications. At lower magnification

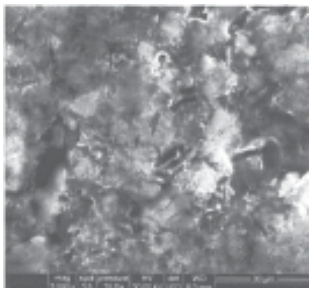

Fig. 4. Pentoxifylline tablets – Magnification: 3000 X

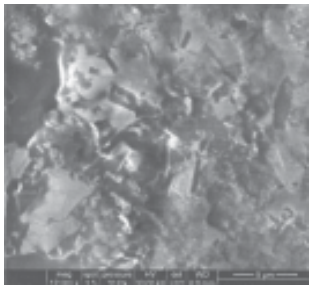

Fig. 5. Pentoxifylline tablets - Magnification: 12000 X

can be observed that the pure pentoxifylline presents acicular crystals. When the magnification was 6000X can be observed that the acicular crystal observed at lower magnification presents also a compact and complex structure due to the heterogeneous crystallization. That leads at presence on the surface of each particle of different planar structures with irregular shapes and sizes.

By comparison in case of SEM pictures obtained for commercial product (SEM depicted in fig. 4 and 5) can be observed that the crystals of active product with high degree of crystallinity are dispersed in to the excipients mass used for product formulation. From the SEM picture recorded at higher magnification can be observed that in the encapsulation process are not taking place any changes into the crystallite structure of drug active ingredient. From both SEM pictures is evident that the commercial product have a compact structure, which can be explained if we are taking into account the occurrence of physical interaction between the active principle and excipients used in drug formulation process [6].

FTIR characterization

FTIR is a very powerful technique used to study complex amorphous systems consisting of more than one component. These techniques based on molecule vibration spectroscopy make it possible to reveal physical or chemical mechanism at the molecular level. The understanding of such mechanism can be a key factor for the quality control of pharmaceutical products [7, 8].

Pentoxifylline is a complex system which contain two heterocyclic ring, one imidazole ring graphed on the pyridine ring, and in this way the vibration frequencies of

Tent. assig.	PEX	PEXR	Tent. assig.	PEX	PEXR
δC-N-H deformation in plan	449 vs	470 vs	δCH deformation band	1258 s	1261 s
νC-N-C stretching	487 vs	487 vs	νC=C aromatic stretching	1459 vs	1480 vs
νN-C=O stretching	616 vs	616 vs	νC=C aromatic	1560 s	1560 s
νCH_2 skeletal vibration	752 vs	753 vs	νN-H stretching	1655 vs	1643 vs
νCH_2 skeletal vibration	763 vs	763 vs	νC=O stretching mode	1701 vs	1715 vs
νSi-O stretching	-	1014 s	νCH stretching mode	2954 vs	2942 s
δCH deformation band	1066 vs	1062 vs	νN-H stretching	3114 s	3116 s
νC-O-C stretching	1164 s	1160 s	ν_{ring} stretching	3312 m	3344 s
νC-O-C stretching	1175 vs	1177 vs	νOH stretching	-	3676 w

vs-very strong; s-strong; m-medium; w-weak

Table 1
THE MAIN ABSORPTION BANDS (cm^{-1}) FOR PEX AND PEXR

complex compound is obtained by using as model the infrared vibration frequencies of benzene, pyridine, pyrimidine, and also of imidizole. In case of five atoms heterocyclic ring the double links have an aromatic character which is inducing ring vibrations and also hydrogen deformations in IR spectrum.

In table 1 are depicted the most prominent bands observed into the recorded FTIR spectrum (spectrum not shown in present paper).

By analyzing the data presented in table 1 can be observed that in both cases of pentoxifylline active substance and also in case of commercial product, the stretching vibration of C=O group for the PEX appear at 1701 cm^{-1}, and for PEXR this vibration is broadened and is shifted at 1715 cm^{-1}.

Also, presence of N-H group lead at stretching vibration observed for PEX at 1655 cm^{-1}, and in case of PEXR this vibration is shifted at 1643 cm^{-1}.

From the FTIR spectrum recorded in case of PEXR can be observed the presence of a supplementary vibration at 1014 cm^{-1} in comparison with the PEX recorded spectra. This intense vibration is associated with the presence of Si-O link from silicone dioxide used as excipent in commercial product formulation. Presence of talk as excipent in drug formulation is not affecting the FTIR spectra because this compound has almost no vibrations present into the FTIR spectra. One other excipient used in drug formulation is magnesium stearate, which presents a poor FTIR spectrum. Magnesium stearate presents a specific vibration band between 2920 and 2851 cm^{-1}. Presence of this specific vibration is associated with presence of ethyl functional group into the stearate molecule [9, 10].

In case of pure lactose (also used as excipient in drug formulation) stretching vibration of OH group is located at 3528 cm^{-1}, and by comparison in case of studied commercial product this vibration has a low intensity and was shifted at 3676 cm^{-1}. Aromatic ring presents a high intensity stretching vibration at 3312 cm^{-1} in case of PEX, and in comparison in case of PEXR this stretching vibration was shifted at 3344 cm^{-1}.

Based on data obtained from the FTIR spectrum recorded in case of PEX and PEXR can say that in commercially product we have physical interactions between the pure pentoxyfilline and all excipients use in drug formulation.

XRD characterization

The XRD technique has a great importance in pharmaceutical physics because it represents the easiest and fastest method to obtain fundamental information

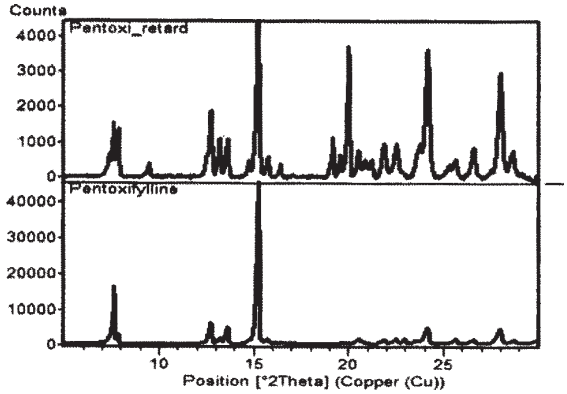

Fig. 6. X-ray diffraction pattern of PEX and PEXR

about the structure of a crystalline substance. Structural analysis by single-crystal X-ray diffraction provides the largest amount of information but is significantly harder to obtain a suitable crystal in case of commercial product. Because the majority of drug substances are obtained as crystalline powders, researchers often use the powder pattern of these substances as a readily obtainable fingerprint to determine structural type. In fact, it is only by pure coincidence that two compounds might form crystals for which the ensemble of molecular planes happens to be identical in all space [11, 12].

XRD spectra presented in figure 6 were recorded for both pure active compounds PEX and for the commercial drug PEXR. From recorded and analyzed pentoxifylline XRD spectra, we can observe presence of all spectral lines presented into the literature, proving that the used compound has the right purity and crystalline structure.

In the commercial product XRD spectra it was observed the presence of many additional spectral lines which were associated with presence of different excipients into the analyzed drug. By analyzing the XRD spectrum recorded in case of commercial produce can be observed the presence of lines specific for lactose, talc and magnesium stearate. Simultaneously the lines specific for pure pentoxyfilline were shifted to higher diffraction agles coupled with some reduction of line intensity [13].

Based on all this data we can say that in the commercial product were observed some physically interactions between the active compound and the used excipients. All of these data are in accordance with information obtained from FTIR spectra and SEM [14].

DSC characterization

The DSC curves of PEX and PEXR are illustrated in figures 7 and 8.

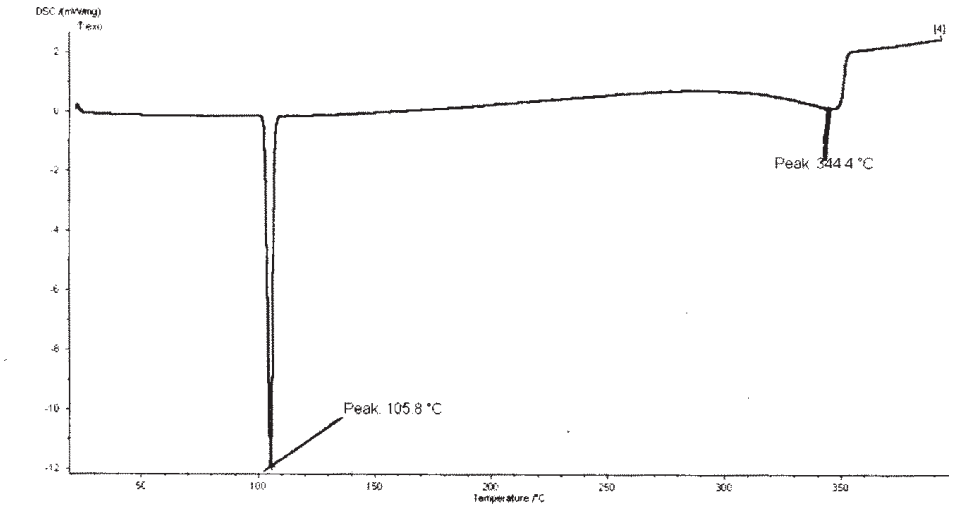

Fig. 7. Differential scanning calorimetry (DSC) of pentoxifylline

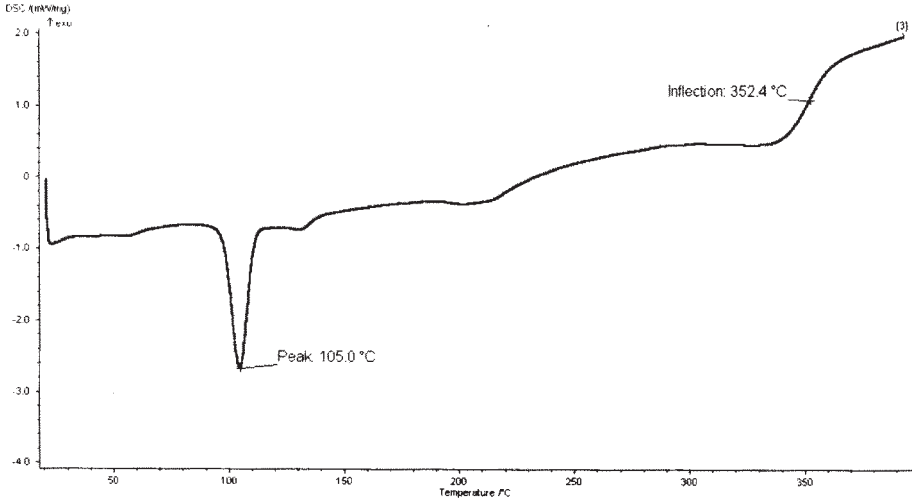

Fig. 8. Differential scanning calorimetry (DSC) of pentoxifylline retard

Analyzing the DSC data depicted in figure 7 can be observed that the pure pentoxyfilline is stable until 105.8°C, when is melt. By increasing the temperature can be observed that the studied compound is stable until 344.4°C, when the chemical decomposition is taking place.

On the other hand, the analysis of the pentoxifylline tablets reveals a slight modification of the curve, the point of melting being lower, at 105°C. This may be caused by the excipients found in the tablet that behave like impurities. PEX retard shows a continuous alteration of the curve thanks to the degradation of the excipients [15, 16].

Conclusions

The pentoxifylline active substance and pharmaceutical product were simultaneously characterized by SEM , FT-IR spectroscopy and X-ray powder diffraction pattern. SEM imaging provides the resolution required to evaluate both the size and shape of nanometer scale particles. The large depth of focus of the SEM reveals fine surface detail, even over large, irregularly-shaped particles.

There are some differences between the FT-IR spectra and the X-ray diffraction spectra of the two compounds which were analyzed, differences due to the nature of the physical interactions. The simultaneous analysis of the SEM, FT-IR and X-ray data constitutes a secure method of control and evaluation in the practice of the pharmaceutical products [17-19].

The analysis of the DSC's results for pentoxifylline, of the active substance and the tablets, concludes that the thermal stability of it isn't influenced by the presence of excipients.

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