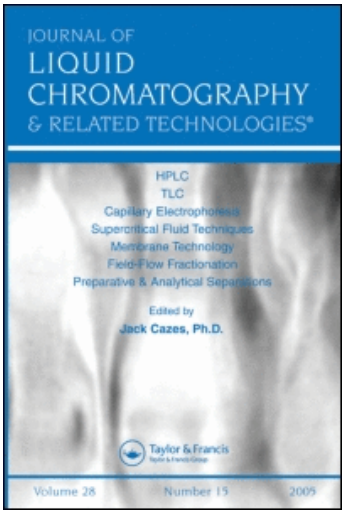

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Use of Thin Layer Chromatography to Evaluate the Stability of Methyl Nicotinate

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Use of Thin Layer Chromatography to Evaluate the Stability of Methyl Nicotinate

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Abstract: Thin layer chromatography with densitometry and spectrodensitometry was used to evaluate the stability of methyl nicotinate. Normal phase thin layer chromatography analysis was performed on silica gel $60\,F_{254}$ with an acetone $+n$-hexane mobile phase. The investigations of chemical stability of methyl nicotinate were performed on silica gel $60\,F_{254}$ at a temperature of 120°C, in an ethanolic solution stored at 8°C, as well as in aqueous and ethanolic solutions stored in ordinary- and quartz-flasks heated at 40°C and exposed to UV radiation ($\lambda = 254$ nm). Methyl nicotinate was only stable in aqueous and ethanolic solutions stored in ordinary flasks at 40°C and exposed to UV radiation ($\lambda = 254$ nm).

Keywords: Densitometry, Normal phase thin layer chromatography, Spectrodensitometry, Stability of methyl nicotinate

INTRODUCTION

The stability of drugs is the time when no visual changes are observed in a particular drug form and after which the contents of the active components are not lower than 90% of the initial contents.[1,2]

The stability of a drug is one of its basic properties. It is understood by reference to physical, chemical, and biological factors of activity. Each

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change in the structure and properties of the form of a drug can lead to loss and weakness of pharmacological activity.[3]

In order to prevent these disadvantageous phenomena, we have to:

1. know the mechanism of drug decomposition under different conditions;
2. know the chemical processes occuring in a drug to counteract them, chemically or physically, i.e., stabilize them.

In research dealing with drug stability, most often the so called accelerated aging tests are used, based on kinetic methods of measurement of decomposition reaction rate under conditions of heightened temperature, increased humidity, access to light, and similar agents having an influence on the course of the reaction.[4]

Methyl nicotinate is used in the pharmaceutical industry as an ingredient in creams and ointments. It acts as a prodrug to enhance the topical penetration of the active substances on the skin.[5,6]

Various studies have shown significant enhancing effects of lipophilic agents such as isopropyl myristate and mineral oil on the skin penetration of methyl nicotinate.[7–9] The explanation for the observed enhancing effects may be an interaction of the lipophilic liquids with the lipid bilayers of the stratum corneum that leads to a decrease of the barrier resistance in the skin.

Methyl nicotinate is also used as an active ingredient in accelerating cosmetics and sun tanning preparations, causing a tingling effect, i.e., feeling the heat, and pinching the skin under particular conditions. The skin becomes better supplied with oxygen and, thus, can yield a quicker suntan effect.[10]

Methyl nicotinate, as well as nicotinic acid, is widely used as a vasodilator by diabetics,[11,12] and schizophrenics and other psychic patients.[13–15]

The purpose of this work was to use thin layer chromatography (TLC) with densitometry to investigate the chemical stability of methyl nicotinate.

EXPERIMENTAL

Chemicals

The components of the mobile phase: acetone (Polish Chemical Reagents (POCh), Poland; analytical grade), and *n*-hexane (POCh, Poland; analytical grade) were used for TLC analysis. A commercial sample of methyl nicotinate (Sigma-Aldrich, Germany) was used as the test solute. The purity of the standard sample was at least 99%.

Standard Solution Preparation

The solution of the commercial sample of methyl nicotinate was prepared in ethanol (POCh, Poland, 96%, analytical grade). Methyl nicotinate (40 mg) was dissolved in 10 mL of ethanol.

Stationary Phase

Glass plates, precoated with silica gel 60 F_{254} (E. Merck, #1.05715, series: 640136123, OB569763, and HX609224), were used to investigate the chemical stability of methyl nicotinate. The plates were prewashed with a mixture of acetone and *n*-hexane (50:50, v/v) and dried for 24 h at room temperature ($18 \pm 1°C$). The plates were then activated at 120°C for 30 min.

Conditions of Research on the Stability of Methyl Nicotinate

Investigation of Methyl Nicotinate Chemical Stability on Silica Gel at 120°C

The plates were cooled to room temperature after their activation and the solution of methyl nicotinate was spotted in the amount of 5 μL (which corresponds to 20 μg of methyl nicotinate) onto the chromatographic plates. Next, the plates were heated at 120°C during 1, 2, 3, 4, 5, 6, and 7 hours. After this time, the standard solution of methyl nicotinate (not heated) was spotted onto chromatographic plates near the heated (120°C) methyl nicotinate.

Investigation of Methyl Nicotinate Chemical Stability in Ethanolic Solution Stored in a Refrigerator

An ethanolic solution of methyl nicotinate was stored in a refrigerator at 8°C for 1 year. After this time, a fresh standard solution of methyl nicotinate was prepared. The solution of methyl nicotinate stored for 1 year at 8°C (the old solution) and a new standard solution of methyl nicotinate were spotted in the amount of 5 μL (which corresponded to 20 μg of methyl nicotinate) onto activated chromatographic plates.

Investigation of Methyl Nicotinate Chemical Stability in Aqueous and Ethanolic Solutions Stored in Ordinary- and Quartz-Flasks at 40°C and Exposed to UV Radiation ($\lambda = 254$ nm)

Solutions of methyl nicotinate were prepared by dissolving of 40 mg of methyl nicotinate in 10 mL ethanol and water, respectively. The solutions

investigated in ordinary- and quartz-flasks were within a distance of 18.5 cm from a UV lamp (Cobrabid, Poland). Ethanolic and aqueous solutions of methyl nicotinate in ordinary- and quartz-flasks were exposed to UV radiation ($\lambda = 254$ nm) and heated to 40°C for 200 h. In the first 40 hours, measurements were carried out at 5 h intervals, for 20 h. The above-mentioned solutions and a standard solution of methyl nicotinate were spotted in the amount of 5 μL onto the chromatographic plates.

Mobile Phases Used in TLC

Acetone +*n*-hexane mobile phase in the volume composition of 40:60 was used to investigate the chemical stability of methyl nicotinate on silica gel at 120°C.

Acetone +*n*-hexane mobile phase in volume composition of 30:70 was used to investigate the chemical stability of:

methyl nicotinate in an ethanolic solution stored for 1 year in a refrigerator (old solution) and the freshly prepared standard ethanolic solution of methyl nicotinate; and
methyl nicotinate in ethanolic and aqueous solutions stored in ordinary- and quartz-flasks heated at 40°C and exposed to UV radiation ($\lambda = 254$ nm).

The above-mentioned mobile phases (50 mL) were placed in classical chromatographic chambers (Camag) and the chambers were saturated with the mobile phases for 30 minutes. The plates were developed to a distance 14 cm at room temperature (18 ± 1°C). The plates were then dried for 24 h at room temperature (18 ± 1°C) in a fume cupboard.

Densitometric and Spectrodensitometric Investigations

Densitometric and spectrodensitometric investigations were performed using a TLC Scanner 3 (Camag, Switzerland) operated in the absorbance mode and controlled by winCATS 1.4.2 software. The radiation source was a deuterium lamp emitting a continuous UV spectrum between 190 and 450 nm. Densitometric scanning was then performed in a multi wavelength mode in the range of 200 to 440 nm, at wavelength intervals of 20 nm at each step. Next, densitometric analysis was then performed at the respective absorption maxima shown in Table 1. The slit dimensions were 8.00 × 0.40 mm, Macro; the optimal optical system was light; the scanning speed was 20 mm s^{-1}; the data resolution was 100 μm $step^{-1}$; the measurement type was remission; and the measurement mode was absorption.

Table 1. The selected results of densitometric analysis of methyl nicotinate in ethanolic solution which was exposed to UV light ($\lambda = 254$ nm) in quartz flask

Time of the exposure to UV radiation ($\lambda = 254$ nm)	R_F of methyl nicotinate (MN) and the products of its chemical changes (P)	Area of peak (AU)[a]	λ_{max}(nm)
0 h	**0.36 (MN)**	**24068**	**221**
5 h	0.14 (P)	1246	288
	0.25 (P)	***4165***	***269***
	0.36 (MN)	**23414**	**221**
20 h	0.08 (P)	1486	291
	0.16 (P)	686	292
	0.21 (P)	1295	292
	0.28 (P)	***11582***	***269***
	0.37 (MN)	**17604**	**221**
40 h	0.06 (P)	2015	289
	0.14 (P)	462	294
	0.18 (P)	3798	291
	0.25 (P)	***16299***	***268***
	0.34 (MN)	**15039**	**221**
60 h	0.14 (P)	2058	274
	0.19 (P)	6131	290
	0.28 (P)	***18843***	***268***
	0.37 (MN)	**10078**	**221**
80 h	0.06 (P)	1561	282
	0.14 (P)	1792	274
	0.20 (P)	14080	290
	0.28 (P)	***20967***	***268***
	0.36 (MN)	**8163**	**221**
	0.50 (P)	1476	274
120 h	0.06 (P)	1101	287
	0.18 (P)	10775	290
	0.25 (P)	***22404***	***268***
	0.35 (MN)	**4535**	**265**
	0.52 (P)	2333	273
160 h	0.07 (P)	1101	284
	0.20 (P)	9026	290
	0.28 (P)	***22758***	***268***
	0.36 (MN)	**2737**	**266**
	0.49 (P)	3372	273
200 h	0.07 (P)	1694	285
	0.19 (P)	6648	290
	0.26 (P)	***22516***	***269***
	0.36 (MN)	**1763**	**267**
	0.48 (P)	806	279
	0.54 (P)	3452	273

[a]Areas of peaks were measured at λ_{max}.

The chromatographic bands obtained on the densitograms were investigated by spectrodensitometric analysis under the following conditions: the slit dimensions were 8.00×0.40 mm, Macro; the optimal system was resolution; the scanning speed was 20 nm s^{-1}; the data resolution was 1 nm $step^{-1}$; the initial wavelength was 200 nm, and final wavelength was 350 nm or 450 nm; the measurement type was remission; and the measurement mode was absorption.

RESULTS AND DISCUSSION

Investigation of Methyl Nicotinate Chemical Stability on Silica Gel at 120°C

The densitograms of standard of methyl nicotinate and methyl nicotinate heated for 1 to 7 h at 120°C on silica gel are presented in Figure 1.

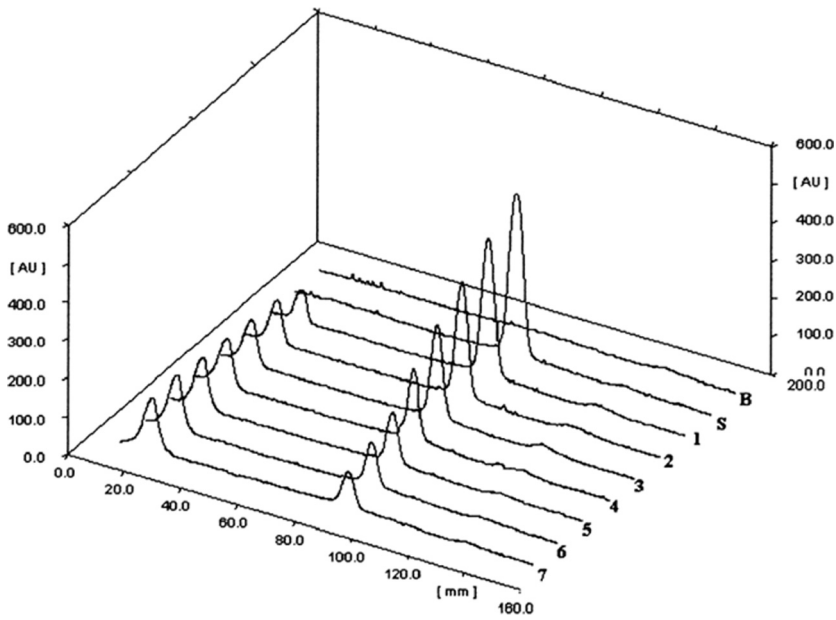


Figure 1. The densitograms of the chromatogram background, the standard of methyl nicotinate and methyl nicotinate heated at 120°C for 1 to 7 h on silica gel; where: B – the chromatogram background; S – the standard of methyl nicotinate; 1 – after 1 h of heating; 2- after 2 h of heating; 3 – after 3 h of heating; 4 – after 4 h of heating; 5 – after 5 h of heating; 6- after 6 h of heating; 7 – after 7 h of heating.

The chromatographic band from the methyl nicotinate standard had an $R_F = 0.48$ and an area of 25957.5 AU. The standard solution of methyl nicotinate had no impurities. Two chromatographic bands with $R_F = 0.01$ and $R_F = 0.48$ were visible on the densitograms of methyl nicotinate which had been heated from 1 to 7 h on the silica gel. The substance remaining at the origin of the chromatogram was a product of chemical change of methyl nicotinate, formed on silica gel during the heating process. The largest amount of the substance was a product of chemical changes of methyl nicotinate formed during 7 h of heating (an area of 9430.3 AU). However, the smallest amount of the substance was a product of chemical change of methyl nicotinate formed during 1 h of heating (an area of 4147.3 AU). The spectrodensitograms of methyl nicotinate which, before the chromatogram development, was heated on silica gel (from 1 to 7 h) and the standard of methyl nicotinate (Figure 2a) and formed a product of chemical change of methyl nicotinate (Figure 2b), respectively are presented in Figure 2. The spectrodensitograms presented in Figure 2a were identical (with $\lambda_{max} = 221$ nm) and showed that methyl nicotinate ($R_F = 0.48$) was present in these bands. The spectrodensitograms of bands corresponding to a product of change of methyl nicotinate (which was heated on silica gel) with an $R_F = 0.01$ have the fundamental absorption bands (λ_{max}) at the wavelength equal to 263 nm in the range of 200 to 350 nm.

Investigation of Methyl Nicotinate Chemical Stability in Ethanolic Solutions Stored at 8°C

The densitometric and spectrodensitometric analyses performed showed that methyl nicotinate undergoes a chemical change during the 365 days of storage in an ethanolic solution in the refrigerator at 8°C. The densitograms of methyl nicotinate derived from a freshly prepared standard solution (Figure 3a) and the old ethanolic solution (Figure 3b) are shown in Figure 3. The methyl nicotinate in ethanolic solution underwent a chemical change during storage. Except for methyl nicotinate, with an R_F value of 0.35, the presence of the substance was a product of a chemical change of methyl nicotinate with $R_F = 0.40$. 91.75% of methyl nicotinate was after 365 days storage of its ethanolic solution at 8°C. The comparison of the spectrodensitograms of methyl nicotinate (MN) coming from the old and freshly prepared ethanolic solutions are shown in Figure 4. These spectrodensitograms are characterized by good agreement. The spectrodensitogram of the product (P) of chemical change of methyl nicotinate ($\lambda_{max} = 265$ nm) is also shown in Figure 4.

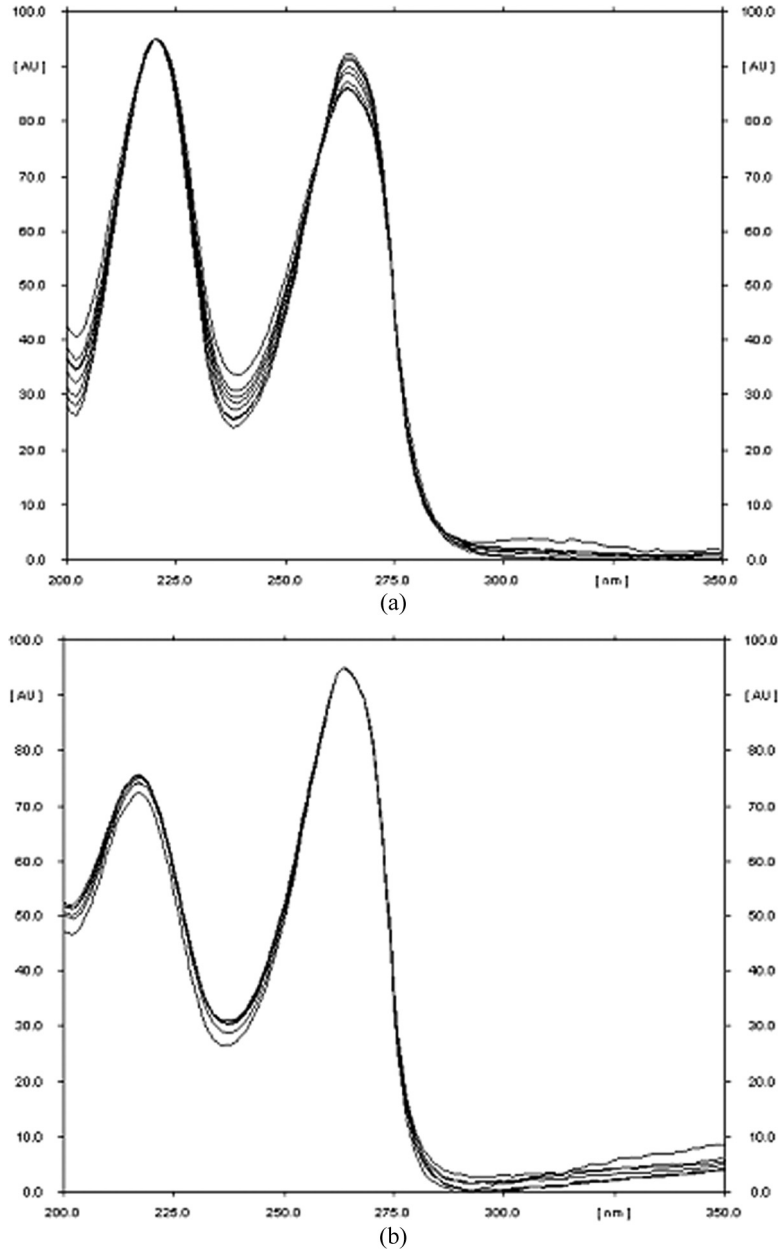


Figure 2. (a) The spectrodensitograms of the standard of methyl nicotinate and methyl nicotinate ($R_F = 0.48$) which, before chromatogram development, was heated at 120°C for 1 to 7 h on silica gel. (b) The spectrodensitograms of the substance with $R_F = 0.01$ formed during heating of methyl nicotinate on silica gel.

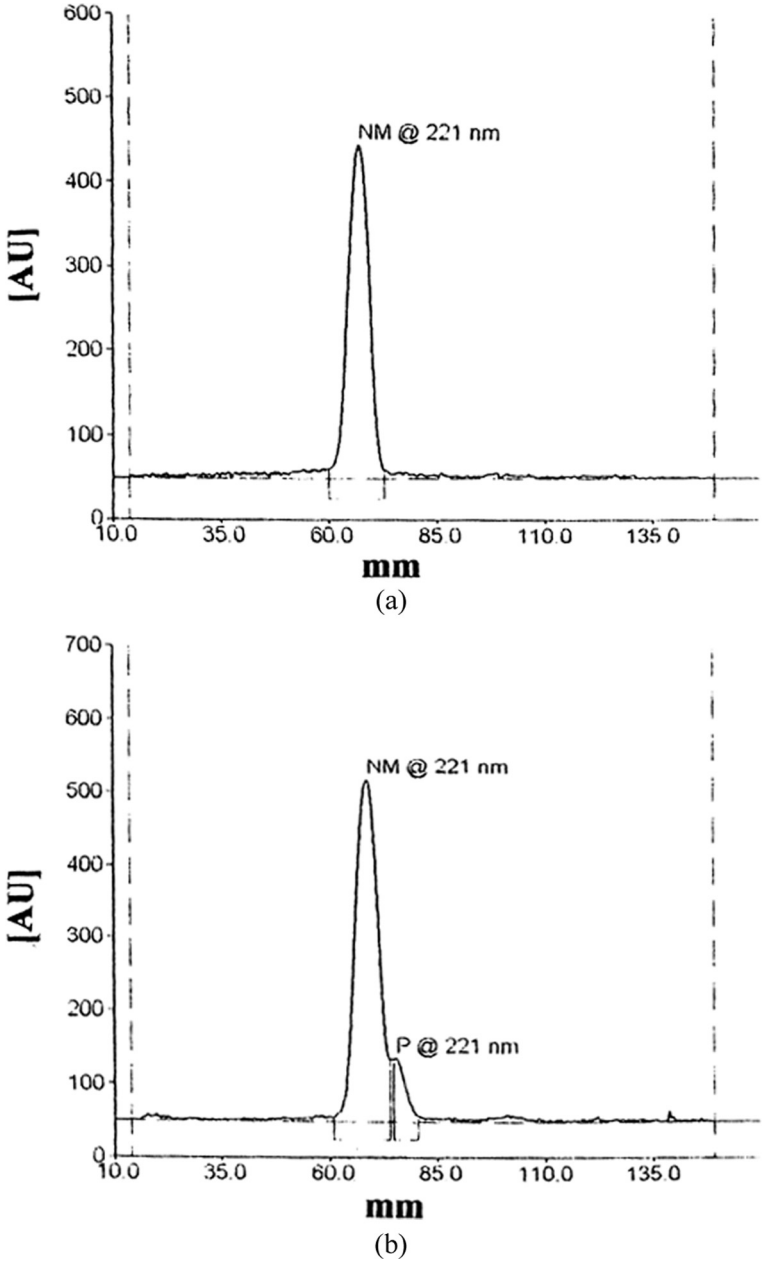


Figure 3. The densitogram of methyl nicotinate from an ethanolic solution: (a) prepared before the experiment; (b) stored in a refrigerator at 8°C for 1 year; where: NM – methyl nicotinate; P – a product of the chemical change of methyl nicotinate.

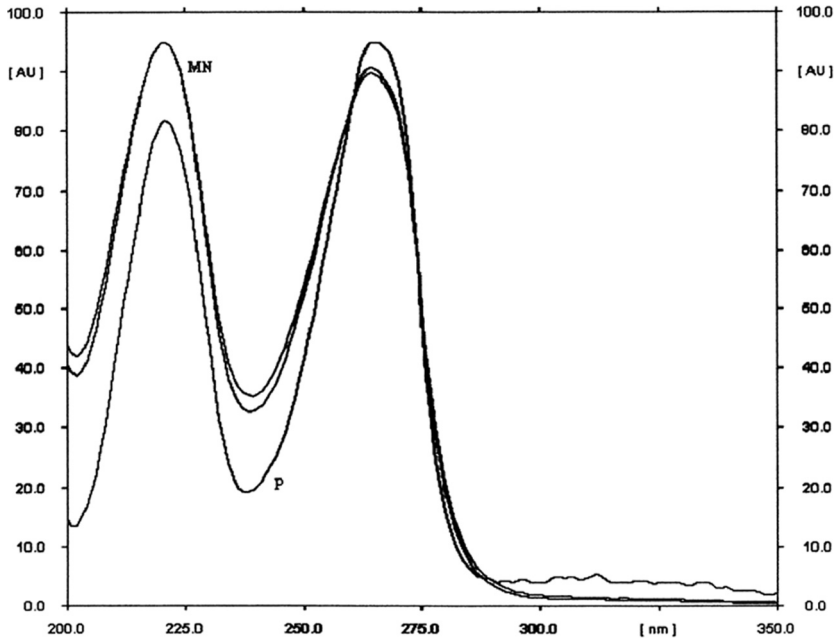


Figure 4. The comparison of the spectrodensitograms of methyl nicotinate (MN, $\lambda_{max} = 221$ nm) in ethanolic solution stored in a refrigerator at 8°C for 1 year and methyl nicotinate coming from a new prepared ethanolic solution as well as the spectrodensitogram of the product (P with $R_F = 0.40$ and $\lambda_{max} = 265$ nm) formed during 1 year of storage of methyl nicotinate in an ethanolic solution at 8°C.

Investigation of Methyl Nicotinate Chemical Stability in Aqueous and Ethanolic Solutions Stored in Ordinary-and Quartz-Flasks Heated at 40°C and Exposed to UV Radiation ($\lambda = 254$ nm)

Investigation of Methyl Nicotinate Chemical Stability in Aqueous Solution

It was found that methyl nicotinate in aqueous solution stored both in ordinary- and quartz- flasks, heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) during 200 h did not undergo chemical changes.

Investigation of Methyl Nicotinate Chemical Stability in Ethanolic Solution

The multi wavelength densitograms of the standard of methyl nicotinate in ethanolic solution and methyl nicotinate in ethanolic solution in

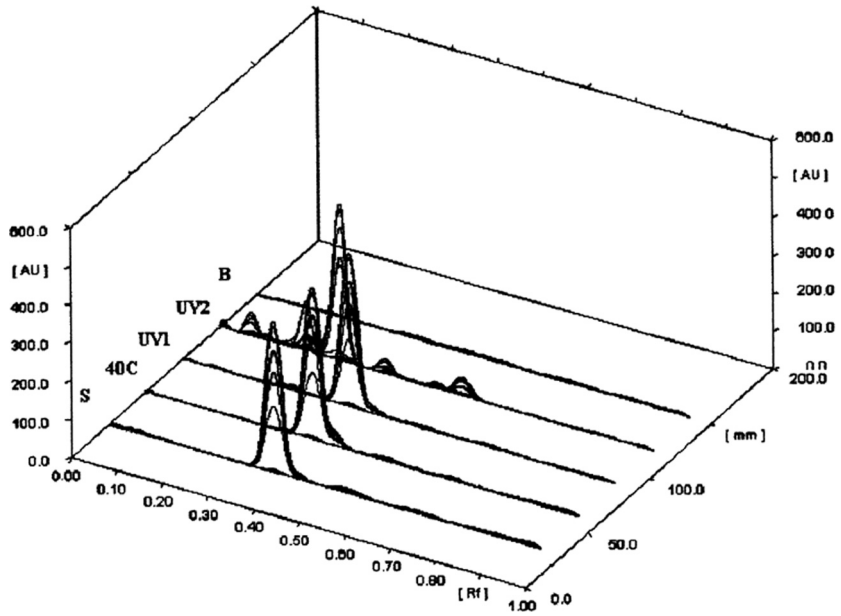


Figure 5. *3D* densitograms recorded in the multi wavelength from 200 to 440 nm of methyl nicotinate from an ethanolic solution, which was heated at 40°C and exposed to UV radiation ($\lambda_{max} = 254$ nm) in ordinary- and quartz- flasks for 200 h. Where: S–the standard of methyl nicotinate; 40 C–heating in temperature of 40°C; UV 1–exposure by UV radiation in ordinary flask; UV 2–exposure by UV radiation in quartz flask; B–chromatogram background.

ordinary- and quartz- flasks, which were heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) by 200 h are shown in Figure 5. One chromatographic band is visible on the densitograms of methyl nicotinate standard, and methyl nicotinate in ethanolic solution, which was heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) in an ordinary flask (UV 1) up to 200 h. It shows that methyl nicotinate in ethanolic solution undergoes no chemical changes under these conditions. From three to six chromatographic bands were visible on the densitograms of methyl nicotinate in ethanolic solution (Figure 6 and Table 1), which were exposed to UV radiation ($\lambda = 254$ nm) in a quartz flask (UV 2) from 5 h to 200 h. It shows that methyl nicotinate undergoes a chemical changes under these conditions. The main product of chemical changes of methyl nicotinate is the substance with R_F equal to about 0.26.

The comparison of areas of chromatographic bands obtained of methyl nicotinate coming from ethanolic solution in the quartz flask exposed to UV radiation ($\lambda = 254$ nm) from 0 to 200 h and the main product of chemical changes of methyl nicotinate are shown in

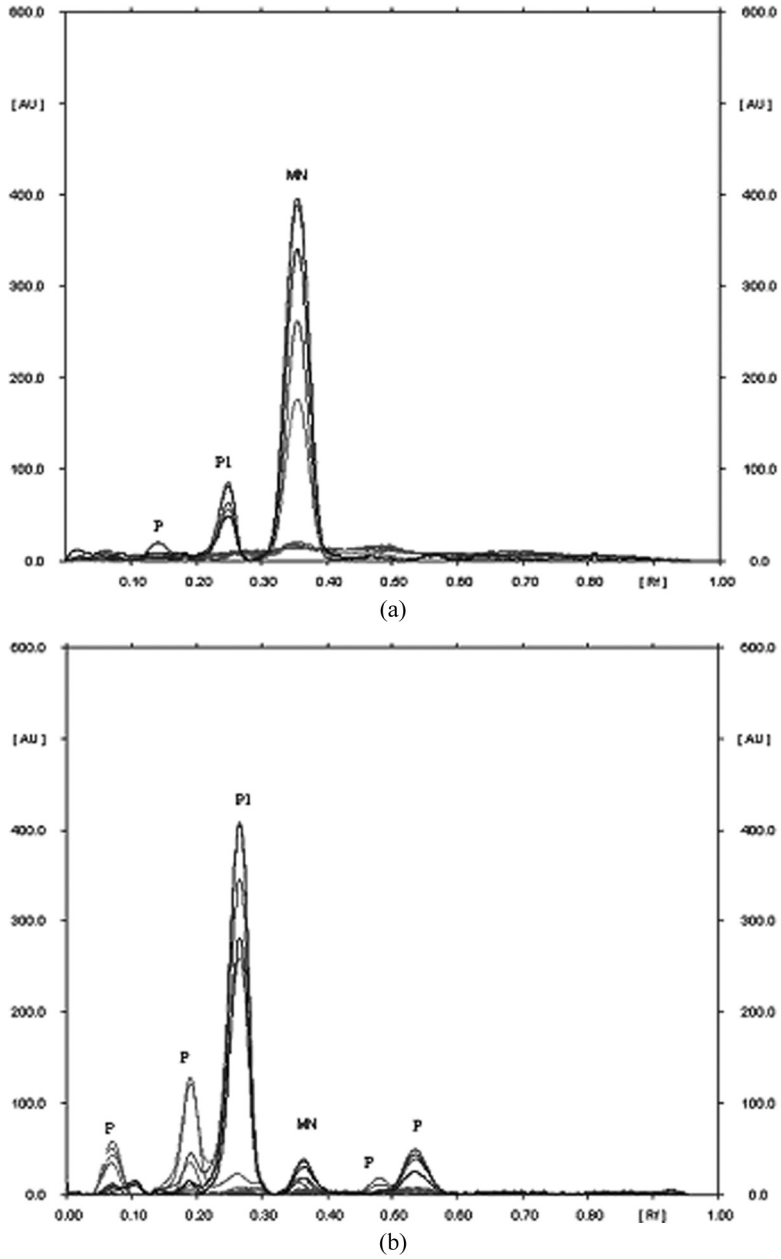


Figure 6. TLC-UV chromatograms recorded in the multi wavelength from 200 to 440 nm of methyl nicotinate coming from ethanolic solution, which was exposed to UV radiation ($\lambda_{max} = 254$ nm) in a quartz- flask for: (a) 5 h and (b) 200 h; where: MN – methyl nicotinate; P – the products of chemical changes of methyl nicotinate; and P1 – main product of chemical changes of methyl nicotinate.

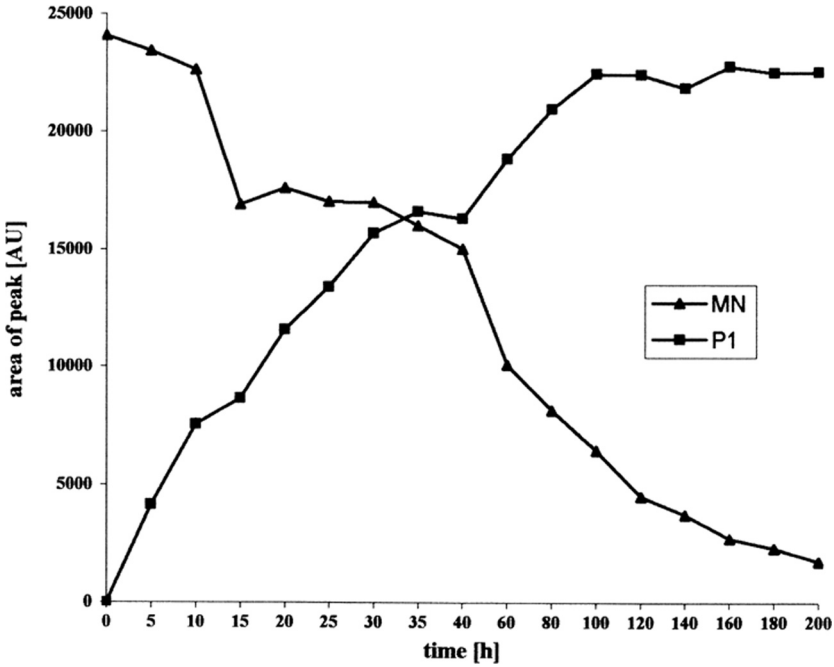


Figure 7. The comparison of areas of chromatographic bands of methyl nicotinate ($R_F = 0.36$ at $\lambda = 221$ nm) in ethanolic solution in a quartz flask exposed to UV radiation ($\lambda_{max} = 254$ nm) from 5 to 200 h and a main product (P1) of chemical change of methyl nicotinate with $R_F = 0.26$ (at $\lambda_{max} = 269$ nm).

Figure 7. The progressive loss of methyl nicotinate, of which the ethanolic solution in the quartz flask was exposed to UV radiation ($\lambda = 254$ nm) from 5 to 200 h was noted. The area of the standard of methyl nicotinate is equal to 24068 AU. The area of 23414 AU of methyl nicotinate in quartz flask was after 5 h of its exposure to UV radiation ($\lambda = 254$ nm). However, only an area of 1763 AU of methyl nicotinate in the quartz flask remained after 200 h of its exposure to UV radiation ($\lambda = 254$ nm). Moreover, a progressive increase of the substance was the main product (P1) of chemical change of methyl nicotinate was observed. The substance with $R_F = 0.26$ and an area of 3913 AU formed after 5 h of the exposure by UV radiation ($\lambda = 254$ nm) of methyl nicotinate in ethanolic solution. However, an area of this substance was 20706 AU after 200 h of the exposure by UV radiation ($\lambda = 254$ nm) of methyl nicotinate in ethanolic solution. The comparisons of the spectrodensitograms of methyl nicotinate in ethanolic solution in ordinary- and quartz- lasks, which were heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) by 5 h and 200 h and the standard of methyl nicotinate are shown in Figure 8.

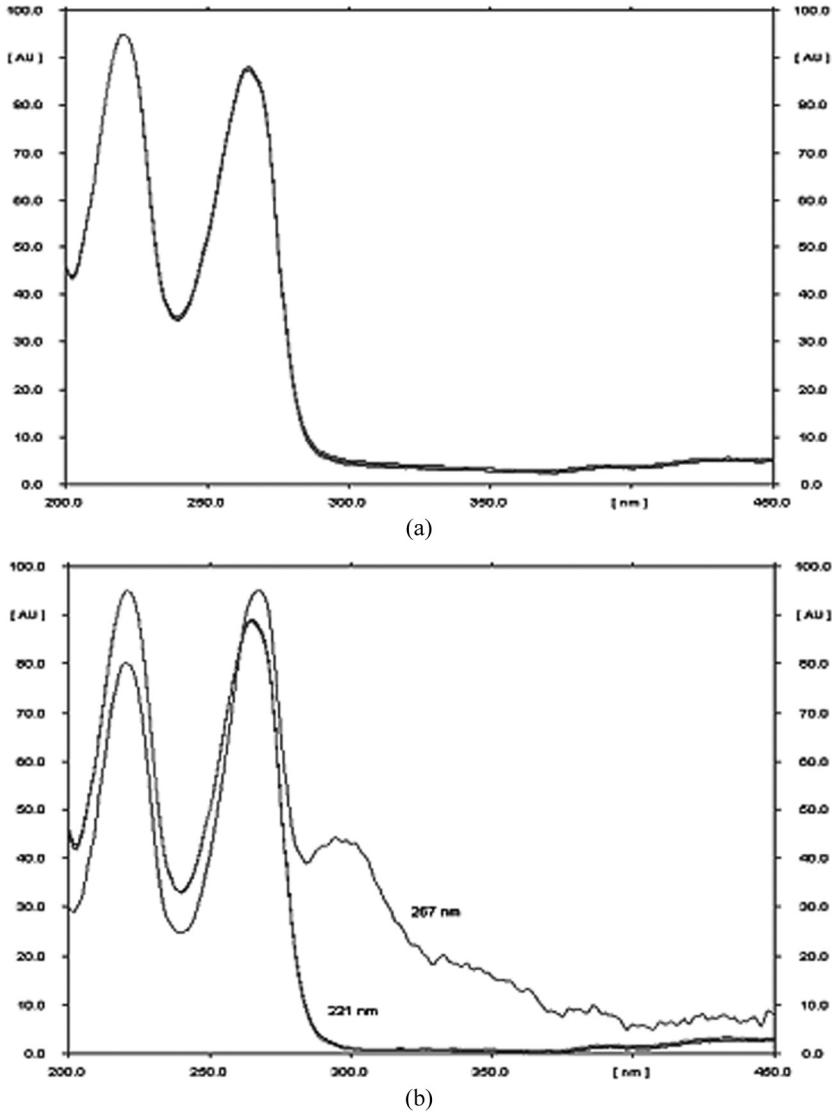
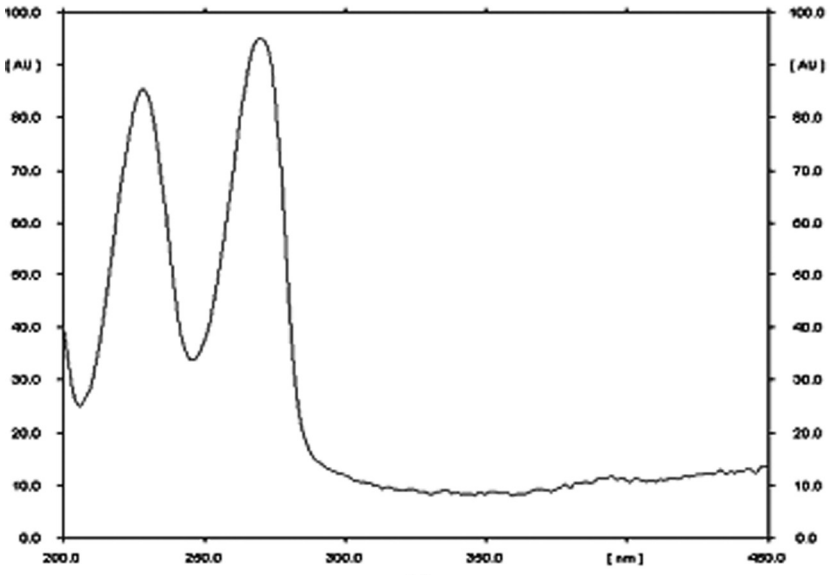
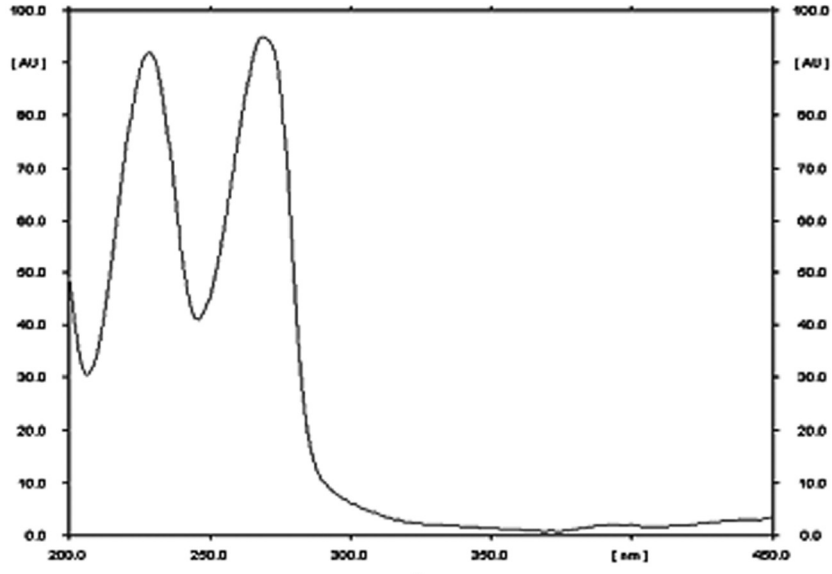


Figure 8. The spectrodensitograms of methyl nicotinate from its ethanolic solutions, which were heated at 40°C and exposed to UV radiation ($\lambda_{max} = 254$ nm) in ordinary- and quartz- flasks: a) for 5 h and the standard of methyl nicotinate ($R_F = 0.36$ and $\lambda_{max} = 221$ nm); b) for 200 h and the standard of methyl nicotinate ($R_F = 0.36$ and $\lambda_{max} = 221$ nm); and for methyl nicotinate in a quartz flask exposed to UV radiation ($\lambda_{max} = 254$ nm) $R_F = 0.36$ and $\lambda_{max} = 267$ nm).



(a)



(b)

Figure 9. The spectrodensitograms of the main product (P1 - with $R_F = 0.26$ and $\lambda_{max} = 269$ nm) of chemical change of methyl nicotinate formed after: a) 5 h and b) 200 h of exposure by UV radiation ($\lambda_{max} = 254$ nm) of methyl nicotinate in ethanolic solution in a quartz flask.

The spectrodensitograms in Figure 8a are identical (with $\lambda_{max} = 221$ nm) and suggest that methyl nicotinate ($R_F = 0.36$) is present in these bands. There was a high spectral correlation of methyl nicotinate ($r = 0.999$).

The spectrodensitograms of methyl nicotinate in ethanolic solution in the ordinary flask, which was heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) for 200 h and the standard of methyl nicotinate are shown in Figure 8b and have the fundamental absorption bands (λ_{max}) at the wavelength equal to 221 nm. However, the fundamental absorption band (λ_{max}) at the wavelength equal to 267 nm for methyl nicotinate exposed to UV radiation ($\lambda = 254$ nm) in the quartz flask was observed. The spectrodensitograms of methyl nicotinate in ethanolic solution in the quartz flask, which was exposed to UV radiation ($\lambda = 254$ nm) from 5 to 80 h have the fundamental absorption bands (λ_{max}) at the wavelength equal to 221 nm. However, the spectrodensitograms of methyl nicotinate in ethanolic solution in the quartz flask have the fundamental absorption bands (λ_{max}) at the wavelength from 265 to 268 nm during its exposure to UV radiation ($\lambda = 254$ nm) from 100 to 200 h.

The spectrodensitogram of the substance with R_F value equal to about 0.26 being the main product of chemical change of methyl nicotinate in an ethanolic solution in the quartz flask, which was exposed to UV radiation ($\lambda = 254$ nm) for 5 h and 200 h are shown in Figure 9. The spectrodensitograms of the bands corresponding to a product of chemical changes of methyl nicotinate in ethanolic solution in the quartz flask (which was exposed to UV radiation ($\lambda = 254$ nm) by 5 h and 200 h) with R_F value equal to about 0.26 have the fundamental absorption bands (λ_{max}) at the wavelength equal to 269 nm (Figures 9a and 9b) in the range of 200 to 450 nm.

CONCLUSIONS

Thin layer chromatography with densitometry and spectrodensitometry was used to evaluate the stability of methyl nicotinate. Heating of methyl nicotinate on silica gel at 120°C for 1 to 7 h caused the formation of the substances being products of its chemical change. These substances, after chromatographic separation, remain at the origin of the chromatogram and have the fundamental absorption bands (λ_{max}) at a wavelength equal to 263 nm. Methyl nicotinate in ethanolic solution undergoes a chemical change during 365 days of storage at 8°C. Except for methyl nicotinate, with an R_F value equal to 0.35, it was stated that the presence of the substance being a product of its chemical changes with R_F value equal to 0.40. Methyl nicotinate in aqueous solution, stored both in ordinary- and quartz- flasks, heated to 40°C and exposed to UV radiation ($\lambda = 254$ nm) for 200 h undergoes no chemical changes. It was found that

methyl nicotinate in ethanolic solution stored in ordinary flasks heated at 40°C and exposed to UV radiation ($\lambda = 254$ nm) for 200 h undergoes no chemical changes. Methyl nicotinate in ethanolic solution stored in a quartz flask underwent a chemical change during its exposure to UV radiation ($\lambda = 254$ nm) for 5 to 200 h. It was noted that a progressive loss of areas of the chromatographic bands obtained for methyl nicotinate, of which an ethanolic solution in quartz flask was exposed to UV radiation ($\lambda = 254$ nm) occurred from 5 to 200 h. It was also stated that a progressive increase of areas of chromatographic bands obtained for the substance with R_F value equal to about 0.26, being the main product of chemical changes of methyl nicotinate formed during exposure by UV radiation ($\lambda = 254$ nm) of methyl nicotinate in ethanolic solution in a quartz flask from 5 to 200 h. It was found that the spectrodensitograms of methyl nicotinate in ethanolic solution in a quartz flask, which was exposed to UV radiation ($\lambda = 254$ nm) from 5 to 80 h has the fundamental absorption bands (λ_{max}) at the wavelength equal to 221 nm. However, the spectrodensitograms of the above-mentioned solution have the fundamental absorption bands (λ_{max}) at the wavelength equal to from 265 to 268 nm during its exposure to UV radiation ($\lambda = 254$ nm) from 100 to 200 h.

Further investigations will concern the identification of the products of chemical changes of methyl nicotinate.

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