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Short Term Monitor of Photodegradation Processes in Ranitidine Hydrochloride Observed by FTIR and ATR-FTIR

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ABSTRACT

The effects of degradation of ranitidine hydrochloride exposed to UVB radiation (λ = 310 nm) and oxygen in a weathering chamber were studied by Fourier Transform Infrared spectroscopy (FTIR) and Attenuated Total Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR). ATR-FTIR profile indicated that the degradation was spatially heterogeneous. Significant amounts of photoproducts were detected only in a directly irradiated layer. Major damage/change was reflected in the appearance of broad, extended group of signals near the wavenumber 3600-3200 cm^{-1} or/and 3500-3400 cm^{-1}. We examined whether FTIR-ATR technique is a great tool to observe the simplest and the first changes on the surface of a substance in powder.

Key words: photodegradation, Fourier Transform Infrared Spectroscopy, ATR, ranitidine hydrochloride

INTRODUCTION

Stability of a drug preparation has to be analysed under practical use conditions[(1)]. Therefore, commercially available forms (tablets, capsules, and suspension etc.) are examined inside and outside packages. Very often the samples are tested during long time and/or under drastic conditions. Sometimes quick information about quality is needed especially in a solid-state substance. Accelerated testing is widely used for the prediction of storage stability and quality, estimation of shelf-lives, and safe storage temperatures of labile products[(2)]. In the food, pharmaceutical and biotechnology industries, products are stressed by testing at high temperatures. The results are then extrapolated to normal storage conditions. Therefore, FDA and other regulatory agencies require such methods to be well designed[(3)]. Screening chemical change of a drug or substance used for drug preparation is usually slow, complicated or expensive method. A conventional way to attain knowledge of chemical substances stability is to identify any ongoing degradation process by means of spectral (MS, NMR, IR, etc.), elemental analysis or chromatography LC, TLC, HPLC[(4)]. Many operations are need before each analysis. Fourier transform infrared spectroscopy (FTIR) is a valuable tool for monitoring such processes in the solid state[(5)]. Unfortunately, it is not a very popular method in pharmacy. No Pharmacopoeia suggests FTIR analysis for drug degradation products. Changes generated after damaging exposition onto different factors (e.g. light, humidity, temperature, and pH) cause transformations with functional groups that show characteristic fingerprints in the IR spectrum. It is also useful to record any changes caused directly on the surface of irradiated compound (or material) on reflection spectra and subsequently on transmission spectra because the spectral path length and the optical density accordingly are too large. This is a fast, relatively cheap and well known method. On the other hand, it has been proven recently that Attenuated total reflectance – Fourier transform infrared spectroscopy (ATR-FTIR) is very practical for fast estimation of polymer surface changes during environmental degradation[(6)], for the study of films subjected to a solution of a drug[(7)], real-time monitoring crystallization processes[(8)] as well as synthesis or adsorption[(9)].

Factors determining the chemical stability of drug substances include intrinsic factors such as the molecular structure of the drug itself and environmental factors, such as temperature, moisture, pH, buffer species, oxygen, ionic strength, and light. Light is an omnipresent factor and very difficult to avoid especially during drug production process. Chemical consequences after drug exposition on light might be detected after a long time and subsequent processes causing radical formation, energy transfer, luminescence and possible generation of dramatic therapeutical effect[(10)]. Drugs can become

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photoreactive just upon administration to a patient. Sometimes the interaction of sunlight with pharmaceutical agents results in toxic reactants which are transported in the blood system[11]. Therefore, the first structural change of drug compound should be recorded as fast as possible.

Ranitidine hydrochloride is a representative example of a very unstable drug component[12]. Humidity, high temperature, light and atmospheric gases (oxygen) bring about the essential structure changes of ranitidine hydrochloride[13-15]. The aim of this work was to show the early changes on the surface of solid state drug substance – ranitidine hydrochloride, after either irradiation or spectrophotometric tests.

N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl] methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine is an H_2 receptor antagonist recommended for the treatment of peptic ulcers[16]. Its chemical structure (Figure 1-I), amine and nitro groups cause many problems, especially during storage[17]. Degradation products or its impurities are sources of bad odour and dark colour on the surface of powder compound. The reactive properties of the substituted 2-nitro-1,1-vinyldiamino entity allow different hydrolytic behaviours of the ranitidine molecule under acidic and alkaline conditions[18]. In solution it undergoes a fast exchange at room temperature, with pseudo-first order pH-dependent kinetics[19]. It has been proven that ranitidine was also degraded in direct photolysis experiments under summertime sunlight at noon[20]. In literature there are no examples of assignation photodegradation process of ranitidine in its solid state. There were tested pharmaceuticals containing ranitidine hydrochloride (40°C, 75% RH, with and without light). Stability of those drugs and total percentage of degradation products were determinated by HPLC method[21]. Ranitidine hydrochloride powder was also tested in different humidity (70, 85, 96, 100% RH) and temperature conditions (45, 55, 65°C)[22]. Generally, ranitidine hydrochloride is described by spectroscopic methods[23]. In the FTIR spectrum, the most labile and changeable regions of wavenumber are those responsible for the presence of amine groups stretching N–H at 3325-3050 cm^{-1}, free –NH at 3270-3200 cm^{-1} and dimethylamino groups give bands at 2820-2780 cm^{-1} [24].

In our experiment on ranitidine stability we used a weathering chamber with a xenone lamp as irradiation source.

MATERIALS AND METHODS

I. *General*

Ranitidine HCl (polymorphic Form 2) bulk powder was purchased from POLPHARMA SA Pharmaceutical Works (Poland). Potassium bromide (anhydrous) was

Signed on spectrum	Wavenumber [cm^{-1}]	Interpretation
A	3260	NH
	3190	NH
B	3100	NH
	3066	CH furane
	3017	CH furane
C	2970	CH aliphatic
	2950	CH aliphatic
	2908	CH aliphatic
	2653	NH
D	2560	NH
E	1620	NH
	1590	NO_2
F	1570	NH
	1472	CC
	1428	CC
G	1380	NO_2
H	1226	CN
	1137	CN
	990	CH
J	806	CH
K	760	CH

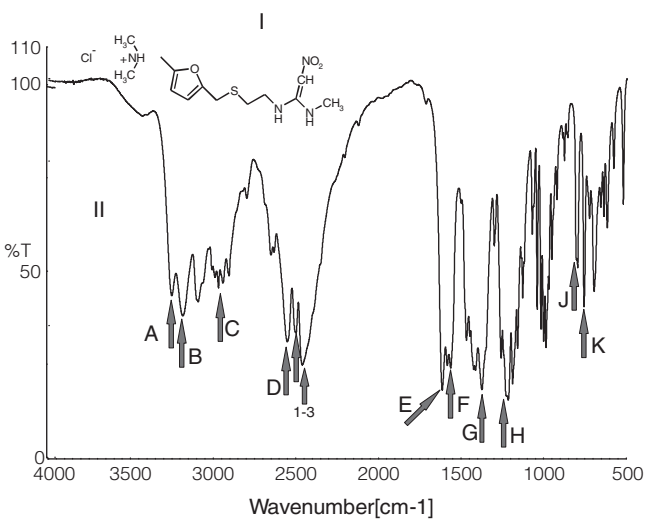

Figure 1. Structure of ranitidine hydrochloride (I) and FTIR spectrum (II) with characteristics (III).

supplied by Merck (Poland). All other chemicals were of analytical grade.

II. *Samples for Irradiation Process*

Prepared material needed the same area for irradiation and for each technique of recording FTIR spectrum. Therefore, the accurately weighed ranitidine hydrochloride powder (1 mg plus potassium bromide to 100 mg) was compressed to discs using hydraulic press machine (Riken Seiki Co., Ltd. Japan) equipped with flat-faced punches and cylindrical die (13 mm i.d.) set a compression force at 10 Mpa; obtained discs were used to record transmission spectra after exposition to light. The pieces of carrier – matt adhesive tape stripes (100 mm × 20 mm, not tracing, not transparent or crystal) were thoroughly covered with 10/15 mg of ranitidine hydrochloride on the whole adhesive part of the tape. The obtained materials were used to record reflection spectra after exposition to light.

III. *Tested Parameters*

Changes in absorption values (ΔA) were studied in the spectral range 4000-900 cm^{-1} between spectrum of not irradiated ranitidine and ranitidine irradiated for a long time.

IV. *Irradiation*

Sample discs and sample adhesive tapes (containing ranitidine hydrochloride) were exposed to UVB irradiation in a Suntest CPS+ Atlas chamber (Accelerated Tabletop Exposure Systems, Germany) equipped with xenone lamp (1.1 to 1.5 kW) and two filters: special window glass and Solar ID65, applied together. Exposure behind window glass is accurated for photostability testing (Indoor Indirect Daylight) of pharmaceutical products according to ICH guideline[1] "Photostability Testing of New Drug Substances and Products". The illuminance was set at two values of exposure power: 280 and 700 [W/m^2] at time (1, 2, 3, 5, 10, 13 15, 30, and 24, 48, 120 h). The irradiation tests were carried out at 25-45°C (respectively to the values of energies). Relative humidity was the same during our investigation.

FTIR spectra of the sample discs were obtained in transmission technique by FTIR-410 Jasco spectrometer (Jasco Corporation, Japan). The spectral data were transformed by normalized function. ATR-FTIR spectra of ranitidine hydrochloride put precisely on adhesive tape and glue were obtained with the horizontal attenuated total reflectance (HATR) accessory (reflectance technique). The internal reflecting element (IRE) was a ZnSe crystal. Spectra were collected in the range 4000-650 cm^{-1} with 32 scans. Acquired spectra were first corrected for background based on the signal recorded for the same ATR crystal, but without the adhesive tape with ranitidine hydrochloride.

RESULTS AND DISCUSSION

This paper presents the possibilities of detecting the very quick photodegradation process in ranitidine hydrochloride by FTIR and ATR-FTIR techniques. We compared the non-irradiated spectra and spectra of drug substance after exposure to light. The most important goal of this study was to choose a FTIR technique that is suitable for monitoring changes on the surface of the substance after contact with ultraviolet irradiation. Our work might be useful to exploit during storage process after synthesis. Furthermore, we committed FTIR method to avoid solution preparation. Destruction of ranitidine determination is carried out only in the solid state.

Firstly we irradiated discs and tapes with ranitidine hydrochloride in the lowest power of weathering chamber 280 W/m^2 for 1, 2, 3, 5, 10, 13 and 15 hours. Afterwards, we prolonged the exposure time to 60 hours and observed ranitidine FTIR and ATR-FTIR spectra after 30, 45 and 60 hours. Lastly, we destructed ranitidine during 120 hours of irradiation.

FTIR spectra of irradiated drug did not give any noticeable difference below 30 hours of irradiation with the exposure power 280 W/m^2 (Figure 2). Discs contained ranitidine and absorbed irradiation but transmission spectra was not sensitive enough for such changes in the whole recorded disc. In a case of tape irradiation, the initial differences between the spectrum of non-irradiated and irradiated drug substances were observed very soon, after 15 hours (Figure 3). The substance in the probes likely intensified the results on the ATR/FTIR spectra. Tapes contained ten times more a substance then discs with KBr. Therefore, effect of a change on the surface of substance was detectable in a very short time (few hours) using the reflection technique. The most sensitive region for absorption changes after irradiation was 3600-2400 cm^{-1}, indicating an increase of absorption values. In addition, the region near wavenumber of 1800-1000 cm^{-1} has changed. A new band has risen at 1670 cm^{-1}. Bands generally maintained their shape and character, but their peaks were very difficult to identify due to extending nature of a region near 3600-2400 cm^{-1}.

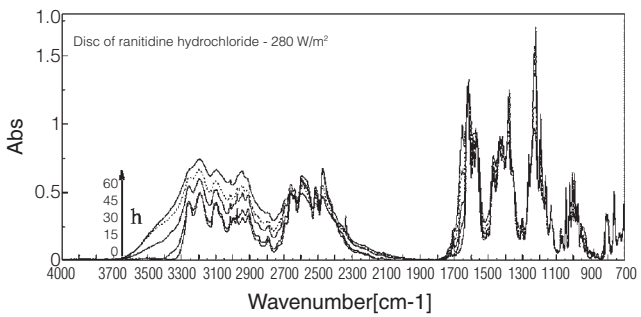

Figure 2. Transmission FTIR for ranitidine hydrochloride irradiated with the exposure power of 280 W/m^2 up to 60 hours.

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Ranitidine hydrochloride irradiated for 60 hours (P = 280 W/m²) showed considerable differences in either the surface or investigated probes. Transmission technique illustrated spectral changes in ranitidine especially in region of 3600-2400 cm^{-1}. Spectrum did not lose its character. Bands were well shaped but absorption values increased (band at 3200 cm^{-1}) by 50%. From equations (1) and (2), we estimated the absorption changes after exposure.

$$\frac{A_1}{A_0}\cdot 100\% \quad (1)$$

$$\frac{A_0 - A_1}{A_0}\cdot 100\% \quad (2)$$

A_1 - absorption value for irradiated substance
A_0 - absorption value for not irradiated substance

The first consequence from exposing ranitidine to light was clearly shown on the irradiated layer (surface of the tape). Two-fold duration of drug photodegradation was needed to create changes on FTIR spectrum comparing with fast answer in ATR spectrum. To examine the amount of photodegradated drug substance simply and quickly, it was better to record ATR spectrum, in which increase of absorbance could be attributed to degradation product.

There were two independent experiments performed for agent impact assessment in photodegradation of ranitidine hydrochloride, in terms time and amount of energy consumed. Firstly all probes were continuously irradiated for 60 hours in the Atlas chamber 280 W/m^2. Secondly the probes were irradiated for 24 hours in the Atlas chamber 700 W/m^2. The same amount of energy of 60 and 48 MJ/m^2 was used. Radiant exposure was irradiance integrated over time. Therefore, the following equation applies:

$$E[\frac{J}{m^2}] = \frac{P[W]}{S[m^2]}\cdot t[\text{sec}]$$, where E = energy, P = power of the weathering chamber, S = area, t = time, J = joule, W = watt, m = meter.

Recorded spectra (transmission and reflection) indicated no differences in the results. Amount of energy used was the only factor creating changes in ranitidine hydrochloride which ultimately led to photodegradation.

Finally we irradiated discs and tapes with ranitidine hydrochloride in the power of weathering chamber 700 W/m^2 24, 48 for 120 hours to achieve total degradation of ranitidine. Spectacular changes on spectrum for photodestructed ranitidine are shown in Figures 4 and 5.

Bands were blurred in the range of 3600-2800 cm^{-1} most of and gradually disappeared in the range of 2700 to 2350 cm^{-1}. A new band arose in 1675 cm^{-1}. Changes were so huge from the spectrum of non-irradiated substance that we obtained significantly (in average about 80% - obtained from equations 1 and 2) different spectra.

The main objective of this work was to monitor ranitidine HCl photodegradation by FTIR method. Particularly, we studied ATR-FTIR, previously described in a case of analysis ranitidine HCl determination[25-30]. Generally, researchers used this technique to study polymorphism of ranitidine HCl. Presented above results (FTIR analysis) might suggest a change of polymorphic Form 2 of ranitidine hydrochloride into Form 1. Specific peak of Form 2-1045 cm^{-1}[29] and its decreasing intensity on the FTIR spectra of tested samples during irradiation process could be responsible for polymorphism change. On the other hand, another characteristic peak

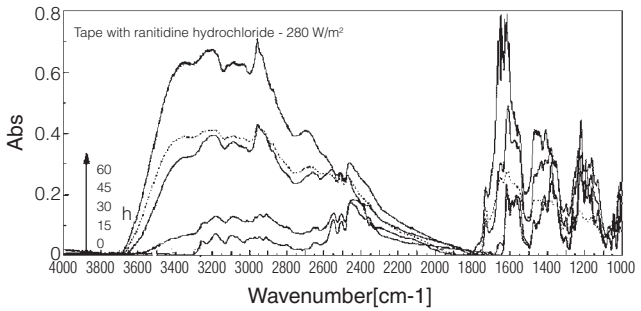

Figure 3. ATR-FTIR for ranitidine hydrochloride irradiated with the exposure power of 280 W/m^2 up to 60 hours.

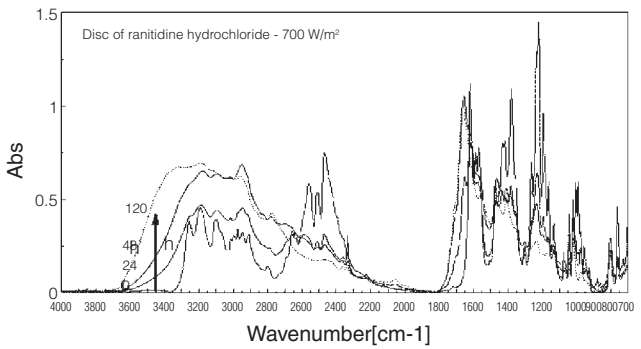

Figure 4. Transmission FTIR for ranitidine hydrochloride irradiated with the exposure power 700 W/m^2 up to 120 hours.

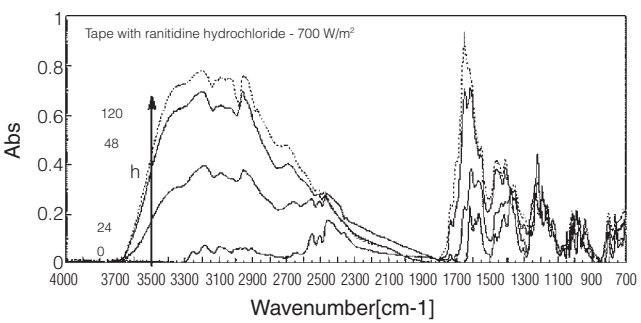

Figure 5. ATR-FTIR for ranitidine hydrochloride irradiated with the exposure power 700 W/m^2 up to 120 hours.

of polymorphic Form 2-1620 cm^{-1}[30] was stable. ^{13}C NMR analysis of the photodegradated sample proved lack of changes in polymorphic Form 2. ^{13}C NMR and melting point of tested samples contradicted that observed process is a polymorphic form change, but a photodegradation process. The most important difference in polymorphic Forms occurred at about 100 ppm - C(2) which was the carbon with nitro group[25]. In this region, the spectrum of Form 1 showed a singlet whereas as opposed to a doublet in Form 2. In our case, spectrum was always doubled either before or after irradiation of samples. Another region to verify polymorphic forms was at 24-25 ppm, where the spectrum was a singlet in Form 1 and a doublet in Form 2. Note that we might observe two doublets in each regions in determinated and irradiated ranitidine hydrochloride. Extensive work was being continuated in a subject of choosing other analytical methods (NMR or CE) suitable for photodegradation detection of a solid-state ranitidine hydrochloride.

During irradiation procedure with the highest power of weathering chamber P = 700 W/m^2, we observed increased temperature up to 45°C. We checked how this increased temperature changed ranitidine hydrochloride itself and also its spectrum using FTIR techniques. Discs and an adhesive tapes containing ranitidine hydrochloride were tightly wrapped with aluminium foil (blank probes, absorption A_0) and were irradiated for 24 hours with P = 700 W/m^2 (absorption A_1). Spectra recorded for blank probes undoubtedly showed no connection with clear changes recorded for irradiated ranitidine spectra influenced by temperature. The biggest differences were observed between spectrum of blank probes and irradiated ones. Any changes in the spectra in the range above 2800 cm^{-1} were very likely caused by stretching N–H from created secondary amines during irradiation and also stretching aliphatic C–H groups.

CONCLUSIONS

The stability of drugs has been studied very frequently in relation to heat, moisture, oxidation and exposure to light[25,26,31]. There are no evidences in literature about studying the first response of drug substance exposure to light and its spectral consequences. Especially pharmaceuticals and drug substances need to be constantly monitored. First contact with degradation factor may cause dramatic pharmacological effect afterwards. Therefore, we recorded the plane of drug substance (reflection technique) and total probe after irradiation test. After a short time of exposure, some changes did occur on the drug surface, but provoked no visible results. Our purpose was to show the efficiency and usability of ATR-FTIR for observing the earliest changes occurring to drug substance, without isolation and identification. The method involved disagreement occurrence detection signal in substance spectrum after absorbing some amount of energy. We chose a particularly sensitive method which could monitor changes in surface structure. We demonstrated that this method was a useful tool to observe the earliest changes on the surface of a drug substance irradiated for a very short time. When measuring the time needed to detect any changes on the surface of ranitidine hydrochloride, FTIR reflection technique was proven more efficient than the transmission technique. During as few as 15 hours of exposure to light (in the power of Atlas chamber 280 kW/m^2), we were able to observe structural changes in ranitidine hydrochloride, but still only on the spectrum recorded by reflection technique. Transmission technique required 30-hour irradiation under the same conditions for the disagreement signal to occur.

ATR-FTIR permits the analysis of all materials with big absorption coefficient and requires neither specialist equipment nor analytes. It is a very useful tool in continuous monitoring of a drug substance during production process or storage. For recording any surface this method enabled to observe the slightest and the first changes occurring after irradiation – much earlier than using the transmission technique.

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