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Evaluation of the photoprotective effect of *β*- cyclodextrin on the emission of volatile degradation products of ranitidine

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Key words: ranitidine, cyclodextrins, photoprotection, HS-SPME- GC-MS, ^{1}H NMR ROESY

Abstract

The process of the photo-excitation of ranitidine hydrochloride (RAN) in a solid state makes visible changes to its colour and generates an unpleasant odour. The purpose of the present study was to observe the protective effects of ˇ-cyclodextrin (CD) complexation as well as the effect of the mixture of two stoichiometries 1:1 and 1:2 (RAN:CD, IC) on the photostability of samples in a solid state. Samples of inclusion complexes (IC) and physical mixtures (PM) were prepared and irradiated for 48 h in a Suntest CPS+ chamber. Irradiated samples were analyzed using nuclear magnetic resonance (1H NMR), infrared spectroscopy (FT-IR), the differential scanning calorimetry method (DSC) and thermogravimetry analysis (TGA). Volatiles were monitored with the use of headspace-solid phase microextraction-gas chromatography–mass spectrometry (HS-SPME-GC–MS). The protective effect of CD was noticed with respect to IC, and also PM. Achieved photostabilization of complexed RAN against photodegradation could be explained due to either the inclusion of the furan part of RAN into the CD cavity as shown by the 1H NMR ROESY (rotation frame nuclear Overhauser effect spectroscopy) spectrum or the screening effect of CD. FT-IR spectra, DSC curves and microscope images of irradiated samples of protected RAN did not indicate any physical changes, such as phase transfer

Introduction

H2 receptor antagonists represented by ranitidine hydrochloride (RAN) belong to a group of medicinal compounds that are very sensitive to environmental exposure, especially light and humidity [1-2]. Apart from the known problems with ranitidine taken in the form of tablets and syrup, there are still unresolved issues surrounding its use in powdered or pure substance form and any possible mechanisms of its instability in a solid state.

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It has been documented that the process of the photo-excitation of ranitidine hydrochloride causes visible colour changes and emits an unpleasant odour [3]. A number of compounds are released during exposition of the solid form of RAN to light [4] and some of these have already been identified [5]. The molecules produced during photodegradation may be responsible for the characteristic strong odour of ranitidine powder generated during its storage and forced light irradiation.

Studies on the photostability of medicinal substances are an important element of the stability testing of drugs [6]. Photodegradation of drug compounds can contribute to a variety of adverse physical effects for the medicinal product, can lead to changes in the physical and chemical properties of the medicinal product and, thus, can effect changes in the pharmacokinetics and eventually lead to unplanned therapeutic effects. The list of environmentally sensitive pharmacological compounds constantly increases; therefore, the search for newly developed methods for the improvement of drug stability is a most vital task. A review of the literature suggests that one method of inhibition of drug degradation is complexation with cyclodextrins – cyclic oligosaccharides (CDs) [7,8]. The photostabilization effect or the photoprotection of different molecules is well documented [9-13]. Protective properties of native CDs (α-, β-, γ-CD) and their derivatives are approached by incorporation of a guest compound inside a cyclodextrin moiety, but this is not always so. Preparation of simple physical mixtures with cyclodextrins is also effective in terms of protective activity [14]. For pharmaceutical applications, the improvement of drug stability and solubility, as well as the biological availability of drug compounds, are necessary features. CDs are used in such pharmaceuticals as the Nicorette Microtab (AB, Sweden) containing betadex (β-CD), Orungal I.V. (Janssen, Belgium) containing 2-hydroxylpropyl-β-cyclodextrin, Bridion (Schering-Plough, Belgium) with a modified β-CD, Flamexim (Chiesi Pharma, Poland), containing piroxicam complexes with β-CD, and others.

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In this paper, we demonstrate the influence of CDs on the emission of volatile photodegradation products from ranitidine hydrochloride powder. The scope of this study is only concerned with the photoprotection of RAN by *β*-CD, as the first step of planned and parallel established general stabilization of RAN. Currently, results are demonstrated as reduced amounts of compounds produced during photodegradation through either formation of inclusion complexes or, the simplest form, through physical mixtures of RAN-CD in two stoichiometries. The effect of supramolecular protection is investigated using the HS-SPME-GC–MS method.

1. Experimental

1.1. Materials

The tested ranitidine hydrochloride (polymorphic Form 2) bulk powder was supplied as a white crystalline powder by Polpharma Pharmaceutical Works (Poland). The *β*-CD CYL-3190 was purchased from CycloLab R&D Ltd (Budapest, Hungary). A Millipore Milli Q-plus system (Millipore, Bedford, USA) was used to purify water for the preparation of complexes.

1.2. Methods

1.2.1. Inclusion complexes and physical mixture preparation

Ranitidine hydrochloride inclusion complexes were prepared using the encapsulation method [15]. Cyclodextrin suspensions were added to the ranitidine hydrochloride solution under continuous stirring. After 48 hours of stirring, solutions were filtered. The filtrate was then cooled at 4 °C overnight and lyophilized using an Alpha 1-2 LD (Christ, Osterode, Germany) freeze-drier. As a result, white, fluffy powders were obtained. Inclusion complexes in a molar ratio of 1:1 stoichiometry of RAN:CD - IC_1:1 and 1:2 stoichiometry, IC_1:2, respectively. Simultaneously, for comparative purposes physical mixtures (PM) were prepared by mechanical mixing substances with the same stoichiometry as for inclusion complexes (PM_1:1 and PM_1:2).

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1.2.2. Irradiation process

The amount of 1g samples of IC_1:1, IC_1:2, PM_1:1 and PM_1:2 were placed in a 20 mL glass vial and sealed with Parafilm. Blank samples were wrapped with aluminum foil. Samples were irradiated in a Suntest CPS+ chamber (Atlas, Gelnhausen, Germany) equipped with a Xenon lamp (1.1 to 1.5 kW) and an electronic device for measuring and controlling both irradiation and temperature inside the box. The solar ID65 standard according to guideline ICH was applied. The illuminance was set at a value of exposure power of 500 [W m^{-2}] for 48 hours.

1.2.3. Inclusion complex and physical mixture characterization

Both inclusion complexes and physical mixtures were characterized using the DSC method, as described previously [16], FT-IR, and nuclear magnetic resonance ^{1}H NMR, 2D-NOESY (Nuclear Overhauser Effect Spectroscopy), 2D-TOCSY (Total Correlation Spectroscopy) and 2D-ROESY (Rotation Frame Nuclear Overhauser Effect Spectroscopy).

Differential scanning salorimeter (DSC) analyses were performed using a Netzsch Phoenix DSC 204 F1 (Netzsch Gerätebau, Germany) equipped with an intercooler system. The samples (1.5–4 mg) were weighed and sealed into aluminum pans. The DSC runs were conducted over a temperature range of 25 – 300 °C at a rate of 10 °C min^{-1}. All tests were run under a nitrogen atmosphere. Thermograms are expressed as the function °C=f(mW), i.e. the temperature of the sample according to heating energy.

FT-IR spectra were recorded and analyzed in solid state using a Jasco 410 instrument (4000-650 cm^{-1} with 32 scans) and KBr pellets of solid samples were prepared using a minipress.

^{1}H NMR spectra were recorded in deuterium oxide (D_2O) on a Gemini Varian 500 MHz spectrometer using TMS as an internal standard at 298 and 305 K (2D-ROESY).

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Microscope images were performed using an Opta-Tech X 2000, equipped with a 9 MP Opta-Tech CMOS digital camera with Opta View software for data acquisition, version 7.1.0.4 (Opta-Tech, Poland). The morphology of samples was examined by means of a scanning electron microscope (Hitachi TM-1000, 198 Japan), with the accelerating voltage was 15 kV.

1.2.4. HS-SPME-GC–MS

The production of volatiles was monitored using the headspace solid phase micro-extraction and gas chromatography mass spectrometry method (HS-SPME-GC-MS) described earlier [5].

Briefly, about 200 mg of the test mixture was placed in a 4 mL glass vial and then sealed with Parafilm. Blank sample - vials containing the same material were wrapped with aluminum foil during the irradiation process. Preconditioned fiber was exposed to the headspace for 30 min at 40 °C. Following extraction, fiber was retracted and introduced into the injection port of a gas chromatograph for desorption (4 min).

Samples were extracted with the use of a carboxen/polydimethylsiloxane SPME fibre (CAR/PDMS, Supelco – 57318U, *d*f = 75 μm) conditioned before extraction in the injection port of a gas chromatograph at a temperature of 290 °C for 60 minutes.

GC–MS analyses were performed using a Varian GC-450 gas chromatograph (Varian Chromatography Systems, Walnut Creek, CA, USA) equipped with a 1079 PTV injector (Programmable Temperature Vaporizing) and a Varian 220-ms (Varian Chromatography Systems, Walnut Creek, CA, USA) ion-trap mass spectrometer. Experimental conditions were: column, 30 m×0.25 mm i.d.×0.25 μm film, VF-5ms (Varian); temperature programme: 35 °C, held for 4 min, increased at a rate of 10 °C min^{-1} to a final temperature of 290 °C and held for 4 min. Helium was employed as the carrier gas at a constant flow of 1 mL min^{-1}. The injector was operated initially in split-less mode for 4 min and then the split vent was kept open (1:20) to the end of the run. Injector temperature was held constant at 290 °C. The GC-MS transfer

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line and ion-trap temperatures were 270 °C and 170 °C, respectively. The ion-trap mass spectrometer was operated in electron impact ionization (EI) mode (70 eV). The mass range scanned in full-scan acquisition mode was *m/z* 30–350.

2. Results and discussion

2.1. Characterization of IC and PM of ranitidine with β-cyclodextrin

Ranitidine susceptibility to degradation is readily noticeable when exposed to humidity or light, as presented in Figs. 1 A1 and 1 A2 as the brown surface of the powder particles. There are also some published reports on the color changes of RAN from white and pale yellow to dark yellow, brown or russet [16,17]. The obtained inclusion complexes of RAN with CD were white and puffy and remained visually unchanged after irradiation (microscope), as presented. The results of SEM analysis were analyzed to investigate the morphologies of inclusion complexes and the physical mixtures of RAN and *β*-cyclodextrin both before and after photodegradation. Irregularly shaped particles are larger for IC than PM, while after photo-irradiation they both become slightly shredded (Fig. 1 - B4, C4). In the case of PM after photo-exposition, the image is almost the same. In contrast, a visible change in the morphology and shape of particles was observed in IC_1:1 freeze-dried products of CD, revealing an apparent interaction in the solid-state. Moreover, the shape of IC_1:1 (Fig. 1 - B3) confirms its amorphous form.

The analysis of thermograms provides interesting information about PM_1:1, for which four peaks can be observed at the temperatures 92, 147, 221 and about 250 °C, respectively (Table 1, Fig. 2A). The first peak (T_1) is characterized by a very high transition enthalpy of about 160 J/g. The enthalpy of the other two peaks is reduced to a value of about 30 J/g for the second (T_2) and to 5 J/g for the third peak (T_3). PM_1:2 (Fig. 2B) and PM_1:1 (Fig. 2A) samples show a similar course for thermograms. For PM_1:2 and PM_1:2_blank, a broad endothermic peak (T_1) with a maximum at about 97 °C is observed.

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For the PM_1:2_UV system, the maximum transition temperature (for T_1 peak) shifted approximately by 8 °C towards lower temperatures. For PM_1:2_blank and PM_1:2_UV, maxima of peaks occur at about 260 °C, in turn, for PM_1:2, this maximum is shifted towards lower temperatures (T_4 = 252 °C). Comparing the enthalpy of fusion for substances of PM systems, for T_2 peaks a reduction was observed in the enthalpy value for PM_1:2_blank and PM_1:2_UV systems as compared to PM_1:2. It is worth noting that the obtained systems are characterized by a closely related course, which may indicate their high levels of stability against UV radiation.

FT-IR spectra recorded for each sample - RAN, PM_1:1, and PM_1:2 - are presented in Supplementary Materials Fig. 1S.

The RAN spectrum presents several characteristic bands, also observed in PM_1:1. The spectrum of a physical mixture coincides with the spectrum of RAN between 2650 and 2450 cm^{-1}. The region of the spectrum of PM near wavenumber 1600-1100 cm^{-1} clearly consists of overlaid bands both for RAN and CD.

FT-IR spectra recorded for RAN and IC_1:1 are presented in Supplementary Materials Fig. 2S. The IC spectrum shows no characteristic bands for RAN in the ranges 3600-3200 cm^{-1}, and 3200-2500 cm^{-1}. Bands corresponding to CD indicate interactions between host and guest compounds. A clear and sharp band characteristic for RAN from C=N stretching vibration (originating from a nitro group) occurs at 1620 cm^{-1}. This may support the hypothesis that this region of RAN is located outside the cyclodextrin cavity in the inclusion complex, which is also confirmed by ^{1}H NMR ROESY. FT-IR spectra of inclusion complexes, as well as physical mixtures with RAN after photodegradation are presented in Supplementary Materials Fig. 3S. Samples after irradiation present no chemical damage either visually or on the infrared spectra.

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^{1}H NMR spectra were recorded for CD, RAN and IC and are presented in Fig. 3. Chemical shift differences for each RAN proton in IC_1:1 and IC_1:2 are typical for such supramolecular systems. Average shifts of particular protons of about 0.167 for IC_1:1 and 0.175 for IC_1:2 can be noted (Table 2).

2D-NOESY (Nuclear Overhauser Effect Spectroscopy) and 2D-TOCSY spectral plots of IC are presented in Fig. 4 and do not reveal any intermolecular cross peaks confirming an inclusion complex structure. Cross-peaks between protons of ranitidine itself are only observed for 4/3, 5/6, 3/(1 and 2), 6/7, 6/8 and 3/12 pairs of protons. Specific interaction between cyclodextrin protons and incorporated ranitidine are observed only on the 2D-ROESY spectrum (Fig. 3). Overlaid spectra with two specific places of interactions CD/1,2 and CD/7 (marked in green) are presented in Fig. 4. RAN protons of methyl groups 1 and 2 (Fig. 4) are bonded with the CD cavity, while the methylene group near the sulfur atom (number 7) is also incorporated in this inclusion owing to the observed CD/7 signal of interaction. Additional weak cross-peaks revealing interactions between protons of RAN (number 4 and 5) are presented in Figs. 3 and 4. This will probably provide an explanation for the photostability of the ranitidine inclusion complex.

2.2. GC-MS analysis

GC-MS chromatograms of irradiated bulk RAN serving as a positive control for the photodegradation process are presented in Fig. 5.

Comparing the number of peaks detected using the same methodology, we observed almost clear chromatograms. Reduced amounts of degradation compounds formed during exposure to light in comparison to the reference sample chromatogram of bulk RAN (Fig. 5). Significant changes between chromatograms recorded for irradiated samples in comparison to blank ones

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are presented in Fig. 6 both for 1:1 and 1:2 complex stoichiometry. The same mass spectra for all peaks were noticed during photodegradation in the cases of IC_1:1 and IC_1:2.

In the case of inclusion complexes, both 1:1 and 1:2 stoichiometry, the most intensive peak in the chromatogram was **I**, an acetaldoxime Rt=1.65 min. The following peaks were identified: **I, III** - thiazole Rt=4.60 min, **IX** - dimethylacetamide Rt=5.98 min, **VI** - dimethylformamide Rt=8.07 min and **XI** as 5-methylfurfural Rt=9.94 min [5].

In the current study, physical mixtures with the same stoichiometry as the inclusion complexes were also prepared and analyzed. In the scientific literature it is documented that, in some cases, even a small amount of cyclodextrins in the reaction mixtures or powders may significantly influence the final effect of the reaction, and specific processes and mechanisms of different chemical reactions. In such a way, it is also possible to achieve different physical or chemical properties of particular chemicals.

Physical mixtures containing RAN and β-CD were irradiated and further analyzed by a HS-SPME-GC-MS method. Surprisingly, acetaldoxime was the only product identified on the chromatograms of blank and irradiated samples of PM_1:1 and also PM_1:2. Peak intensity was significantly lower in PM than in IC.

Acetaldoxime is detected in most samples containing RAN and also the bulk one, but not in the blank sample of IC and bulk RAN after the freeze-drying process, which was performed in order to verify such circumstances. This effect may be related to the fact that it is so volatile that during the lyophilisation process it is completely removed from samples. However, it is generated during irradiation, also in blank samples (Fig. 6).

Reducing the amount of cyclodextrins in the physical mixtures from stoichiometry 1:1 to 1:0.1 was also tested in order to test photoprotective activity. These results indicate a not so

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spectacular protection of RAN during photo-irradiation, as is the case with PM_1:1. Fewer peaks are observed on the GC-MS chromatogram (Supplementary Materials Fig. 4S). It is important to underline the role of cyclodextrins in the stability of the solid sample physical mixture. Depending on the energetic system of the molecule occurring in the environment or surrounding CD (IC & PM) in the excited state induced by e.g. radiation, both an increased and an inhibited photodegradation effect can be observed [18]. The energetic system of ranitidine has not been described in detail; however, it is known which part of the molecule is sensitive to the quanta of electromagnetic radiation in the UV-Vis. Based on the positive photoprotection results observed for the particles and blocking against the emission of volatile degradation products for both IC and PM, we tend to conclude that both the change in the energy status of molecule, as well as the shielding of CD play a significant role. One should also mention that CDs are known for their high affinity towards volatile compounds [19]. It is therefore possible to inhibit or reduce the degree of volatility of unwanted molecules through their complexation [20]. It is highly probable that during the exposure of ranitidine, several photoprotection mechanisms occur simultaneously.

In effect, not so many photodegradation products are generated.

The beneficial role of β-cyclodextrins towards ranitidine photostability, observed as a decrease in the generation of volatile products during irradiation, is documented in this study. In physical mixtures, RAN is protected more efficiently than in inclusion complexes. The number of detected peaks in the PM chromatograms is lower than that for IC; moreover, these peaks are less intense. The results obtained for PM_1:1 and PM_1:2 both indicate quite comparable protective effects of cyclodextrins and appear very promising.

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The results obtained in this study indicate that ranitidine hydrochloride complexes with β-CD are more resistant to irradiation than free (bulk) RAN. This is a confirmation of the protective properties of cyclodextrins.

3. Conclusions

It can be concluded that the successful photoprotection of ranitidine in solid state due to the presence of cyclodextrins in the form of a physical mixture and inclusion complex was achieved. In the light of the qualitative research we performed, significantly reduced emissions of volatile degradation products were observed in the physical mixture of RAN compared to those obtained for free ranitidine after photo-irradiation. These observations are in agreement with visual and microscope images of irradiated samples of inclusion complexes and mixtures with β-cyclodextrin. Protection of ranitidine against photodegradation in such supramolecular systems could be explained due to the inclusion of the sulfur atom from the RAN molecule and also the furan part. Nevertheless, the screening effect of β-cyclodextrin in the physical mixture improved the statement of its protective properties. Moreover, no bad odor is any longer noticed for samples of RAN after irradiation.

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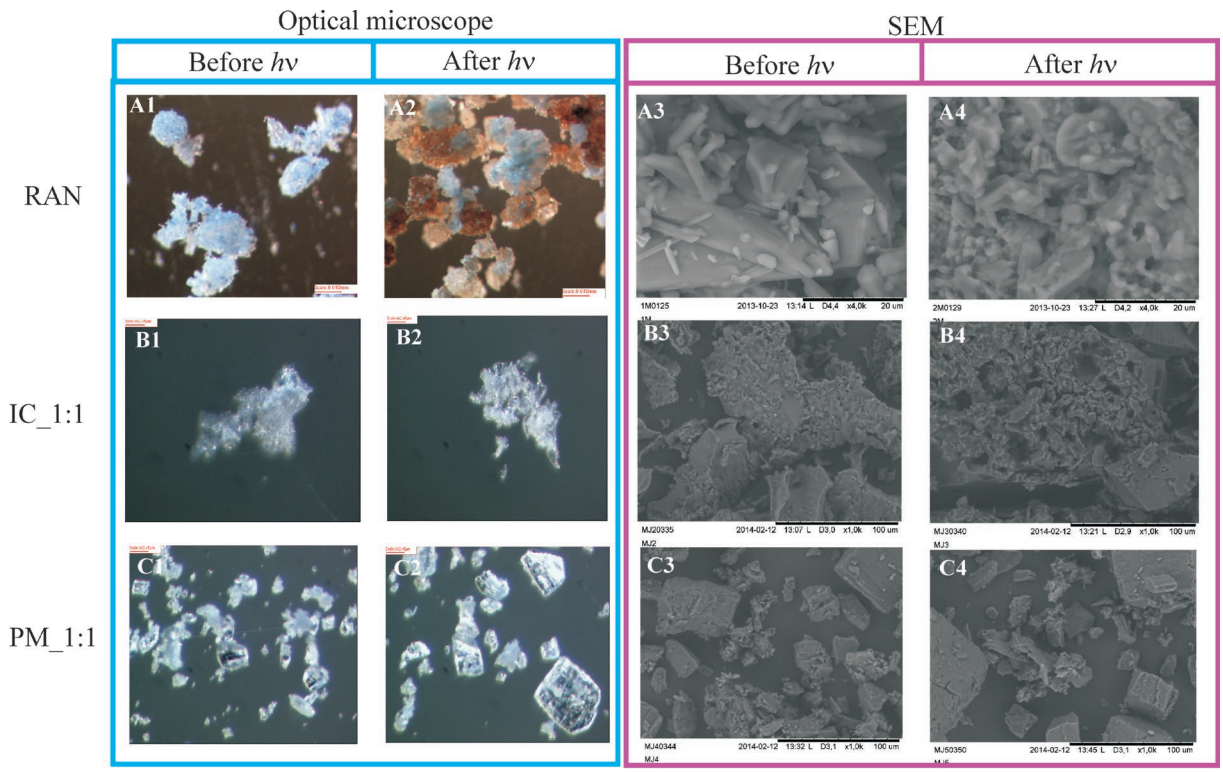

Fig. 1. Particles (1 and 2 - optical microscope; 3 and 4 - SEM) before (1,3) and after irradiation (2,4) of RAN (A), IC_1:1 (B), PM_1:1 (C)**.**

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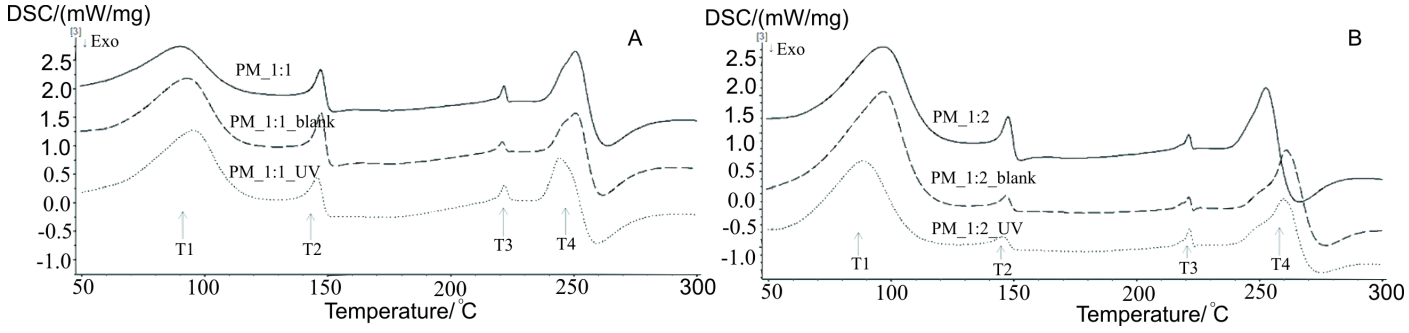

Fig. 2. DSC curves of PM_1:1 (A) and PM_1:2 (B) before and after irradiation.

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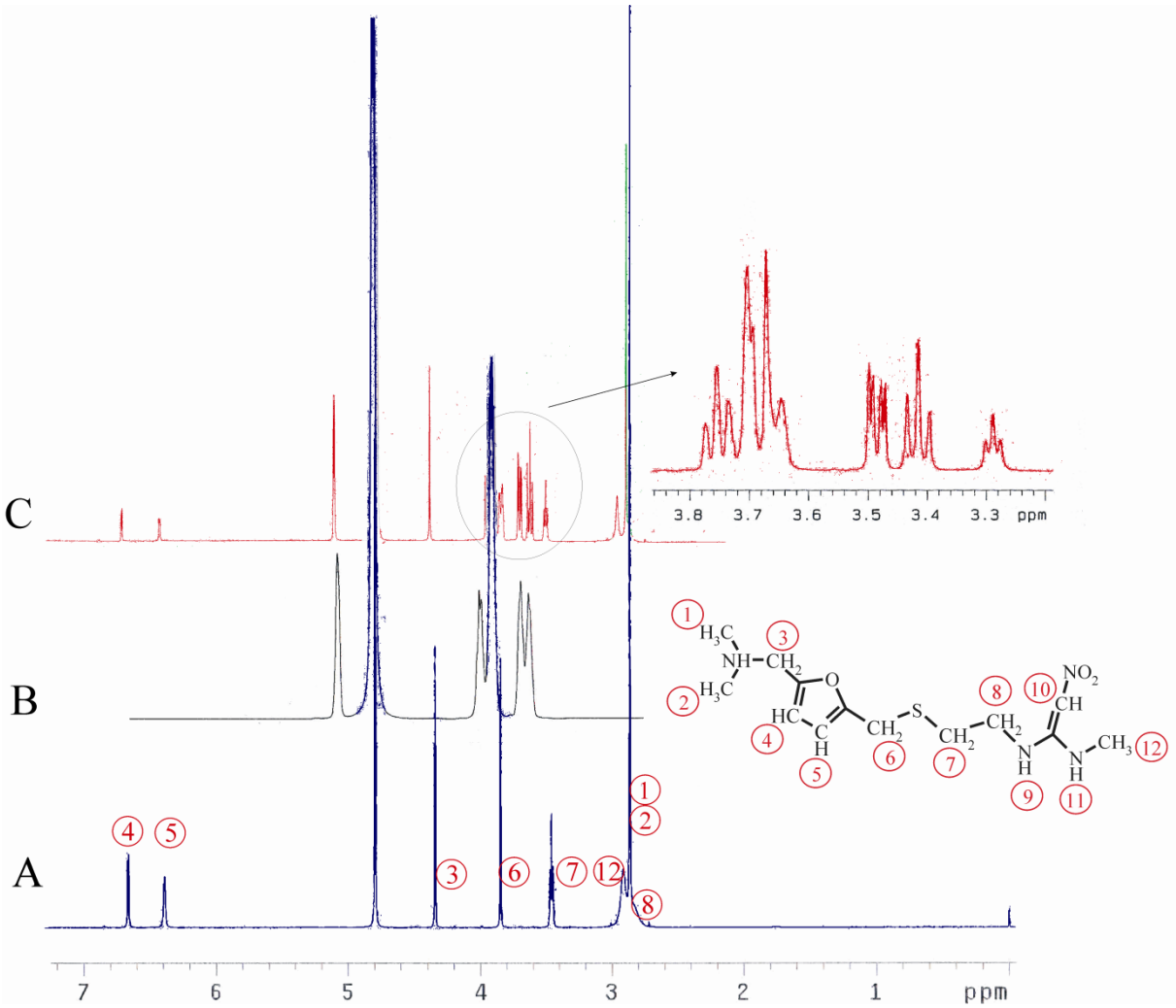

Fig. 3. ^{1}H NMR spectra of A) RAN, B) CD and C) IC_1:1.

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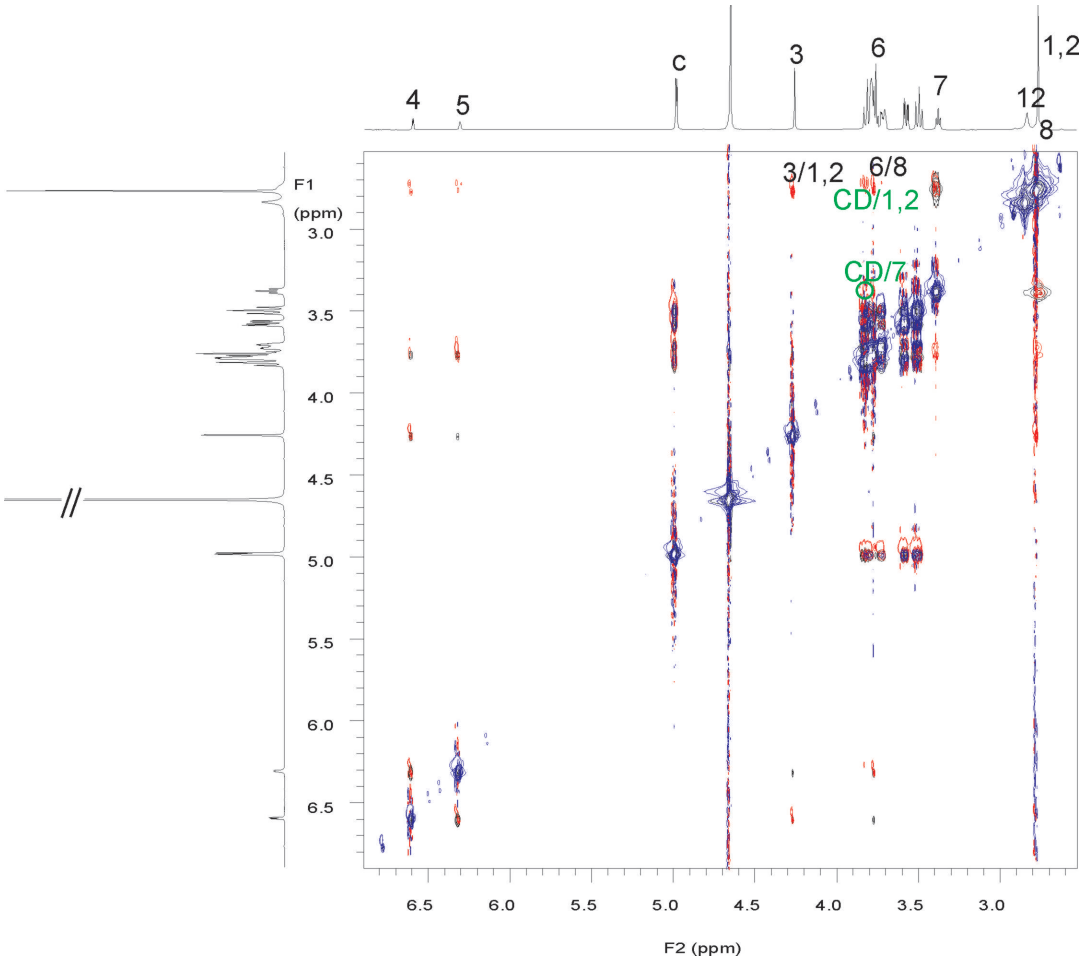

Fig. 4. Two dimensional overlaid spectra ROESY, NOESY and TOCSY of IC_1_1 and indicated interactions.

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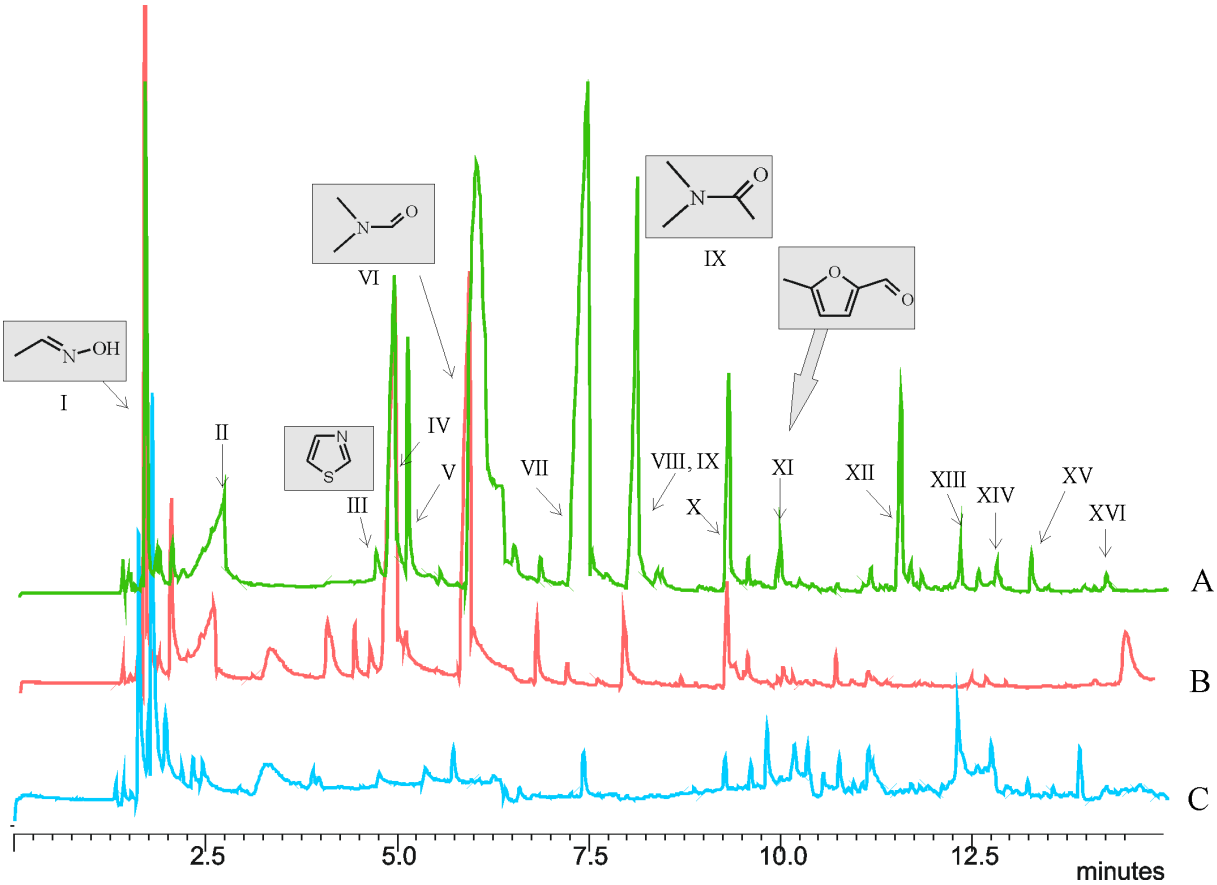

Fig. 5. GC-MS chromatogram obtained for A) bulk RAN; B) IC_1:1 and C) PM_1:1 powders after photo-exposition for 48 h in a Suntest CPS+ chamber and evaluated compounds. Roman numbers are described and identified [5].

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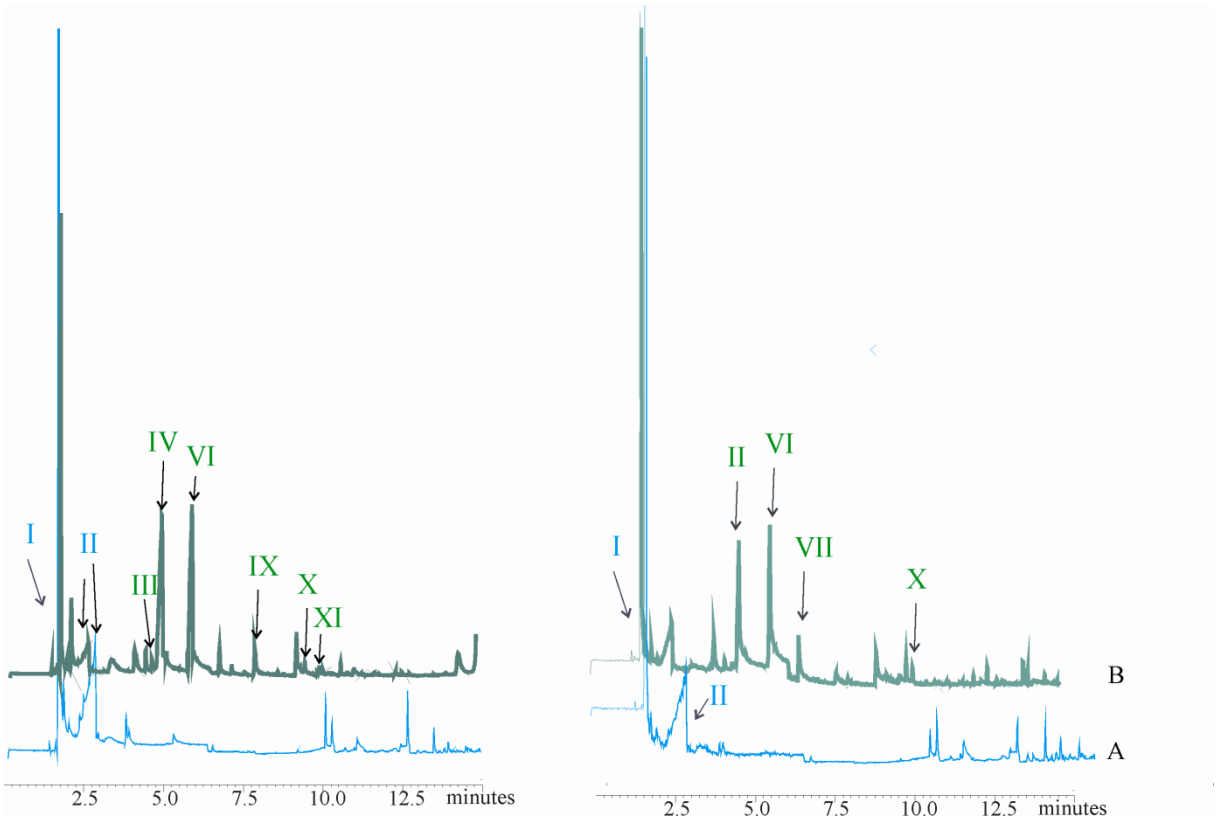

Fig. 6. GC chromatogram of organic compounds released during photo-excitation of IC_1:1 (left) and IC_1:2 (right). Roman numbers are described and identified [5].

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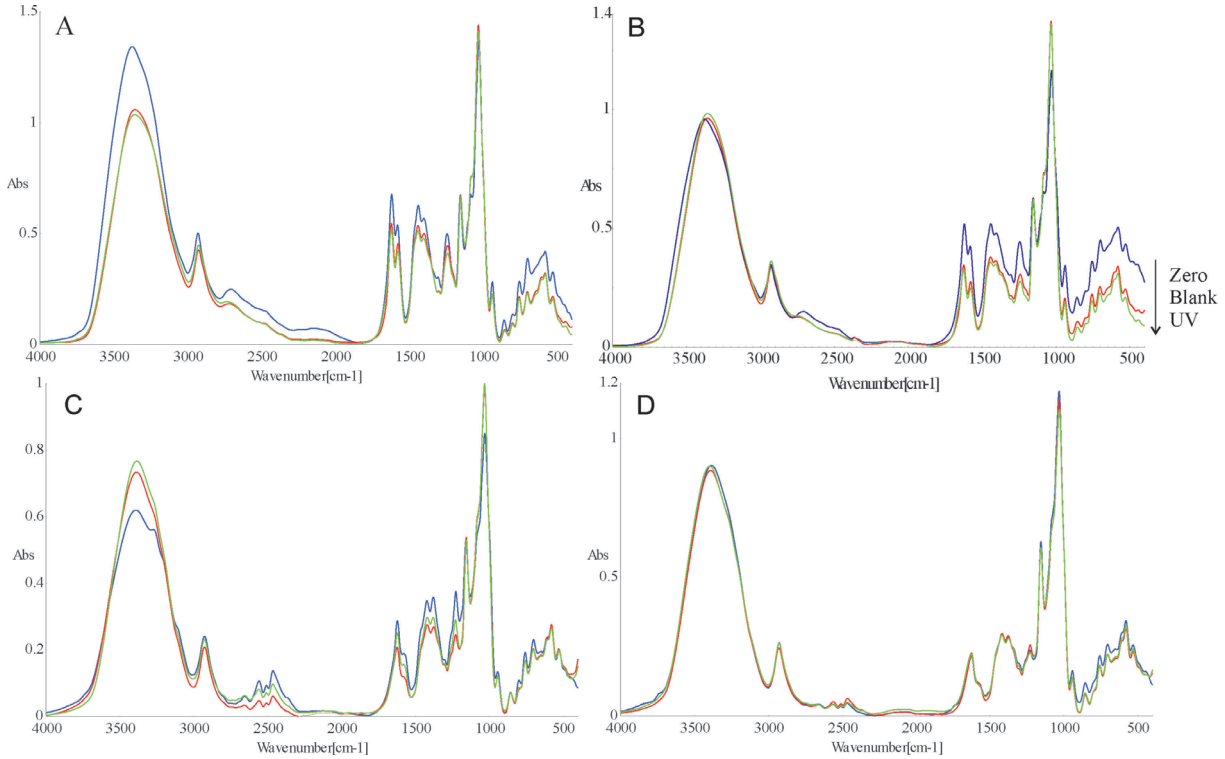

Fig. 7. FT-IR spectra of samples A) IC_1:1, B) IC_1:2, C) PM_1:1, D) PM_1:2 assigned as zero, blank and photoirradiated for 48 h.

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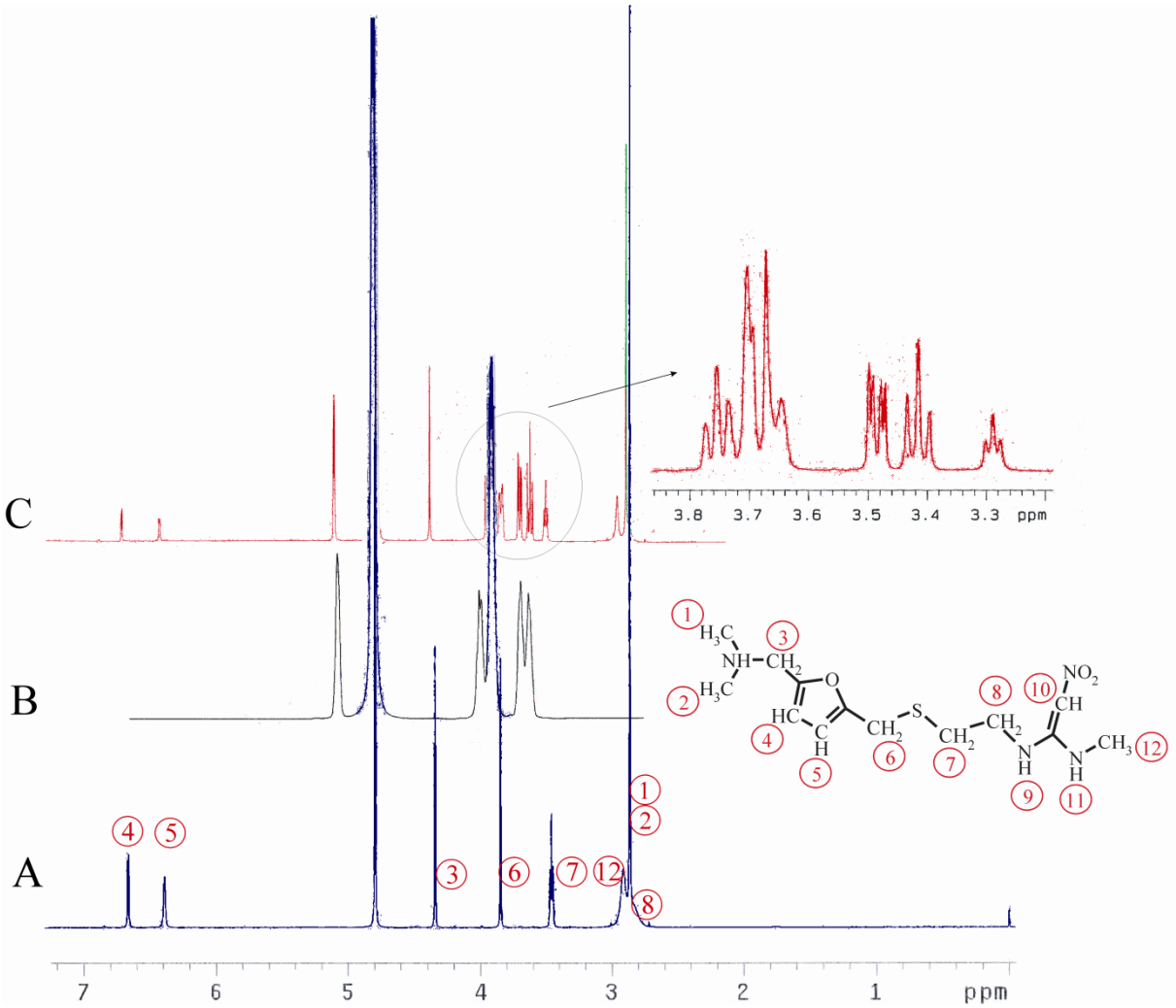

Fig. 8. ^{1}H NMR spectra of a) RAN, b) CD and c) IC_1:1.

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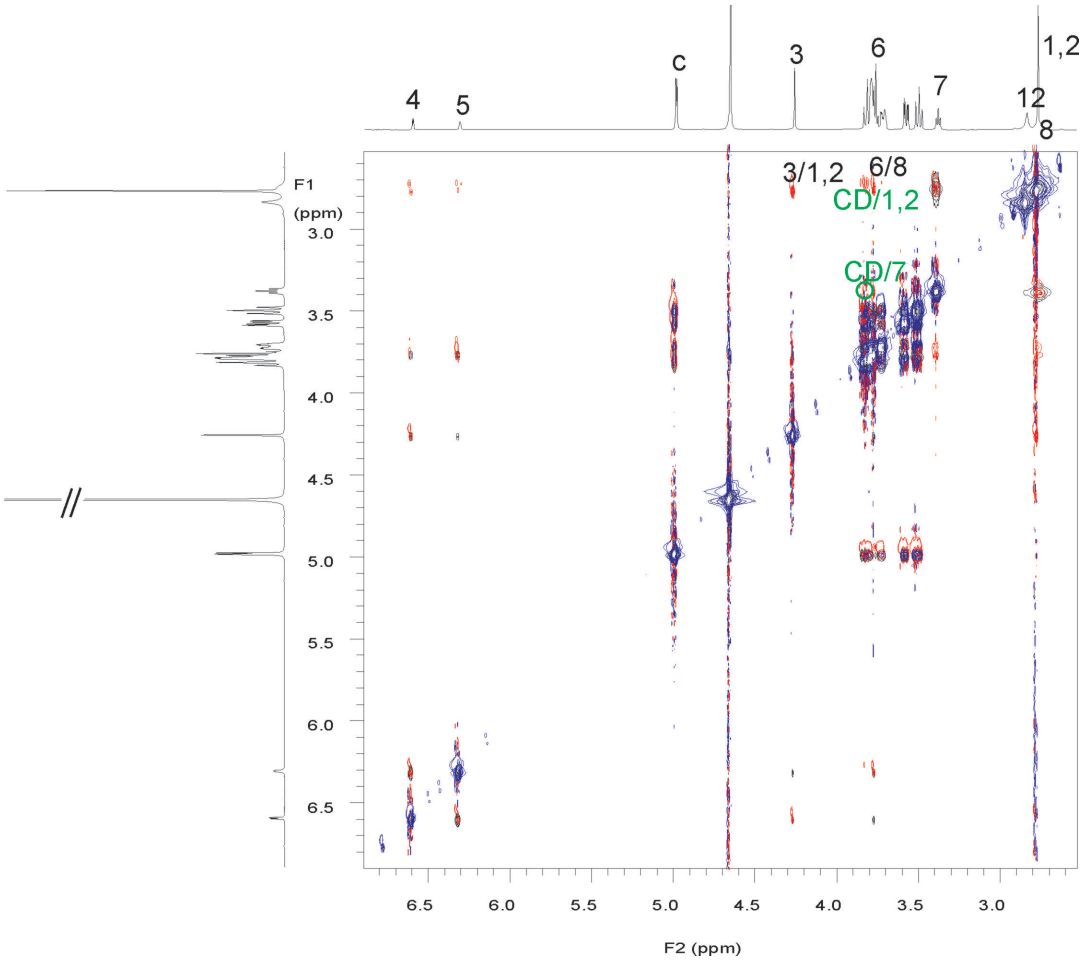

Fig. 9. Two dimensional overlaid spectra ROESY, NOESY and TOCSY of IC_1_1 and indicated interactions.

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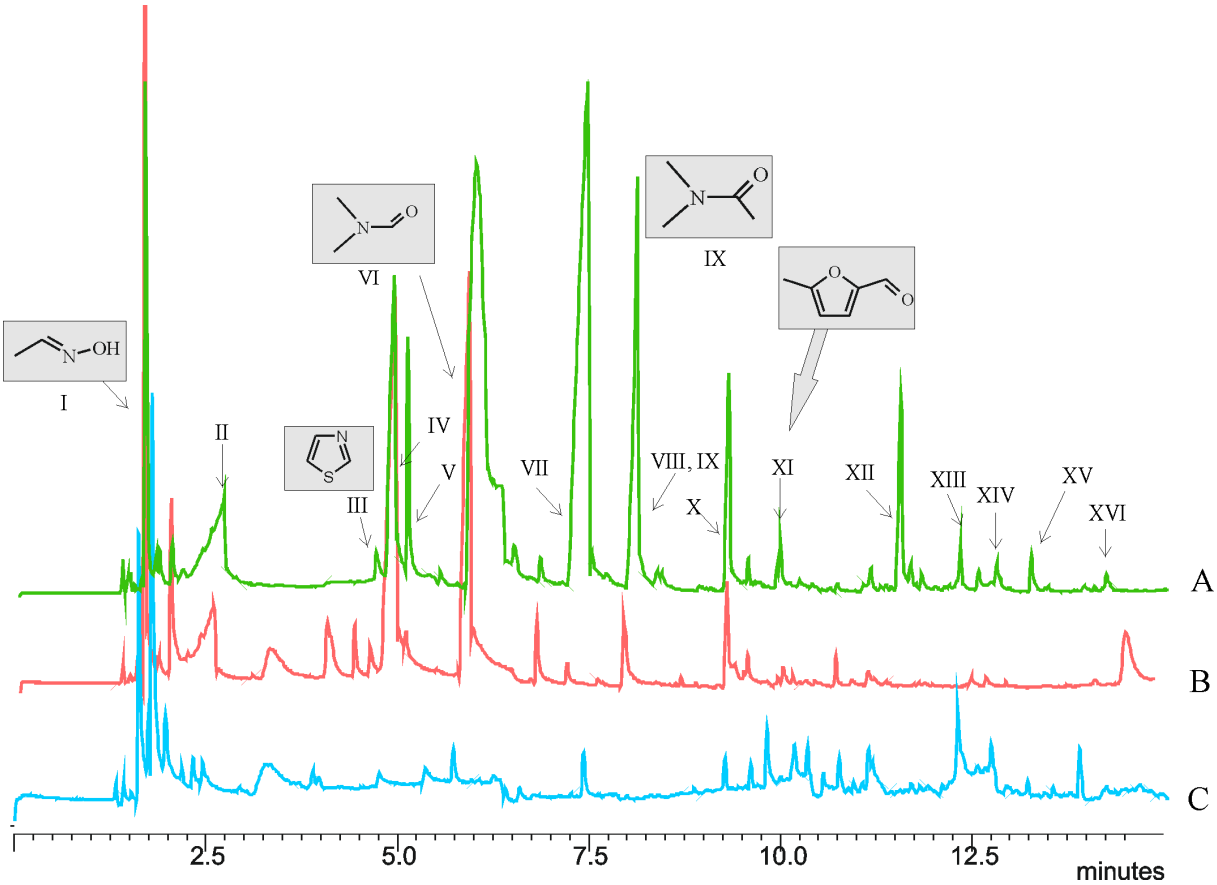

Fig. 10. GC-MS chromatogram obtained for A) bulk RAN; B) IC_1:1 and C) PM_1:1 powders after photo-exposition for 48 h in a Suntest CPS+ chamber and evaluated compounds.

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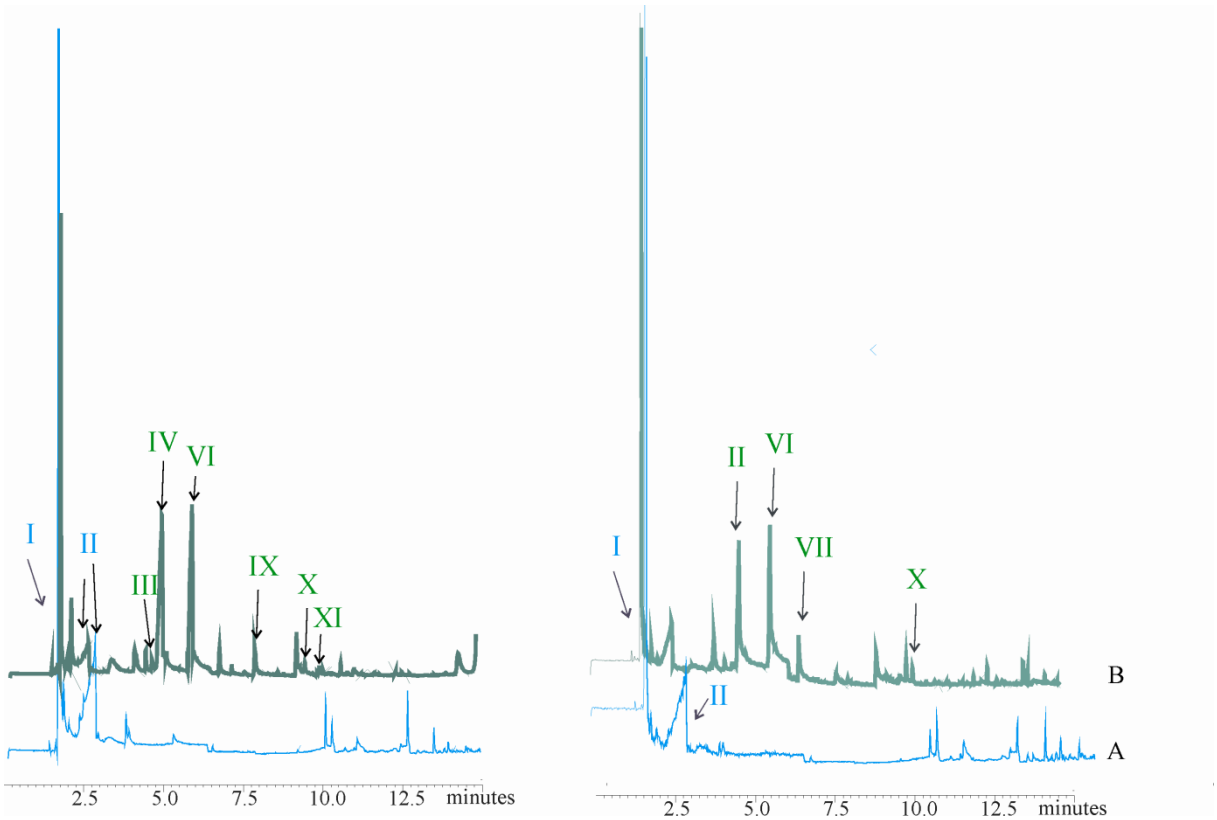

Fig. 11. GC chromatogram of organic compounds released during photo-excitation of IC_1:1 (left) and IC_1:2 (right).

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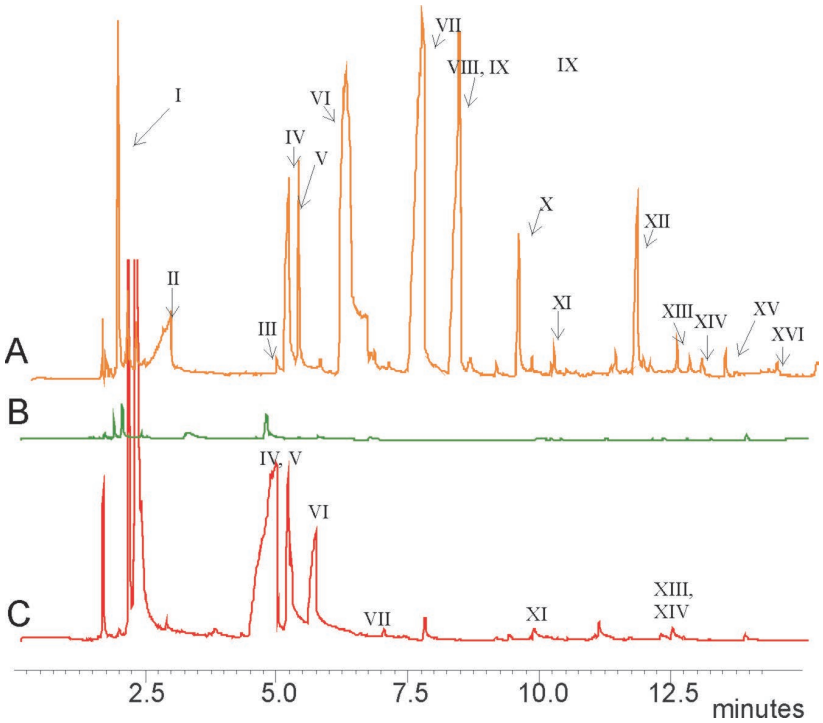

Fig. 12. GC-MS chromatogram of irradiated samples for 48h: A) RAN, B) PM_1:1 and C) PM_1:0.1

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Table 1. Summary of the peak maxima and the enthalpy change for PM mixtures registered using DSC.

Sample	Peak maxima [°C] T_1; T_2; T_3; T_4	Enthalpy changes [J/g] T_1; T_2; T_3
PM_1_1	90.1; 147.2; 221.8; 250.6	155.7; 26.8; 4.6
PM_1_1_blank	92.9; 147.2; 221.2; 250.9	157.0; 32.7; 4.0
PM_1_1_uv	95.1; 145.8; 222.0; 244.2	218.4; 29.7; 6.3
PM_1_2	97.4; 147.5; 221.3; 252.9	171.7; 18.7; 3.4
PM_1_2_blank	96.8; 146.7; 221.4; 250.6	277.7; 6.6; 3.1
PM_1_2_uv	88.9; 145.4; 221.7; 259.5	137.7; 7.4; 4.2

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Table 2. Chemical shifts (^{1}H NMR) of proton signals for RAN, inclusion complexes IC_1:1, IC_1:2 [ppm].

Assigned protons of RAN	**Chemical shifts [ppm]**		
	RAN	**IC_1:1**	**IC_1:2**
4	6.670	6.504	6.495
	6.663	6.498	6.490
5	6.392	6.222	6.218
3	4.343	4.168	4.159
6	3.849	3.704	3.703
7	3.471	3.435	3.434
	3.458	3.417	3.415
	3.446	3.397	3.395
12	2.914	2.751	2.746
1,2,8	2.865	2.678	2.672

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Evaluation of photoprotective effect of β-cyclodextrin on the emission of volatile degradation products of ranitidine

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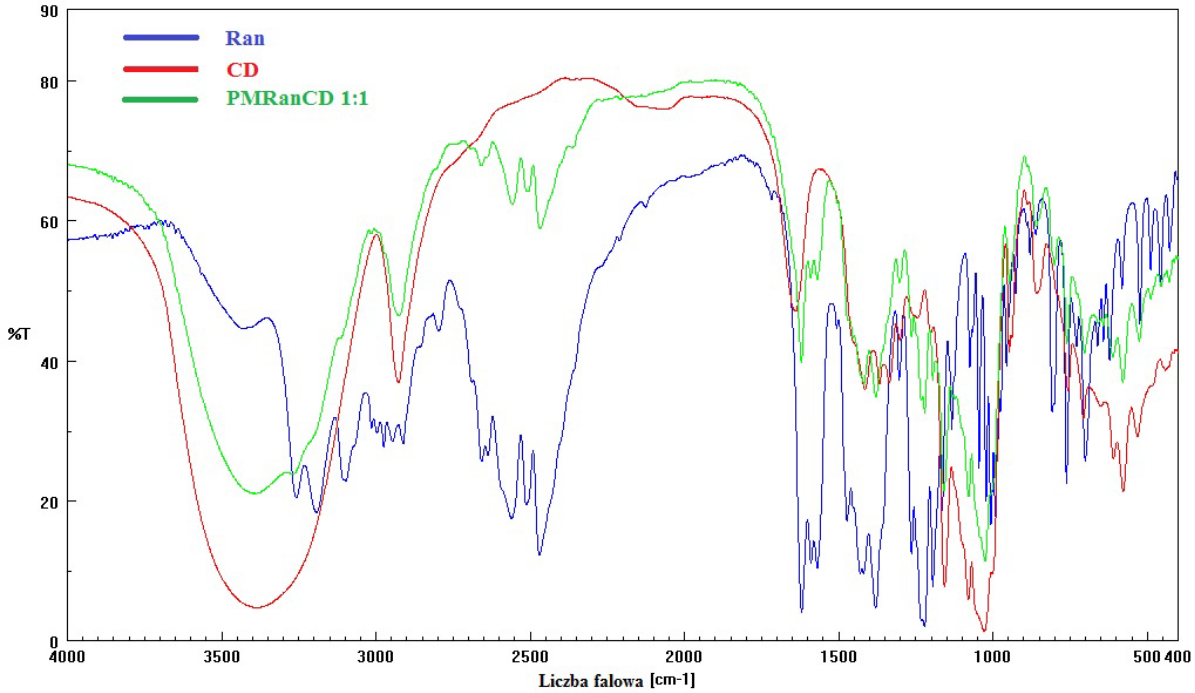

Fig. 1S. FT-IR spectra of RAN, CD and PM_1:1.

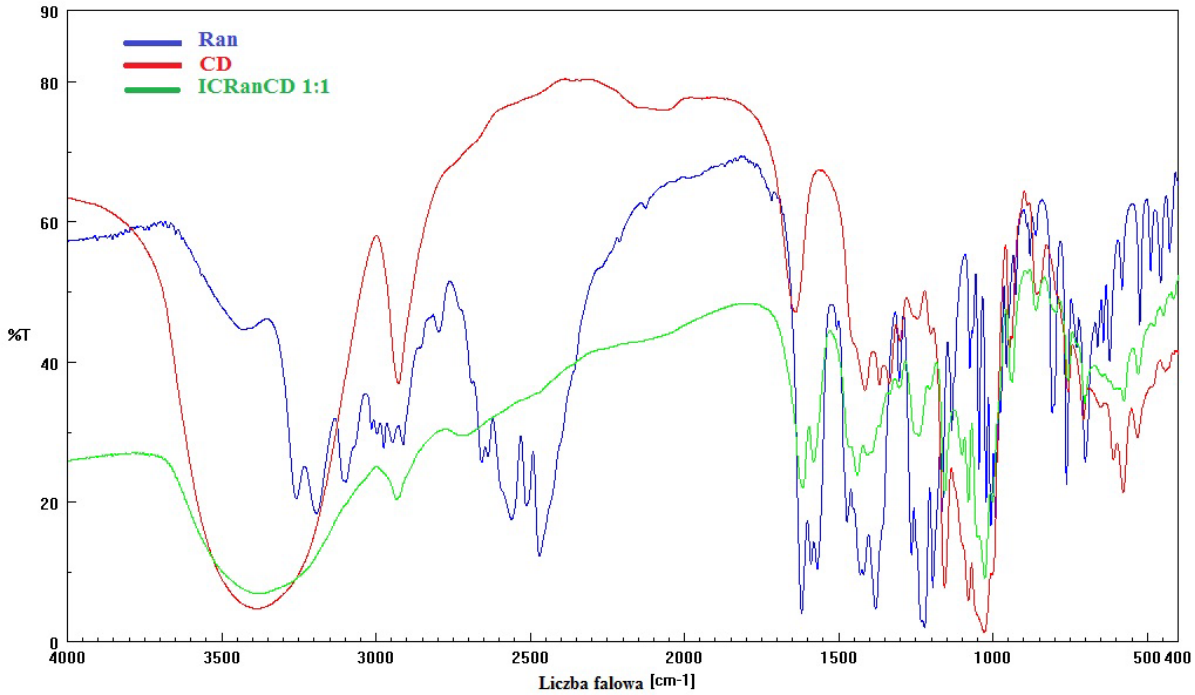

Fig.2S. FT-IR spectra of RAN, CD and IC_1:1.

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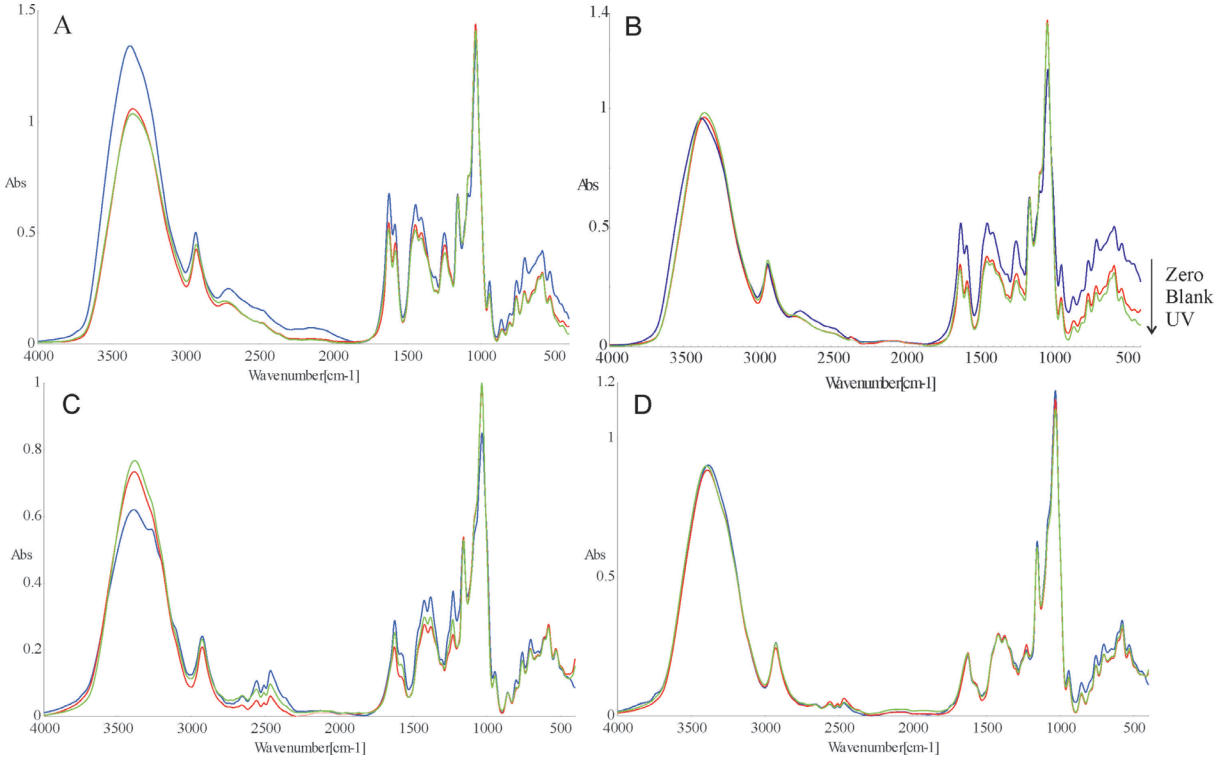

Fig. 3S. FT-IR spectra of samples A) IC_1:1, B) IC_1:2, C) PM_1:1, D) PM_1:2 assigned as zero, blank and photoirradiated for 48 h.

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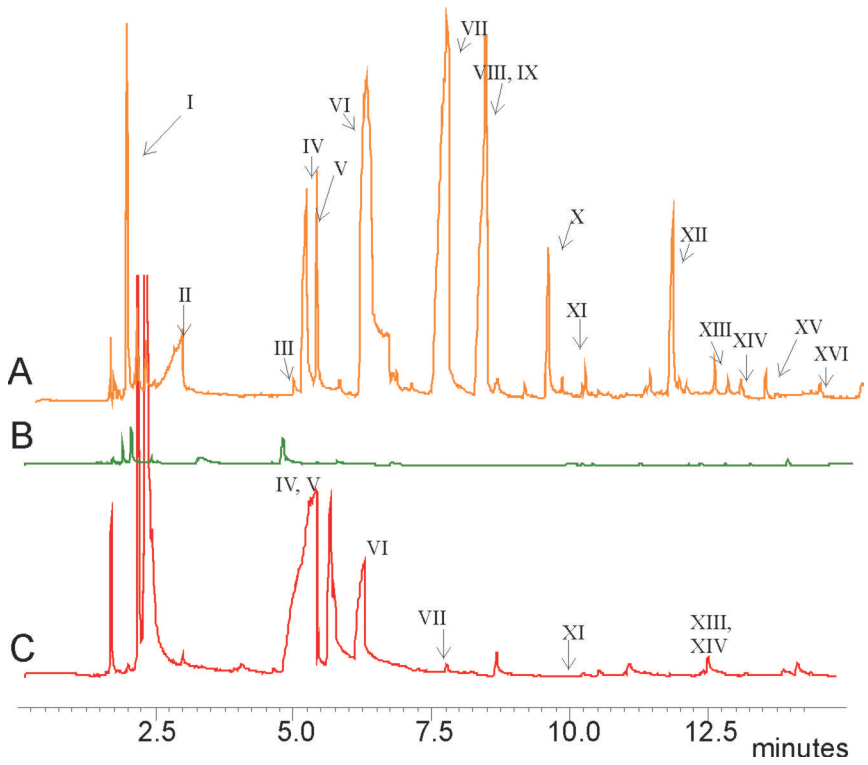

Fig. 4S. GC-MS chromatogram of irradiated samples for 48 h: A) RAN, B) PM_1:1 and C) PM_1:0.1. Roman numbers are described and identified [5].

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