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Influence of Radiation Treatment on Pharmaceuticals—A Review: Alkaloids, Morphine Derivatives, and Antibiotics

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ABSTRACT

A survey was made of the relevant literature on experimental irradiation of alkaloids, morphine derivatives, and alkaloids; the results of 98 investigations of 67 different substances from 33 different sources were compiled and discussed. Twenty-one substances were investigated more often than once, 12 of them twice, 2 of them three times. The most data are available for morphine hydrochloride (six studies), atropine sulfate (seven studies), chloramphenicol (eight studies), streptomycine (five studies), and tetracycline (four studies). Irradiation was carried out in the dose range 5–750 kGy, in most cases between 10 and 60 kGy.

INTRODUCTION

The sterilization of thermolabile medical devices, such as catheters or one-way syringes, with ionizing radiation is successfully practiced in many countries. Furthermore, it is possible to sterilize pharmaceutically active substances with ionizing radiation. Since 1987 radiation sterilization of pharmaceuticals has been admissible in the Federal Republic of Germany provided that a special permission procedure for each substance and manufacturing company is adhered to.

In 1978 we started collecting results of radiation-induced chemical changes in pharmaceuticals using the relevant literature (6). Now, results of 500 experimental irradiations of 300 substances, based on 130 different sources from the years 1922–1987 are available. About 77% of these substances were examined once, 11% twice, 6% three times, 1% four times, 1.5% five times, 1% six times, 1% seven times, 0.5% eight times, 0.5% nine times, and 0.5% ten times, respectively, by appropriate working groups.

The substances were irradiated in pure form (solid substances or liquids), as aqueous solutions, and (less frequently) in soluble organic media; primarily with cobalt-60 gamma rays but also with electron- and x-rays. The applied doses ranged between several kGy and nearly 1 MGy.

Since different terms for the chemical substances have been used in the different sources, we prefered, in general, international nonproprietory names (INN) as

substance names instead of trade or chemical names. So we changed the substance name given in the original paper into the INN, if necessary.

The multitude of examinations necessitated a classification of substances into various substance groups. These are: alkaloids and morphine derivatives, barbiturates, antibiotics (without penicillin and sulfonamide), penicillins, sulfonamides, enzymes, hormones, vitamins, carbohydrates, adjuvants (without carbohydrates), and other substances.

In this paper we describe our results obtained for alkaloids, morphine derivatives, and antibiotics, starting with a description of the results for the individual substances. Then tables are provided where the results are classified by specific criteria, for example, actual decay, number and identity of decomposition products and comparison of irradiated solutions with solutions of separately irradiated components. At the end a short discussion of the results is presented.

RESULTS FOR THE INDIVIDUAL SUBSTANCES

The substances were present in solid form or as aqueous solutions with and without radioprotectors. In some cases, the components were irradiated separately prior to dissolution.

The substances examined are discussed in alphabetical order.

First, alkaloids and morphine derivatives, then antibiotics. Where necessary, the results have been subdivided into those for solid substances, solutions, solutions with radioprotectors, and irradiation of the individual components.

Alkaloids and Morphine Derivatives

Apomorphine Hydrochloride

Apomorphine hydrochloride in the form of a 1% aqueous solution became discolored and was partly decomposed when irradiated at 60 kGy. The thin-layer chromatogram showed decomposition products in several interfused zones. Increasing absorbed doses resulted in an increasing decomposition of the dissolved substance of 5% at 10 kGy, 10% at 20 kGy, and 42% at 60 kGy (30).

Atropine Sulfate

Solid Substance

Atropine sulfate in solid form was irradiated at a dose of 25 kGy. Its decomposition amounted to 1% (8).

Other authors (12,33) found slight but noticeable discoloration coupled with progressive depression of melting point as the radiation dose increased. Also loss of weight occurred and both samples failed the British Pharmacopoeia test for apoatropine. Simple aqueous solutions of the irradiated solid were clear but off-white.

Altorfer (1) detected at least 4 products of radiolysis at 25 and 50 kGy. Two of them could be identified by thin-layer chromatography as apoatropine and tropanol. Furthermore, the melting point suffered a strong depression and the melting range widened. The originally white powder was discolored to yellow by irradiation at 50 kGy. The ultraviolet (UV) spectrum indicated decomposition. The assay showed that there was no loss in potency (99.5–101.0%). Switek and Modrzejewski (32) found that atropine sulfate showed little change in color at doses of 25 and 50 kGy. This change was more marked on heating at 160°C for 3 hr. Melting point, UV spectrum, thin-layer chromatogram (TLC), and pH value remained unchanged. Schulte and Henke (30) detected a decomposition of not more than 2% by thin-layer chromatography in solid substance irradiated at 60 kGy.

Diding et al. (7) used gamma and electron radiation at 25 and 50 kGy for their experiments on atropine in powder form sealed in polyethylene tubes. "None of the irradiated samples complied in all respects with the pharmacopoeia tests. The lowering of melting range and pH, and the increase in reducing impurities are more pronounced in the Co-60 treated samples. The potency is also somewhat lower after Co-60 treatment. The results from the other tests (UV absorption and TLC) also indicate more marked changes in the Co-60 treated samples."

Solution

Decomposition of aqueous solutions of atropine sulfate at concentrations of 0.05%, 0.1%, 0.2%, and 0.5% by gamma irradiation was inversely proportional to the concentration. A 0.5% solution showed a decomposition of 9.4%, a 0.2% solution a decomposition of 20.4%, and a 0.05% solution a decomposition of 57% (8).

Pandula et al. (24) irradiated a 0.1% atropine solution and found six new spots in the paper chromatogram. "The irradiated solution showed an increase in absorption. A significant deterioration was recorded in the absorption curve of the irradiated atropine solution in comparison with that of the non-irradiated." They also studied the effect of increasing radiation doses on the decomposition. The changes in 0.1% atropine solution were: 5 kGy, 21%; 10 kGy, 38%; 20 kGy, 53%; and 30 kGy 71% decomposition. Furthermore, the ef-

fect of increasing concentrations on the degree of decomposition was tested in 0.1%, 0.2%, 1.0%, and 2.0% atropine solutions. The ampoules tested were irradiated simultaneously and uniformly at a dose of 25 kGy. The extent of the decomposition decreased with increasing concentration. The 0.1 % solution showed a decomposition of 39% whereas the 2.0% solution showed a decomposition of only 4%. Furthermore the effect of dose rate between 0.1 and 2.5 kGy/hr on the decomposition was examined. The solutions tested were irradiated in each case with a total dose of 10 kGy. On the basis of the data obtained it could be seen that the destruction of the atropine solution was higher when the dose rate was below 1 kGy/hr. On the other hand, the change was found to be practically independent of the dose rate above 1 kGy/hr.

Schulte and Henke (30) also detected increasing decomposition with increasing absorbed doses. Irradiation of a 1.5% aqueous solution resulted in 10% decomposition at 10 kGy, 17% at 20 kGy, and 37% at 60 kGy. The thin-layer chromatogram showed decomposition products in several interfused zones. In their experiments, decomposition was independent of the dose rate. Solutions irradiated at 60 kGy in dose rates of 0.03, 0.05, 0.09, 0.21, and 0.41 kGy/hr showed the same decomposition of 37%.

In the experiments of Switek and Modrzejewski (32), a 2% solution was irradiated at 25 and 50 kGy. The pH value decreased and, in both cases, there were two decomposition products, probably tropic acid and apoatropine. The changes after autoclaving for 60 min at 120°C were similar but weaker. After autoclaving for 20 min at 120°C, no decomposition products could be detected by thin-layer chromatography.

Altorfer (1) detected six decomposition products after irradiation of a 1% aqueous solution at 25 kGy. One of them could be identified as tropanol.

In the experiments of Horne (12) and those reported by the Association of the British Pharmaceutical Industry (33) "the injection solution (1%) was completely inactivated at both dose levels (25 and 250 kGy); the colour changing to pale straw. There was a reduction in pH from 4.3 to 3.15 at 250 kGy and a multi-dose solution containing chlorbutol showed a slight haze."

Solution with Radioprotectors

Pandula et al. (24) irradiated a 0.1% atropine solution containing (sodium) sulfite under nitrogen atmosphere at 25 kGy (1 kGy/hr). No color changes were observed; the pH value of the solution changed slightly; only atropine could be identified in the paper chromatographic test, and the spots which were characteristic of the irradiated solutions were not found; only a small change in the absorption spectra was recorded; the loss of active atropine was not more than 4%.

Addition of 0.5% sodium pyrosulfite to a 1.5% solution which was irradiated at 20, 40, and 60 kGy had no stabilizing effect; the thin-layer chromatogram showed decomposition products from an absorbed dose of 20 kGy (30).

Altorfer (1) irradiated an eye drop preparation (1% solution) containing the auxiliary substances boric acid, borax, toloconium methylsulfate, or phenylmercuric nitrate, and methylcellulose at 25 kGy. He detected only one decomposition product by thin-layer chromatography. The decomposition was smaller than in the solution without additional substances.

Addition of 0.2% potassium pyrosulfite to a 0.2% aqueous solution resulted in a reduction of the decomposition from 20.4% (without additional substance) to 3.5%. No decomposition products could be detected by thin-layer chromatography after addition of 0.5% S-(2-aminoethyl)-isothiouroniumbromide-hydrobromide or 0.2% tetiol as well as 0.2% potassium pyrosulfite (8).

Separate Irradiation of the Components

A 1.5% aqueous solution of atropine sulfate, the components of which had been irradiated separately at 60 kGy and mixed 24 hr later, had a decomposition of less than 2% measured by thin-layer chromatography (30). Decomposition of a 1% solution treated in a similar way and irradiated at 25 kGy was less than 0.5% (1).

Cocaine Hydrochloride

Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography and photometry when analyzing the irradiated (60 kGy) solid substance. Gamma irradiation of a 2% aqueous solution resulted in discoloration and partial decomposition. The thin-layer chromatogram showed decomposition products in several interfused zones. In the photometric assay they found decomposition increasing in an almost linear mode with absorbed dose from 5% (10 kGy) to 10% (20 kGy), and to 24% (60 kGy). Addition of 0.5% sodium pyrosulfite prevented decomposition in the 2% solution irradiated at 20, 40, and 60 kGy. Irradiation of water and the solid substance separately at 60 kGy, followed by the preparation of a solution after 24 hr, did not result in decomposition products detectable by thin-layer chromatography.

Codeine Phosphate

Solid Substance

Gamma irradiation of codeine phosphate in solid form at 25 and 50 kGy resulted in a significantly darker appearance only; melting point, UV spectrum, thin-layer chromatogram, and pH value remained unchanged. Discoloration was more intense following heating at 160°C for 3 hr (32).

No decomposition product could be detected by thin-layer chromatography even at a dose of 750 kGy (30).

Solution

Irradiation of a 2% aqueous solution at 25 and 50 kGy resulted in partial decomposition (changes in color, thin-layer chromatogram, and pH value). Simultaneously with irradiation, the solution was heated in a autoclave at 120°C for 20 and 60 min. The autoclaved solution showed similar but weaker changes, which were less pronounced in the solution with the shorter heating time. This solution did not show any changes in the thin-layer chromatogram as well (32).

Schulte and Henke (30) found 8 decomposition products by thin-layer chromatography in a 2% solution irradiated at 60 kGy. In the photometric assay they found decomposition increasing almost linearly with increasing absorbed doses from 5% (10 kGy) to 16% (20 kGy), and to 55% (60 kGy).

Solution with Radioprotectors

An addition of 0.5% sodium pyrosulfite did not produce a stabilizing effect in the 2% solution irradiated at 20, 40, and 60 kGy. Decomposition was observed from 20 kGy (30).

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a 2% solution 24 hr later, did not result in decomposition products detectable by thin-layer chromatography (30).

Dihydroergocristinmethane Sulfonate

The microcrystalline powdered substance did not show any changes in photometry and thin-layer chromatogram after gamma irradiation at 50 kGy (34).

Emetine Dihydrochloride

Irradiation of a solution for injection at up to 25 kGy resulted in only weak changes detectable by infrared spectroscopy (2).

Ephedrin Hydrochloride

Solid Substance

UV absorption showed a decomposition of 1% (8) and 1–2%, respectively (23), following irradiation at 25 kGy. The melting point decreased by 1°C (8) and 2°C (23); there were no indications of changes in color and polarity (8,23).

Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography in the solid substance irradiated at 60 kGy.

Solution

In aqueous solutions irradiated at 25 kGy, decomposition increased with decreasing concentration from 16.3% (8) and 18% (23), for 0.5% solutions, to 85% (8) and 95% (23), for 0.05% solutions. A decomposition product was found by gas chromatography, the 1% solution showing a decomposition of 6% at 25 kGy absorbed dose (8).

Schulte and Henke (30) detected 10% decomposition by photometric assay in a 2% solution irradiated at 60 kGy; the color changed and the thin-layer chromatogram showed decomposition products in several interfused zones.

Solution with Radioprotectors

Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography after addition of 0.5% sodium pyrosulfite to a 2% aqueous solution irradiated at 20, 40, and 60 kGy.

Irradiation of a 1% aqueous solution in the presence of 0.2% potassium pyrosulfite decreased decomposition from 8.5% to 5.8%. AET (0.5%) or tetiol (0.2%) had similar protective effects: in all three cases it was not possible to detect any decomposition products by paper chromatography (8).

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a 2% solution 24 hr later, did not result in decomposition products detectable by thin-layer chromatography (20).

Ergometrine Maleate

Even after 250 kGy, the assay, determined by UV absorption or colorimetrically with dimethylamine benzaldehyde, was virtually unchanged. Horne reported (12):

No trace of ergometrinine could be shown by chromatography. At both levels of irradiation (25 and 250 kGy) the melting point was slightly reduced. A 2% solution in water of the salt irradiated at 25 kGy was yellow in color and faintly opalescent, at 25 kGy it was a greenish brown color with a flocculent, insoluble deposit. Both solutions still gave a blue fluorescence under UV, but had a slightly elevated pH.

When irradiated in solution (0.125 mg/ml sealed under nitrogen) the changes were more marked. Even at 25 kGy, the colorimetric assay showed only 10–20% of the original activity, and at neither level did the solution exhibit any blue fluorescence with UV. It is interesting, that even with such marked degradation as shown colorimetrically the UV absorption figures for both the irradiated solutions were still about 75% of the control values. Chromatography showed no trace of either ergometrine or ergometrinine. The pH of the solution had risen from 3.1 control to 4.8 at 25 kGy and 5.6 at 250 kGy. The irradiated samples passed the BP test for toxicity.

In another report (8), discoloration of the grey/white powder with increasing dose through pale cream to a buff color was observed; no odor developed. The melting point was depressed from 197°C to 195°C at 250 kGy. The BP assay showed little loss of potency; at 250 kGy assay was 98% and UV absorption 96%. Chromatography of the irradiated material showed no trace of ergometrinine. A 2% aqueous solution before irradiation was colorless, bright with a blue fluorescence in UV light, and pH 4.1 At 25 kGy the solution was yellow and opalescent or flocculent; at 250 kGy, greenish brown with a flocculent insoluble deposit. Solutions of irradiated material showed a blue fluorescence and at higher dosage the pH increased to 4.3.

The solution for injection (0.125 mg/ml and 1.0 mg/ml) was more markedly affected; "originally colorless, it became pale brown and opalescent at 25 kGy and buff colored with a dark brown precipitate at 250 kGy. There was an increase in pH from 3.1 to 4.7 (at 25 kGy) and 5.58 (at 250 kGy). The BP assay showed the potency as 6% at the higher dose. Chromatography of the irradiated solution showed no fluorescent spots" (8).

Ethylmorphine Hydrochloride

Solid Substance

Gamma irradiation of ethylmorphine hydrochloride in solid form at 25 and 50 kGy resulted in a weak discoloration; melting point, UV spectrum, thin-layer chromatogram, and pH values remained unchanged (32).

Gopal et al. (10) observed that a solution of this substance irradiated at 25 kGy conformed to the specifications of the Indian Pharmacopoeia 1966 and National Formulary XII, except for a slight change in color. The absorption maxima and minima (283 and 260 nm) were nearly identical for the color and irradiated samples. The chromatograms of the control and irradiated samples showed only a single zone.

Solution

Irradiation of a 2% aqueous solution at 25 and 50 kGy resulted in partial decomposition. The color changed to yellow, the pH value dropped, and the thin-layer chromatogram showed an oxidation product. Autoclaving at 120°C for 20 and 60 min produced similar but weaker changes, which were less pronounced in the solution with the shorter heating time. This solution did not show any changes in the thin-layer chromatogram (32).

Hydrocodone Hydrochloride

This substance was analyzed by Reisch et al. (29). The solid substance showed only small differences from the standard after irradiation at 60 kGy. In aqueous solutions (1.5% and 1%) the amount of unchanged substance decreased in an almost linear mode with increasing doses. The 1.5% solution showed a decomposition of 12.6% whereas a 17.6% decomposition was measured in the 1% solution, both irradiated at 10 kGy. Irradiation at 20 kGy resulted in a decomposition of 21.4% in the 1.5% solution, and in a decomposition of 27.7% in the 1% solution. At 60 kGy, decomposition was 37.1% (1.5% solution) and 42.1% (1% solution).

Hydrocodone Hydrogentartrate

Solid Substance

The solid substance irradiated at 25 kGy only showed a small increase in UV absorption, indicating a decomposition of 0.5% (8).

Pandula et al. (23) found a 1–2% decomposition in the solid substance irradiated at 25 kGy. They could not detect any decomposition products by polarography.

Similarly, Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography.

Solution

Aqueous solutions at concentrations between 0.05% and 0.5% were irradiated at 25 kGy (8,23). Solutions

at the lower concentration showed marked changes. With increasing concentration, decomposition decreased: from 49% in the 0.05% solution to 9% in the 0.5% solution (8). A 2% solution showed a decomposition of 4% at 25 kGy absorbed dose (8).

Schulte and Henke (30) found an increasing decomposition with increasing doses in 1.5% aqueous solutions, from 17% (10 kGy), to 24% (20 kGy) and 41% (60 kGy).

Solution with Radioprotectors

Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography after addition of 0.5% sodium pyrosulfite to a 2% aqueous solution irradiated at 20, 40, and 60 kGy.

Irradiation of a 2% aqueous solution at 25 kGy in the presence of potassium pyrosulfite (0.2%), AET (0.5%), or tetiol (0.2%) reduced decomposition. Without protective substances decomposition was 4.4%; in the presence of potassium pyrosulfite it was 2.2%, and of AET 2.5%. In all three cases no decomposition products could be detected after irradiation (8).

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a 2% solution after 24 hr, did not result in decomposition products detectable by thin-layer chromatography (30).

Hydromorphone Hydrochloride

Solid Substance

Reisch et al. (29) observed only small differences from the control after irradiation of the solid substance at 60 kGy. No decomposition products were detectable by thin-layer chromatography (29,30).

Solution

In aqueous solutions, the loss of active substance was more pronounced in solutions with lower concentrations. With increasing doses, the amount of unchanged substance decreased in an almost linear mode. The 0.5% solution showed complete decomposition at 100 kGy, 47% decomposition at 20 kGy, and 30% decomposition at 10 kGy; whereas the 1% solution showed a decomposition of 24% at 10 kGy, of 39% at 20 kGy, and of 64% at 60 kGy. Reisch et al. (29) reported that aqueous solutions of this morphin derivative were hydroxylated by gamma rays preferable in 1-position.

Even in a 1.5% solution examined by Schulte and Henke (30) decomposition increased with increasing dose. At 10 kGy, 38% was destroyed, at 20 kGy half of the substance was destroyed, and at 100 kGy all of the substance was destroyed. They found eight radiolysis products in a 1.5% solution irradiated at 60 kGy.

Levomethadone Hydrochloride

Solid Substance

Schulte and Henke (30) analyzed the solid substance, aqueous solutions with and without radioprotectors, and the components irradiated separately. Decomposition of the solid substance irradiated at 60 kGy was estimated by thin-layer chromatography to be a maximum of 2%.

Aqueous Solution

In a 2% aqueous solution, decomposition increased with increasing doses. At 10 kGy, 12% was destroyed; at 20 kGy 25% and 60 kGy 52% was destroyed. Seven radiolysis products were detected after irradiation at 60 kGy.

Solution with Radioprotectors

Addition of 0.5% sodium pyrosulfite to a 2% aqueous solution had no stabilizing effect. The thin-layer chromatogram showed decomposition following a 20 kGy absorbed dose.

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a solution after 24 hr, resulted in decomposition of less than 2% as detected by thin-layer chromatography.

Methadone Hydrochloride

Solid Substance

Reisch et al. (29) analyzed the solid substance and the solution. The solid substance showed only small differences from the standard after irradiation at 60 kGy. The thin-layer chromatography indicated small amounts of a decomposition product.

Aqueous Solution

In aqueous solutions the decomposition increased with increasing doses. Solutions of lower concentrations exhibited higher decomposition levels than solutions of higher concentrations. A 20 kGy absorbed dose destroy-

ed 31% of the active substance in the 0.5% solution, 26% in the 1% solution, and 13% in the 5% solution. A 60 kGy absorbed dose destroyed 71% in the 0.5% solution, 54% in the 1% solution, and 24% in the 5% solution (29).

Morphine Hydrochloride

Solid Substance

Irradiation of the solid substance at 25 kGy resulted in a decomposition of about 5% (8). Pandula et al. (23) estimated the decomposition by thin-layer chromatography to be 1–2%; they did not find any other changes. Even after irradiation at 60 kGy the solid substance showed only small differences from the control (29). Schulte and Henke (30) could not detect any decomposition products by thin-layer chromatography after irradiation at this dose level.

Switek and Modrzejewski (32) could not observe any changes after irradiation at 25 kGy. Simultaneous heating of the substance at 160°C for 3 hr led to a noticeable discoloration.

Solution

Aqueous solutions were more sensitive to irradiation, with solutions of low concentrations undergoing intensive changes. At 25 kGy absorbed dose, the decomposition was inversely proportional to the concentration. A 0.5% solution showed a decomposition of 20% (8) or 30% (23), whereas a 0.05% solution was decomposed by 80% (8,23).

Decomposition increased with increasing doses. In a 1% solution, decomposition increased from 13% at 10 kGy to 26% at 20 kGy, 36% at 30 kGy, and to 59% kGy (29). Decomposition of a 2% solution was lower, namely 5% (30) and 8% (29) at 10 kGy, 17% (30) and 20% (29) at 20 kGy, and 58% at 60 kGy (30). In the experimaents by Schulte and Henke (30), decomposition at 60 kGy was independent of the dose rate (2.8 and 21 kGy/hr). They found four radiolysis products by thin-layer chromatography following irradiation at 60 kGy.

Irradiation of a 2% aqueous solution at 25 and 50 kGy resulted in partial decomposition, as well as in changes in color, pH value, and thin-layer chromatogram. An autoclaved solution (120°C for 20 and 60 min) showed similar but less pronounced changes (32).

Bonet-Maury et al. (2) observed small changes only by infrared spectrography after irradiation at 2.5 and 25 kGy.

Solution with Radioprotectors

Addition of 0.2% potassium pyrosulfite to a 2% solution reduced decomposition from 15% (without addition) to 5% (UV measurement) and 9% (polarographic measurement). Addition of 0.5% AET reduced decomposition to 7% (UV) and 9% (polarogr.) whereas 0.2% tetiol led to a decomposition of only 4% (polarogr.). In the presence of potassium pyrosulfite, only one decomposition product was found, whereas two decomposition products were observed when no substances were added (8).

Schulte and Henke (30) did not observe any decomposition by thin-layer chromatography after addition of 0.5% sodium pyrosulfite to a 2% aqueous solution and irradiation at 20, 40, and 60 kGy.

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a solution after 24 hr, did not result in decomposition products detectable by thin-layer chromatography (30).

Morphine Sulfate

Morphine sulfate, in the form of dry powder and 1.5% aqueous solution was irradiated by Horne (12):

> Both powder and solution changed color on irradiation, passing from a pale lemon at 25 kGy to a bright yellow at 250 kGy. However, a solution prepared from the irradiated powder was clear, as was the irradiated solution. In neither case was a significant change in the pH noted. No loss of potency could be detected in the irradiated solution, but there was a slight fall in its optical rotation.
>
> After irradiation the solid salt showed a fall in anhydrous morphine content (84% initially, falling to 82% at the low level, and 81.5% at the high level of irradiation) with an increase in the amount of other alkaloids. The pH of solutions prepared from untreated samples fell from 4.6 to 4.4 to 4.3.

According to the Association of the British Pharmaceutical Industry (33), the originally white powder was discolored by irradiation and following 250 kGy was a "bright mustard yellow." "Aqueous solutions of the material were colored but clear and showed no change in pH; there was some decrease in anhydrous morphine content and an increase in the amount of other alkaloids

was found." An irradiated solution (0.25 g in 1 ml) remained clear but changed to a yellow color; no loss of potency or change in pH was noted but there was a decrease in the optical rotation of the solution.

Oxycodone Hydrochloride

Solid Substance

Reisch et al. (29) found a decrease in optical rotation of about 15% and detected small amounts of a decomposition product after irradiation of the solid substance at 60 kGy; melting point, infrared spectrogram, and the pH value of the aqueous solution remained unchanged.

Schulte and Henke (30) could not observe any decomposition by thin-layer chromatography and colorimetry in the substance irradiated at the same dose.

Solution

In aqueous solutions the amount of unchanged substance decreased in an almost linear mode with increasing doses. Decomposition was higher in solutions of lower concentrations. A 2% solution was discolored and partly decomposed. With increasing doses, the colorimetric assay showed a linear decomposition increasing from 14% (30) or 15% (29) at 10 kGy absorbed dose, to 34% (30) or 47% (29) at 60 kGy. Schulte and Henke (30) found eight radiolysis products by thin-layer chromatography at 60 kGy absorbed dose. In a 1% solution, decomposition was more marked, increasing from 19% at 10 kGy, to 26% at 20 kGy, and to 56% at 60 kGy (29).

Solution with Radioprotectors

Addition of 0.5% sodium pyrosulfite to a 1% aqueous solution had no stabilizing effect. The thin-layer chromatogram showed decomposition at a 20 kGy absorbed dose (30).

Separate Irradiation of the Components

Separate irradiation of water and the solid substance at 60 kGy, followed by the preparation of a solution after 24 hr, did not result in decomposition products detectable by thin-layer chromatography (30).

Papaverine Hydrochloride

Solid Substance

Gamma irradiation of papaverine hydrochloride in solid form at 25 and 50 kGy caused discoloration; melting point, ultraviolet absorption spectrum, thin-layer chromatogram, and pH value remained unchanged. The color change was more marked on heating at 160°C for 3 hr (32).

Solution

Irradiation of a 2% aqueous solution at 25 and 50 kGy resulted in partial decomposition (changes in color, thin-layer chromatogram, and pH value). An autoclaved solution (120°C for 20 and 60 min) showed similar but less pronounced changes (32).

Pethidine Hydrochloride

Solid Substance

Reisch et al. (29) observed only small differences from the standard after irradiation of the solid substance at 60 kGy. No decomposition products were detectable by thin-layer chromatography (29,30).

Solution

With increasing doses, the amount of unchanged substance decreased in an almost linear mode. In aqueous solutions, the loss of active substance was more pronounced in the solutions of lower concentration. Decomposition increased in a 5% solution from 16% (29) and 14% (30) at 10 kGy to 20% (29) and 25% (30) at 20 kGy, and to 30% (29) and 70% (30) at 60 kGy. Decomposition was more pronounced in a 1% solution: 16% at 10 kGy, 26% at 20 kGy, and 70% at 60 kGy (29). Schulte and Henke (30) found six radiolysis products in a solution irradiated at 60 kGy.

Solution with Radioprotectors

No decomposition after addition of 0.5% sodium pyrosulfite to a 1% aqueous solution irradiated at 20, 40, and 60 kGy was observed by thin-layer chromatography (30).

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 60 kGy followed by the preparation of a solution after 24 hr did not result in decomposition products detectable by thin-layer chromatography (30).

Pilocarpine Hydrochloride

Solid Substance

Diding et al. (7) reported that the solid substance still conformed to the specifications of the Nordic Pharm-

acopoeia after being exposed to electron or gamma irradiation at doses of 25 and 50 kGy. They did not observe any differences associated with the different irradiation modes.

Altorfer (1) detected decomposition of less than 0.1% after irradiation at 50 kGy.

Solution

Decomposition of a 1% aqueous solution was 10–15% at 25 kGy absorbed dose (1).

Solution with Radioprotectors

Altorfer (1) irradiated an eye drop preparation (1% solution) containing the auxiliary substances boric acid, borax, toloconium methylsulfate, or phenylmercuric nitrate and methylcellulose at 25 kGy. Decomposition was the same as in the 1% aqueous solution.

Separate Irradiation of the Components

Separate irradiation of water and solid substance at 25 kGy followed by the preparation of a 1% solution after 24 hr did not result in any decomposition products detectable by thin-layer chromatography (1).

Reserpine

The powdered substance showed changes in color and ultraviolet spectrum after irradiation at 50 kGy. The amount of decomposition products, also present in the unirradiated substance, increased with irradiation (34).

Scopolamine Hydrobromide

Schulte and Henke (30) analyzed the solid substance, aqueous solutions with and without radioprotectors, and the components irradiated separately. They did not find any decomposition in the solid substance irradiated at 60 kGy using thin-layer chromatography or a colorimetric method.

A 2% aqueous solution changed color following irradiation. The thin-layer chromatogram showed decomposition products in several interfused zones. Increasing absorbed doses resulted in increasing decomposition of the dissolved substance from 12% at 10 kGy and 16% at 20 kGy to 29% at 60 kGy. Decomposition at 60 kGy was independent of dose rate (2.8 and 21 kGy/hr).

Addition of 0.5% sodium pyrosulfite to a 2% aqueous solution had a stabilizing effect. The thin-layer chromatogram did not show any decomposition after irradiation at 20, 40, and 60 kGy.

Separate irradiation of water and solid substance at 60 kGy, followed by the preparation of a solution after 24 hr, did not result in any decomposition detectable by thin-layer chromatography.

Sparteine Sulfate, Strychnine Sulfate

Irradiation of solutions for injection resulted in changes in the infrared spectrum at 2.5 kGy absorbed dose, increasing with increasing doses (2).

Theophylline

Rasero (28) irradiated theophylline solutions at concentrations of 0.1, 0.5, 1 and 5 g/liter at up to 200 kGy. Visual examination showed that irradiation led to the development of a slight yellow color in the solution. This yellow tint became more pronounced at higher solution concentrations and higher absorbed doses. The pH remained relatively constant. Conversely, the solutions of higher concentrations exhibited lower degradation than the solutions of lower concentrations. Solutions of theophylline of higher concentrations showed a higher amount of hydroperoxide but there was no decrease in the level after a certain point. The polyethylene or glass containers used for the solutions did not have an effect on the results.

Antibiotics

Amphotericine B

On irradiation of amphotericin B in the dry state at doses up to 100 kGy, no changes in the antibiotic activity were observed. A solution of unknown concentration in DMSO was completely destructed after receiving a dose of 25 kGy (9).

Antibiotics of the Streptomycin Group

Some antibiotics of the streptomycin group [dihydrostreptomycin sulfate, pasomycin (*p*-aminosalicylic salt of dihydrostreptomycin), streptomycin, streptopenicillin] were irradiated by Pochapinsky et al. (25). A dose of 25 kGy and even a dose of 80 kGy did not increase the toxicity of any of the preparations. They did not differ from the control samples in respect to their hypotensive activity and pyrogenic effect. All antibiotic preparations of the streptomycin group retained their antibiotic activity under normal storage conditions after irradiation at up to 80 kGy.

Antibiotics of the Tetracycline Group

Pochapinsky et al. (27) irradiated some antibiotics of the tetracycline series (chlortetracycline, nystatine, oxytetracycline, polymyxin, tetracycline). They found that all the tested antibiotics, after irradiation at 25 kGy and even after a dose of 80 kGy, did not differ from control (unirradiated) samples in their chemotherapeutic and pharmaceutical properties, as well as in their antimicrobial spectra. They observed a slight deterioration of the crystals in all the antibiotic preparations studied following irradiation.

Bacitracin

Zinc bacitracin in solid form was irradiated at doses of 25 and 250 kGy. The pale cream color remained unchanged at a dose of 25 kGy, but there was a 7% decomposition. At 250 kGy the decomposition was 25% and discoloration was observed (12).

Cefadroxil

Jacobs (19) irradiated cefadroxil powder at doses up to 50 kGy. He found that "cefadroxil monohydrate is virtually unaffected at the 25 kGy dose. Slight decomposition is discernible, however, at the 50 kGy dose level. These conclusions are illustrated by the relatively low mean G(-) value of 9."

Cefalexin

Cefalexin in the dried state was irradiated by Jacobs (15,17,21). Microbiological assays showed loss in potency from 1% (10 kGy) to 3% (25 kGy) and to 7% (50 kGy). None of the other tests, however, seemed to support this observation, possibly suggesting that the magnitude of radiolysis was slight.

Cefaloridine

Cefaloridine powder is apparently unaffected by radiation doses of up to 50 kGy (15,17,21).

Similarly Fleurette et al. (9) observed no changes in the antibiotic activity on irradiation of cefaloridine in the dry state at doses up to 100 kGy. An aqueous solution of unknown concentration lost its antibiotic activity after receiving a dose of 25 kGy.

Cefalotin

Jacobs et al. irradiated cefalotine in the dry state. They came to the following conclusion:

> "From the earlier data (15,17,21) it is apparent that gamma-irradiation somewhat reduces the potency of cephalothin (cefalotin). This reduction, on the basis of UV absorbance, chemical assay, and specific optical rotation measurements, is around 3.1% following a 50 kGy dose, and 2.2% (or 97.8% purity) as determined by UV absorbance alone. HPLC data indicate a percentage recovery of 94.88%. The free acid was examined in the present study (14) and the sodium salt in the earlier study (15,17,21), but this fact is not thought to contribute significantly to any variation in response" (14).

Cefalotin in the dry state was irradiated by Fleurette et al. (9) at doses up to 100 kGy. They observed a loss of antibiotic activity from 2% at 25 kGy to 13% at 100 kGy. An aqueous solution of unknown concentration lost its antibiotic activity completely after receiving a dose of 25 kGy (9).

Cefamandole

Jacobs et al. (13) irradiated cefamandole nafate in the dry state at doses up to 50 kGy. "Irradiated cefamandole nafate tended to be off-white or cream in color and its solutions were intense yellow." HPLC analysis of 50 kGy irradiated samples indicated, for cefamandole nafate, an 89.3% recovery (13). Jacobs et al. found 0.95% total radiolysis product peaks (as percent relative to estimated total peak area of unirradiated samples determined by HPLC analysis) at 10 kGy, 1.55% at 25 kGy, and 1.79% at 50 kGy, respectively. "The discrepancy between the percent of recovery and total radiolysis product peak values . . . may be attributed, in part, either to peaks that remained undetected at the UV wavelengths utilized or to the extinction coefficients of degradates that differed widely from cefamandole."

Cefapirin Sodium

Gamma irradiation reduced the potency by about 2% at 25 kGy absorbed dose and 4% at 50 kGy, respectively, as indicated by the chemical assay results. Radiolysis products were in too small a concentration to be detected by TLC (15,17,21).

Cefazolin

Jacobs (19) irradiated cefazolin sodium powder at doses up to 50 kGy. His conclusion was that "gamma radiation only slightly reduces the potency of cefazolin (mean G(-cefazolin) of 9). Consideration of the HPLC

recovery of 99.5% reduces the G-value for the 50 kGy data to 3, and the mean value to 8."

Ceforanide

A G-value of < 1 was observed for irradiated ceforanide powder at a dose of 25 kGy (19).

Cefotaxime

Jacobs (19) irradiated cefotaxime powder at doses up to 50 kGy. His conclusion was that "No significant breakdown of cefotaxime could be detected using any of the analytical techniques adopted, even following the 50 kGy radiation dose. This is reflected in a low mean G(-cefotaxime) value of 1."

Cefoxitin Sodium

Jacobs et al. (14,18) irradiated cefoxitin sodium at doses up to 50 kGy.

> Comparison of the chromatograms for the irradiated and unirradiated cefoxitin indicates the presence of at least 3 or 4 radiolysis product peaks with retention times shorter than that for the cefoxitin peak, and one large peak with a longer retention time. Nevertheless, the HPLC data support the earlier conclusions as to the high radiation stability of cefoxitin sodium. A contributory factor to the radiation stability of this compound may be its low water content, which has been found to be less than 0.5% (Jacobs, unpublished data), whereas with most antibiotic powders in our hands, this value is closer to 4%. Furthermore, it has previously been suggested (18) that cefoxitin's chemical structure, with a 3-carbamoxyloxymethyl moiety substituted into the dihydrothiazine ring, may play an important role in this compound's radiation chemistry."

Recovery as determined by HPLC was 97.86% at 50 kGy absorbed dose (14).

Cefradine

Jacobs (19) irradiated cefadrine monohydrate in the dry state at doses up to 50 kGy. He found that this substance "is radiation labile and undergoes very significant degradation at the 25 kGy dose level, as illustrated by the high G(-cefradine H_2O) of 130." Microbiological and chemical assay values were close, at 89% (microbiol.) and 88% (chem.) at 25 kGy absorbed dose and 67% (microbiol.) and 71% (chem.) at 50 kGy.

Chloramphenicol

Solid Substance

Chloramphenicol was relatively stable on irradiation. Two working groups (8,9) found no decomposition at doses between 25 and 100 kGy. Others reported discoloration at 16 kGy and 25 kGy, respectively (3,23). Diding et al. (7) found that after 25 kGy from either a Co-60 source or a linear electron accelerator, chloramphenicol did not meet some of the Nordic Pharmacopoeia quality requirements. Altorfer (1) estimated decomposition at these doses at up to 1–2% and detected at least five radiolysis products by TLC. Schulte and Henke (30) reported a decomposition of 1.5% at 60 kGy.

Solution

Irradiation of a 1% aqueous solution at 25 kGy caused marked decomposition. Altorfer (1) detected 11 unidentified radiolysis products by TLC.

At 25 kGy, decomposition in a 0.1% aqueous solution was 41% (8,23) measured by polarography, whereas UV measurement showed only 19% (8). The same measurements on a 0.05% solution gave values of 62% (polarographic measurement) (8,23) and 31% (UV) (8). Thus decomposition was inversely proportional to the concentration.

Schulte and Henke (30) detected 84% decomposition in a 0.25% solution irradiated at 80 kGy.

Solution with Radioprotectors

Altorfer (1) irradiated a chloramphenicol eye drop preparation (0.5% solution) containing boric acid, borax, toloconium methylsulfate or phenylmercuric nitrate, and methylcellulose at 25 kGy, and detected marked decomposition.

In a 0.25% solution containing boric acid, decomposition was about 23% at 40 kGy absorbed dose. The solution was discolored and there was a pH value drop (31).

Addition of 0.2% potassium pyrosulfite to a 0.1% aqueous solution resulted in a reduction of the decomposition from 42% (without additional substance) to 23%. Addition of 0.5% AET reduced decomposition to 19%, whereas 0.2% tetiol led to a decomposition of 32% (polarography) (8).

The antibiotic activity of a solution of unknown concentration in ethanol was completely destroyed on irradiation at 25 kGy (9).

Separate Irradiation of the Components

A 0.25% aqueous solution of chloramphenicol, the components of which had been irradiated separately at 80 kGy and mixed 24 hr later, showed a decomposition of less than 2% measured by thin-layer chromatography (30). A solution of the same concentration was treated in a similar way and irradiated at 25 kGy by Altorfer (1). He could not detect new decomposition products except the five he found upon irradiation of the solid substance.

Chlortetracycline

Countroulis et al. (4) irradiated chlortetracycline ("aureomycin") in the dry state at a dose of about 16 kGy. They reported no appreciable overall differences in potency between the irradiated and unirradiated samples. There was no change in color, nor apparent change in solubility.

Holland et al. (11) exposed chlortetracycline in the dry state to gamma irradiation at up to 110 kGy, and in organic and aqueous solutions. No changes in the UV absorption spectrum of the dry substance were produced at dose up to 100 kGy. The antibiotic activity was also retained up to 50 kGy. Electron spin resonance (ESR) data for the dry substance irradiated at 25 and 50 kGy indicate the formation of mono- or biradicals by abstraction of hydrogen atoms. After dissolving samples which had been irradiated in the solid state in an aqueous solution, a process of proton transfer from the solvent to the damaged molecule took place. Increasing the irradiation dose from 25 to 50 kGy led to an increased concentration of free radicals from $N = 2 \times 10^{16}$ spins/g (25 kGy) to $N = 2.6 \times 10^{16}$ spins/g (50 kGy). In 0.01–0.1% aqueous solutions decomposition by gamma irradiation was inversely proportional to the concentration. A 0.01% aqueous solution displayed a complete loss of its antimicrobial activity at 3 kGy. The thin-layer chromatogram showed two new spots under UV light, following 2 kGy absorbed dose, the intensity of which is dependent on the radiation dose delivered. The radiation effect in aqueous solutions was significantly reduced by the addition of mercaptoethanol.

The results of Pochapinsky (27) are reported in an earlier section (Antibiotics of the Tetracycline Group).

Colistin

Colistine (polymyxine E) in the dry state was irradiated at doses up to 100 kGy by Fleurette et al. (9), who reported no changes in the antibiotic activity. An aqueous solution of unknown concentration completely lost its antibiotic activity after a dose of 25 kGy (9).

Dihydrostreptomycin

The irradiated powder showed no discoloration or loss in potency at 25 kGy absorbed dose. A 250 kGy dose changed the color of the originally white powder into a pale brown, aqueous solutions being clear, pale brown. Solutions of the untreated sample were clear and colorless. Decomposition amounted to about 5% at 250 kGy (12).

For the results of Pochapinsky (25), see under Antibiotics of the Streptomycin Group.

Erythromycin, Framycetin, Fusidic Acid, Gentamycin, Kanamycin, Lincomycin, Minocyclin, and Nalidixic Acid

The substances were irradiated in dry state (solid substance) and as aqueous solutions of unknown concentration by Fleurette et al. (9).

Solid Substance

Erythromycin, gentamycin, lincomycin, minocyclin, and nalidixic acid showed no loss of antibiotic activity at doses of up to 100 kGy when irradiated in dry state. Framycetin retained its activity up to 70 kGy, but lost 4% of its activity at 80 kGy and 6% at 100 kGy, respectively. Fusidic acid and kanamycin showed no loss of antibiotic activity at 25 kGy, but at higher doses displayed increasing loss of activity with increasing dose. At 50 kGy potency was reduced by 3% (fusidic acid) and by 5% (kanamycin); and at 100 kGy, 16% (fusidic acid) and 7% (kanamycin) reductions were observed.

Solution

The antibiotic activity of an aqueous solution of unknown concentration of erythromycin displayed a retention of 9% at 25 kGy absorbed dose, and 12% at 50 kGy. Solutions of framycetin, fusidic acid, gentamycin, kanamycin, lincomycin, minocyclin, and nalidixic acid showed a complete loss of their antibiotic activity at 25 kGy.

Neomycin Sulfate

Neomycin sulfate was irradiated at 25 and 250 kGy. An aqueous solution of the irradiated powder changed from clear and colorless to very pale yellow at 25 kGy, and to orange at 250 kGy. At both dose levels loss in potency was about 4% (12).

Fleurette et al. (9) irradiated neomycin in the dry state and as an aqueous solution of unknown concentration. In the dry state the substance showed no loss of its antibiotic activity at doses of up to 60 kGy. At higher doses loss of activity was 8% at 70 kGy and 15% at 100 kGy. A aqueous solution of unknown concentration had a complete loss of its antibiotic activity after receiving a dose of 25 kGy.

Oleandomycin

Oleandomycin displayed no loss of its antibiotic activity at doses up to 70 kGy, but at 80 kGy potency was reduced by about 1%, and at 100 kGy by about 2%. An aqueous solution of unknown concentration was completely destroyed after receiving a dose of 25 kGy (9).

Oxtetracycline

Countroulis et al. (4) irradiated oxytetracycline ("terramycin") in the dry state at a dose of about 16 kGy. They reported no appreciable overall differences in potency between the irradiated and unirradiated samples, and no change in color nor apparent change in solubility.

Holland et al. (11) exposed oxytetracycline to gamma irradiation of up to 110 kGy in the dry state, and in organic and aqueous solutions. In the dry state exposures up to 50–100 kGy produced no changes in the UV absorption spectrum. The antibiotic activity was also retained at 50 kGy. The ESR data for the substance irradiated in the solid state at 25 and 50 kGy indicate that the formation of mono- or biradicals by abstraction of hydrogen atoms occurs during this process. When dissolving irradiated samples into an aqueous solution, a process of proton transfer from the solvent to the damaged molecule takes place. Increasing the irradiation dose from 25 to 50 kGy led to an increased concentration of free radicals from $N = 1 \times 10^{14}$ spins/g (25 kGy) to $N = 1.8 \times 10^{14}$ spins/g (50 kGy). A 0.01% aqueous solution lost its antimicrobial activity at 3 kGy.

For the results of Pochapinsky (27), see under Antibiotics of the Tetracycline Group.

Paromomycin

Fleurette et al. (9) irradiated paromomycin in the dry state and as aqueous solution of unknown concentration. In the dry state the substance showed no loss of its antibiotic activity at doses of up to 60 kGy. At higher doses, loss of activity was 12% at 70 kGy and 11% at 100 kGy. The aqueous solution lost its antibiotic activity after receiving a dose of 25 kGy.

Polymyxin

Polymyxin sulfate was irradiated at 25 and 250 kGy. The appearance changed from a "white crystalline powder" to a "faintly off-white crystalline powder" at 25 kGy and to a "cream crystalline powder (definite caramel odour)" at 250 kGy. Assay was 6940 units/mg (unirradiated), 7960 units/mg (25 kGy), and 9136 units/mg (250 kGy). Chromatography of hydrolyzed and unhydrolyzed materials before and after irradiation showed no abnormal spots (12).

For the results of Pochapinsky (27), see under Antibiotics of the Tetracycline Group.

Pristinamycin

Increasing loss of antibiotic activity with increasing dose was observed on pristinamycin irradiated in dry state. At 25 kGy the substance lost 2% of its activity, and at 100 kGy 15%. A aqueous solution of unknown concentration had a complete loss of its antibiotic activity after receiving a dose of 25 kGy (9).

Rifampicin

Crippa et al. (5) irradiated rifampicin in the dry state at a dose of 20 kGy:

> The chromatographic and NMR analysis, carried out on irradiated samples, did not show notable molecular alterations. The ESR spectrum of irradiated samples proved unchanged as regards resonance characteristics. The signal intensity, on the contrary, was increased in the irradiated samples up to a factor of about 5 with respect to the unirradiated samples. . . . A careful estimation of the quantitative effects of radiation brings us to the conclusion that no more than 1 part per 100,000 is damaged with a dose of 20 kGy.

Rifampicin irradiated in the dry state showed no loss of its antibiotic activity at doses of up to 70 kGy. At higher doses loss of activity was 2% at 80 kGy, and 15% at 100 kGy. A solution of unknown concentration in methanol was completely destroyed after receiving a dose of 25 kGy (9).

Streptomicillin

Pochapinsky et al. (26) irradiated streptomicillin (a combination of streptomycin and penicillin) in the dry state at a dose of 25 kGy. The assay values immediately after irradiation and 2 years later (storage at room temperature) showed no significant difference between ir-

radiated and control samples. Also, there was no difference in toxicity and pyrogenic effect.

Streptomycin

Countroulis et al. (4) irradiated streptomycin HCl in the dry state at a dose of about 16 kGy. There appeared to be no appreciable overall differences in potency between the irradiated and unirradiated samples. A slight change in color, from white to gray, was noted in the irradiated samples.

Streptomycin sulfate was irradiated by Horne (12). The originally white powder changed color to cream at 25 kGy and brown at 250 kGy. Aqueous solutions of the powder changed their appearance from clear and colorless (unirradiated), to clear and pale yellow (25 kGy), and clear and pale brown (250 kGy). Decomposition increased from 3% at 25 kGy to 5% at 250 kGy.

For the results of Pochapinsky (25), see under Antibiotics of the Streptomycin Group.

Streptomycin powder retained its antibiotic activity at doses up to 25 kGy but lost 2% at 50 kGy and 8% at 100 kGy, respectively. An aqueous solution of unknown concentration showed a complete loss of antibiotic activity after receiving a dose of 25 kGy (9).

Tetracycline

Jacobs (16) irradiated tetracycline hydrochloride powder at doses up to 150 kGy. "On the basis of TLC, m.p. and NMR analyses, a 25 kGy radiation dose produces no apparent change in tetracycline HCl." Specific optical rotation measurements were within the limits of the European Pharmacopoeia. Following a 150 kGy radiation dose, a faint additional spot was visible in the thin-layer chromatogram.

Diding et al (7) studied the effects of both gamma and electron radiation on the chemical and microbiological properties of tetracycline hydrochloride powder after treatment with 25 and 50 kGy. All irradiated samples were well within the limits of the Ph. Nord in optical rotation, light absorption, chemical assay, and TLC test.

> In this [TLC] test, the same number of secondary spots were obtained from the irradiated and untreated samples. Two of the impurity spots, one of which could be identified as anhydrotetracycline, located above the main spot were somewhat more intense in the case of irradiated samples. . . . The tests made with tetracycline hydrochloride showed that this substance revealed only insignificant changes resulting from irradiation treatment.

No difference between Co-60 treatment and accelerator treatment was noted.

Chen et al. (3) irradiated tetracycline powder and as an 0.2% aqueous solution. There was no major change in the powder after irradiation up to 50 kGy, but there were some marked changes in aqueous solutions. Comparison with other sterilization methods (e.g., autoclaving or dry heat) showed that irradiation was the method of choice for the powder.

For the results of Pochapinsky (27), see under Antibiotics of the Tetracycline Group.

On irradiation of tetracycline powder at doses up to 100 kGy, no changes in the antibiotic activity were observed. An aqueous solution of unknown concentration was completely destroyed after receiving a dose of 25 kGy (9).

Tobramycin, Vancomycin, and Virginiamycin

Vancomycin powders showed no loss of antibiotic activity at doses of up to 80 kGy. At 100 kGy vancomycin lost 2% of its antibiotic activity. Tobramycin and virginiamycin showed increasing loss of activity with increasing dose. Tobramycin showed a loss of antibiotic activity of 5% at 25 kGy and 37% at 100 kGy, where as virginiamycin showed a loss of 4% at 25 kGy and 19% at 100 kGy. Aqueous solutions of unknown concentrations of vancomycin and virginiamycin were completely destroyed after receiving a dose of 25 kGy. Solutions of tobramycin displayed a loss of activity of 67% at 25 kGy and were completely destroyed after receiving a dose of 50 kGy (7).

Viomycin

Viomycin sulfate powder was irradiated by Jezowska-Trebiatowska et al. (22) at doses up to 1.2 MGy. The results of spectroscopic (IR, NMR, UV) studies and amino acid analyses of the irradiated substance, as well as precipitation and examination of radiolysis products, enabled elucidation of degradation pathways induced by gamma radiation. The studies indicated a decomposition of about 1–2% at 25 kGy.

Tabulated Data

The results for the individual substances are summarized in Table 1. It gives an overview of literature,

radiation mode, physical condition, irradiation dose, decomposition, investigation methods, and decomposition products. Tables 2–6 show the results classified by specific criteria in a clearly arranged form. They give an overview of specific questions such as decomposition, dependence of decomposition on dose, and dependence of decomposition on concentration. In each table, part A covers alkaloids and morphine derivatives, and part B covers antibiotics.

Explanatory Notes for Tables 1–6

Absorbed dose	Absorbed dose, in kGy: Tables 1 and 2.
Changes in investigation method	The authors of the original papers found changes in the irradiated substance with the method mentioned: Tables 2, 3, 4, and 6.
Concentration (conc.)	Concentration of the irradiated solution, %: Tables 3, 4, and 6.
Decomposition	Degree of decomposition: Tables 2, 3, 4, and 6.
Decomposition	Number and identity of decomposition products: Tables 1 and 5.
Investigation methods	Investigation method used: Table 1.
Irradiation (irr.)	Gamma (g) or electron (e) irradiation: Table 1.
Irradiation (irr.) mode	Irradiation of the ready-to-use solution or irradiation of the components, i.e., irradiation of the solid substance and separate irradiation of the solvent followed by the preparation of the solution: Table 6.
Reference (Ref.)	Data source: Tables 1–6.
Physical condition	Condition in which the substance is irradiated: Table 1.
Substance	Name of the substance in short form; e.g., atropine instead of atropine sulfate: Tables 1–6.

Abbreviations Used in the Tables

abs±	absorption maximum and minimum
aq. solution	aqueous solution
chem	chemical analysis
chrom	chromatography
col	color
cont	content
DSC	differential scanning calorimetry
DTA	differential thermal analysis
ESR	electron spin resonance
extract	extraction
GC	gas chromatography
HPLC	high performance liquid chromatography
hyp	hypotensive activity
IR	infrared
IR*	infrared after freeze drying of the aqueous solution
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
NMR*	name after freeze drying of the aqueous solution
oro	optical rotation
PC	paper chromatography
pH	pH value
PhInd	specifications of the Indian Pharmacopoeia
PhNord	specifications of the Nordic Pharmacopoeia
PhUSSRIX	specifications of the State Pharmacopoeia USSR IX
phome	photometrically
pogra	polarography
pot	potency
pyr	pyrogenic properties
sol	solubility
solid subst.	solid substance
spect	spectrophotometry
titr	titration
TLC	thin layer chromatography
tox	toxicity
UV	ultra violet spectrum
view	visual view (appearance)
wt	weight

Table 1A

Results for Individual Substances: Alkaloids and Morphine Derivatives

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Apomorphine-HCl	(30)	g	1% aq. solution	10, 20, 40, 50, 60 kGy 5, 10, 22, 30, 42%	cont, TLC view	Several
Atropine sulfate	(1)	g	Solid substance	25, 50 kGy Max. 0.5% TLC, UV, view, wt	chem, cont, GC, IR, mp, NMR, oro,	2-4 (apoatropine, tropanol)
			1% aq. solution	25 kGy Yes	pH, GC, oro, TLC, view, oro, IR*, NMR*	6 (tropanol)
Components irradiated separately			1% aq. solution	25 kGy Max. 0.5%	GC, pH, oro, TLC, view, IR*, NMR*	
Preparation as eye drops with radioprotectors			1% solution	25 kGy Yes, but smaller	GC, pH, TLC, view, IR*, NMR* as in aq. sol.	1
Atropine sulfate	(32)	g	Solid substance	25 50 kGy Changes in: col	pH, mp, TLC, UV, col	None
			2% aq. solution	25, 50 kGy Yes	pH, TLC, UV, view	2 (tropa acid, apoatropine)
Atropine sulfate	(30)	g	Solid substance	60 kGy 2%	TLC	
			1.5% aq. solution	10, 20, 40, 60 kGy 10, 17, 28, 37%	cont, TLC, view	Some
Addition of 0.5% $Na_2S_2O_5$			1.5% solution	20, 40, 60 kGy Yes	TLC	None
Components irradiated separately			1.5% aq. solution	60 kGy About 2%	TLC	1
Atropine sulfate	(7)	g, e	Solid substance	25, 50 kGy 1, 2%	IR, PhNord, TLC, UV	2
Atropine sulfate	(24)	g	0.1% aq. solution	5, 10, 20, 30 kGy 21, 38, 54, 71%	cont, PC, UV	6
25 kGy at different concentrations				Conc.: 0.1 0.2 0.5 1.0 2.0% Decomp.: 39 18 10 5 4%	UV	
10 kGy at different dose rates (UV)			0.1% aq. solution	2500, 2000, 1500, 1000, 500, 250, 100 Gy/h 28, 23, 26, 29, 40, 58, 62%		
Atropine sulfate	(12,33)	g	Solid substance	25 50 kGy changes in: col, mp	mp, pot, view	
			Aq. solution	25 250 kGy 100%	mp, pot, view	1 (1) Apoatropine
Atropine sulfate	(8)	g	Solid substance	25 kGy 1%	col, mp, PC, pogra, UV	None
25 kGy at different concentrations				Conc.: 0.50, 0.20, 0.10, 0.05% Decomp.: 9, 20, 40, 57%	col, PC, pH, pogra, UV	3
0.2% solution with protective substances, 25 kGy			With 0.2% $K_2S_2O_5$ With 0.5% AET With 0.2% tetiol	3.5% Measurement impossible	col, PC pH, pogra, UV	None None None

Cocaine hydrochloride	(30)	g	Solid substance	60 kGy None	cont, TLC	None
			2% aq. solution	10, 20, 40, 60 kGy 5, 10, 17, 24%	cont, TLC view	Some
Addition of 0.5% $Na_2S_2O_5$			2% solution	20, 40, 60 kGy: None	TLC	None
Components irradiated separately			2% aq. solution	60 kGy None	TLC	None
Codeine phosphate	(30)	g	Solid substance	60, 750 kGy None	cont, TLC	None
			2% aq. solution	10, 20, 40, 60 kGy 5, 16, 32, 55%	cont, TLC, view	8
Addition of 0.5% $Na_2S_2O_5$			2% solution	20,40,60 kGy Yes	TLC	None
Components irradiated separately			2% aq. solution	60 kGy None	TLC	None
Codeine phosphate	(32)	g	Solid substance	25, 50 kGy Changes in: col	mp, pH, TLC, UV col	None
			2% aq. solution	25, 50 kGy Yes	pH, TLC, UV, view	1
Dihydroergocristrimethane sulfonate	(34)	g	Solid substance	50 kGy None	TLC, phome	None
Emetine dihydrochloride	(2)	g	Solution for injection	2.5, 25 kGy Small	IR	
Ephedrine hydrochloride	(23)	g	Solid substance	25 kGy 1–2%	col, mp, pogra, UV	
25 kGy at different concentrations				Conc.: 0.50, 0.20, 0.10, 0.05% Decomp.: 18, 38, 63, 95%	col, pH, pogra, UV	
Ephedrine hydrochloride	(30)	g	Solid substance	60 kGy None	TLC	None
			2% aq. solution	60 kG 10%	cont, TLC view	Some
Addition of 0.5% $Na_2S_2O_5$			2% solution	20 40 60 kGy None	TLC	
Components irradiated separately			2% solution	60 kGy None	TLC	None
Ephedrine hydrochloride	(8)	g	Solid substance	25 kGy 1%	col, mp, PC, pogra, UV	None
25 kGy at different concentrations				Conc.: 1.0, 0.50, 0.20, 0.10, 0.05% Decomp,: 6, 16, 41, 64, 85%	col, extract PC, pH, pogra, UV	1
1% solution with protective substances				10 kGy 25 kGy		
			Without prot. subst.	1.6% 5.8%	col, extract	
			With 0.2% $K_2S_2O_5$	5.7% 8.5%	PC, pH, pogra,	None
			With 0.5% AET	Protective effect	UV	None
			With 0.2% tetiol	Protective effect		None

(*continued*)

Table 1A Continued

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Ergometrine maleate	(8)	g	Solid substance	25, 250 kGy		
				None	col, mp	
			0.0125%, 0.1%	25, 250 kGy	col, pH, TLC,	
			aq. solution	94%	cont	
Ergometrine maleate	(6)		Solid substance	5, 250 kGy	cont (2 methods),	No ergometrine
				Changes in: col, mp, pH,	chrom, pH, view	could be detected
			0.0125%	25, 250 kGy	cont (2 methods),	by chromatograpy
			aq. solution	80–90%	chrom, pH, view	in solution or
				25, 25%		solid substance
Ethylmorphine hydrochloride	(32)	g	Solid substance	25 50 kGy	pH, mp, TLC,	None
				Changes in: col	col	
			2% aq. solution	25 50 kGy	pH, TLC, UV,	1
				Yes	view	
Ethylmorphine hydrochloride	(10)	g	Solid substance	25 kGy	abs±, PhInd,	
				Changes in: col	TLC, view	
Hydrocodone hydrochloride	(29)	g	Solid substance	60 kGy	col, IR, mp,	None
				Changes in: oro	oro, pH, TLC	
			aq. solution	10, 20, 40, 60 kGy	col, cont,	
			1.5%	13, 21, 28, 38%	IR, mp, oro,	1
			1.0%	18, 28, 35, 42%	pH, TLC	
Hydrocodone hydrogentartrate	(23)	g	Solid substance	25 kGy	col, pogra,	
				1–2%	mp, UV	
25 kGy at different concentrations				Conc.: 0.50, 0.20, 0.10, 0.05%	col, pH,	
				Decomp.: 9, 16, 27, 49%	pogra, UV	
Hydrocodone hydrogentartrate	(30)	g	Solid substance	60 kGy	TLC	None
				None		
			1.5% aq. solution	10, 20, 40, 60 kGy	cont, TLC,	Some
				17, 24, 32, 41%	view	
Addition of 0.5% $Na_2S_2O_5$			2% solution	20, 40, 60 kGy	TLC	
				None		
Components irradiated separately				60 kGy	TLC	None
			Solution	None		
Hydrocodone hydrogentatrate	(8)	g	Solid substance	25 kGy	col, PC, pogra,	None
				0.5%	titr, UV	
25 kGy at different concentrations				Conc.: 2.0, 0.50, 0.20, 0.10, 0.05%	col, PC, pH,	2
				Decomp.: 4, 9, 16, 27, 49%	pogra, UV	
2% solution with protective subtances, 25 kGy			With 0.2% $K_2S_2O_5$	2.2%	col, PC,	None
			With 0.5% AET	2.5%	pH, pogra, UV	None
			With 0.2% tetiol	Protective effect		None
Hydromorphone hydrochloride	(30)	g	Solid substance	60 kGy	TLC	None
				none		
			1.5% aq. solution	10 20 40 60 160 kGy	cont, TLC,	6
				38 50 66 82 100%	view	

Components irradiated separately				60 kGy	TLC	None
			Solution	none		
Hydromorphone hydrochloride	(29)	g	Solid substance	60 kGy	col, IR, mp,	None
				changes in: oro	oro, pH, TLC	
			Aq. solution	10, 20, 40, 60, 80, 100 kGy	col, cont,	
			0.5%	30, 47, 64, 81, 83, 100%	IR, mp, oro,	1
			1.0%	24, 39, 51, 64, —, —%	pH, TLC	
Levomethadone	(30)	g	Solid substance	60 kGy	TLC	None
				About 2%		
			2% aq. solution	10, 20, 40, 60 kGy	cont, TLC,	7
				12, 25, 41, 52%	view	
Addition of 0.5% $Na_2S_2O_5$			2 % solution	20 40 60 kGy	TLC	
				Yes		
Components irradiated separately				60 kGy	TLC	1
			Solution	About 2%		
Methadone hydrochloride	(29)	g	Solid substance	60 kGy	col, IR, mp,	1
				changes in: TLC	oro, pH, TLC	
			aq. solution	10, 20, 40, 60 kGy	col, cont, IR,	
			0.5%	16, 31, 56, 71%	oro, pH, TLC	4
			1.0%	11,26,38,54%	cont	
			5.0%	—, 13, 18, —%	cont	
Morphine hydrochloride	(23)	g	Solid substance	25 kGy	col, pogra,	
				1-2%	mp, UV	
25 kGy at different concentrations				cont.: 0.50, 0.20, 0.10, 0.05%	col, pH,	
				decomp.: 29, 42, 43, 80%	pogra, UV	
Morphine hydrochloride	(32)	g	Solid substance	25, 50 kGy	pH, mp, TLC,	None
				None	col	
			2% aq. solution	25, 50 kGy	pH, TLC, UV,	
				Yes	view	2
Morphine hydrochloride	(29)	g	Solid substance	60 kGy	col, IR, mp,	None
				Changes in: oro	oro, pH, TLC	
			aq. solution	10, 20, 40, 50 kGy	col, cont, IR,	
			2%	8, 20, 31, 43%	oro, pH, TLC	2
			1%	13, 36, 50, 59%	cont	
Morphine hydrochloride	(30)	g	Solid substance	60 kGy	cont, TLC,	None
				None		
			2% aq. solution	10, 20, 40, 60 kGy	cont, TLC,	4
				5, 17, 39, 58%	view	
Addition of 0.5% $Na_2S_2O_5$			2% solution	20, 40, 60 kGy	TLC	
				None		
Components irradiated separately				60 kGy	TLC	None
			Solution	None		

(continued)

Table 1A Continued

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Morphine hydrochloride	(8)	g	Solid substance	25 kGy	col, PC, pogra,	2
				About 5%	mp, UV	
25 kGy at different concentrations				Conc.: 2.0, 0.50, 0.20, 0.10, 0.05%	col, PC, pH,	2
				Decomp. (UV): 15, 20, 45, 60, 80%	pogra, UV	
				Decomp. (pogra): 15, 30, 42, 43, 80%		
2% solution with protective substances, 25 kGy			With 0.2% $K_2S_2O_5$	5% (UV), 9% (pogra)	col, PC,	1
			With 0.5% AET	7% (UV), 9% (pogra)	pH, pogra, UV	
			With 0.2% tetiol	— (UV), 7% (pogra)		
Morphine hydrochloride	(2)	g	Solution for injection	2.5, 25 kGy	IR	
				Small		
Morphine sulfate	(12,33)	g	Solid substance	25, 50 kGy	oro, pH, pot, view	
				Changes in: col, pH, oro	morph. anhydride cont.	
			1.5% aq. solution	25 kGy	oro, pH, pot, view,	
				Very low (oro)	morph. anhydride cont.	
Oxycodone hydrochloride	(30)	g	Solid substance	60 kGy	cont, TLC	None
				None		
			2% aq. solution	10, 40, 60 kGy	cont, TLC,	8
				14, 26, 34%	view	
Addition of 0.5% $Na_2S_2O_5$			1% solution	20 40 60 kGy	TLC	
				Yes		
Components irradiated separately				60 kGy	TLC	None
			Solution	None		
Oxycodone hydrochloride	(29)	g	Solid substance	60 kGy	col, IR, mp,	1
				Changes in: oro, TLC	oro, pH, TLC	
			Aq. solution	10, 20, 40, 50 kGy	col, cont,	
			2%	15, 19, 28, 48%	IR, mp, oro,	2
			1%	19, 26, 40, 56%	pH, TLC	
Papaverine hydrochloride	(32)	g	Solid substance	25, 50 kGy	pH, mp, TLC,	None
				Changes in: col	UV, col	
			2% aq. solution	25, 50 kGy	pH, TLC, UV,	2
				Yes	view	
Pethidine hydrochloride	(30)	g	Solid substance	60 kGy	TLC	None
				None		
			5% aq. solution	10, 20, 40, 60 kGy	cont, TLC,	6
				14, 25, 46, 70%	view	
Addition of 0.5% $Na_2S_2O_5$			1% solution	20, 40, 60, kGy	TLC	None
				None		
Components irradiated separately				60 kGy	TLC	None
			Solution	None		

Pethidine hydrochloride	(29)	g	Solid substance	60 kGy Changes in: oro	col, IR, mp, oro, pH, TLC	None
[a]Commercial (Hoechst)			Aq. solution	10, 20, 40, 60 kGy	col, cont,	
			5%[a]	15, 19, —, 24%	IR, mp, oro,	
			5%[b]	16, 20, 24, 30%	pH, TLC	
[b]Freshly prepared			1%[b]	16, 26, 46, 70%		
Pilocarpine hydrochloride	(1)	g	Solid substance	25, 50 kGy Changes in: col, DSC, mp	chem, cont, DSC, GC, IR, mp, NMR, oro, TLC, UV, view, wt	None
			1% aq. solution	25 kGy 10–15%	pH, GC, oro, TLC, view, oro, UV-vis, IR*, NMR*	Some Tropanol
Components irradiated separately			1% aq. solution	25 kGy None	GC, pH, oro, TLC, view, IR*, NMR*	None
Preparation as eye drops with radioprotectors			1% solution	25 kGy Yes, but smaller as in aq. sol.	GC, oro, TLC, view UV-vis, IR*, NMR*	Some
Pilocarpine hydrochloride	(7)	g, e	Solid substance	25, 50 kGy None	IR, DTA, PhNord, TLC, UV	
Reserpine	(34)	g	Solid substance	50 kGy Changes in: col, UV	col, spect, TLC	
Sparteine sulfate	(2)	g	Solution for injection	2.5, 25, 100 kGy Yes, increasing with dose	IR	
Strychnine sulfate	(2)	g	Solution for injection	2.5, 25, 100 kGy Yes, increasing with dose	IR	
Scopolamine hydrobromide	(30)	g	Solid substance	60 kGy None	cont, TLC	None
			2% aq. solution	10, 20, 40, 60 kGy 12, 16, 23, 29%	cont, TLC, view	Some
Addition of 0.5% $Na_2S_2O_5$			2% solution	20, 40, 60 kGy None	TLC	None
Components irradiated separately			Solution	60 kGy None	TLC	None
Theophylline	(7)	g	Aq. solution	10, 20, 30, 36, 80 kGy	col, cont,	
			0.1%	52, 75, —, 93, —%	H_2O_2	
			0.5%	16, 20, 38, —, 55%		

Table 1B

Results for Individual Substances: Antibiotics

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Amphotericine B	(9)	g	Solid substance	25–100 kGy		
				None	pot	
			?% aq. solution in DMSO	25 kGy Complete		
Bacitracine	(12)	g	Solid substance	25, 250 kGy 7, 25%	pot, view	
Cefadroxil	(19)	g	Solid substance	25, 50 kGy +1, 1% (chem) +1, 3% (pot)	cont, mp, oro, UV, pH, pot, TLC	None
Cefalexine	(15,17,21)	g	Solid substance	10, 25, 50 kGy 0.3, 1.1, 0.8% (chem) 3, 3, 7% (pot)	cont, NMR, oro, pot, spect, TLC	None
Cefaloridine	(15,17,21)	g	Solid substance	10, 25, 50 kGy +2.6, +2.1, +3.1% (chem) (15, 17) +1, 0, +1% (chem) (21) 4, 1, 8 (pot) (15,17,21)	cont, NMR, oro, pot, spect, TLC	None
Cefaloridine, chloramphenicol, colistin, gentamycin, lincomycin minocyclin, nalidixic acid, tetracycline	(9)	g	Solid substance	25–100 kGy None	pot	
			?% aq. solution	25 kGy Complete		
Cefalotin	(15,17,14,21)	g	Solid substance	10, 25, 50 kGy +1.3, 0, +2.2% (chem) (15,17,21) —, —, 5.1% (chem) (14) 7, 9, 10% (pot) (15–21)	cont, HPLC, NMR, oro, pot, spect, TLC	None by TLC (15,17,21) 3–4 by HPLC (14)
Cefalotin	(9)	g	Solid substance	25, 50, 75, 100 kGy 2, 6, 8, 13%	pot	
			?% aq. solution	25 kGy Complete		
Cefamandole	(13)	g	Solid substance	10, 25, 50 kGy +5, +4, +3% (chem) 1, 1, 1% (pot)	cont, HPLC, oro, pot, TLC	2–3 by HPLC
Cefapirine sodium	(15,17,21)	g	Solid substance	10, 25, 50 kGy 0.8, 1.7, 3.4% (chem) (15) 0.8, 1.7, 3.9% (chem) (17) 0.8, 0.7, 3.9% (chem) (21) 4, 7, 12% (pot) (15–21)	cont, NMR, oro, pot, spect, TLC	None
Cefazolin	(19)	g	Solid substance	25, 50 kGy 2, 1% (chem) 8, 6% (pot)	cont, mp, oro, UV pH, pot, TLC	1 by HPLC (50 kGy)
Ceforanid	(19)	g	Solid substance	25 kGy 0% (chem) 4% (pot)	cont, mp, oro, UV, pH, pot, TLC	None

Cefotaxim	(19)	g	Solid substance	25, 50 kGy	cont, mp,	None
				0, 0.3% (chem)	oro, UV	
				+5, +3% (pot)	pH, pot, TLC	
Cefoxitine sodium	(14,18)	g	Solid substance	25, 50 kGy	cont, HPLC,	3–5 by HPLC (14)
				—, 2%	mp, oro,	
					pH, spect, TLC	None by TLC (18)
Cefradine	(19)	g	Solid substance	25, 50 kGy	cont, mp,	1 by TLC
				12, 29% (chem)	oro, UV	
				11, 33% (pot)	pH, pot, TLC	
Chloramphenicol	(1)	g	Solid substance	25, 50 kGy	chem, cont,	5
				Max. 1.5%	DSC, GC, IR, pH, mp, NMR	
					oro, TLC, UV, view, wt	
			1% aq. solution	25 kGy	pH, GC, oro, TLC,	11
				Yes	UV, view, IR*, NMR*	
Components irradiated separately			0.25% aq. solution	25 kGy	GC, pH, oro, TLC,	5
				Yes	UV, view, IR*, NMR*	
Preparation as eye drops with radioprotectors			0.5% solution	25 kGy	GC, pH, oro, TLC,	Some
				Yes	UV, view, IR*, NMR*	
Chloramphenicol	(23)	g	Solid substance	25 kGy	col, pogra,	
				None	mp, UV	
25 kGy at different concentrations				Conc.: 0.1, 0.05%	col, pH,	
				Decomp.: 41, 62%	pogra, UV	
Chloramphenicol	(30)	g	Solid substance	60 kGy	cont, TLC	
				1.5%		
			0.25% aq. solution	80 kGy	cont, TLC	15
				84%		
Components irradiated separately			0.25% aq. solution	80 kGy	TLC	1
				About 2%		
Chloramphenicol	(17)	g,e	Solid substance	25, 50 kGy	cont, DTA, IR,	Not complying
				<1% (chem)	pot, pHNord, TLC	with PhNord
				<3% (pot)		
Chloramphenicol	(31)	g	0.25% aq. solution with boric acid	40 kGy	cont, pH, NaCl-cont,	
				23%	boric acid-cont, view	
Chloramphenicol	(4)	g	Solid substance	16 kGy		
				None	col, pot, sol	
Chloramphenicol	(8)	g	Solid substance	25, 50 kGy	col, IR, mp,	None
				None	pc, pogra, UV	
25 kGy at different concentrations				Conc.: 0.10, 0.05%	col, PC, pH,	1
				Decomp.: 19, 31%	pogra, UV	
0.1% solution with protective substances, 25 kGy			With 0.2% $K_2S_2O_5$	Small reduction of decomposition, measurement impossible	col, PC, pH, pogra,	1
			With 0.5% AET		UV	1
			With 0.2% tetiol			1
Chloramphenicol	(9)		See Cefaloridine (9)			
Chlortetracycline, oxytetracycline	(4)	g	Solid substance	16 kGy		
				None	col, pot, sol	

(*continued*)

Table 1B Continued

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Chlortetracycline	(11)	g	Solid substance	10–50 kGy: small		
cycline				50–100 kGy: yes	col, ESR, pot,	
			?% aq. solution	2 kGy: decomp. inversely	TLC, UV	
				prop. to the conc.		2 at 4 kGy
addition of mercapto-ethanol				Radiation effect is significantly reduced		
Chlortetracycline sodium, nystatine, oxytetra-cycline HCl, polymyxin HCl, tetracycline HCl	(27)	g	Solid substance	25 80 kGy No diff. from control	PhUSSRIX	
Colistin	(9)		See Cefaloridine (9)			
Dihydrostreptomycin sulfate	(25)	g	Solid substance	25 kGy	col, hyp,	
				2% (chem) after sto-	pot, pH,	
				4% (pot) rage for	pyr, sol,	
				1 year at room temp.	tox	
Dihydrostreptomcin sulfate	(12)	g	Solid substance	25, 250 kGy None, 5%	pot, view	
Erythromycine	(9)	g	Solid substance	25–100 kGy		
				None	pot	
			?% aq. solution	25, 50 kGy		
				9, 12%		
Framycetin	(9)	g	Solid substance	25–70, 80, 100 kGy		
				None, 4, 6%	pot	
			?% aq. solution	25 kGy		
				Complete		
Fusidic acid	(9)	g	Solid substance	25, 50, 70, 100 kGy		
				0, 3, 10, 16%	pot	
			?% aq. solution	25 kGy		
				Complete		
Gentamycin	(9)		See cefaloridine (9)			
Kanamycin	(9)	g	Solid substance	25, 50, 70, 100 kGy		
				0, 5, 5, 7%	pot	
			?% aq. solution	25 kGy		
				Complete		
Lincomycin	(9)		See cefaloridine (9)			
Minocyclin	(9)		See cefaloridine (9)			
Nalidixic acid	(9)		See cefaloridine (9)			
Neomycin	(9)	g	Solid substance	25–60, 70, 100 kGy		
				None, 8, 15%	pot	
			?% aq. solution	25 kGy		
				Complete		
Neomycin sulfate	(12)	g	Solid substance	25, 250 kGy	pot, view	
				About 4%		
Nystatine	(27)		See chlortetracycline sodium (27)			

Oleandomycin	(9)	g	Solid substance	25-70, 80, 100 kGy	
				None, 1, 2%	pot
			?% aq. solution	25 kGy	
				Complete	
Oxytetracycline	(4)		See chlortetracycline (4)		
Oxytetracycline	(11)	g	Solid substance	50 kGy	
				None (pot)	col, ESR, pot,
			0.01% aq. solution	3 kGy	TLC, UV
				Complete (pot)	
Oxytetracycline HCl	(27)		See chlortetracycline sodium [27]		
Paromomycin	(9)	g	Solid substance	25-60, 70, 100 kGy	
				None, 12, 11%	pot
			?% aq. solution	25 kGy	
				complete	
Pasomycin	(25)	g	Solid substance	25 kGy	col, hyp,
				2% (chem) after storage	pot, pH,
				for 1 year at room temp.	pyr, sol,
				+2% (pot)	tox
Polymyxin HCl	(27)		See chlortetracycline sodium		
Polymyxin	(12)	g	Solid substance	25, 250 kGy	pot, view
				+14, +32%	
Pristinamycin	(9)	g	Solid substance	25, 50, 70, 100, kGy	
				2, 5, 9, 15%	pot
			?% aq. solution	25 kGy	
				Complete	
Rifampicin	(5)	g	Solid substance	20 kGy	ESR, NMR,
				Very small	TLC
Rifampicin	(9)	g	Solid substance	25-70, 80, 100 kGy	
				None, 1.6, 2.4%	pot
			?% aq. solution	25 kGy	
				Complete	
Streptomicillin	(26)	g	Solid	25 kGy substance	col, cont,
				3% (pot) after storage	pot, pH
				for 2 years at room temp.	pyr, tox
				+2% (chem)	
Streptomycin	(9)	g		25, 50, 70, 100 kGy	
			Solid substance	0, 2, 5, 8%	pot
			?% aq. solution	25 kGy	
				Complete	
Streptomycin calcium chloride complex	(25)	g	Solid substance	25 kGy	col, hyp,
				+0.3% (chem) after storage	pot, pH,
				for 1 year at room temp.	pyr, sol,
				+3% (pot)	tox

(*continued*)

Table 1B Continued

Substance; comment	Ref.	Irr.	Physical condition	Absorbed dose; decomposition	Investigation methods	Decomposition products
Streptomycin HCl	(4)	g	Solid substance	16 kGy None	col, pot, sol	
Streptomycin sulfate	(12)	g	Solid substance	25, 250 kGy 3, 5%	pot, view	
Streptomycin sulfate	(25)	g	Solid substance	25 kGy 2% (chem) after storage for 1 year at room temp. +6% (pot)	col, hyp, pot, pH, pyr, sol, tox	
Streptopenicillin (streptomycin sulfate)	(25)	g	Solid substance	25 kGy 4% (chem) after storage for 1 year at room temp. +6% (pot)	col, hyp, pot, pH, pyr, sol, tox	
Tetracycline	(9)		See cefaloridine (9)			
Tetracycline HCl	(7)	g, e	Solid substance	25 50 kGy <1% (chem) <2% (pot)	cont, DSC, IR, PhNord, pot, TLC	
Tetracycline HCl	(27)		See chlortetracycline sodium (27)			
Tetracycline HCl	(16)	g	Solid substance	25–150 kGy 4% (pot)	NMR, oro, mp, pot, TLC, UV	1 by TLC (150 kGy)
Tobramycin	(9)	g	Solid substance	25, 50, 75, 100 kGy 5, 19, 27, 37%	pot	
			?% aq. solution	25, 50 kGy 67, 100%		
Vancomycin	(9)	g	Solid substance	25–80, 100 kGy None, 2%	pot	
			?% aq. solution	25 kGy Complete		
Viomycin	(22)	g	Solid substance	25 kGy 1–2%	GC, IR, MS, NMR, UV, ESR	
Virginiamycin	(9)	g	Solid substance	25, 50, 70, 100 kGy 4, 11, 11, 19%	pot	
			?% aq. solution	25 kGy Complete		

Table 2A

Decomposition of Solid Substances: Alkaloids and Morphine Derivatives

Substance	Ref.	Absorbed dose (kGy)	Changes in investigation method	Decomposition (●● = 1%; ○ = no decomp.)[a]
Atropine	(1)	25/50	col, mp, TLC, UV	●
	(7)	25/50	PhNord	●●●●
	(8)	25	UV	●●
	(12,33)	25/50	col, mp	
	(30)	60	TLC	●●●●
	(32)	25/50	col	○
Cocaine	(30)	60	—[b]	○
Codeine	(30)	60/750	—	○
	(32)	25/50	col	○
Dihyhroergocristin-methansulfonate	(34)	50	col	○
Ephedrine	(8)	25	mp, UV	●●
	(23)	25	mp, UV	●●●●
	(30)	60	—	○
Ergometrine	(12)	25/250	col, mp, pH	
Ethylmorphine	(10)	25	col	○
	(32)	25/50	col	○
Hydrocodone[c]	(29)	60	oro	○
Hydrocodone[d]	(8)	25	UV	●
	(23)	25	UV	●●●●
	(30)	60	—	○
Hydromorphone	(29)	60	oro	○
	(30)	60	—	○
Levomethadone	(30)	60	TLC	●●●●
Methadone	(29)	60	TLC	●
Morphine[c]	(8)	25	UV	●●●●●●●●●●
	(23)	25	TLC	●●●●
	(29)	60	oro	○
	(30)	60	—	○
	(32)	25/50	—	○
Morphine[e]	(12,33)	25/50	col, pH, oro	
Oxycodone	(29)	60	oro, TLC	●
	(30)	60	—	○
Papaverine	(32)	25/50	col	○
Pethidine	(29)	60	oro	○
	(30)	60	—	○
Pilocarpine	(1)	25/50	col, DSC, mp	○
	(7)	25/50	—	○
Reserpine	(34)	50	col, UV	●
Scopolamine	(30)	60	—	○

[a]○: no decomposition by TLC.
[b]—: no changes.
[c]Hydrochloride.
[d]Hydrogentartrate.
[e]Sulfate.

Table 2B

Decomposition of Solid Substances: Antibiotics

Substance	Ref. dose[a]	Absorbed (kGy)	Changes in content (● = 1%; ○ = no decomp.) Increase	Decrease	chem, pot[b]
Amphotericine B	(9)	25		○	pot
Bacitracine	(12)	25		●●●●●●●	pot
Cefadroxil	(19)	25	●		chem
			●		pot
Cefalexine	(15,17,21)	25		●	chem
				●●●	pot
Cefaloridine	(15,17,21)	25	●●		chem (15,17)
				○	chem (21)
				●	pot (15,17,21)
	(9)	25		○	pot
Cefalotin	(9)	25		●●	pot
	(15,17,21)	25		○	chem
				●●●●●●●●●	pot
	(14)	50		●●●●●	chem
Cefamandole	(13)	25	●●●●		chem
				●	pot
Cefapirine sodium	(15,17,21)	25		●	chem (15,17)
				●	chem (21)
				●●●●●●●	pot (15,17,21)
Cefazolin	(19)	25		●●	chem
				●●●●●●●●	pot
Ceforanid	(19)	25		○	chem
				●●●●	pot
Cefotaxim	(19)	25		○	chem
				●●●●●	pot
Cefoxitin sodium	(14,18)	50		●●	chem
Cefradine	(19)	25		●●●●●●●●●●●●	chem
				Δ7	pot
Chloramphenicol	(1)	25		●●	chem
	(4)	16		○	pot
	(7)	50		●	chem
				●●●	pot
	(8)	25		○	chem
	(9)	25		○	pot
	(23)	25		○	chem
	(30)	60		●●	chem
Chlortetracycline	(4)	16		○	pot
sodium	(11)	50		Small	chem
	(27)	25		○	chem
	(9)	25		○	chem
Colistin	(9)	25		○	pot
Dihydrostreptomycin-	(12)	25		○	pot
sulfate	(25)	25		●●	chem
				●●●●	pot
Erythromycin	(9)	25		○	pot
Framycetin	(9)	25		○	pot
Fusidic acid	(9)	25		○	pot

(*continued*)

Table 2B *Continued*

Gentamycin	(9)	25	○	pot
Kanamycin	(9)	25	○	pot
Lincomycin	(9)	25	○	pot
Minocyclin	(9)	25	○	pot
Nalidixic acid	(9)	25	○	pot
Neomycin	(9)	25	○	pot
Neomycin sulfate	(12)	25	●●●●	pot
Nystatine	(27)	25	○	chem
Oleandomycin	(9)	25	○	pot
Oxytetracycline	(4)	16	○	pot
	(11)	50	○	pot
Oxytetracycline HCl	(27)	25	○	chem
Paromomycin	(9)	25	○	pot
Pasomycin	(25)	25	●●	chem
			●●	pot
Polymyxin HCl	(27)	25	○	chem
Polymyxin	(12)	25	●●●●●●●●●●●●	pot
Pristinamycin	(9)	25	●●	pot
Rifampicin	(5)	20	Very small	chem
	(9)	25	○	pot
Streptomicillin	(26)	25	●●●	chem
			●●	pot
Streptomycin	(9)	25	○	pot
Streptomycin HCl	(4)	16	○	pot
Streptomycin sulfate	(12)	25	●●●	pot
	(25)	25	●●	chem
			●●●●●	pot
Streptomycin–calcium chloride complex	(25)	25	●	chem
			●●●	pot
Streptopenicillin	(25)	25	●●●●	chem
			●●●●●	pot
Tetracycline	(9)	25	○	pot
Tetracycline HCl	(7)	50	●	chem
			●●	pot
	(16)	25	●●●●	pot
	(27)	25	○	chem
Tobramycin	(9)	25	●●●●●	pot
Vancomycin	(9)	25	○	pot
Viomycin	(22)	25	●●	chem
Virginiamycin	(9)	25	●●●●	pot

[a]Mainly 25 kGy dose level.

[b]Chem = chemical assay; pot = microbiological assay (potency).

Table 3

Decomposition of 1–2% Aqueous Solutions of Alkaloids and Morphine Derivatives in the Dose Range 10–25 kGy

Substance	Ref.	Concentration %	Changes in investigation method	Decomposition (●●●● = 10%)
Apomorphine	(30)	1		●●●●
Atropine	(1)	1	TLC	
	(24)	1		●●
		2		●●
	(30)	1,5	TLC	●●●●●●●
	(32)	2	pH, TLC	
Cocaine	(30)	2	col, TLC	●●●●
Codeine	(30)	2	TLC	●●●●●●
	(32)	2	col, pH, TLC	
Ephedrine	(8)	1		●●
Ergometrine	(8)	2	col, pH	
Ethylmorphine	(32)	2	col, pH, TLC	
Hydrocodone[a]	(29)	1		●●●●●●●●●●
		1,5		●●●●●●●●
Hydrocodone[b]	(8)	2		●●
	(30)	1,5		●●●●●●●●●
Hydromorphone	(29)	1		●●●●●●●●●●●●●●●
	(30)	1,5		●●●●●●●●●●●●●●●●●●●●
Levomethadone	(30)	2	TLC	●●●●●●●●●
Methadone	(29)	1		●●●●●●●●●
Morphine[a]	(8)	2		●●●●●●
	(29)	1		●●●●●●●●●●●●●●
		2		●●●●●●●●
	(30)	2	TLC	●●●●●●●
	(32)	2	col, pH, TLC	
Morphine[c]	(12,33)	1,5	col, oro	
Oxycodone	(29)	1	col	●●●●●●●●●●
		2		●●●●●●●●
	(30)	2	col, TLC	●●●●●●
Papaverine	(32)	2	col, pH, TLC	
Pethidine	(29)	1		●●●●●●●●●●
Pilocarpine	(1)	1	TLC	●●●●●●
Scopolamine	(30)	2		●●●●●●

[a]Hydrochloride.
[b]Hydrogentartrate.
[c]Sulfate.

Table 4A

Decomposition of 1–2% Aqueous Solutions of Alkaloids and Morphine Derivatives in the Dose Range of 40–60 kGy

Substance	Ref.	Concentration (%)	Changes in investigation method	Decomposition (●●● = 10%)
Apomorphine	(30)	1		●●●●●●●●●●●●
Atropine	(30)	1,5	TLC	●●●●●●●●●●
Cocaine	(30)	2	col, TLC	●●●●●●
Codeine	(30)	2	TLC	●●●●●●●●●●●●●●●●
Ephedrine	(30)	2	col, TLC	●●●
Hydrocodone[a]	(29)	1		●●●●●●●●●●●●
		1,5		●●●●●●●●●●
Hydrocodone[b]	(30)	1,5		●●●●●●●●●●●●
Hydromorphone	(29)	1		●●●●●●●●●●●●●●●●●●
	(30)	1,5		●●●●●●●●●●●●●●●●●●●●●●●●
Levomethadone	(30)	2	TLC	●●●●●●●●●●●●●●
Methadone	(29)	1		●●●●●●●●●●●●●●●●
Morphine[a]	(29)	1		●●●●●●●●●●●●●●●●●
		2		●●●●●●●●●●●●
	(30)	2	TLC	●●●●●●●●●●●●●●●●●
Oxycodone	(29)	1	col	●●●●●●●●●●●●●●●●
		2		●●●●●●●●●●●●●●
	(30)	2	col, TLC	●●●●●●●●●
Scopolamine	(30)	2		●●●●●●●●●

[a]Hydrochloride.
[b]Hydrogentartrate.

Table 4B

Decomposition of Aqueous Solutions of Antibiotics

Substance	Ref.	Concentration (%)	Absorbed dose (kGy)	Decomposition (● = 5%)
Cefaloridine, cefalotin, chloramphenicol colistin, framycetin, fusidic acid, gentamycin, kanamycin, lincomycin, minocyclin, nalidixic acid, neomycin, oleandomycin, paromomycin, pristinamycin, rifampicin, streptomycin, vancomycin, virginiamycin	(9)	?	25	Complete
Chloramphenicol	(1)	1	25[a]	
	(23)	0.1	25	●●●●●●●●
		0.05	25	●●●●●●●●●●●●
	(30)	0.25	80	●●●●●●●●●●●●●●●●●●
	(8)	0.1	25	●●●●
		0.05	25	●●●●●●
Chlortetracycline	(11)	0.01	3	Complete
Erythromycine	(9)	?	25	●●
			50	●●●
Oxytetracycline	(11)	0.01	3	Complete
Tobramycin	(9)	?	25	●●●●●●●●●●●●●
			50	Complete

[a]Altorfer (1) made no comment on the percentage of decomposition, but he found 11 additional spots by TLC.

Table 5A

Number and Identity of Decomposition Products in Irradiated Aqueous Solutions of Alkaloids and Morphine Derivatives

Substance	Ref.	Decomposition products
Apomorphine	(30)	Several
Atropine	(1)	6 (tropanol)
	(24)	6
	(30)	Several
	(32)	2 (probably tropa acid and apoatropine)
Cocaine	(30)	Several
Codeine	(30)	8
	(32)	1
Ephedrine	(8)	1
	(30)	Several
Ergometrine	(8)	No ergometrinine detectable
Ethylmorphine	(32)	1
Hydrocodone[a]	(29)	1
Hydrocodone[b]	(8)	2
	(23)	Several
	(30)	Several
Hydromorphone	(29)	4
	(30)	6
Levamethadone	(30)	7
Methadone	(29)	4
Morphine[a]	(8)	2
	(29)	2
	(30)	4
	(32)	2
Oxycodone	(29)	2
	(30)	8
Papaverine	(32)	2
Pethidine	(30)	6
Pilocarpine	(1)	Several (tropanol)
Scopolamine	(30)	Several

[a]Hydrochloride.
[b]Hydrogentartrate.

Table 5B

Number of Decomposition Products in Irradiated Aqueous Solutions of Antibiotics

Substance	Ref.	Concentration (%)	Absorbed dose (kGy)	Decomposition products
Chloramphenicol	1	1	25	11 (TLC)
	30	0.25	80	15 (TLC)
	8	0.05–0.1	25	1 (PC)
Chlortetracycline	11	?	4	2 (TLC)

Table 6A

Comparison of Irradiated Solutions (a) with Solutions of Separately Irradiated Components (b): Alkaloids and Morphine Derivatives

Substance	Ref.	Concentration (%)	Irr. mode	Changes in investigation method	Decomposition (●● = 10%; ○ = no decomp.)[a]
Atropine	(1)	1	a	TLC	[b]
	(30)		b		●
	(30)	1.5	a	TLC	●●●●●●●
			b		●
Cocaine	(30)	2		col, TLC	●●●●●
			b		○
Codeine	(30)	2	a	TLC	●●●●●●●●●●●
			b		○
Ephedrine	(30)	2	a		●●
			b		○
Hydrocodone	(30)	1.5	a		●●●●●●●●
			b		○
Hydromorphone	(30)	1.5	a		●●●●●●●●●●●●●●●
			b		○
Levomethadone	(30)	2	a	TLC	●●●●●●●●●
			b		●
Morphine	(30)	2	a	TLC	●●●●●●●●●●●
			b		○
Oxycodone	(30)	2	a	col, TLC	●●●●●●●
			b		○
Pethidine	(30)	5	a		●●●●●●●●●●●●●
			b		○
Pilocarpine	(1)	1	a	TLC	●●●
			b		○
Scopolamine	(30)	2	a		●●●●●●
			b		○

[a]○: no decomposition by TLC.
[b]Altorfer (1) made no comment on the percentage of decomposition, but he found six radiolysis products.

Table 6B

Comparison of Irradiated Solutions (a) with Solutions of Separately Irradiated Components (b) and Irradiated Solutions with Radioprotectors (c): Antibiotics

Substance	Ref.	Concentration (%)	Abs. dose (kGy)	Irr. mode	Decomposition	Decomposition products
Chloramphenicol	(1)	1	25	a	Yes	11
		0.25	25	b	Yes	5
		0.5	25	b	Yes	Some[a]
	(8)	0.1	25	a	19%	1
		0.1	25	c	Red.[b]	1
	(30)	0.25	80	a	84%	15
		0.25	80	b	2%	1
	(31)	0.25	40	c	23%	—
Chlortetracycline	(11)	?	2.5	c	Red.[c]	—

[a]Number not detectable.
[b]Small reduction of decomposition, measurement impossible.
[c]The radiation effect was significantly reduced in comparison with the irradiated solution without radioprotectors.

DISCUSSION

Alkaloids and Morphine Derivatives

Solid Substances

As can be seen in Table 2A, half of the solid substances did not show any decomposition. In the group of substances where results from different sources were available, atropine was decomposed in four investigations up to 2%. Only in one publication was no decomposition detected. In the case of morphine hydrochloride, two investigations mentioned a decomposition of up to 5% whereas three did not mention any decomposition. In the case of ephedrine and hydrocodone hydrochloride, decomposition was found in two of three investigations.

Decomposition products were found in the substances atropine (2–4, apoatropine and tropanol could be identified), methadone (1), morphine (2) and oxycodone (1).

Aqueous Solutions

Most of the aqueous solutions had a concentration between 1% and 2%, and were irradiated at 10 to 25 kGy or 40 to 60 kGy. Therefore, only this concentration and dose range are considered in Tables 3A and 4A. Irradiation resulted in a more or less pronounced radiolysis in all studied pharmaceutical substances, with rare exceptions. Decomposition depends upon the material and increases with incremental dose and falling concentration.

In most irradiated solutions, decomposition products were found (Table 5A), but only a few were identified.

Comparison of irradiated solutions with solutions irradiated separately was made in two investigations. The results are presented in Table 6A. In all cases the solution was more affected by radiation than the separately irradiated components.

Antibiotics

Solid Substances

About half of the solid substances did not show any decomposition (Table 2B). In the group of substances where results from different sources were available, chloramphenicol showed less than 1.5% decomposition in one investigation and no decomposition in three investigations, respectively, when irradiated at doses of 25 kGy. Two more investigations on chloramphenicol irradiated at doses of 50 and 60 kGy, respectively, found decomposition of less than 1.5% also. Tetracycline lost up to 3% of its potency when irradiated at doses up to 50 kGy (3 investigations). In another investigation of solid tetracycline, no decomposition was found by chemical analysis.

Aqueous Solutions

About two thirds of the investigations on irradiation of aqueous solutions were made by Fleurette et al. (9) on solutions of unknown concentration (Table 4B). Twenty-two substances were completely destroyed at 25 kGy absorbed dose. The rest showed decomposition between 9% and 67%, respectively, at 25 kGy absorbed dose.

CONCLUSION

Radiation sterilization of solid substances would certainly raise less problems than radiation sterilization of solutions. However, the major problem in evaluating the health risks of irradiated pharmaceuticals is not that of the chemical changes but of the toxicological and pharmaceutical consequences of radiolysis. As this question has been considered only in a small number of investigations, most of which are neither recent nor extensive ones, the present study does not give a conclusive answer.

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