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Influence of Irradiation Sterilization on Polymers Used as Drug Carriers—A Review

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ABSTRACT

A survey was made of the influence of irradiation sterilization on relevant natural, semisynthetic, and synthetic polymers used for drug carrier systems. The first part of the review deals with some general aspects of irradiation treatment and its use in the sterilization of pharmaceuticals. The second part reviews the information available in the literature on polymeric biomaterials used for carriers after irradiation sterilization. The influence of irradiation sterilization has been described for polyester, poly(ortho ester), different synthetic hydrogels, silicone derivatives, cellulose-derivatives, hyaluronic acid, different glucosides, collagen, and gelatine. Also, some limitations concerning the use of high-energy radiations for sterilization are given.

***Key Words**: Beta irradiation; Drug carriers; Gamma irradiation; Irradiation sterilization; Polymeric biomaterials; Review*

INTRODUCTION

Irradiation sterilization of pharmaceutical preparations has become popular in the recent years. Conventional methods such as dry or moist heat sterilization often cause degradation and hydrolysis of the devices used; and ethylene oxide (EO), due to residual amounts, often causes toxicological problems. However, irradiation sterilization may also change the properties of drug delivery formulations and therefore must be used cautiously.

This review focuses on the changes of polymeric drug delivery systems and biomaterials due to irradiation treatment. Delivery systems become more and more important as drug carriers for drug targeting or controlled release. They are often susceptible to heat sterilization

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and must either be sterilized with high-energy radiations or be prepared aseptically. Initially, irradiation sterilization of pharmaceuticals has been investigated for active compounds and for medical devices. Only in recent years with the development of parenteral delivery systems have high-energy radiations been used to sterilize such carriers.

The effects of irradiation sterilization on therapeutic agents, medical devices, articular implants, and liposomes will not be treated in this article. However, this discussion can be found in the recently published review by Jacobs (1) and Boess et al. (2) on the effects of gamma radiation on therapeutic agents. Together with earlier reviews by Goppal (3) and Jacobs (4), most of the available literature until 1992 covers the effects of gamma sterilization on drugs. For more than 30 years, the use of ionizing radiation for sterilization has been the method of choice for medical devices intended for single use such as hemodialysers, oxygenators, blood bags, syringes, blood transfusion sets, and tubing. A series of publications evaluates the advantages and disadvantages of the different methods and their validation procedures (5–11). Also the possibility of the reprocessing of such devices, and therefore of their multiple uses, have been investigated (12). Premnath et al. (13) recently published a review on articular implants, especially those made of ultrahigh molecular weight polyethylene (UHMWPE), and the reader can refer to this publication. Liposomes do not belong to the group of polymeric drug carriers, and are therefore not considered in this review. They are vesicles made of phospholipid layers which present a particular interest for drug delivery systems, food industry, and biochemistry. The mechanism of ionizing radiation on liposomes, specifically biological membranes, has been reviewed by Stark (14) and completed by Katsaras et al. (15) and Tinsley et al. (16). Other authors have suggested sterilizing liposomal drug carriers by high energy radiations (17–20).

The review is structured into two parts. The first part is a short introduction to different irradiation sterilization methods. In the second part, the influence of irradiation treatments on polymeric drug carriers is discussed. A table with an overview of the relevant literature is given for the different classes of polymers that have been investigated.

BASICS OF GAMMA AND ELECTRON-BEAM STERILIZATION

The two high-energy radiation types used for sterilization of pharmaceuticals, preservation of food, decontamination of packaging materials, and sanitation of cosmetics are gamma (γ) and beta (β) radiations. Radiations are also used in therapeutics (e.g., treatment of cancer), organic synthesis, and the preparation or cross-linking of polymers.

Gamma Radiation

Gamma-ray photons are emitted by many radioactive isotopes or sources. The principal sources for industrial applications are cobalt-60 (^{60}Co) and cesium-137 (^{137}Cs), with the former being by far more common. Cobalt-60, with a half-life of 5.3 years, is produced by neutron bombardment of the inactive cobalt-59. Each disintegrating ^{60}Co atom causes the emission of a beta particle with an energy of up to 0.3 million electron volts (MeV), and two gamma photons with an energy of 1.17 and 1.33 MeV, while an atom of stable nickel-60 is produced (21,22). Gamma-ray processing is a slow but continuous procedure. The rays are able to penetrate completely through the product even when contained in hermetically sealed packages.

Beta Radiation

Beta radiations are produced as beam of high-energy electrons. Electron accelerators suitable for the sterilization of medical products can produce electron energies ranging from 0.1 to 15 MeV. There are generally two types of electron-beam accelerators used for sterilization: a direct-current accelerator usually generates electron beams of less than 5 MeV, and a linear electron accelerator generates pulsed 10 MeV beams (7,23). The electron beams used for sterilization are generated and accelerated in a vacuum until they reach high-energy levels, after which they can pass through a thin metal window and travel through several tens of meters of air. Either just before or just after leaving the vacuum, the beam is magnetically scanned across the whole product as it moves past on a conveyor or product carrier (6,11). A major disadvantage of this technique is the limited product penetration. Ten MeV electrons penetrate only about 5 cm of a material with density of 1.0 g/cm^3 before they lose all their energy and reach thermal equilibrium with the material (6).

The Effects of Radiations

The interaction of high-energy radiation with matter proceeds through three main processes: (i) the reaction with the nucleus producing new nuclear arrangements or

structures; (ii) the displacement of these nuclei, giving a new atomic or molecular arrangement, and (iii) the interaction with orbital electrons, so that there are no changes in the nuclear structure, and atomic rearrangements occur indirectly due to the different electron systems (24). The amount of energy deposited per unit-mass of materials is called the absorbed dose, one kilojoule of energy deposited per kilogram of materials being equal to one kilogray (1 kGy = 1 J/g or 0.24 cal/g = 0.1 Mrad). Approximately 5–30 kGy are required to sterilize a product, depending on the initial bioburden and the response of the pathogenic agents to radiation. Two theories have been proposed for the lethal action of ionizing radiation on microorganisms. The direct action theory postulates that the radiation induces ionization of the DNA of the microorganism. The indirect action theory suggests that the primary step involves the formation of free radicals, e.g., peroxides, or other molecules in the medium, subsequently inducing secondary reactions in the DNA of the microorganism (25). Electron beam sterilization was found to be more effective than γ sterilization (26) in killing bacteria, while only γ irradiation seemed to be effective for inactivating bacterial endotoxine (27,28).

The two irradiation sterilization methods differ in their interaction with matter. While γ rays show high penetration and low dose rate, scanned electron beams possess low penetration and high dose rate (6). The interaction of ionizing radiation with matter is represented in Fig. 1. Gamma radiation sterilization typically takes between 6 and 24 h, but electron beam sterilization can take less than 1 min to reach the required dose (7). Gamma ray sterilization has found better acceptance than electron beam sterilization due to its superior penetration abilities (29). Therefore, many more investigations are available about γ irradiation of drug delivery systems and the major part of this review is focused on this sterilization method.

Pharmacopoeial Requirements

The choice of the dose in irradiation sterilization is an important matter because pharmacopoeias request a high sterility assurance level (SAL). The SAL for a product sterilized in the terminal container is set at 10^{-6}—that is, one chance out of one million to find a contaminated element (30). For aseptically prepared preparations, the SAL is set at 10^{-3}. Furthermore, pharmaceutical products are often affected by irradiation sterilization, in a dose-dependent manner. To ensure a

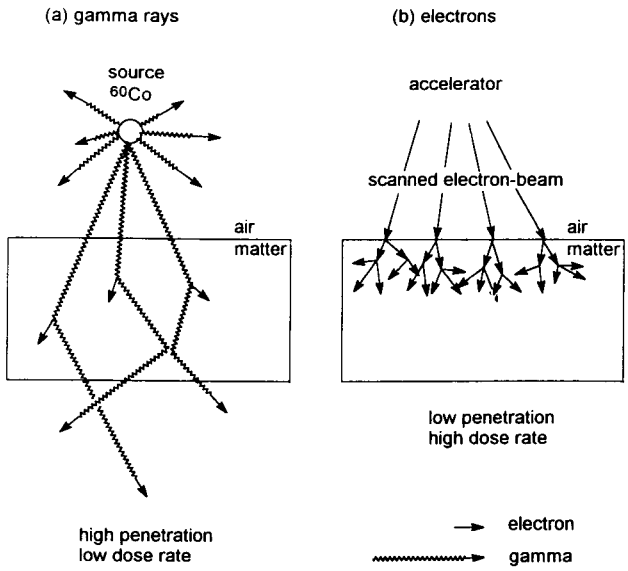

Figure 1. The interaction of (a) gamma rays and (b) electrons with matter (6).

safe product, it is absolutely necessary to carefully validate the sterilization method.

In many cases, the required assurance level can be achieved by using a uniform treatment dose of 25 kGy (2.5 Mrad), as recommended by pharmacopoeia (31). This dose is considered adequate from the microbiological viewpoint for pharmaceutical products that have been produced in accordance with good manufacturing practice (GMP). This dose is clearly higher than necessary in many cases. Lower doses may be employed, provided that the SAL of 10^{-6} can be reached. The use of lower doses should be validated by evaluating the initial bioburden and its resistance to irradiation, and by determining the SAL (31). As biological indicator for irradiation sterilization, *Bacillus pumilis* is required by the European Pharmacopoeia and the USP. Different validation procedures using *Bacillus pumilis* E 601 as radioresistant indicator bacterium have been proposed (30,32–35).

Sterilization Conditions

The conditions under which irradiation occurs can significantly influence the properties of the final materials. In the presence of oxygen or air, free radicals produced in polymers by radiation are often rapidly converted into peroxidic radicals. The fate of these radicals is dependent upon the nature of the irradiated ma-

terial and on other parameters such as temperature, total dose, dose rate, and sample size (36). Another important parameter is the solvent. Since the presence of a solvent leads to an additional interaction possibility, pharmaceutical devices are generally more stable when irradiated in the absence of any solvent. The effect is particularly marked when a product is dissolved in water (24). When a solution is irradiated, the main effect is to dissociate the solvent into free radicals which may attack the solute (the "indirect effect"). The following moieties with oxidative or reductive activity may be observed after irradiation of aqueous or alcoholic solutions (37):

e^-_{solv}, ·H, $\cdot CH_2OH$, H_2	reductive moieties
·OH, H_2O_2	oxidative moieties
$HO_2\cdot/O_2^-\cdot$	pH-dependent, either oxidative or reductive

In the presence of oxygen, the formation of $HO_2\cdot$, $O_2^-\cdot$ is favored; argon prevents the formation of O_2, $HO_2\cdot/O_2^-\cdot$; and ascorbic acid prevents the formation of ·OH, e^-_{solv}, ·H, $\cdot CH_2OH$, $HO_2\cdot/O_2^-\cdot$ (37). More detailed information about the radiolysis of water molecules has been given by Antoni (38). Generally, it is recommended that the sterilization be at a low temperature since the reactivity of the above described degradation products is reduced and the damages can be limited.

Sterilization Effects on Polymers

Radiation generally interacts with polymers in the same manner as described above. Alterations in the molecular structures of the polymers appear as changes in the chemical or physical properties. The two major mechanisms of degradation or changes taking place in a polymer as it is subjected to radiation are: (i) chain scission occurring as a random rupturing of bonds, which reduces the molecular weight and the viscosity of the polymer or (ii) cross-linking which results in the formation of large three-dimensional networks (36). Usually, both mechanisms occur simultaneously. Whether the reaction will be characterized by a predominance of scission or cross-linking depends on several factors including the chemical structure of the materials to be irradiated, the dose, the environment of the material during irradiation, and the heat of polymerization. As a result of chain scission, very low molecular weight fragments, gas evolution, and unsaturation may occur. Cross-linking generally results in increased tensile strength, while impact strength decreases and the polymer becomes increasingly brittle with increased dose (36).

INFLUENCE ON IRRADIATION STERILIZATION ON SYNTHETIC POLYMERIC DRUG DELIVERY SYSTEMS

Polyesters

General Aspects

Due to their favorable histocompatibility, polyesters are the most widely investigated biodegradable polymeric carriers for drug delivery systems. The principal polymers of this family are homo- and copolymer derived from lactic and glycolic acids: poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers, poly(lactic-co-glucolic acid) (PLGA). Initially, PLA, PGA, and their copolymers were developed for use as synthetic, absorbable sutures in the 1960s and early 1970s (39). In recent years, drug-charged micro- and nanoparticulate systems, implants, and inserts have been reported for a large field of applications.

Since polyesters are not stable when exposed to high moisture and temperatures, irradiation sterilization was checked as an alternative sterilization method. The influence of irradiation sterilization, principally γ irradiation, has been investigated by different authors. PGA was intensively studied by Chu et al. (40). They postulated that the predominant effect of γ irradiation on PGA sutures was chain scission because of the reduction in mechanical properties of PGA upon γ irradiation. The scission process has been speculated to occur through free radical formation. A hypothetical reaction pathway has been proposed (Fig. 2). Chu also suggested that due to the so-called "cage effect," the scission of the polymer chain could be more severe in the amorphous regions. A cage effect is a concept that involves the recombination of initial radicals before they can diffuse out of an active cage and undergo reactions other than recombination elsewhere (41). Since the crystalline regions of PGA act as effective cages because of their structure, the trapped free radicals can recombine and reduce the number of effective scissions (40). The mechanical integrity of the suture seems to be maintained by these regions (42). However, as γ irradiation leads to a preferential fragmentation into amorphous regions, the irradiation specimens become more susceptible to hydrolysis, which is reflected in faster pH decrease (40) as well as in faster loss of tensile strength in vitro and/or in vivo (40,43–45). Also for PLA and PLGA, it has

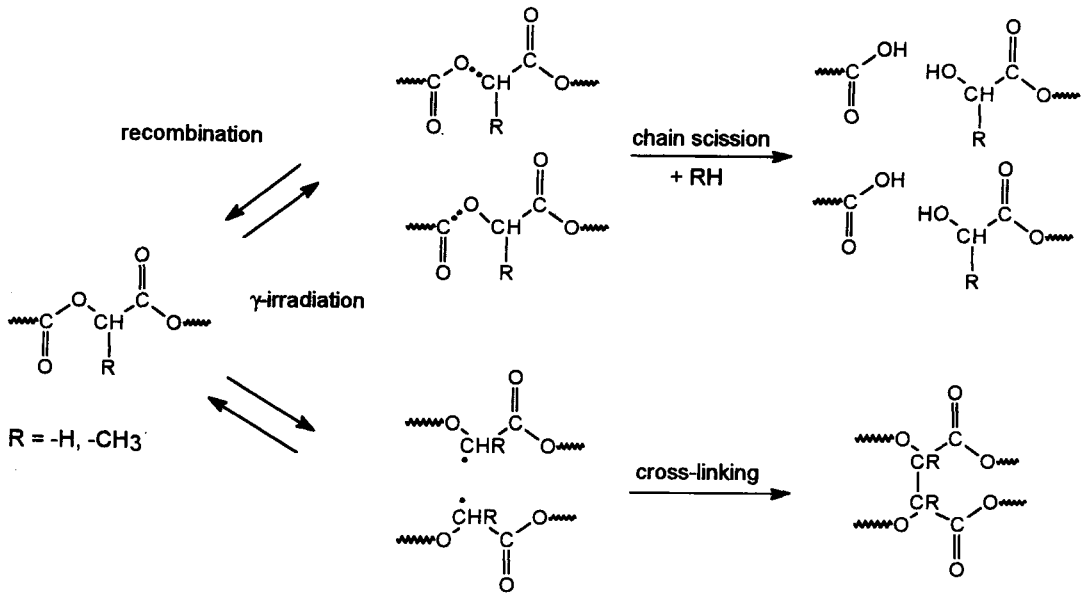

Figure 2. Hypothetical degradation mechanisms of PLG upon γ irradiation (40,47).

been observed that crystalline regions present in a polymer are not greatly affected by γ irradiation, while changes appear to be primary in the amorphous regions (46).

PLA and PLGA seem to be more susceptible to radiation degradation than PGA, but the former is more resistant to hydrolytic degradation. The difference in response to radiation is due to the chemical structure of the constituents (glycolic and lactic acids). The methyl group of lactic acid lowers the probability for recombination of radical pairs resulting from radiation chain scission because of steric hindrance, and increases degradation probability (48). An interesting aspect that has not been considered until now is the dependence of the influence of the configuration of lactic acid on the effects of irradiation. While d-PLA and l-PLA are of a semicrystalline nature similar to that of PGA, dl-PLA is amorphous in nature. Due to its amorphous nature, dl-PLA may be more susceptible to irradiation degradation than d-PLA or l-PLA.

Investigations concerning molecular weight have shown that the decrease in the number average molecular weight (M_n) is irradiation dose-dependent (42). However, opinions on how the molecular structure may be changed by irradiation are divergent. While Gilding et al. (42) and Hausberger et al. (49) observed a predominant effect of γ irradiation on number-average molecular weight M_n and only slight reductions in weight-average molecular weight M_w, they concluded that terminal segments of the PGA groups are preferentially cleaved. Consequently, the polydispersity index ($I = M_w/M_n$) of the irradiated polymer increased. It was explained that the large amount of low molecular weight material was formed by a so-called unzipping mechanism. On the other hand, Chu et al. (40), and more recently Volland et al. (47) and Yoshioka et al. (50), observed a chain scission mechanism which did not affect the polydispersity index I, since the chain is cleaved in a random fashion by γ irradiation. The long-term behavior and degradation of γ irradiation treated polyester have been established quantitatively by Hausberger et al. (49). A substantial effect on initial molecular weight distribution and onset of mass loss was demonstrated. However, no effect on rate-of-mass loss was observed.

Another phenomenon, which may occur in irradiated polymers, has been observed by Gupta et al. (51,52). They studied the effect of γ irradiation on PLA in air and in a nitrogen atmosphere. At higher dosages (>250 kGy), they observed a simultaneous mechanism of chain scission and cross-linking, which may be due to the cleavage of the ester linkage (increase in COOH end

groups) and hydrogen abstraction at the quaternary carbon atom sites. Furthermore, they observed that the presence of air led to faster polymer degradation in terms of both chain scission and cross-linking, and that the melting point decreased with dose.

Under in vivo conditions, γ irradiated PGA sutures have been shown to degrade faster than unirradiated samples (53). This difference might be related to a decrease in the molecular weight of the irradiated specimens. Thus, it is impiortant to bear in mind that the properties and useful lifetime's of PLA–PGA implants can be significantly affected by radiation, even though there might be no immediate visual change.

Polyester-Based Drug Delivery Systems

In recent years, the influence of γ sterilization on different polyester-based drug delivery formulations has been studied. Generally, it has been observed that the irradiation sterilization process could heavily degrade the polymer by decreasing the molecular weight, the mechanical properties, and the viscosity. Reports in the literature of irradiation treatment on drug release from different drug delivery systems are contradictory. While some authors (54–56) reported in vitro release from polyester-based drug delivery systems to be unaffected by γ sterilization, other groups (47,57–61) noted significant changes in both the positive and negative sense.

Studies focusing on the influence of irradiation sterilization on polyester-based drug delivery, principally microspheres, have recently been published. Spenlehauer et al. (58,59) reported that different cisplatin-loaded PLA or PLGA microspheres irradiated with 37.7 or 28.4 kGy showed a sharp decrease in polymer molecular weight, regardless of the composition of the polymer or copolymer. Indeed, the lifetimes of the microspheres were significantly affected, because the degradation continued in storage. The degradation was more pronounced for polymers with higher amounts of glycolic units, which had been varied from 10% to 25%. Without irradiation, the microspheres showed an initial slow release rate in vitro for approximately 60 days, after which an uncontrolled and massive release of cisplatin was observed. When the microspheres were γ irradiated, the same slow initial release rate was observed, but only over a period of 8 days; after this time the remaining cisplatin was massively released (58,59).

Volland et al. (47) investigated the influence of different irradiation doses (7–35 kGy) on PLGA with a monomer ratio of 50:50 based microspheres with or without drug. Captopril, an antihypertensive drug, was taken as the model drug substance. The microspheres were sterilized under various conditions, such as in the presence of humid air and oxygen. As expected, a decrease in molecular weight was found, but the effect of moisure and oxygen on the loss of molecular weight was not very pronounced, compared to the samples sterilized under a vacuum. Furthermore, it was found that high molecular weight polymers were much more affected by irradiation sterilization than lower molecular weight polymers. The same authors suggested that shorter chain lengths will favor recombination. This may be explained by taking into consideration the "cage effect" (see above) of primary formed radicals (40). Since chain mobility decreases with increasing molecular weight, the radical lifetime increases and competitive reactions become more predominant.

Concerning in vitro release kinetics, the authors found that the release behavior of captopril microspheres are γ irradiation was influenced by both the initial polymer molecular weight and the irradiation dose. For low and medium molecular weight microspheres (16.5 and 51.5 kDa, respectively), a dose-dependent acceleration of release was observed. A significant increase of captopril release rate and changes in the release profile due to faster polymer degradation were observed for high molecular microspheres (66 kDa), which have been rationalized on a basis of drastic changes in mechanical properties. The release studies also demonstrated that the polymer and the drug interact during the sterilization process.

Yoshioka et al. (56) elucidated the effect of γ irradiation (5–100 kGy) on the release characteristics of progesterone-loaded PLA microspheres. A dose-dependent polymer decomposition, including hydrolysis, has been reported. Doses of up to 25 kGy, the glass transition temperature (T_g), and the initial drug release rate were not significantly changed. However, irradiation at 100 kGy caused a significantly increased initial release rate. In the second phase, an abrupt increase in release rate was observed when the T_g was lowered below 37°C (set point of the release studies). The authors suggested that the polymer decomposition caused by irradiation may accelerate polymer decomposition in the release media and shorten the time required for T_g to become lower than 37°C. They concluded that the release rate will not be significantly affected by irradiation at doses of up to 25 kGy if the microspheres are designed to complete drug release before the T_g reaches 37°C. In a second study, Yoshioka et al. (50) investigated the possibility of controlling the drug release rate of PLA microspheres

by γ irradiation. The suggestion is based on the assumption that the release rate of microspheres is governed by the T_g. The T_g value may be influenced by γ irradiation without altering other physical properties of the microspheres such as the surface area and particle size other than the molecular weight of the polymer. Low molecular weight microspheres would have other physical properties. It has been shown that the initial release rate of progesterone from PLA microspheres increased as T_g decreased in response to γ irradiation (doses of 5–1000 kGy). The decrease in T_g depended on the irradiation dose, which indicated to the authors that the release rate can be controlled by irradiation dose. It was suggested that the time period before the start of the rapid release of above described two-phase profile, with a slow initial release followed by a rapid release after the T_g was lowered below 37°C, could be controlled by altering the irradiation dose.

However, γ irradiation for polymers, including PGA, PLA, and PLGA, is not without risk because of potentially toxic by-products, especially toxic monomers and oligomers. It seems that this method makes sense only when it offers clear and significant advantages over the other methods available; but in this case, the dose should be set as low as possible to avoid associated risks. An overview of the above discussed literature about irradiation treatment of polyester is given in Table 1.

Poly(Ortho Ester)

Poly(ortho esters) (POEs) are a group of solid or viscous hydrophobic degradable polymers, which under certain conditions can undergo a heterogeneous erosion process confined to the polymer–water interface (63). Due to the moisture sensitivity of POE and its susceptibility to degradation at elevated temperature (64), conventional methods such as dry heat or steam sterilization cannot be used, nor can ethylene oxide sterilization because of toxicological risks. Therefore, the most suitable practical terminal sterilization method for POE seems to be irradiation sterilization. Table 2 presents the following discussed works about irradiation treatment of POE. A study on solid POE has shown that irradiation treatment with 25 kGy reduced initial flexural yield strength by 60%, had a negligible effect on initial modulus, and markedly increased degradation rate (65). Semisolid POE after γ irradiation showed a molecular weight and a dynamic viscosity decrease resulting from backbone cleavage at a dose lower than 20 kGy and structural degradation at doses higher than 20 kGy (66). It has also been shown that due to the preparation procedure, the initial bioburden of POE is low. Therefore, the dose to achieve a product SAL of 10^{-6} may be less than 25 kGy. Doses between 15 and 20 kGy, depending on the POE molecular weight, lead to a sterile product, and by using doses in this range, the degradation of POE by backbone scission can be limited (66). A comparative study investigated the differences between γ- and electron-beam sterilization of POE and compared them to an aseptic preparation method (67). Furthermore, the addition of protecting agents such as the antioxidant α-tocopherol and the sterilization under nitrogen monoxide, which may neutralize free radicals, have been investigated. However, both sterilization methods, as well as the addition of protective agents, lead to accelerated polymer degradation (67). After irradiation treatment, the release rate of drug is definitively accelerated. It seems that electron beam sterilization is slightly less destructive than γ sterilization. The addition of α-tocopherol had the most positive effect on POE. It was concluded that terminal sterilization by irradiation treatment leads to fast polymer degradation and changes the properties of POE. Therefore, it is preferable to prepare injectable drug delivery systems of POE aseptically. Aseptically prepared POE showed better biocompatibility after subconjunctival injection compared to γ-sterilized POE (68,69).

Synthetic Hydrogels

Hydrogels are slightly cross-linked hydrophilic polymers or copolymers that form a three-dimensional network or matrix that can hold water or an aqueous solution. They are widely used as viscosifiers for injectable solutions and topical ocular formulations. One way to create three-dimensional networks is to expose aqueous solutions of monomers to ionizing radiation. Synthetic cross-linked hydrogels formed by irradiation treatment are described for poly(ethylene oxide) (70), poly(vinyl alcohol) (71), poly(N-vinylpyrrolidine) (72), poly(acrylamide-maleic acid) (73), and poly(di(methoxyethoxy)phosphazene) (74), among others. The formation of cross-linked hydrogels by irradiation treatment will not be discussed in this context, since it has been presented in a number of reviews (72,75,76). However, the formation and sterilization of hydrogels may occur simultaneously, which can be considered an advantage for the preparation of a sterile formulation.

Poloxamer, Poloxamine

Simultaneous formation and sterilization by γ irradiation has been proposed for the hydrogels poloxamer and

Table 1

Influence of Irradiation Sterilization on Polyesters and Its Drug Carrier Systems

Polymer	Dosage Form and Active Compound	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
PGA	Suture	0–400	Degradation mechanism: simultaneous chain scission (predominant) and cross-linking	(40)
PGA	Suture	0–200	In vivo degradation of irradiated PGA.	(53)
PGA/ PLGA	Suture	0–200	PLGA is more susceptible than PGA to radiation degradation.	(48)
PLA/ PLGA	—	0–25 Water Vapor pressure 0.75 Pa to 2.8 kPa	Decrease in M_w or intrinsic viscosity at 25 kGy: 30% to 60%, depending on water vapor pressure.	(46)
PLA	—	0–25 Water vapor pressure 0.75 Pa to 2.8 kPa	Decrease in M_w or intrinsic viscosity at 25 kGy: 20% to 60%, depending on water vapor pressure. Linear relationship between M_w and irradiation dose.	(62)
PLGA	Suture	0–35	Decrease in M_w or intrinsic viscosity at 25 kGy: 50%–60%. Degradation mechanism: cleavage of terminal segments. Linear relationship between M_w and irradiation dose.	(42)
PLA	Powder	0–1200 Air, N_2, RT	Degradation mechanism: at higher doses (>250 kGy) simultaneous chain scission and cross-linking.	(51,52)
PLGA	Microparticles	15–55 Dry ice (–78.5°C)	Decrease in M_w or intrinsic viscosity at 25 kGy: 10%-20%. Degradation mechanism: cleavage of terminal segments.	(49)
PLA/ PLGA	Microspheres; cisplatin	28.4, 37.7 Dry air	Decrease in M_w or intrinsic viscosity at 25 kGy: 30%–40%. In vitro release decreased from 60 to 8 days. Accelerated degradation.	(58)

PLA/ PLGA	Microspheres; cisplatin	28.4, 37.7 Dry air (10% RH)	Decrease in M_w or intrinsic viscosity at 25 kGy: 40%–50%. In vitro release decreased from 60 to 8 days. Accelerated degradation.	(59)
PLGA	Microspheres; captopril	7–35 Vacuum, air (54% RH), humid air (98.5% RH) dry ice (–78.5°C)	Decrease in M_w or intrinsic viscosity at 25 kGy: 10%–40%, depending on M_w. Distinct influence on in vitro release rate depending on initial M_w. Linear relationship between M_w and irradiation dose. Accelerated degradation by chain scission mechanism. Interaction between drug and polymer during irradiation.	(47)
PLA	Microspheres; progesterone	5–100, resp. 5–1000 dry air (0% RH), humid air (96% RH)	Decrease in M_w or intrinsic viscosity at 25 kGy; 30%–40%. Two phase release profile at >25 kGy, no significant change in initial release rate; at 100 kGy, increased initial release rate (release rate depends on T_g). Dose-dependent increase in carboxylic acid content, and decrease in T_g.	(50,56)
PLA/ PLGA	Microspheres; norethisterone	20	Decrease in intrinsic viscosity at 25 kGy: 30%–40%.	(43)
PLGA	Microspheres; luteinizing hormone-release hormone	16,29,33	Decrease in intrinsic viscosity at 25 kGy: 30%–40%. Triphasic in vitro release; changes in the second and third phase after irradiation.	(57)
PLGA	Microspheres; tripotoreline	25	Distinct influence on in vitro release rate depending on initial M_w.	(60)
PLGA	Microspheres; melatonin	25, 57.5 Water vapor pressure 0.075 Pa to 2.8 kPa anoxia or 110 kPa oxygen	In vitro release not significantly affected.	(55)
PLA	Microspheres; piroxicam	15	Zero-order in vitro release after 36 h.	(61)

[a]γ irradiation, unless indicated otherwise.

Table 2

Influence of Irradiation Sterilization on Poly(Ortho Ester) and Its Drug Carrier Systems

Polymer	Dosage Form and Active Compound	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
POE	Ointment	1–40 Dry ice (–78.5°C), inert atmosphere	Decrease in M_w or intrinsic viscosity at 25 kGy: 60%–70%. Doses >20 kGy: structural changes. Validation of sterility at 20 kGy.	(66)
POE	Implant	25.2 Room air, RT	Reduction of the initial flexural yield strength by 60%.	(65)
POE	Ointment; 5-fluorouracil	20 (γ and EB) Dry ice (–78.5°C), Ar or N_2O	Decrease in M_w or intrinsic viscosity at 25 kGy: 40%–50%. In vitro release $t_{50\%}$ decreased from 51 hr to 9 hr.	(67)
POE	Ointment	20 Dry ice (–78.5°C), Ar	Subconjunctival biocompatibility after γ-sterilized and aseptically prepared POE.	(68,69)

[a]γ irradiation, unless indicated otherwise.

poloxamine. Poloxamers are block copolymers of poly(oxyethylene)-poly(oxypropylene), and poloxamines contain, additionally, ethylenediamine in their structure. They both form micelles in aqueous solutions. Exposure to irradiation of up to 12 kGy induced gelation of the poloxamer solutions at a lower concentration than in nonirradiated systems by inducing the formation of cross-links between adjacent micelles (77,78). The treatment with radiation doses of up to 4 kGy changed the intermicellar interaction, which caused a pronounced effect on the flow properties of the gel, with the transition from a plastic to a pseudoplastic flow (79).

Polyacrylate

Cross-linked poly(acrylic acid) (PAA) are polymers that form hydrogels with excellent mucoadhesive properties (80), and that are mainly known under the trade name Carbopol®. They are widely used as viscosifiers in the pharmaceutical and cosmetic industries. The effect or irradiation treatment of Carbopol gels is a controversial issue that has been much discussed in the literature. Adams et al. (81) compared the effects of γ irradiation and autoclaving gels based on Carbopol 940 and 941. Before γ sterilization and after autoclaving, the tested gels were pseudoplastic systems with a high yield value. Some loss of viscosity occurred in autoclaving, whereas after γ irradiation (30 kGy), the gels were Newtonian liquids of considerably reduced viscosity. Moreover, ethanol was found to be a good protecting agent for Carbopol gels. The addition of 5–10% ethanol did not affect the pseudoplastic behavior of the gel; only the viscosity was reduced (81). No explanation for this phenomenon has been given. Opposite observations have been made by Deshpande et al. (82), who claimed that autoclaving caused marginal changes in viscosity and did not affect the consistency of the gel, whereas γ irradiation (25 kGy) increased viscosity substantially and gave rise to a brittle gel. However, in vivo studies have shown that the radiation treatment of a pilocarpine containing polyacrylic gel did not influence the biological response of the formulation (82).

As an alternative to conventional eye drops, Alani (83) proposed an ophthalmic rod made of a nontoxic acrylic plastic. The rods were sterilized by γ radiation at 33 kGy. No specific tests on the influence of the sterilization method on the polymeric device were performed; however, no toxic, inflammatory, or degenerative reactions were observed during the long-term daily treatment of rabbit eyes.

Polyethylene Glycol (PEG)

PEGs are used in ophthalmic ointment bases and as nonaqueous vehicles for injections. Bhalla et al. (84,85) investigated the feasibility of sterilizing some PEGs by γ radiation. The physicochemical and pharmacological properties of γ-sterilized PEG 400, 1500, and 4000 were compared to those of control- and heat-sterilized samples. No significant alteration in viscosity, freezing point, hydroxyl value, average molecular weight, and degradation products were observed for any of the PEGs tested. While irradiated PEG showed no change in color, all heat-sterilized samples showed a slightly yellowish tinge. The pH value of all irradiated samples was not significantly varied, whereas some heat-sterilized samples showed a considerable pH decrease. Since the pharmacological tests concerning irritation and acute toxicity showed no significant changes as compared to the untreated samples, it was concluded that radiation sterilization is a suitable sterilization method for PEGs (84). The above discussed studies on hydrogels are summarized in Table 3.

Silicone Derivatives

The influence of γ sterilization and exposure to elevated temperatures on various key properties of a silicon-based (α,ω-*bis*(4-methacryloxybutyl)-poly(dimethylsiloxane) ocular drug delivery systems have been investigated by Bawa et al. (86). Both the resistance to hydrolysis and the mechanical properties of films containing gentamicin as a model drug were found to be unchanged after γ sterilization (25 kGy) and exposure to elevated temperatures (40°C over 3 months). The drug release rates of the devices were found to be affected by γ irradiation and exposure to heat. A slowdown of the release rates was observed, which may be due to an additional cross-linking of the polymeric matrix caused by irradiation. However, how can additional cross-linking influence only the drug release and not the physicochemical properties of a device? A distinct influence on the release after γ irradiation has also been observed by Burns et al. (87) for nonerodible porous matrix implants of a silicone elastomer (Silastic®). While some batches of implants showed after irradiation (12.5, 25 kGy) a significantly increased cumulative release of a luteinizing hormone-releasing hormone analog, others did not show any significant difference. No explanations were given for the differences observed in the release rates. An overview about γ irradiation on silicon derivatives is given in Table 4.

Table 3

Influence of Irradiation Sterilization on Hydrogels and Its Drug Carrier Systems

Polymer	Dosage Form and Active Compound	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
Poloxamer	Hydogel	0–45.6 Aqueous solution, N_2O, RT	Increased viscosity after irradiation due to the formation of cross-link. Formation of micelles depending on irradiation dose.	(77)
Poloxamine	Hydrogel	0–12 Aqueous solution, RT	Increased viscosity after irradiation. Evaluation of the rheological properties.	(79)
Poloxamine	Hydrogel	0–24 Aqueous solution, N_2O, RT	Transition from a plastic to a pseudoplastic flow at doses over 4 kGy. Increased gel strength.	(78)
PEG 400, 1500, 4000	Hydrogel	25	Unchanged M_w after irradiation at 25 kGy. No significant alteration of physicochemical characteristics, content of degradation products, and biocompatibility.	(84,85)
Carbopol	Hydrogel	30 25°C	The pseudoplastic systems became Newtonian liquids with reduced viscosity after irradiation. Ethanol as protecting agent (only slightly reduced viscosity).	(81)
Carbopol	Hydrogel; pilocaprine	25 Aqueous solution	Increased viscosity after sterilization (brittle gel). Biological activity not influenced.	(82)
Acryl-plastic	Ocular device; tropicamide, oxybuprocaine, fluoresceine	32.9	No apparent changes in the devices after sterilization.	(83)

[a]γ irradiation, unless indicated otherwise.

Table 4

Influence of Irradiation Sterilization on Silicone Based Drug Delivery Systems

Polymer	Dosage Form and Active Compound	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
Dimethyl-siloxane-derivative	Ocular device; gentamycin	25	Slowdown of the relase rate, due to additional cross-linking. Mechanical properties unchanged.	(86)
Silicone-elastomer	Implant; luteinizing hormone-releasing hormone	12.5, 25 Dry ice (-78.5°C)	Cululative in vitro release: by some batches, significantly changed; by others, no significant change.	(87)

[a]γ irradiation, unless indicated otherwise.

INFLUENCE OF IRRADIATION TREATMENT ON NATURAL AND SEMISYNTHETIC POLYMERS AND ON THEIR DRUG DELIVERY SYSTEMS

A large number of natural and semisynthetic polymers are used as pharmaceutical excipients and drug carrier materials. Some general aspects of irradiation-induced changes in polysaccharides and polypeptides have been investigated by Antoni (38). Concerning the irradiation of polysaccharide molecules, it has been found that the primary effects on its constituent units is dehydrogenation and decomposition, with the release of gaseous hydrogen, carbon monoxide, and carbon dioxide. No general, uniformly valid rule can be set for the radiosensitivity of proteins, due to their individual functions and their structural/conformational differences. The most widely used representative of this class of products on which the influence of irradiation treatment has been investigated will be discussed in this context.

Polysaccharides

Cellulose Derivatives

Cellulose derivatives are a rich source of semisynthetic polymers that can be used as pharmaceutical excipients. They are frequently used as carriers, binders, or stabilizing agents in formulations, such as solid formulations, gels, or suspensions. Often such preparations need to be sterile. However, radiation-treated cellulose derivatives are not excluded from damages. The decomposition is caused in a dose-dependent manner by random fractures in the main chain (88), leading to a severe and immediate drop in viscosity (89,90).

The stability of sodium carboxymethylcellulose (NaCMC) powder after irradiation (doses of up to 25 kGy) has been tested by Sébert et al. (91). The influence of such treatment on the functional properties of NaCMC, especially on the formulation of gels, suspensions, tablets, and sustained-release parenteral dosage forms, has been investigated. It has been observed that the impact of γ rays on NaCMC is marked from 15 kGy. Upward ruptures of glycosidic linkages induce a modification of the rheological behavior causing in particular a noticeable decrease in viscosity. Consequently, these changes must be considered for pharmacotechnical applications, even if the influence on the functional properties seems to be moderate. The authors estimated that the stability of suspensions could be impaired by an increase in particle sedimentation, that gel formation could be disturbed, and that the release of drugs from sustained-release parenteral dosage forms based on diffusion could be modified. On the other hand, the binding capacity seems to be improved. Concerning the tabletting properties, it has been reported that γ irradiation has no deleterious effect. El-Bagory et al. (92) compared three irradiated direct compression excipients (microcrystalline cellulose Avicel PH102), spray-processed lactose, pregelatinized starch (Sta-Rx-1500), and maize starch with the untreated excipients. No differences were found between the tabletting properties of the irradiated and nonirradiated materials. These results are no surprise, since tabletting capacity is a phenomenon involving the surface of the polymer, while viscosifying properties depend on molecular weight of the polymer and its structure in solution. Also, the biocompatibility of irradiated cellulose derivatives does not seem to be markedly affected by γ irradiation sterilization. Studies on ethylcellulose microspheres implanted in a small area of the brain have shown that no neural toxicity was induced up to 9 months after placement (93).

Hyaluronic Acid

Due to its good biocompatibility and tolerance, hyaluronic acid (HA), an altering copolymer of N-acetyl-D-glucosamine and D-glucuronic acid, is a widely used natural polysaccharide for pharmaceutical and cosmetic applications. In the solid state, HA behaves like other polysaccharides when treated with γ radiations; a drop of the intrinsic viscosity due to glycosidic cleavage is the most widely observed consequence of radiation action on HA. The depolymerization proceeds through radical formation. Balazs et al. (94) described the radiation-induced degradation pathway for HA as follows (Fig. 3). Extreme excitation following γ irradiation could remove the oxygen *p*-electron to produce an intermediate (I) that would give rise to glycosidic cleavage. The intermediate carbonium ion (II) would react rapidly with water. Simultaneously, the presence of the uronic acid group could labilize the hydrogen atom at C-5 and eliminate the H. Such a radical (III) would be stabilized by resonance interactions with the carboxylic group. Armand et al. (95) proposed that the polyanion HA be protected by forming a molecular complex with cetyl pyridinium cations, an antiseptic compound. The protection from irradiation damages is based on inter- and intramolecular energy transfer effects observed in carbohydrate systems. The consequence of this energy transfer is a reduction of free radicals in the system. In solution, the susceptibility of hyaluronic acid to radiation damage is due to the reaction with major products of water radiolysis (94).

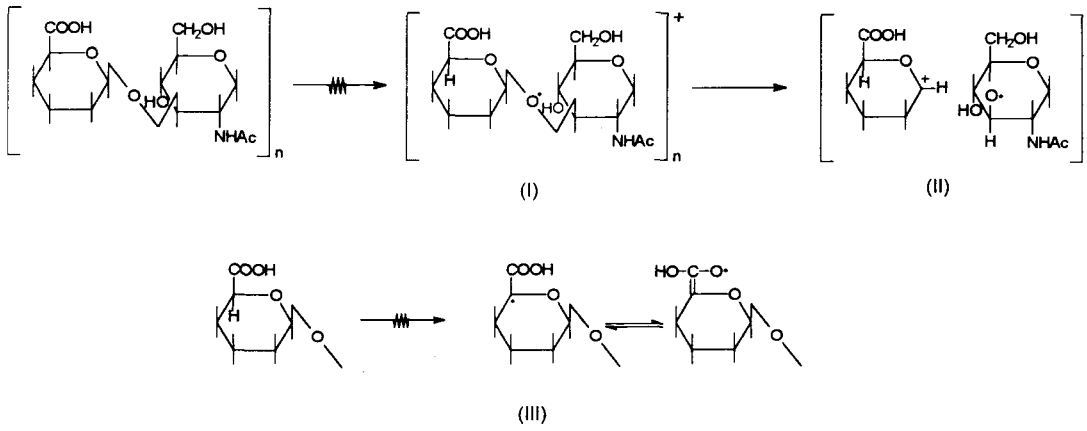

Figure 3. Hypothetical degradation pathway for hyaluronic acid after irradiation (95).

Vegetable Gums and Other Glucosides

Natural plant hydrocolloids such as acacia, alginate tragacanth, or xanthan may increase the viscosity of aqueous systems. Therefore, they are often used as viscosifiers for ophthalmic or other drug solutions that must be sterile when applied. Due to their nature and methods of production, vegetable gums normally contain microorganisms. Gums, like other polysaccharides, are affected by irradiation treatment. The treatment results in the splitting of glucosidic bonds with the formation of stable free radicals (38). Acacia gum, sodium or calcium alginate, tragacanth, and xanthan gums all showed irradiation-induced decrease in viscosity due to a reduction in the degree of polymerization (81, 90,96–98). It seems that irradiation is not an appropriate method for the sterilization of gums, since even small radiation doses (< 10 kGy) have a pronounced effect on their viscosity (97). However, other sterilization methods, such as dry or moisture heat or ethylene oxide treatments, also caused polymer degradation (98). The most frequently used sterilization method for gums is autoclaving. Also, the radiolysis of complex glucosides is caused mainly by radiation-generated ·OH radicals and hydrolysis in the glucosidic linkages (99). The influence of irradiation treatment on natural and semisynthetic polysaccharides is shown in Table 5.

Irradiation Treatment of Polypeptidic Biomaterials

Collagen

Due to its favorable properties, e.g., high biocompatibility and low immunogenicity, biological collagen is a well-suited material for many medical applications. Collagen consists of three polypeptide chains (α-chains) which form a helix, connected by interchain hydrogen bonds (100). The physical and chemical properties of collagen are determined by intra- and intermolecular covalent bonds (cross-link).

Since it is difficult to maintain the native structural integrity of the fibers, it is not easy to sterilize collagen. Gamma irradiation is widely used for sterilization and cross-linking of polypeptidic biomaterials. However, opinions about the safety of this method differ. Earlier studies reported that only extremely high doses (> 100 kGy) caused a breakdown of the helical structure, whereas differences in the rigidity characteristics of native and sterilized collagen, as well as significant changes in the sub-unit composition of the polypeptides, have been noticed at lower doses (101).

More recently, Cheung et al. (102) have shown that, in soluble collagen and reconstituted fibrils, a significant number of collagen molecules are cleaved by γ radiation even at 10 kGy. The damage became more severe as the radiation doses increased. No difference has been noticed between the collagen samples in solution and lyophilized collagen. Similar results have been obtained for fibrous collagen networks obtained from purified dermis (103, 104).

The other phenomenon that occurs by irradiation treatment of collagen is cross-linking. While Liu et al. (105) and Pietrucha (106) observed a marked cross-linking of collagen at already lower irradiation doses (up to 30 kGy), Cheung et al. (102) have reported that doses over 75 kGy may compensate for the damage of peptide bonds by the formation of cross-links. Cross-linking decreased the solubility of collagen and increased the

Table 5

Influence of Irradiation Sterilization on Natural and Semisynthetic Polysaccharides Used as Drug Carriers

Polymer	Irradiated Form	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
NaCMC	2% Aqueous solution	0.28–0.85	Decrease in intrinsic viscosity at 0.57 kGy: 40%–60%. Profound destruction.	(89)
NaCMC	Powder	0–25 RH 5%	Decrease in M_w at 25 kGy: >70%. Physical, chemical, and pharmacotechnical properties markedly changed by radiation doses ≥ 15 kGy.	(91)
Cellulose, lactose, starch	Powder	0–25	No differences in tabletting properties before and after irradiation. No affect on the effectiveness of maize starch after radiation.	(92)
EC	Microspheres	29.8	Biocompatibility.	(93)
HA		0.1–100 Gy (γ and EB) Vacuum or Ar	Description of a degradation pathway.	(94)
HA		15, 30 Vacuum, −201°C or 20°C	Protection of hyaluronic acid with cetylpyridine.	(95)
Acacia	Powder	25	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: up to 20%. Viscosity measurements on solutions of 2%, 5%, 10%, prepared after irradiation.	(96)
Alginate	Powder	25	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: >70%. Viscosity measurements on solutions of 0.1%; 0.3%, 0.5%, prepared after irradiation.	(96)
Alginate	Powder	23.15	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: >70%. Viscosity measurements on solutions of 3%, prepared after irradiation.	(98)
Tragacanth	Powder	1–50	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: >70%. Reduction in intrinsic viscosity even at low irradiation doses (<10 kGy).	(97)
MC, Tragacanth	Hydrogel	30 25°C	Decrease in intrinsic viscosity, resp. M_2 at 25 kGy: >70%. The pseudoplastic systems became Newtonian liquids with reduced viscosity after irradiation.	(81)
Starch	Powder	5–25 Air or N_2	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: 60%–70%.	(90)
NaCMC	Powder	5–25 Air or N_2	Significant reduction in intrinsic viscosity (25 kGy).	(90)
Xanthan	Powder	5–25 air or N_2	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: 10%–20%.	(90)

[a]γ irradiation, unless indicated otherwise.

resistance of collagen to collagenase degradation (105), while the integrity of the helix seemed to be preserved (102).

Damages of irradiation treatment to collagen occur through radiation-generated radicals, principally hydroxyl radicals ·OH and superoxide ions $O_2^-\cdot$, as well as radicals derived from amino acids. The reaction of hydroxyl radicals ·OH with collagen resulted in polymerization (107). Shieh et al. (107) suggested that free radicals in irradiated dry collagen may have longer lifetimes compared to free radicals in collagen of higher moisture contents. Monboisse et al. (108) tried to quantify the interaction between a suspension of collagen fibrils and the superoxide ion, $O_2^-\cdot$, formed by electron beam or by γ irradiation at low doses (between 8 and 1200 kGy). $O_2^-\cdot$ can be expected to react with collagen molecules by more than one mechanism. It has been estimated that the sensitivity to hydrolysis of peptide bonds depends on the amino acid residues present in the vicinity or on the secondary structure of the molecule. In addition, some of the free radicals might react with the amino acid residue side chains without leading to peptide linkage hydrolysis. A kinetic interpretation of the phenomena has been suggested as follows (108):

(i)	$O_2^-\cdot$ + collagen	→	$coll_1\cdot$ + $coll_2^-\cdot$ + H_2O_2 or O_2
(ii)	$coll_1\cdot$ + $coll_2\cdot$	→	collagen
(iii)	$coll_1\cdot$ (or $coll_2\cdot$) + collagen	→	products + 4-hydroxyproline containing peptides

Reaction (i) corresponds to the trapping of $O_2^-\cdot$ by collagen fibrils, giving two (or more) radicals, $Coll_1\cdot$ and $Coll_2\cdot$, that can recombine to form collagen according to reaction (ii) (recovering process) in competition with reaction (iii) which symbolizes the step(s) toward hydroxyproline-containing peptide release.

The mechanism of radiation cross-linking of collagen is not well understood. It has been assumed that, after irradiation, degradation and cross-linking occur simultaneously. Cross-linking seems to be favored by the absence of oxygen, presence of water, and low radiation dose. The cross-linking seems to be due mainly to the stability and/or biodegradation of collagen (106,109). At high doses of γ radiation (75 kGy), if cross-links can form very near the cleavage sites, the integrity of the helix may be preserved (102). Early animal work and clinical experience indicated that the immune response to cross-linked collagen was negligible (109).

A recent study published by Olde Damink et al. (110) compared the influence of sterilization by ethylene oxide (EO) and by γ irradiation on the in vitro degradation of collagen. During EO sterilization, reaction of the gas with the free amino groups of collagen was observed, which resulted in a decreased helix stability, as indicated by a lowering of the shrinkage temperature (T_s). The mechanical properties of collagen were not significantly altered. Gamma sterilization was induced as reported above, with chain scission resulting in a decrease of both the tensile strength and the high strain modulus of non-cross-linked and cross-linked collagen (110).

Gelatine

Due on its origin, gelatine is naturally contaminated by bacteria. The use of irradiation for decontamination causes a shortening of chain length and a decrease in viscosity (111). However, the treatment of gelatine with dry heat or ethylene oxide (EO) also affects gelatine (112). While dry heat sterilization renders the gelatine insoluble, EO sterilization is unsuitable because it has poor penetration and leaves residues. Therefore, γ sterilization seems to be the most suitable method. Irradiation treatment changes the physicochemical properties of gelatine as follows: while the primary structure is hardly affected, the secondary and tertiary structures seem to be more susceptible to the treatment (113). However, the susceptibility to the changes depends on the type of gelatine, and the changes only slightly affect the properties of gelatine in pharmaceutics (113). The above discussed influences of irradiation treatment on polypeptides are summarized in Table 6.

COMBINATION OF ASEPTIC PREPARATION AND IRRADIATION TREATMENT

A combination of an aseptic preparation procedure and high-energy radiation treatment has been proposed for total parenteral nutrition solutions (TPN). TPN solutions generally contain amino acids, glucose, lipids, electrolytes, vitamins, and trace elements. Due to the susceptibility of their components, TPN solutions cannot be sterilized by traditional methods, and must be prepared aseptically. Under standard conditions, the aseptic preparation methods lead to a SAL value of 10^{-3}. To minimize the risk of microbiological contamination of these formulations, Koornhof et al. (114) investigated the effect of low-dose γ irradiation on aseptically admixed preparation. The results showed that a minimum absorbed radiation dose as low as 1.5 kGy improved the SAL from 10^{-3} to less than 10^{-8} for the

Table 6

Influence of Irradiation Sterilization on Natural and Semisynthetic Polypeptides Used as Drug Carriers

Polymer	Irradiated Form	Absorbed Dose [kGy][a] and Physical Conditions During Irradiation Treatment	Comments	Ref.
Collagen	Freeze-dried, neutral salt soluble, acid-soluble	0–100 Vacuum, 22°C	Decrease in M_w at 25 kGy: 30% to 60%, depending on the type of collagen. Peptide bond fission, differences in rigidity characteristics and subunit composition. No breakdown of the helical structure.	(101)
Collagen	Fibrils, acid-soluble, calfskin	0.008–1.2 kGy	Evaluation of a degradation mechanism.	(108)
Collagen	soluble	3–300 RT, liquid N_2 (77°K), RH: 31%, 69%, 100%	Polymerization of collagen with ·OH-radicals. Free radiacals in dry proteins have longer lifetimes compared to free radicals in collagen of higher moisture content.	(107)
Collagen	human amnion	2.5–25 RT	Cross-link, as a dose-dependent effect.	(105)
Collagen	Rat skin Type 1	0–75 Solution and lyophilized	Cleavage of collagen molecules even at 10 kGy weaken the helical structure. At 75 kGy: if cross-linking occurs near cleavage bond, the helical structure may be preserved.	(102)
Collagen	Prosthesis, bovine collagen	25–30 (EB)	Simultaneous cross-linking and sterilization.	(106)
Collagen	Dermal, sheep	25; Standard EO sterilization apparatus	Compairison of the two methods. EO seems to be more advantageous.	(110)
Gelatine	Solid state type: calfskin	0–155 Vacuum	Decrease in intrinsic viscosity, resp. M_w at 25 kGy: 20%–30%, resp. M_w 50%–60%. Molecular degradation.	(111)
Gelatine	Granules, capsules types nonspecified	3–60	Reduction in specific viscosity: for granules: 20% at 10 kGy, 35% at 20, 30 kGy. for capsules: 20% at 10 kGy, 35% at 20, 30 kGy.	(112)
Gelatine	Different types (basic and acid)	1–25	Decrease in M_w at 25 kGy: 10% to 40%, depending on the type of gelatine.	(113)

[a]γ irradiation, unless indicated otherwise.

investigated microorganisms belonging to the *Klebsiella, Serratia*, and *Enterobacter* genera. These bacteria have been found to be the most common contaminants of TPN. At an absorbed dose as high as 8.3 kGy, no measurable changes in the amino acid, electrolyte, glucose, and lipid components of the solutions have been detected. Therefore, it has been concluded that these findings may have important implications for the enhancement of microbiological safety levels of aseptically prepared intravenous fluids in general.

Since nearly all polymeric drug carriers are dose-dependent and are affected by irradiation treatment, the combination of aseptic preparation and high-energy radiation treatment at low doses is an interesting approach to improving the microbiological safety and to limiting the degradation of such drug delivery systems.

LIMITS OF IRRADIATION STERILIZATION

A few comparative studies of different biomaterials and formulations have shown that in some cases irradiation treatment is less adaptable than other sterilization methods. As already discussed above, Carbopol gels may be better sterilized by moisture heat than by irradiation treatment (81,82,115). Alginate is less affected by sterilization as a gel by autoclaving or in a dry state by ethylene oxide (98). For PLA, Gogolewski et al. (116) proposed a thermal treatment, which seemed to be better adapted for the polymer than γ sterilization. The molecular weight of tyrosine-derived polycarbonates, a new group of biodegradable implant materials, was less damaged after ethylene oxide sterilization than after γ irradiation (117). Talc used for pleurodesis may be sterilized by different methods, including γ sterilization, but the method is too expensive compared to dry heat sterilization (118).

Another aspect that limits the use of high-energy radiations for sterilization is the formation of toxic degradation products. An example has been given by Shintani et al. (119,120), who observed the formation of the potentially toxic and carcinogenic degradation compound 4,4′-methylenedianiline after irradiation of polyurethane (119,120). The reports in the literature are controversial. Other authors, Albanese et al. (121), evaluated the in vitro biocompatibility of heparinized material based on polyurethane and poly(amido-amine). They concluded that γ rays would be a suitable method of sterilization for such devices since no toxic response was noticed (121).

CONCLUSION

The use of high-energy radiations to sterilize pharmaceuticals is already well established in the field of active compound and medical devices. Indeed, many questions in the field of drug delivery systems have received no answers until now. If only it could be better understood how polymers are affected by high-energy radiations, better means might be devised for stabilizing the polymer. However, in Switzerland, several γ sterilized drug delivery systems such as Decapeptyl® Retard (Ferring), Zoladex® (Zeneca), Sandostatine® (Sandoz), and Suprefact® (Roussel) are already commercially available.

It has been shown that γ sterilization is a highly critical process step when developing new drug delivery systems, and therefore it should be carefully evaluated at an early stage in the development program. With the exception of the finding that radiolysis by irradiation may be prevented or reduced at low temperatures, and/or in the absence of oxygen, there are no general rules to predict the effect of irradiation on a biomaterial or a drug carrier system. Nearly all the polymers discussed undergo transformation when exposed to radiations. In most cases, an accelerated degradation of the drug carrier induced by a molecular weight decrease was observed. However, it has also been shown that the use of high-energy radiation for the sterilization of pharmaceuticals is not without risks and must be carefully evaluated in order to identify possible toxic degradation products. There is very little information on this important point. The irradiation-induced degradation has been carefully evaluated for only a few biomaterials. For most polymers discussed, especially the synthetic biomaterials, the investigations have focused on the physicochemical changes in the properties. It may be concluded that specific and sensitive physicochemical, toxicological, immunological, clinical safety, and efficacy tests must establish whether the effects of irradiation such as chain cleavage or other structural damages are not potentially dangerous.

ABBREVIATIONS

EC	Ethylcellulose
HA	Hyaluronic acid
MC	Methylcellulose
NaCMC	Sodium carboxymethylcellulose
PEG	Polyethylene glycol
PGA	Poly(glycolic acid)

PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
POE	Poly(ortho ester)
Ar	Argon
EB	Electron beam
N_2O	Nitrous oxide
N_2	Nitrogen
RT	Room temperature
Irr.	Irradiation
M_w	Weight average molecular weight
M_n	Number average molecular weight
RH	Relative humidity
T_g	Glass transition temperature

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