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Research Paper

Electron Beam and Gamma Radiolysis of Solid-State Metoclopramide

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Purpose. Study the radiolysis of solid-state metoclopramide hydrochloride at various absorbed doses. Elucidate the structure of the degradation products to gain information on the radiolysis mechanisms.
Methods. Solid-state metoclopramide samples were irradiated at several doses with gamma rays and high-energy electrons to evaluate the influence of the dose rate. High-performance liquid chromatography with a diode array detector was used to measure the chemical potency as a function of the absorbed dose and to quantify the degradation products. The characterization of degradation products was performed by liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry.
Results. The degradation of solid-state metoclopramide after irradiation was negligible. No qualitative or quantitative differences were observed between gamma and electron beam irradiations (no dose rate effect). Four degradation products that were similar to metoclopramide were detected in trace levels (below 0.1% of the drug concentration) and were not unique to irradiation because they were found in lower amounts in unirradiated metoclopramide. The major degradation product formed after radiation was due to the loss of the chlorine atom from the metoclopramide molecule.
Conclusion. Solid-state metoclopramide is radioresistant from a chemical point of view and therefore could be a suitable candidate for radiosterilization studies by either gamma rays or high-energy electrons.

KEY WORDS: final products analysis; HPLC–DAD; LC–MS; metoclopramide hydrochloride; radiolysis.

INTRODUCTION

Radiosterilization (sterilization by exposure to ionizing radiation) is a terminal sterilization method and therefore may be performed on drugs in their final container without any significant rise in temperature. Furthermore, the reference dose of 25 kGy guarantees a sterility assurance level (SAL) of 10^{-6} (1,2). However, this method leads to the formation of radiolytic products that may be responsible for color and odor modifications (3,4). The advantages of radiosterilization will more likely lead to its more widespread application in the near future. However, there is still a lack of knowledge on the mechanisms leading to the formation of final radiolytic products. The radiolysis mechanisms have to be studied to predict the sensitivity of a solid drug toward ionizing radiation from a chemical point of view as well as to determine the optimal irradiation conditions to lower the drug degradation. The characterization of the final products contribute to the determination of the radiolysis mechanisms.

Amongst the different sterilization methods, radiosterilization is the first choice for thermosensitive solid-state drugs (5). For these, radiolytic products are generally present in such low amounts that very sensitive techniques are required for their analysis (6,7). Up to now, many studies were devoted to the determination of radicals trapped in the solid matrix, but few have been performed on final products and on the mechanism leading to their formation (8,9). As past studies have shown that no direct correlation may be established between trapped radicals and final products (6,10), electron spin resonance (ESR) studies should be considered as an additional method to detect irradiated drugs, as is the case of irradiated foods (11). Therefore, only chromatographic techniques are suited to determine the radiostability of a drug.

Metoclopramide is a drug from the benzamide group used as an antiemetic that can be administered intravenously to patients undergoing chemotherapy, radiotherapy, or gastroenterological exams to prevent the nausea and vomiting induced by these treatments (12). Metoclopramide can also be injected to patients suffering from acute migraine (13). Being a thermosensitive drug, metoclopramide could be a good candidate for radiation sterilization. Moreover, radiation effects on the numerous chemical bonds that are present in that molecule could be studied.

Previous ESR studies on irradiated solid-state metoclopramide (14) have shown the formation of carbon-centered radicals that are hypothesized to originate from the cleavage

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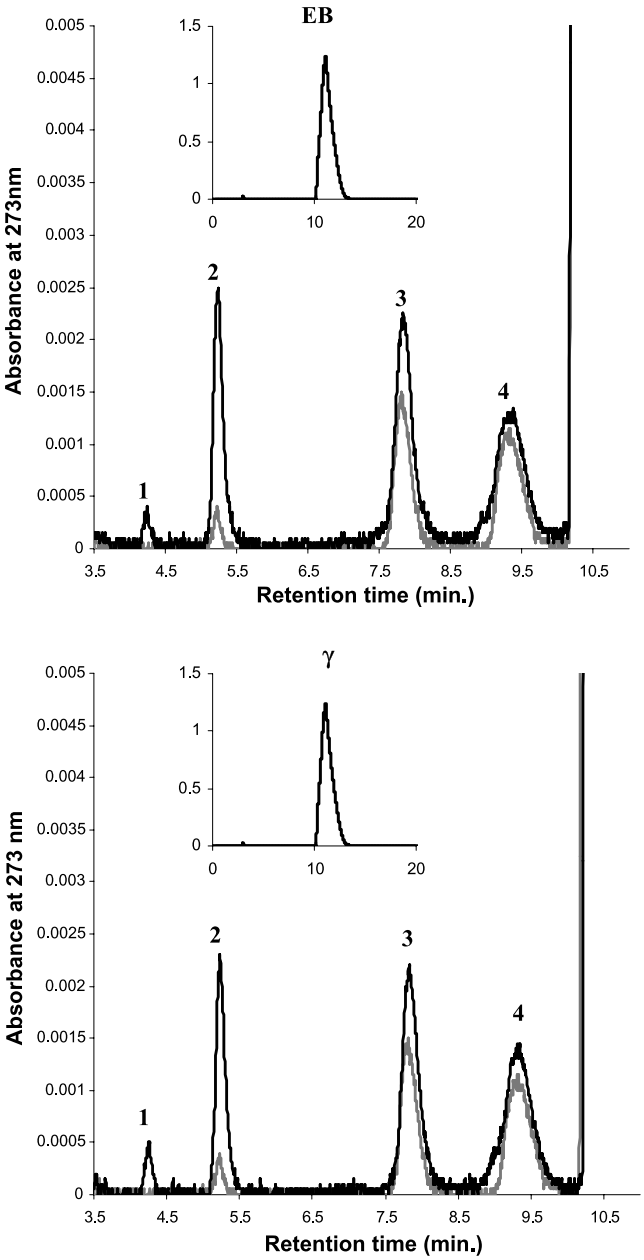

Fig. 1. Overlay of the chromatograms at 273 nm zoomed on the degradation product peaks for unirradiated (lighter chromatogram) and 25-kGy irradiated (darker chromatogram) solid metoclopramide. γ, 25-kGy gamma irradiated; EB, 25-kGy electron beam irradiated. An extended view is inserted above each zoomed chromatogram.

of the amide bond, but the final products have not been investigated. In this work, solid-state metoclopramide hydrochloride was irradiated at various doses with gamma rays and high-energy electrons to investigate the influence of the dose rate on the radiolysis of metoclopramide. For some solid-state irradiated molecules, it was observed that the dose rate might have an influence on the radiolysis mechanism (10). pH and color changes were assessed, and the loss of metoclopramide (chemical potency) as a function of the absorbed dose was measured. Final products were quantified by high-performance liquid chromatography with a diode array detector (HPLC–DAD) and characterized after liquid chromatography–tandem mass spectrometry (LC–MS–MS) analyses to gain information on the radiolysis mechanisms and to determine whether the final products are directly linked to the radical observed in ESR.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride (4-amino-5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxybenzamide) monohydrate crystals with minimum 99% purity were purchased from Sigma-Aldrich (St. Louis, MO, USA) and were stored in the dark at room temperature. The crystals contained 5% of crystallization water. Ammonium acetate was from UCB

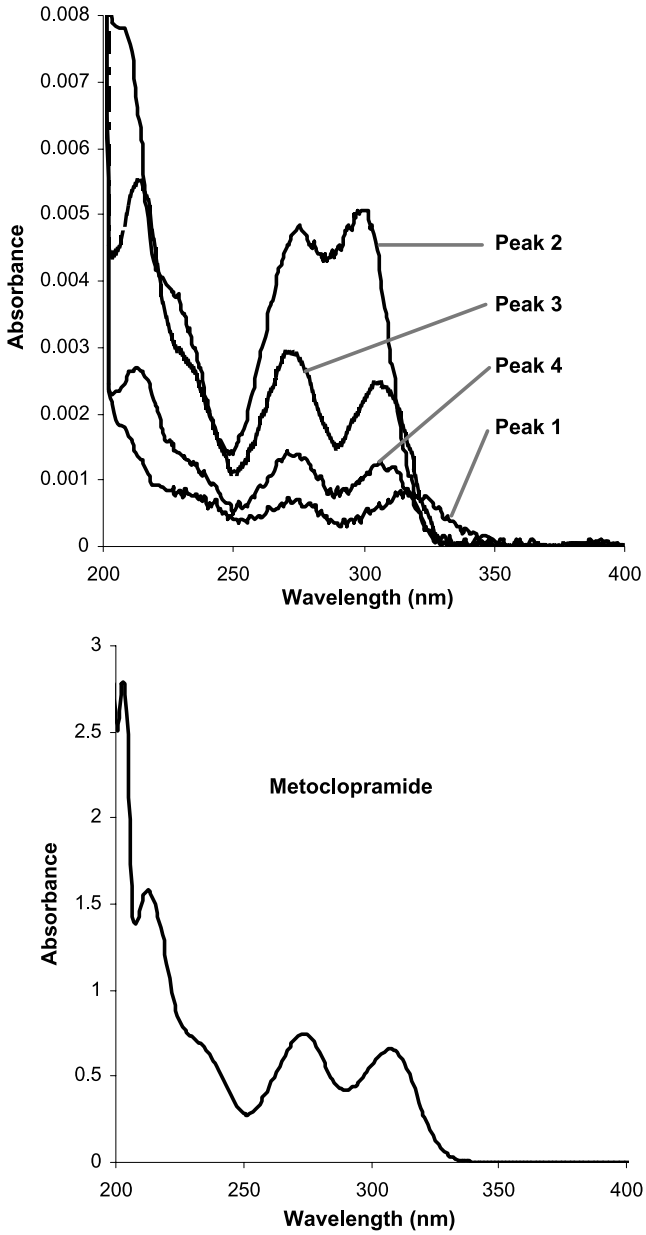

Fig. 2. Overlay of the UV spectra of degradation products peaks; UV spectrum of metoclopramide.

(Brussels, Belgium). HPLC supra-gradient acetonitrile was supplied by Biosolve (Amsterdam, the Netherlands). Deionized water was generated in our laboratory with a Milli-Q system from Millipore (Bedford, MA, USA). Nitrogen was supplied by Air-Liquide (Liège, Belgium).

SOLID-STATE SAMPLES FOR IRRADIATION

Metoclopramide hydrochloride monohydrate crystals were irradiated in sealed glass vials under an atmosphere of nitrogen at room temperature.

Irradiation Sources and Dosimetry

Gamma Rays

Gamma irradiations were performed with a panoramic ^{60}Co chamber (UCL, Louvain-La-Neuve, Belgium). The dose rate was 300 Gy h^{-1}. The source was calibrated with alanine dosimetry. Alanine pellets were supplied and analyzed by Risø National laboratory (Roskilde, Denmark) (15). The absorbed doses were 0, 1.5, 10, 15, and 25 kGy.

Electron Beam

For electron beam irradiations, a double-beam linear electron generator was used (Mölnlycke, Waremme, Belgium). The calculated dose rate was 6×10^7 Gy h^{-1}. The beam power of each electron generator was 16 kW, and the electrons were delivered in pulses of 374 and 377 Hz. The speed of the conveyor belt was adjusted to achieve the desired dose. The dose delivered the samples was monitored by measuring the absorbance of polymethylmethacrylate (PMMA) films that were pasted on the samples. The measured absorbed doses were 0, 15, 25, and 60 kGy. For the electron beam irradiations, only a few seconds were needed to achieve the desired dose, contrary to the gamma irradiations that required many hours.

HPLC-DAD System

The system was composed of a Merck-Hitachi (Darmstadt, Germany)L-6200 Intelligent Pump equipped with a Merck-Hitachi AS-2000 autosampler with a 20-µl sample loop and a Merck-Hitachi L-4500 diode array detector (DAD). The Merck-Hitachi D-7000 HPLC system manager software (HSM) version 4.0 was used. Chromatographic separation was achieved on a 250 × 4-mm Merck LiChrospher® 60 RP Select B column, 5 µm particle size. The mobile phase consisted of 18% acetonitrile and 82% ammonium acetate 10-mM aqueous solution adjusted to pH 5 with glacial acetic acid.

Analyses were performed in triplicate at room temperature with a flow rate of 1 mL min^{-1} The absorbance was measured between 200 and 700 nm. The chosen wavelength for quantification was 273 nm. The chemical potency was evaluated by injecting solutions corresponding to 10^{-3} M in metoclopramide. The percentage of metoclopramide recovery was calculated from the ratio of the areas under the curve (AUC) of the metoclopramide peak between irradiated and nonirradiated samples (1,2,16). To detect and quantify degradation products, solutions corresponding to 10^{-2} M in metoclopramide were injected. The degradation products were quantified with a calibration curve and were expressed as a percentage of the initial drug concentration. The calibration curve was made with metoclopramide solutions ranging from 7.5×10^{-7} to 5×10^{-6} M and was validated by a statistical analysis (XLStat; Addinsoft, Paris, France). The limit of detection and quantification was, respectively, 3 and 10 times the signal-to-noise ratio.

LC–UV–MS System

The LC–MS system consisted of a Merck-Hitachi L 6200 Intelligent Pump, a Rheodyne® (Bensheim, Germany) 7125 manual injection valve equipped with a 20-µl sample loop, a Kontron (Hertfordshire, UK) HPLC-322 UV detector, and a Thermo-Finnigan (Waltham, MA, USA) MAT LCQ® Advantage ion-trap mass spectrometer with an atmospheric pressure chemical ionization (APCI) source. The Xcalibur® 1.3 software was used. The chromatographic conditions were the same as in the HPLC–DAD analyses, and the solutions were injected in triplicate.

The following MS conditions were used: positive ion mode, capillary temperature, 180°C; APCI vaporizer temperature, 500°C; sheath gas flow, 70 arbitrary units; source voltage, 6 kV; capillary voltage, +35 V; discharge current, 5.0 µA; tube lens offset, +40 V. Full MS scans of 50–700 units were performed.

Table I. HPLC–DAD Quantification of the Four Degradation Peaks from Solid-State Metoclopramide Irradiated by Gamma Rays (γ) and High-Energy Electrons (EB) at Various Absorbed Doses

Absorbed dose (kGy)	Irradiation	Peak 1 mean percentage (%) (n = 3)	Peak 2 mean percentage (%) (n = 3)	Peak 3 mean percentage (%) (n = 3)	Peak 4 mean percentage (%) (n = 3)	Sum of peak percentages (%)
0	–	<LOD	<LOQ	0.011	0.011	0.023
1.5	γ	<LOD	<LOQ	0.013	0.012	0.025
10	γ	<LOQ	<LOQ	0.015	0.014	0.030
15	γ	<LOQ	<LOQ	0.016	0.015	0.031
15	EB	<LOQ	<LOQ	0.017	0.015	0.032
25	γ	<LOQ	0.011	0.018	0.016	0.046
25	EB	<LOQ	0.011	0.018	0.016	0.045
60	EB	<LOQ	0.032	0.028	0.024	0.083

The amounts of the degradation products are expressed as a percentage of the initial drug concentration.

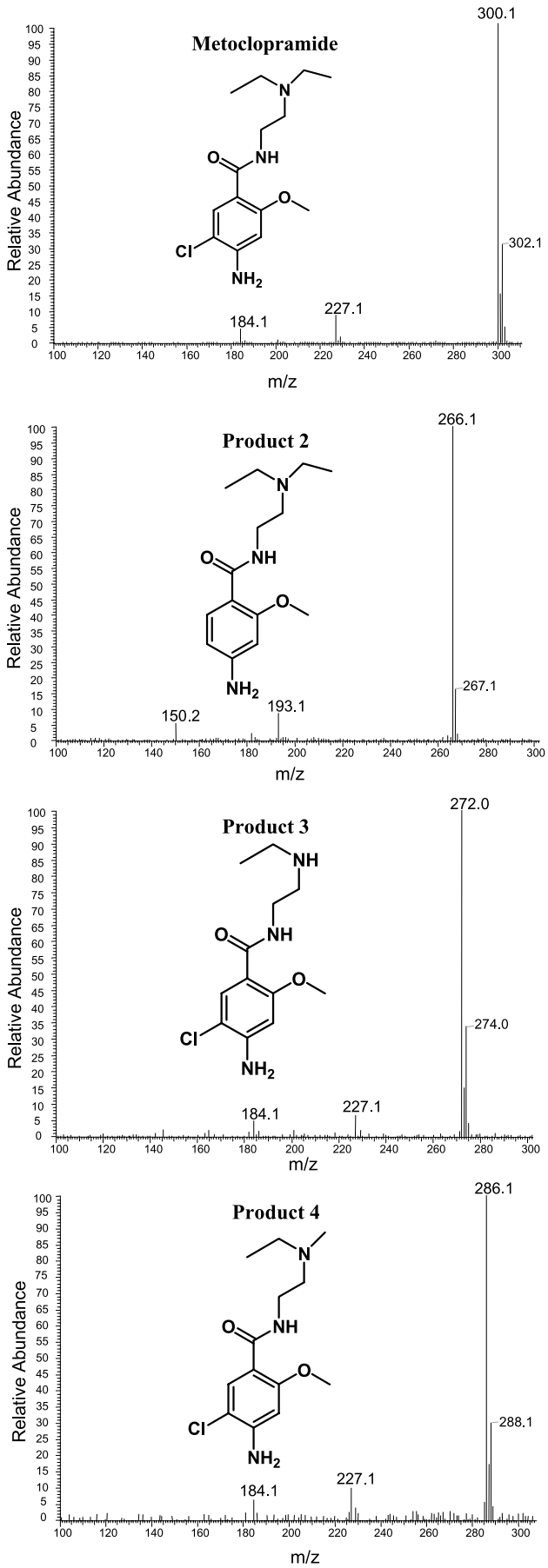

Fig. 3. Characterization of the degradation products by LC–MS: mass spectra and chemical structures of metoclopramide and degradation products 2, 3, and 4.

pH Measurements

A Hanna Instruments (Bedfordshire, UK) pH-meter HI 9025 microcomputer was used. Samples were dissolved prior to measurement to obtain 5-mg mL^{-1} solutions.

RESULTS

Physico-Chemical Changes

Solid-state metoclopramide changes from white to yellow after irradiation. However, the color is heat-reversible, and a colorless solution is obtained after dissolution of the irradiated drug.

No significant differences in pH ($P = 0.8$) can be seen after dissolution of the samples. The mean pH value is 5.5.

Chemical Potency Test

All samples show 100% metoclopramide recovery even after an irradiation of 60 kGy. A statistical test shows no difference ($P = 0.87$) between irradiated and nonirradiated samples.

Analysis of Degradation Products

An overlay of the chromatograms zoomed on the degradation products for unirradiated, 25-kGy gamma rays and 25-kGy electron beam solid-state irradiated metoclopramide samples is presented in Fig. 1. Chromatograms of irradiated metoclopramide show four peaks (numbered from 1 to 4). Peaks 2, 3, and 4 are also present in the unirradiated samples. Similar chromatograms with the same degradation peaks are observed for both electron beam and gamma irradiated samples at similar absorbed doses.

The degradation products have very similar absorbance spectra as metoclopramide, as may be seen in Fig. 2. Therefore, and in accordance to European Pharmacopoeia and European Agency for the Evaluation of Medicinal Products (EMEA) guidelines (1,16), it is assumed that they have the same response factor as metoclopramide at 273 nm.

The quantification results for the degradation products are in Table I. The concentration of product 1 always remains below the limit of quantification. The amount of degradation products increases with the absorbed dose but remains very low (below 0.1% of the drug concentration), even at high doses (60 kGy). As suggested by the chromatographic profiles, no significant difference ($P = 0.65$) in the amount of degradation products is observed when irradiations are performed with gamma rays or accelerated electrons.

Identification of Degradation Products By LC–MS

Even if the percentages of all final products are far below the identification threshold of 0.1% recommended by the EMEA (16), their characterization by LC–MS is nevertheless

important to understand the radiolysis mechanisms behind their formation. Peak 1 could not be detected by the mass spectrometer even in the negative mode or with an electrospray ionization source (ESI). For the other peaks, ions corresponding to protonated molecules $[M+H]^+$ are observed: for example, metoclopramide with an exact mass of 299.1 shows a mass-to-charge ratio (m/z) of 300.1. Fragmentation of all the pseudomolecular ions is performed to elucidate the structures of the degradation products by their fragmentation patterns.

The MS spectra of metoclopramide are in Fig. 3. The fragmentation of metoclopramide, in Fig. 4, leads to a major fragment with $m/z = 227.1$, corresponding to the loss of 73 m/z that can be attributed to the diethylamino group located at the end of the lateral chain; another ion (m/z = 184.1) is obtained after the loss of the *N*,*N*′-diethylethylene diamine group (116 m/z).

Structural hypotheses for the degradation products may be deduced from their mass spectra: by determining whether or not the product has a chlorine atom, by following the odd–even rule (an odd mass corresponds to an odd number of nitrogen atoms, and an even mass corresponds to an even number of nitrogen atoms, respectively), and by analyzing the fragmentation scheme of the pseudomolecular ion to locate whether the modifications have occurred on the aromatic ring or on the lateral chain.

The mass spectra and the structures of the degradation products detected in peaks 2, 3, and 4 are shown in Fig. 3. The MS and MS^2 results are summarized in Table II, and the structure of the major MS^2 fragments are in Fig. 4.

Peak 2 shows a product with m/z 266.1. This product has lost the chlorine as may be seen by the absence of the ^{37}Cl isotope in the MS spectrum. After fragmentation, the pseudomolecular ion gives a major fragment with m/z = 193.1 (loss of 73 m/z).

Peaks 3 and 4 show m/z of, respectively, 272.0 and 286.1. Both products have the ^{37}Cl isotope and the same major fragment with $m/z = 227.1$ as metoclopramide. Therefore, the modifications are located on the diethylamino group from the lateral chain and may correspond to the loss of an ethyl group for product 3 (m/z = 272.0) and of a methyl group for product 4 (m/z = 286.1).

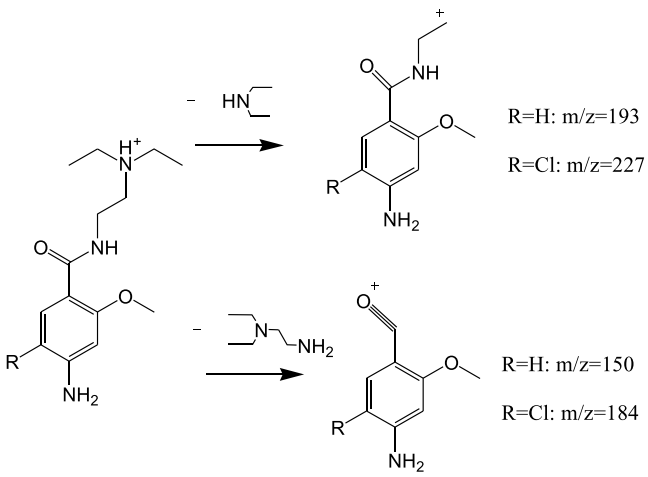

Fig. 4. Fragmentation schemes for metoclopramide and product 2 leading to the major MS–MS fragments.

Table II. m/z Values and Main MS–MS Fragments of the Pseudomolecular Ions of Metoclopramide and Degradation Products 2, 3, and 4

Peak	m/z of pseudomolecular ion	m/z of main MS–MS fragments
2	266.1	193.1; 150.0
3	272.0	227.1; 184.1
4	286.1	227.1; 184.1
Metoclopramide	300.1	227.1; 184.1

DISCUSSION

Color Modification

A change in color is frequently reported after the exposure of a drug toward ionizing radiation (19,20). The coloration can either be due to the formation of a radiolytic product that absorbs in the visible region and gives a colored solution after dissolution (20,21) or, as in our case, to electrons trapped in the solid matrix that may be responsible for the color.

Color centers might be generated either by an electron missing from a normally occupied position, leading to a "hole color-center," or by the presence of one extra electron, which leads to an "electron color-center." They absorb in the visible region of the spectrum and are widely described in irradiated glasses (18,22). When the sample is heated, electrons and holes trapped into the defects recombine and the color disappears. Trapped electrons may recombine with cations during the dissolution process, leading to a colorless solution, as observed in this study.

Chemical Potency

Solid-state metoclopramide hydrochloride is radioresistant, as it undergoes a negligible chemical degradation after high irradiation doses. The solid crystalline matrix should favor the deactivation of excited molecules rather than their decomposition. Moreover, the products resulting from bonds cleavages remain trapped into the crystalline matrix (except $H^{\bullet}$ that can diffuse) and could recombine (17,18). However, as some solid-state irradiated drugs show a major degradation (3,19), this effect is not only due to the solid matrix but is strengthened by the presence of an aromatic ring in the metoclopramide molecule that disperses the absorbed energy throughout the entire aromatic system (15,17). The aromatic system seems to be effective at longer distances, as only little modifications on the lateral chains occur (17).

Final Product Analysis

Even if peak 1 is detected only after irradiation, it may be present at a lower level in the unirradiated drug and therefore may not be unique to radiolysis. All radiolytic products have the same chromophore as metoclopramide, which suggests structures similar to the parent compound as confirmed by the LC–MS experiments.

Peak 2 corresponds to the major degradation product formed after irradiation of the drug in the solid state, as it

shows the highest increase with the absorbed dose. This product (m/z = 266.1) results from the loss of the chlorine atom located on the benzamide ring. The chlorine seems to be less protected than the other substituents against radiolysis. The loss of the chlorine atom occurs through dissociative electron capture: the chlorine atom captures an electron and then dissociates as Cl^-. This effect is favored because the resulting radical is stabilized by the aromatic ring (17). As the chloride ions cannot diffuse easily through the solid matrix, some stay close to the ionization site and may recombine during the dissolution process to reform metoclopramide.

For peak 3, product 3 is formed after the homolytic cleavage of the N–C σ bond that results into a nitrogen-centered radical and an ethyl radical. The radicals may undergo dismutation to give rise to molecular products.

For peak 4, only little change in the concentration of the product (m/z = 282.1) is observed between the irradiated and the unirradiated samples. The loss of the methyl group on the tertiary amino group is due to the homolytic cleavage of the C–C σ bond located in the α position of a heteroatom.

The small radicals (ethyl and methyl) formed by the ionization could either form volatile radiolytic products after termination reaction or react with adjacent molecules to form products with a higher molecular weight than the parent drug, as observed in previous studies (8). In the performed LC–MS analyses, no product with a higher m/z than metoclopramide is detected. A dynamic extraction gas chromatography linked to mass spectrometry (GC–MS) experiment (4) was realized on irradiated solid-state samples, but no volatile products were detected. From the structure of the degradation products, the formation of some volatile products such as methane, ethane, and molecular chlorine was expected, but none of these are observed. This could result from the cage effect that favors the geminate recombination of the fragments, giving rise to the parent drug. Therefore, the volatile products are not present in sufficient amounts to allow their detection by GC–MS.

Influence of the Dose Rate

In this study, no quantitative or qualitative differences are observed between gamma and electron beam irradiations. These observations indicate a negligible influence of the dose rate (in the range from 300 to 6×10^7 Gy h^{-1}) on the radiolysis mechanisms of solid-state metoclopramide, as previously observed for other drugs (20).

Link between Radicals and Final Products

The structure of the final products are not explained by the radical observed in ESR by Damian (14) that was thought to result from the breakage of the bond between the carboxy and the nitrogen of the amide group. If a breakage of that bond occurs, the resulting radicals recombine almost completely so that no final products resulting from this breakage are detected. This observation may support a previous hypothesis that final products may not originate directly from radicals (6,10). If final products were directly related to radicals, radicals centered on the nitrogen (loss of the ethyl), on the benzylic carbon (loss of chlorine), and on the carbon adjacent to the nitrogen (loss of the methyl) should also be observed by ESR.

CONCLUSION

The chemical potency test does not show any difference between irradiated and unirradiated samples; therefore, solid metoclopramide may be qualified as radioresistant, as it is able to withstand high irradiation doses without any significant loss. At the reference dose of 25 kGy, four degradation products are detected in trace level (below 0.1% of the drug concentration) in irradiated samples. The degradation products are not unique to irradiation, as they are present at a lower level in unirradiated samples and their structures, elucidated by tandem LC–MS, are similar to that of metoclopramide, although they are not directly related to the radical observed in electron paramagnetic resonance (EPR), which shows that all the breakages do not lead to detectable final products.

The dose rate does not seem to have a major influence on the radiolysis mechanisms of solid-state metoclopramide, as no qualitative or quantitative differences are observed between gamma and electron beam irradiated samples. This study shows that, from a chemical point of view, radiosterilization of solid-state metoclopramide by either gamma rays or high-energy electrons is conceivable.

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