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REVIEW ARTICLE

Radiation Effects on Pharmaceuticals

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Summary

Nowadays, sterilization process is used for the benefit of humans in different areas of daily life. This includes the sterilisation of medical supplies and pharmaceuticals, in particular agent and auxiliary materials, decontamination of medical equipment, and decontamination of industry, for example drug-herb and vegetable products are used in broad areas. Gamma irradiation sterilisation methods stand out, with numerous advantages. Day by day, those who use this method are applying them in more fields, and the product has gained increasingly widespread use. In fact, according to official authorities in many countries, it has been accepted as a method and has become routine since it was introduced. With regard to pharmaceutical products, gamma irradiation sterilisation has been used and records show the continuous development of the method for sterilisation. Recent studies have focused on many different pharmaceutical products, active and auxiliary substances, active ingredients in drugs, and new drug delivery systems, and discuss the effects of radiation sterilisation on the work. Especially after irradiation, which is much used in the control of analytical studies and reviews, and sterility controls over time, these methods are developing rapidly. The investigation into the use of gamma radiation continues; a new development began to attract attention: the use of e-beam irradiation sterilisation. Increased attention in the developments and studies of this subject, with focus on gamma radiation sterilisation of pharmaceuticals, will become more important in the future.

Key Words: *Sterilisation, radiation sterilisation, sterilisation of pharmaceuticals, pharmaceutical sterilisation, gamma irradiation sterilisation, E-Beam irradiation sterilisation.*

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Radyasyonun Farmasötikler Üzerine Etkileri

Özet

Günümüz koşullarında sterilizasyon işlemi birçok alanda insanlığın yararına kullanılmaktadır. Özellikle tıbbi cihazlar ve ilaç sterilizasyonu, etkin madde ve yardımcı madde, tıbbi cihazlar dekontaminasyonu, endüstride drog-bitki ve bitkisel ürünlerin dekontaminasyonu gibi çok geniş bir alanda kullanılmaktadır. Bu amaçla kullanılan sterilizasyon yöntemlerinden gama radyasyonuyla sterilizasyon işlemi getirdiği avantajlar ile ön plana çıkmaktadır. Gün geçtikçe daha fazla alanda ve üründe kullanım bulan bu yöntem giderek daha yaygın bir kullanıma kavuşmuştur. Hatta birçok ülkede otoritelerce kabul edilerek resmi, kabul edilir bir yöntem olarak uygulanmaya başlanmıştır ve rutin hale gelmiştir. Farmasötik ürünlerin sterilizasyonunda gama radyasyonun kullanılması, uzun süredir sürdürülen ve üzerinde sürekli gelişme kaydedilen bir yöntem olarak sterilizasyonda giderek yaygınlaşan bir yöntem haline gelmiştir. Son zamanlarda yapılan çalışmalarla birçok değişik farmasötik bitmemiş ürün, etkin ve yardımcı maddelerle, ilaç etkin maddelerinin, yeni ilaç taşıyıcı sistemlerin radyasyonla sterilizasyonu ve bunun etkileri üzerinde çalışılmaktadır. Özellikle ışınlama sonrası yapılan analitik incelemeler ve sterilite kontrolleri çalışmaların kontrolünde fazlaca kullanılmakta ve bu yöntemler de hızla gelişmektedir. Gama radyasyonun kullanımı ve araştırılması devam ederken, yeni bir gelişme olarak e-beam radyasyonuyla sterilizasyonun da kullanımı dikkat çekmeye başlamıştır. Bu konudaki süregelen gelişmeler ve çalışmaların artışı; farmasötiklerin gama radyasyonu ile sterilizasyonunu gelecekte daha önemli hale getirecektir.

Anahtar Kelimeler: *Sterilizasyon, Radyasyonla Sterilizasyon, Farmasötiklerin Sterilizasyonu, Gama Radyasyonuyla Sterilizasyon, E-Beam Radyasyonuyla Sterilizasyon.*

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INTRODUCTION

The effect of radiation on pharmaceuticals is known in general, and gamma irradiation sterilisation has an impact on pharmaceuticals to be investigated. One of the applications of radiation sterilisation in healthcare, the use of pharmaceuticals as a method of sterilisation, was accepted by the IAEA in 1967. In recent years, for commercial use, an increase in the number of gamma irradiators of medical devices has been seen, and the application of this method has been seen in the pharmaceutical and cosmetic industries. Gamma rays are the most important method for the sterilisation of pharmaceuticals, due to the high ability to penetrate the sterile packaging of pharmaceutical and cosmetic products, and the fact that the final heat during the process did not increase their traceability or ability to deliver effective and helpful for the heat-sensitive substances in packaging materials or operations. Gamma rays are also easier to control, secure, reliable and provides a fast process. The residue used was purified gases and the process does not require post-quarantine measures and the product obtained has no harmful effect on the environment (1).

Gamma radiation, as the first image BP 1963 (British Pharmacopoeia) and USP XVII (U.S. Pharmacopoeia), are included in the sterilisation process, and a sterilisation dose of 25 kGy is proposed as the method (2).

However, the level of sterility in some products requires doses of 1-15 kGy due to the microbial load (bioburden) (3,4).

The main groups of pharmaceuticals studied by gamma irradiation sterilisation are listed as follows:

1. ANTIBIOTICS AND OTHER DRUGS

A) Solid Systems:

In general, solid-state systems show a lower loss of activity after ionising radiation than other systems.

B) Aqueous Solutions and Suspensions:

In aqueous solutions and the basic component of water suspensions, as a result of excitation, ionisation and high-energy gamma-rays generated and released by dissociation radiolysis products, especially hydrogen, hydroxyl radicals, hydrated electrons and hydrogen peroxide in the environment, that can result in as decomposition substances. For this reason, the use of radiation sterilisation in aqueous solutions and suspensions of various organic compounds is not possible. However, the alkali and alkaline earth elements and alkali metals, chlorides and phosphates, as well as the aqueous solutions of citrates and lactates of alkaline metals were not affected by radiation sterilisation. For example, in a solution of 0.9% NaCl solution, an irradiation change of 25 kGy does not occur. In some cases, the irradiation of freeze dried aqueous solutions is possible. For example, a significant loss of activity was seen in insulin and heparin irradiated aqueous solutions, whereas freeze dried solutions were found to be resistant to radiation. However, cold irradiation as a method is regarded expensive and difficult to implement (2).

Radiation resistance identified within the active substances constitute the largest group of antibiotics. Semi-synthetic penicillins, especially beta-lactam antibiotics (amoxicillin trihydrate, fluoksasiklin sodium, methicillin sodium) and cephalosporins (sephaleksin, sephaloridin, cefadroxil sodium, cefotaxime) showed no significant loss of activity when irradiated. Tetracycline hydrochloride, chloramphenicol, gentamycin, neomycin, streptomycin sulphate antibiotics in a dry powder form were irradiated, and there was no loss of activity (Table 1) (2).

a) Penicillins:

An aqueous solution of sodium benzyl penicillin radiolysis as a result of sterilisation by irradiation, penicillin OH side chain in the benzene ring by reaction between a hydroxy benzyl penicillin, and also the formation of beta-lactam ring fragmented OH's penilloic benzyl and benzyl in the form of penicilloic acid formation was observed. Reaction with aqueous benzyl penicillin electrons ultimately causes molecular arrangements such as the formation of benzyl peniloik acid degradation products; therefore, the sterilisation of an aqueous solution of

Table 1. Ionizing Radiation-Solid Pharmaceuticals Activity Loss (5).

ANTIBIOTICS	DOSE (kGy)	LOSS OF ACTIVITY (%)
Chlortetracycline	17.9-100	0
Oxytetracycline	17.9-100	0
Chloramphenicol	17.9	0
Tetracycline hydrochloride	80	0
Streptomycin hydrochloride	25	0
Sodium benzyl penicillin	25	0
Phenoxy methyl penicillin	25	0
Benzathine penicillin	25	0
Dihydrostreptomycin	25	0
Potassium benzyl penicilin	17.9	0
Polymyxin	80	0
Colimycin	80	0
Nystatin	80	0
Mycerin	80	0
Sulphapyridine	25 and 250	0
Sulphatiazole	25 and 250	0
Streptomycin sulphate	25	3
Streptomycin sulphate	250	5
Dhydrostreptomycin	250	5
Neomycin sulphate	25	4
Sodium benzyl penicillin	250	3
Benzathine penicillin	250	3
Phenoxymethyl penicillin	250	3
Zinc bacitracin	25	7.1
Zinc bacitracin	250	26.7

benzyl penicillin by radiation was not possible (6).

In a study of groundnut oil as a carrier, using a procaine ester of penicillin, about 1-2% decomposition was observed after 40 kGy dose. The radiolysis products found were benzyl penillo aldehyde and benzyl penaldic acid (7).

In the study by Dimitrova and colleagues, DMSO (dimethyl sulphoxide) in the 5-10 kGy gamma-irradiated solution of amoxicillin trihydrate did not cause a loss of biological activity of penicillin, so a radiation dose of 25 kGy, was found to be a suitable sterilisation dose (8).

Loss of microbial activity was observed in 50 kGy irradiation of benzyl penicillin. A 50 kGy radiation dose in powder forms of ampicillin, metampsillin, carbenicillin and ticarcillin was stable (9).

A semi-synthetic penicillin series of 25kGy observed stability for, anhydrous ampicillin, ampicillin trihydrate, ampicillin sodium, oxacillin sodium, sodium kloksasilin, dikloksasilin sodium, potassium, and carbenicillin disodium hetasillin (9).

In the study by Jacobs using ampicillin and its esters and 25 and 50 kGy doses of radiation, the microbiological and chemical properties of ampicillin sodium, pivampicilin, talampicilin were examined and some changes in the radiolysis was observed; it was concluded that low doses must be used for decontamination (10) .

b) Cephalosporins:

Jacobs's study of four member cephalosporins of beta-lactam antibiotics observed radiolysis of various degrees in powder forms undergoing the sterilisation process. For cefazolin sodium, sefodroksil monohydrate, and seforanid, 25 kGy and 50 kGy doses were tested using degrees of melting, chemical and microbial quantification, UV absorption, the degree of optical rotation, TLC, HPLC, pH change test and sterility tests. In conclusion, cefazolin sodium, cefodroxyl monohydrate, cefaronid, cefotaxime CGP 9000 dihydrate can be sterilised with a generally accepted dose of 25 kGy. 1% decomposition was observed to not result in the formation of a toxic product. In addition, sterilisation was not possible under these circumstances for sefadrin mono hydrate (11).

According to Fleurette, a salt sterilization dose of 50 kGy in cephaloridin, found a loss of activity of between 2.3% and 5.7%; a loss of antimicrobial activity was not observed (9).

The study of the radiation sterilisation of commercial preparations of lyophilised cefazolin sodium included four different doses of 5, 10, 25 and 40 kGy irradiation, and stability tests were performed to determine the physicochemical and microbiological properties. The study results were compatible with the active substance with electron spin resonance, which has been found to occur in two radicals. In two commercial lyophilised preparations subjected to radiation, increasing radiation doses and sterilisation process affected the antimicrobial activity. Pharmaceutical dosage forms are about 10 kGy dose of the SAL. Staining characteristics of the studied commercial preparations can be sterilised at low doses (outside 25 kGy). As a result, commercial freeze-dried parenteral products and active substances of cephazolin sodium's parenteral preparations could be sterilized by gamma irradiation at lower doses than 25 kGy (12).

c) Neomycin and Other Aminoglycoside Antibiotics:

The studies by Jacobs and the International Association of Medical Protesis Manufacturers (ABPI), observed a 5% reduction in the activity of streptomycin sulphate, and neomycin sulphate as a result of sterilisation with 25kGy (6).

Irradiation with 35 kGy decreased tobramycin sulphate activity by 5% (6), and Fleurette's study of tobramycin using 25 and 50 kGy reported decreases of 4.4% and 18.5% decrease (9).

Bhalla et al. failed to find a reduction in neomycin sulphate, prednisolone and hydrocortisone acetate after the ointments were radiation sterilised, although a slight colour change effect was seen (13).

In Kimoru and colleagues study, radiation sterilisation of 0.1% or 1% akrinol solutions increased in proportion to the decomposition observed with increasing radiation doses. Although a certain level of degradation occurred in Akrinol solution with 25 kGy of radiation dose, this dose was found suitable for the sterilisation of the solution (14).

d) Tetracyclines:

Jacobs et al. found that tetracycline hydrochloride and its ophthalmic ointment was sterilised with 10 and 25 kGy doses, and also saw change in the UV absorptions, specific optical rotation, TLC, changes in the degree of melting, NMR, and microbial changes in the amount examined. At 25 kGy TLC, no significant changes in the degree of melting and in the NMR were observed. Low initial doses of 10 kGy were determined to be sufficient for sterilisation (15).

e) Sulphonamides:

Philips et al. studied sodium sulphacetamide powder and ointments containing 20-30 % sulphacetamide solutions were sterilized by 20% to 30%, which explained sterilisation with 4% decomposition (16).

Fleurette's study observed a decrease of antimicrobial activity for co-trimoksazol (trimethoprim + sulphamethoxazole) with a decreased dose of 50 kGy (9).

Trigger and Cadwell reported a slight reduction in effect with a 25 kGy dose in 10% eye drops and 5% sulphasetamide eye ointment (17).

Olguner studied the sulphonamide group of three active ingredients (sulphacetamide sodium, sulphamethoxazole and sulphafurazol) with radiation sterilisation of commercial preparations and their ophthalmic or parenteral on 5, 10, 25 and 50 kGy doses. As a result of a study, a sterilisation dose of 25 kGy can be concluded to be more effective than lower doses of radiation for the the three active substance powders and solution, commercial preparations in the form of ophthalmic suspensions and parenteral solutions adopted for pharmacopoeias (4).

f) Other Antibacterial Agents:

Rhee et al. studied the powder form of chloramphenicol and erythromycin and found that, at 50 kGy, they were stable after irradiation. The solution lost 90% of the activity of chloramphenicol after a dose of 15 kGy (18).

No loss of activity was seen by Fleurette when studying rifampicin, amphotericin B, and nitrofurantoin in the solid-state with 50 kGy radiation doses (9).

Tsuji et al. did not observe a decrease in the activity of basitrasin irradiated at 18 kGy (19).

According to a study by Moore and Wilkins, in which a metranidazol solution (pH 7) was prepared under a nitrogen atmosphere followed by gamma-irradiation sterilisation, the G value was 0.96. Oxadiazole groups and imino-ketone were found to be the radiolysis products (20).

Some of the beta-lactam group of antibiotics (Merophenem Trihydrate, Piperacillin Monohydrate, Sultamicillin Tosylate) were studied using 1, 3, 6, 10 and 15 kGy doses, with gamma radiation and formation of products were detected by the ESR method. The ESR results showed that all antibiotics can be sterilized by gamma irradiation (21).

2. ENZYMES AND HORMONES

Gopal reported that the proteolytic activity of papain decreased with the increase in irradiation doses when the activity was detected after 18 and 30 kGy (22).

Morimoto et al. used a dose of 0.5 kGy, followed by trypsin and kallikrein, after a dose of 1 kGy kimotripsinin completely inactivated an aqueous solution (23).

Fujimoto mentioned that the powder form of bromelain containing thermoase is radiorezistant to sterilization; whereas Kotaka et al found that the proteolytic activities of bromelain (like amylase, protease) after 30 kGy irradiation decreased by <10%, 24-42 % and 20-42%, respectively (25).

Indian health authorities use sterilisation by radiation for use in wound healing ointments sutilain, as well as in chymotrypsin-containing ointments, which is accepted by the American authorities (6).

In addition, triptorelin's i.m. (intramuscular) injection solutions are sterilised by radiation in France (6).

In the study by Andreeva and colleagues, blood cell enzyme immobilised polymeric catheters (carboxyethyl cellulose immobilized trypsin, immobilized acetyl cellulose profezim) were treated with a dose of 25 kGy to irradiate films with immobilised trypsin, and the effects of proteolytic enzymes showed a very large loss. With increasing doses (40-60 kGy), enzyme inactivation was increased, but low doses of 25 kGy were reported to not provide complete sterilization (26).

Similarly, Saad and colleagues reported a minimal change in the activity of an oily solution of testosterone at an androgenic-sterilising dose of 25 kGy. After irradiation sterilisation, no changes were observed in testosterone propionate oil carriers using polarimeter-IR-UV spectrophotometry (27).

Bussey and colleagues observed a 1% loss of effect for corticosteroids after sterilisation with 1.3 kGy. This suggests that this substance is not suitable for sterilisation by radiation (28).

Gopal and colleagues studied hydrocortisone, hydrocortisone acetate, prednisolone acetate and prednisolone with 25 kGy, and found that the radiation dose resulted in very little degradation. Radiation sterilised hydrocortisone and chymotrypsin ointments are accepted in India (29).

Although affected by gamma radiation, solid-state beclomethasone dipropionate and beclomethasone ointment containing propylene glycol and methanol, which are registered in B.P., are sensitive to radiation (30).

Pituitary hormone TSH was found to be active a month after sterilisation at a dose of 25 kGy, but the activity of vasopressin during this period decreased. Growth hormone ACTH, human menopausal gonadotropin and luteinising hormone were ineffective following sterilisation by radiation (31).

3. VITAMINS

In an argon-saturated solution of thiamine, radiolysis products increased with increasing thiamine concentration (32).

Similarly, thiamine, riboflavin, pyridoxine, nicotinamide, and two multivitamin preparations containing Ca-pantothenate state were observed to be strong enough to be sterilised as a result of electron irradiation (33).

L'vova and colleagues found that ascorbic acid in the solid form is resistant to 25 kGy of radiation, but that the deterioration and decay increased significantly with increasing concentrations of beta and x-ray radiolysis of dilute solutions, and also that degradation is more common in a nitrogen atmosphere (34).

Cyanocobalamin (B12) and hidrosiyanokobalamin (B12a) vitamins were studied; no significant degradation was observed with the aqueous electron and OH attacks. This was prevented by a suitable protecting radical, as well as decomposition, at the lowest freezing temperature (33).

Radiation sterilisation of aqueous solutions of pyridoxal-5-phosphate resulted in an increased dose and concentration, and radiochemical, hydrolytic decomposition and oxidation (35).

Thiamine hydrochloride, riboflavin, calcium pantothenate, nicotinamide, pyridoxal HCI and cyanocobalamin decay was observed in a study up to 10 kGy. These included ascorbic acid and nicotinamide, which have a protective effect (36).

It has been reported aqueous calcium pantothenate (B3) solutions at -196 degrees can be sterilised by radiation (37).

In the study by Dijoke and his colleagues, particularly with active ingredients such as vitamin A. rapidly decaying radiation sterilisation of ointments was shown to be sufficient for 10 kGy gamma radiation sterilisation (38).

4. ALKALOIDS AND MORPHINE DERIVATIVES

Degradation was observed in neostigmine bromide in powder form as a result of irradiation doses of 25-45 kGy in Jacobs and Leupin's study. Nasal and ophthalmic ointments containing 5% dexapentol showed very little effect as a result of the decrease (39).

Atropine sulphate eye ointments sterilisation at a dose of 25 kGy under the result of a weak decomposition and similarly Belladonna leaves sterilized by gamma irradiation at 3.1 kGy dose caused loss of main alkaloid (atropine) (17).

A very significant amount of morphine led to a decrease in opium after 6 kGy radiation sterilisation (40).

Increasing radiation dose in 2% solutions of morphine, hydromorphine, oxycodeine, hydrocodeine, pethidine and methadone showed a significant reduction in their activities (39). Similar results were observed for ephedrine and morphine by Chakchir and Bobkow (41).

After irradiation dose of 25 kGy, pilocarpines were found to still carry the desired properties of Pharmacopoeias (39).

20% caffeine-sodium benzoate maintained its original pH after the irradiation dose of 25 kGy over 3 years (42).

5. CONTROLLED DRUG RELEASE SYSTEMS

These drugs are used for fixed amounts of the active ingredient is required in the bloodstream. Oral tablets, oily solutions, suspensions, skin patches, pellets for subcutaneous administration, and nanospheres, microspheres, liposomes, niosomes are used as formulations (43-45).

Controlled drug delivery systems are required for melatonin, ampicillin, mitomycin C, DMSA, DTPA (4).

PLG (Polylactic coglicolic acid) and PLGA (Polylactic gluconate) studies were performed using microspheres; a change was found in drug release characteristics following sterilisation by radiation, despite the decrease of the polymer's molecular weight (46).

Mucoadhesive Microspheres containing Sodium Sulphetamide were investigated in a study conducted on *in vitro* and *in vivo* properties; microspheres require a sterilisation dose of 25 kGy (47).

Chitosan microspheres containing Flurbiorofen as the active ingredient were studied in order to examine the release of gamma-sterilisation (at 25 kGy) process parameters affecting the preparation of polymer dose (48).

6. RADIOPHARMACEUTICALS

As reported by Bochkarev et al., I-131-labelled radiopharmaceuticals (for radiation sterilisation) resulted in radiochemical decomposition. However, a suitable radiation dose was 10 kGy (49).

Gopal, and Sundaram reported decreased activity in I-131-labelled human serum albumin, rose bengal and hippuran which had been sterilised by radiation (50).

7. DECONTAMINATION OF PLANT ORIGIN RAW MATERIALS

Radiation is used for decontamination, because of the processes used in the production of raw materials of vegetable origin, which usually have a high microbial load (Tragacantha, Gummi arabicum, Amylum, senna, ergot, Belladonna extract, etc.). Plantal drug doses were as low as 1 kGy in some researches, even if the therapeutic properties of plants reduced their microbial load to acceptable levels without causing any observed changes (2). In addition to the active substances of the pharmaceutical and cosmetic industries, widely used products such as talc, lactose, starch, bentonite, and kaolin, and excipients such as sodium CMC can also be sterilised by radiation (2).

For vaseline, paraffin or natural products, such as polyethylene glycol, and silicone ointment (which may be synthetic), radiation sterilization of pharmaceuticals seems to be the most promising. Currently, many of the ophthalmic and dermal ointments containing antibiotics, steroids or alcoloids can easily be sterilized by gamma irradiation due to the radiorezistance of those active substances in ointment bases.

As well as pharmaceutical products, these products are used as carriers for containers (collapsible aluminium tubes, the empty bottles made of polyethylene and polystyrene, gelatine capsules with the rubber, low density polyethylene and aluminium caps), and the pharmaceutical preparations used for the filtration membranes can be effectively sterilised by gamma radiation (2).

This comparative study on the subject blank hydroxypropylmethylcellulose and gelatine hard capsules using irradiated gamma and beta radiation as a result of the checks carried out, found that the ionising radiation sterilisation process has been concluded and the terms of sanitation (51).

Similarly, sterilization of disposable medical supplies (52) and sterilization of raw materials for cosmetics products (53) also can be accomplished by gamma irradiation.

5-10-15-30 kGy doses were found to be effective for anti-cancer agents such as cyclophosphamide and doxorobicin (in the powder format) with regard to the sterilisation process; cyclophosphamide, degradation products, colour changes and the possible lack of sterilisation of low-dose radiation

Table 2: Radiation Sterilisation of Various State Competent Authorities Permitted Control of Medicines in Pharmaceutical Products (2).

PHARMACEUTICALS PRODUCTS OPHTHALMIC OINTMENTS	DOSES (kGy)	COUNTRIES
Mercuric oxide	25	Australia
Sodium sulphacetamide(6%)	"	Australia, U.K
Oxytetracycline	"	Bangladesh
Chlortetracycline (1%)	"	U.K., U.S.A
Tetracycline HCl (1%)	"	U.K., U.S.A, Israel, India, Indonesia
Atropine Sulphate (6%)	"	U.K., India
Gentamycin Sulphate	"	India
Corticosteroid	"	Some European Countries
Neomycin	"	India, Some European Countries
Polymxycin-B sulphate	"	India
Zinc bacitracin	"	India
Penicillium G (Na)	"	India
Hydrocortisone	"	India
Aureomycine	"	U.K., Some European Countries
Chloramphenicol	"	U.K., India, Norway
OPHTHALMIC SOLUTIONS		
Physostigmine Salicylate (Oily suspension)	"	Australia
Tetracycline (1%) (Oily suspension)	"	U.K.
Contact Lens Saline Aerosol	"	U.K.
Cataline-Na Tablets	"	Some European Countries
LOCAL OINTMENTS		
Chloramphenicol (1%)	"	Norway
Tetracycline (3%)	"	U.K.
Neomycine Sulphate (in PEG)	"	India
HCA (in PEG)	"	India
Alfa Chymotrypsin (in PEG)	"	India
Chlorhexidine wound bandage	"	India
Framycetin sulphate (Adsorbed to parafin wound bandage)	"	Indonesia
Debrisan	"	U.K., India
POWDERS IN LOCAL		
Neomycin	"	Australia, India
Bacitracin	10-15	Australia, India
Talc	15	Indonesia,U.S.A.
Amylum (for surgical gloves)	15	India, Australia, Indonesia
VEGETABLES AND ANIMALS ORIJIN RAWS		
Rauwolfia serpentia (powder)	5	India
Ergot (powder)	25	India
Belladonna extract (dried)	"	India
Papain	"	India
Pancreatin	"	India
Semen Physilli	10	Australia
Gaviscon	25	Australia
Dried Plantal Drogs	15	Indonesia, India
ANTIBIOTICS		
Tetracycline HCI (Powder, i.m/i.v)	25	U.K., Norway, U.S.A.
Tetracycline HCI (Powder, for ophthalmic ointments)	25	Indonesia
DRUGS IN VETERINARY MEDICINE		
Oxfenadazol	3	Australia
Quinapyramine prosalt	25	India

sterilisation process was not appropriate. For doxorubicin, sterilisation is possible at the optimum dose of 25 kGy (54).

25, 100, 1000, 2000 and 3000 kGy radiation sterilisation was carried out on NSAI (Non-Steroidal Anti-Inflammatory) active substances (the ketoprofen powder), and radiolytic decomposition products were investigated. The active ingredient of ketoprofen in powder form was found to be resistant to sterilisation even at high doses (55).

Sultamicillin tosylate antibiotic powder was sterilised at 3, 6, 10 and 15 kGy radiation doses and stability after sterilisation, at room temperature and other temperatures, was investigated by the method of ESR (56).

It was reported that the antibiotic sulphathyazole can be sterilized by 10 kGy irradiation dose depending on the physical, chemical, biological and microbiological results obtained with sulphathyazole powder active substance and its model ophthalmic solutions irradiated at 10, 25 and 40 kGy (57).

As a result of various doses of radiation sterilisation in the antibiotics latomoxef and cephtriaxone changes and free radicals were examined as a result of the application to determine the time limit of 25 kGy: for latomoxef it was found to be 140 days, and for cephtriaxone was 115 days (58).

After sterilisation by irradiation, the changes in the antibiotic cephalosporin group Cefoperazone ESR (Electron Spin Resonance) were determined by the formation of free radicals and the duration limit of a 25 kGy dose of 140 days was identified (59).

Aminoglycoside antibiotics, sisomycin, tobramycin, and paromomycin were shown to form free radicals as a result of the sterilisation process at a dose of 25 kGy of gamma irradiation, and changes in the EPR (Electron Paramagnetic Resonance) were examined by spectrophotometry. Sterilisation results in free radical formation, as a result of a long period of storage that affect the speed of changes (60).

Another study on the effect on the heart drug doputamin HCl, examining the effects of radiation and radiation-sterilised products, did not make a comparison of the active substance (61).

Gamma radiation sterilization of dispers systems like liposomes, niosomes and sphingosomes with 25 kGy, significant degradation occurred. The formulation ingredients were irradiated in powder form instead of aqueous dispersion at lower doses than 25 kGy. No significant change in ingredients were obtained with the control tests. The researchers reported that further studies have to be done for the changes in physical behaviour of these dispertions prepared with the irradiated lipids and phospholipids, and the interaction of them with biological systems (62).

In order to increase the gamma radiation stability, microemulsified and microemulsion systems were irradiated and w/o microemulsion system was found to be the most preventing system from degradation of prednisolone (63).

In another study related to drug delivery systems, instead of eye drops containing gentamicin and vancomycin, minitablets formulations were used, which have shown the availability of radiation sterilisation (64).

Skin products were used in a study of the natural polyphenol resveratrol, and the effect of radiation on resveratrol hydrogel formulations was investigated (65).

Levonorgestrel containing progestin contraceptive microspheres were sterilised by radiation dose of 25 kGy, release of the active substance did not differ before or after treatment (66).

On radiation sterilisation of herbal drugs sold in markets in Brazil (some flower types), irradiation was shown to be a useful method for prevention of this (67).

In another study, *Gummi arabicum* was used as an excipient for the decontamination of fungi; 3, 7, 10 and 15 kGy of radiation sterilization was carried

out and investigated the effect of the rheologic characteristics of *Gummi arabicum* (68).

Different doses of gamma radiation are used in veterinary practice, subject to a study of salmonella toxoid vaccine. Analysis of gamma irradiation for sterilisation of the vaccine led to approval of the use of the method of sterilization in the end (69).

PLGA microspheres containing the active ingredient Thienorfin were used to study the effects of gamma radiation sterilisation; post-HPLC (High Performance Liquid Chromatography), SEM (Scanning Electron Microscopy) and laser particle size analysis was used and the method was found to be suitable with no significant change (70).

Nystatin niosomes contain two different formulations and neutral or negatively charged preparations were sterilized by 25 kGy of gamma irradiation. Then, niosomes prepared in experimental animals *in vivo* conditions in the body were examined after administration and found to be effective for parenteral administration compared with the nystatin (71).

Sparfloksazin *in situ* gel formulation was assessed for the treatment of experimentally increased bacterial keratitis; six different formulations were prepared and sterilized by gamma irradiation. The formulations that were sterilized by gamma irradiation were subjected to evaluation *in vitro* and *in vivo -5,4,3-* formulations were more effective in vivo. When conventional eye drops were compared with alternative formulations the last group was determined to be more effective in mice with regard to increased bacterial keratitis theraphy (72).

Following microparticle formulations containing levonorgestrel used as a contraceptive systems were irradiated at the dose of 25 kGy. Active substance release from the microparticles throughout one month was detected depending on the pharmacokinetic results (73).

A prospective study of radiation sterilization of an aqueous solution of human insulin investigated for drug concentration, excipients and radiation temperature. Loss of activity was observed in doses of 10 kGy without excipients. Ascorbic acid in aqueous solution and oxydised gluthation in frozen solution were found as the best degradation blocking agent caused by irradiation (74).

Following gamma irradiation of Aspirin (2 - asetoksibenzoik acid) at room temperature, three types of electron spin resonance studies of radicals were observed to occur (75).

Pharmaceutical products containing the active ingredient formoterol fumarate were irradiated with gamma-irradiation. The samples were tested by HPLC and ESR spectroscopy and showed very little degradation. A 25 kGy dose of irradiation dose was determined (76).

In a prospective study of irradiated aqueous solutions of metoprolol tartrate, different dose rates were investigated with regard to radical changes. Degradation was usually observed due to an attack of hydroxyl radicals. Dose rates used in the sterilisation effect were reduced and the loss of very high doses decreased (77).

The application of different doses of gamma radiation in chloramphenicol was investigated using SEM, TLC, UV and X-ray methods (78).

On fluoroquinolone and cephalosporin antibiotics, followed by various doses of radiation sterilisation process, the optical and colorimetric parameters were examined; all of the flurokinolon antibiotics were radiation resistant and only Cefdinir was found to be resistant from the cephalosporins (79).

Sterilisation and sedimentation stability of doksurubisin-linked polynanoparticles (Polibuthilcyanoacrilate nanoparticles) was unaffected by aggregation following 10-35 kGy doses of gamma irradiation; the appropriate dose of radiation was determined to be a dose of 15 kGy (80).

A prospective study of carbon nanotube dispersions reached the conclusion that a 28 kGy dose of gamma radiation and was suitable and can be applied effectively in industrial situations (81).

Biomaterial proteins were studied with regard to various methods of sterilisation, and the tissue engineering was compared; gamma radiation sterilisation was found to be the most appropriate method for Sericin (82).

Recently, e-beam (electron-beam) radiation has come to the fore compared to gamma radiation due to advantages in areas such as medical equipment, medicines, etc. (83).

E-beam irradiation sterilisation studies investigated some solid active ingredients, such as beta-blockers (acebutolol, metoprolol, alprenolol, atenolol, pindolol, propranolol), and the results were subjected to sterilisation process doses of 25-40 kGy (84).

Solid, metoclopramide HCl, was studied using HPLC and LC-UV-DAD-MS systems for e-beam and gamma radiation effects, and both methods were found to be applicable for sterilisation (85).

Another study also investigated the e-beam radiation with regard to the effect on solid sulphamethoxazole (86).

CONCLUSION

Many studies have investigated gamma radiation sterilisation of pharmaceuticals, and most of these studies have contributed to making a valid method of sterilisation. Health authorities in most countries have adopted these methods. The sterilisation of pharmaceutical products is based on gamma irradiation, so the measurement process is also important to evaluate the changes. As a result, and especially with regard to newly developed pharmaceuticals (new drug delivery systems, biotechnology products, radiopharmaceuticals, etc.), work is still continuing on this topic, so developments on the subject are recorded every day.

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