Cent. Eur. J. Phys. • 9(6) • 2011 • 1536-1539
DOI: 10.2478/s11534-011-0075-7

VERSITA

Central European Journal of **Physics**

Preliminary spectroscopic investigation of tacrolimus TiO_2 system

Research Article

Mihai Todica[1]*, Luciana Udrescu[1]

1 *"Babes-Bolyai" University, Faculty of Physics, M. Kogalniceanu No 1, 400084 Cluj-Napoca, Romania*

Received 07 June 2011; accepted 25 August 2011

Abstract: The effect of air and UV exposure on the tacrolimus was observed by Raman and UV VIS spectroscopy. For moderate time exposure the chemical structure of tacrolimus is not affected. The absorption property of tacrolimus was enhanced by addition of TiO_2.

PACS (2008): 82.70.Dd; 82.70.Gg; 82.70.Kj

Keywords: tacrolimus • TiO_2 • system • Raman spectroscopy • UV absorption

1. Introduction

In many clinical dermatological applications the pharmaceutical product is directly displayed on the surface of the skin on thin layers, without other protection. In these circumstances the product is in permanent contact with the air or other external aggressive factors, as either the UV radiation or mechanical solicitations [1, 2]. The action of these factors facilitates the degradation of the chemical bonds or the oxidation of the components of the pharmaceutical product. For clinical applications the interest is to maintain unaffected, as long as possible, the properties of the active medical substance and to protect the skin against the aggressive actions. Tacrolimus is a medical active substance used for the treatment of athopic dermatitis, designed for direct application on the surface of the skin [3, 4]. It provides only a weak protection against UV radiation in the domain 291 nm. Usually the protection against UV radiation is enhanced by adding TiO_2, which is well tolerated by the biological tissues at small concentration [5, 7]. The aim of our work was to observe the behavior of this medical substance when submitted to a moderate period of time of air and UV exposure, with the possibility to enhance the UV absorption property by addition of TiO_2. The investigations were done by methods sensitive on the molecular scale, *i.e.:* Raman and UV VIS spectroscopy.

2. Materials and methods

We investigated the pharmaceutical form of tacrolimus used for medical applications. The samples were analyzed in initial state and after addition of TiO_2. The initial samples, without TiO_2, were kept in open air, for different intervals of time, in the dark and at room temperature. The

*E-mail: mihai.todica@phys.ubbcluj.ro

Springer

samples with TiO_2 were obtained by mixing the tacrolimus and TiO_2 for many hours. For spectroscopic investigations the samples were displayed on thin films on microscope glasses. The Raman investigations were performed with R 3000 CN systems, with excitation power 150 mW at wavelength $\lambda = 785$ nm. For UV VIS investigation we used Jasco V-670 system with a scan speed 200 nm/min, UV VIS bandwidth 2 nm, and NIR bandwidth 8 nm.

3. Results and discussions

The main effect of long period of time air exposure, under normal conditions (1 atm pressure and room temperature), is the evaporation of water and possible oxidation of some components of the product, located on the surface of the sample. The apparition of new chemical compounds can be signalized by spectroscopic measurements. Raman spectra are determined by the vibration of the chemical bonds and can reveal every change of the molecular structure of the sample. The existence of new compounds like the oxides, are responsible for the apparition of new vibration bands in the spectrum. These new bands should be easily observed by comparison of the spectrum of the initial sample and the spectrum of the sample after air exposure. The spectra of the tacrolimus in initial state and after 3 hours of air exposure are presented in Fig. 1. The two spectra are very similar and contain the main vibration bands at the same wavelength. Some of these bands are: in the domain 300-400 cm^{-1} C-C aliphatic chain bend; 804-889 cm^{-1} domain C-O-C- rock; 1082-1300 cm^{-1} domain C-O stretch; 1381-1440 cm^{-1} C-H domain bend[1] [6]. However the spectrum of non exposed sample is much smoother, and the vibration bands appears with a small amplitude in the domain 200-400 cm^{-1}. This effect is determined by the dispersion effect of water contained in this sample. For the sample kept long time in contact with the air a small quantity of water evaporates, the dispersion effect is reduced and the structure of tacrolimus is not masked by water. The similarity between the two spectra indicates there is no modification of the molecular structure of tacrolimus after few hours of air exposure. In the second stage of our work we tested the chemical stability of the tacrolimus under UV exposure. In medical applications the interval of time between two successive applications of the pharmaceutical product on the skin is 3-4 hours [1, 7]. In the worst cases the skin is exposed to UV irradiation throughout this period of time, (*i.e.* sun bath exposure).

[1] *http://www.horiba.com/fileadmin/uploads/Scientific/Documents/Raman/bands.pdf*

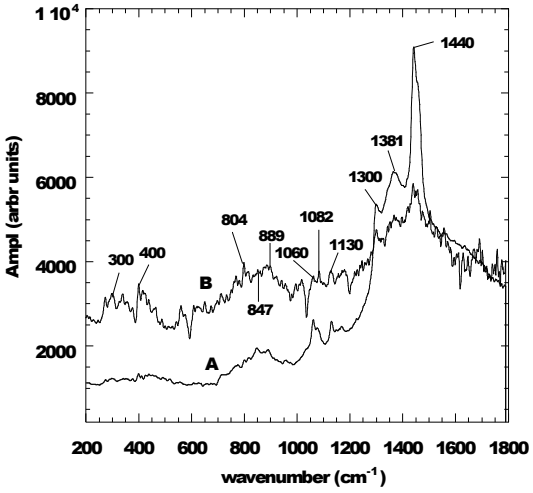

Figure 1. The Raman spectra of tacrolimus in initial state (curve A) and after 3 hours air exposure (curve B).

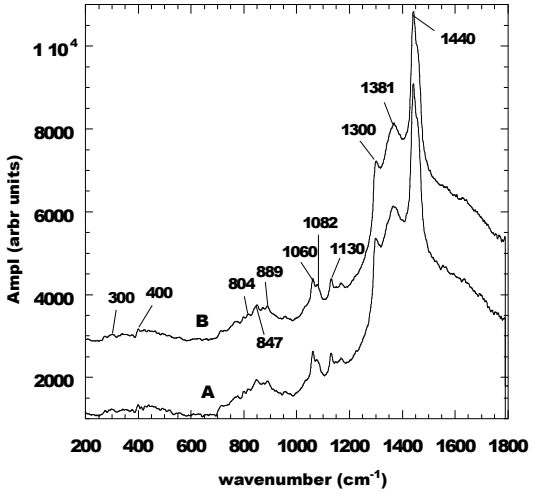

Figure 2. The Raman spectra of non irradiated tacrolimus (curve A) and after 4 hours UV irradiation (curve B).

We taken into account this aspect when we irradiated our samples. The samples were irradiated with a VL 215 G lamp at wavelength 254 nm and intensity 76 mW/cm^2, during different intervals of time. In order to observe possible modifications on the molecular scale induced by irradiation, we compared the Raman spectrum of the non irradiated sample with the spectrum of the irradiated one. The spectra of the non irradiated sample and of the sample UV irradiated for 4 hours are very similar (Fig. 2). This behavior demonstrates no modification of the chemical structure of tacrolimus. Enhancement of the protection against UV radiation is one of the requirements frequently imposed on products designed for skin care. Usually this

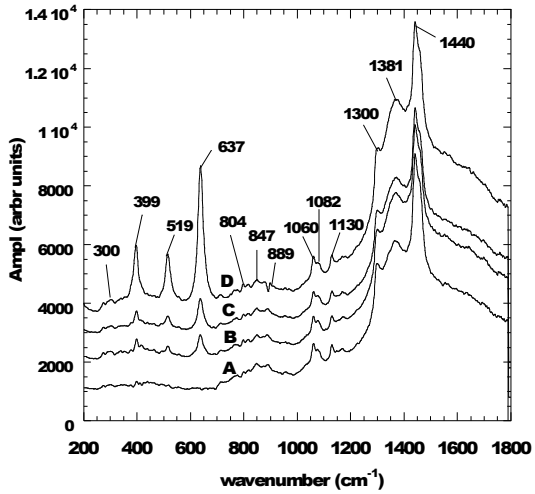

Figure 3. The Raman spectra of the samples: the tacrolimus in initial state (curve A), the tacrolimus with 3% of TiO_2 (curve B), the tacrolimus with 5% of TiO_2 (curve C) and the tacrolimus with 10% of TiO−2 (curve D).

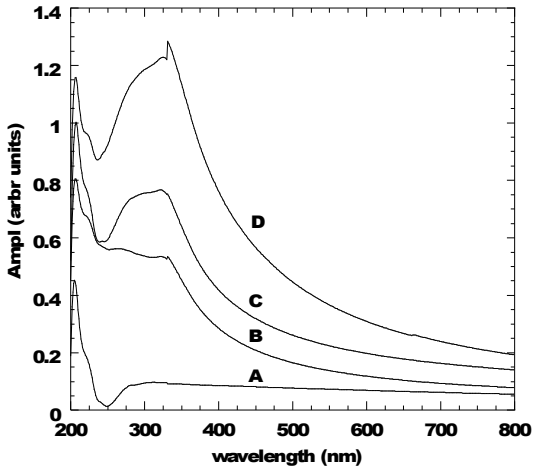

Figure 5. The UV-VIS absorption spectra of samples: the tacrolimus in initial state (curve A), the tacrolimus with 3% of TiO_2 (curve B), the tacrolimus with 5% of TiO_2 (curve C) and the tacrolimus with 10% of TiO_2 (curve D).

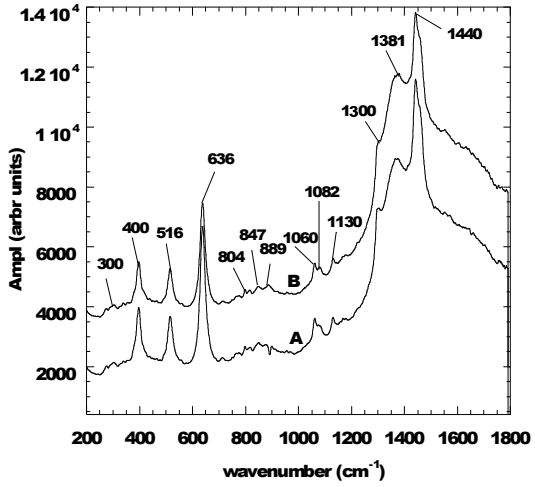

Figure 4. The Raman spectra of non irradiated tacrolimus with 10% TiO_2 (curve A) and after 4 hours UV irradiation (curve B).

effect is obtained by addition of different inert compounds to the pharmaceutical product. TiO_2 is known as one of the substances characterized by very good absorbance in the UV domain and also for its compatibility with biological tissues [8]. For practical interest the TiO_2 must not interact with tacrolimus. One of the aims of our study was the observation of eventually interaction between tacrolimus and TiO_2 and, the absorbance of UV radiation after addition of TiO_2. The eventually interaction can be probed by comparing the Raman spectra of samples in initial state and after addition of TiO_2. These spectra are shown in Figure 3. The characteristic vibration bands of tacrolimus appear clearly in all the spectra at the right wavenumber. In the domain 800 - 1500 cm^{-1} the difference between the spectra of samples with different TiO_2 concentrations are very small. The shape and the amplitude of the spectra didn't change and the vibration bands appear at the same wavenumber as for the sample without TiO_2. Modifications can be observed in the domain 200 - 800 cm^{-1}. Supplementary bands appear at 399 cm^{-1}, 519 cm $^{-1}$ and 637 cm−1 for the samples containing TiO_2. As reported in literature, in the domain 200-800 cm^{-1} TiO_2 exhibits three vibration bands at 399, 519 and 637 cm^{-1} [9]. These bands appear in our spectra at the right wavenumber, but their amplitudes increase with the concentration of TiO_2. This effect clearly indicates the contribution of TiO_2 to the spectra. The band at 399 cm^{-1} is superposed on the vibration bands at 400 cm^{-1} of the tacrolimus and cannot be clearly separated from this one. Thus the characteristic bands of tacrolimus and TiO_2 appear unmodified in our spectra. These observations demonstrate the fact that TiO_2 does not interact with tacrolimus and the chemical structure of both components is not modified. The system tacrolimus TiO_2 appears as a dispersion of TiO_2 in the matrices of tacrolimus. As for the pure samples we tested the stability of system tacrolimus-TiO_2 under UV exposure. The time of exposure was chosen in accord with the medical applications, from 1 to 4 hours, and the Raman spectra were recorded at 1 hour interval. Figure 4 show the spectra of sample with 10% TiO_2 before and after 4 hours irradiation. No modification can be observed. The vibration bands appear at the same wavenumber in both spectra and the amplitude is practically the same. The properties of system tacrolimus-TiO_2 remain unchanged

after irradiation. However we expect an enhancement of UV absorption property after addition of TiO_2. Indeed, the UV-VIS absorption spectra show the increase of the absorbance in the domain 250-350 nm with the increase of TiO_2 concentration (Fig. 5). This observation is in accordance with other results reported in literature [10]. For medical applications an important conclusion results from this study, the UV absorption property can be enhanced by addition of TiO_2, but the chemical properties of the tacrolimus remains unchanged.

4. Conclusions

The direct contact between the air and tacrolimus, at normal temperature and room temperature, for time intervals up to three hours don't affect the chemical structure of the active substance. This behavior is revealed by Raman spectroscopy. Similar behavior is observed after moderate UV exposure. The chemical structure is not modified. The absorption property is enhanced by the inclusion of TiO_2 in the tacrolimus matrix. Raman analysis indicates no chemical interaction between tacrolimus and TiO_2. The system tacrolimus-TiO_2 remains stable even after few hours of UV exposure.

Acknowledgment

The author Luciana Udrescu wishes to pass thanks for the financial support provided from programs co-financed by the SECTORAL OPERATIONAL PROGRAMME HUMAN RESOURCES DEVELOPMENT, Contract POSDRU 6/1.5/S/3 – "Doctoral studies: through science towards society".

References

[1] D. W. Clegg, A. A. Collyer, Irradiation effects on polymers (Springer, New York, 1991)
[2] K. Hane et al., Iyakuhin Kenkyu 23, 33 (1992)
[3] J. J. Russell, Am. Fam. Physician 15, 1899 (2002)
[4] C. Pascual, A. B. Fleischer, Skin Therapy Letter 9, 1 (2004)
[5] H. Ruixia et al., Appl. Surf. Sci. 256, 5000 (2010)
[6] A. Kelen et al., World intellectual property organization (WIPO), Geneva, Switzerland, HU P0600097, Mar. 1, 2007
[7] T. Gambichler et al., J. Am. Acad. Dermatol. 55, 882 (2006)
[8] R. Yanagisawa et al., Exp. Biol. M. 234, 314 (2009)
[9] H. C. Choi et al., Vib. Spectrosc. 37, 33 (2005)
[10] J. Zhang et al., J. Phys. Chem. B 110, 927 (2006)