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Review

The effects of irradiation on controlled drug delivery/controlled drug release systems

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Abstract

The research of radiation effects on drugs over the past 60 years has mainly dealt with radiation sterilization of individual active pharmaceutical ingredients (APIs) in the form of pure substances or injectable solutions. However, the emergence of novel systems for drug administration and targeting via controlled drug delivery (CDD) and/or controlled drug release (CDR) has extended the use of irradiation with respect to pharmaceuticals: the capacity of radiation to act as an initiator of crosslinking has been used in the manufacturing and modification of a number of polymeric carriers with an added advantage of reducing the microbial load of products at the same time. The application of irradiation to these novel systems requires the understanding of radiation action not only on APIs alone but also on drug carriers and on the functioning of the integral CDD/CDR systems. In this paper, the significance of CDD/CDR systems is considered with a special emphasis on the role of irradiation for sterilization and crosslinking in the developments over the past 15 years. Radiation sterilization, crosslinking and degradation of the principal forms of drug carrier systems and the effects of irradiation on the release kinetics of APIs are discussed in light of radiation chemical principles. Regulatory aspects pertaining to radiation sterilization of drugs are also considered. Relevant results are summarized in tabular form.
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Keywords: Drug; Drug carrier; Drug delivery; Drug release; Drug targeting; Hydrogel; Liposome; Natural polymer; Radiation crosslinking; Radiation sterilization; Regulation; Release kinetics; Synthetic polymer

1. Introduction

Recent efforts in drug development resulted in a number of controlled drug delivery (CDD) systems consisting of a drug encapsulated within a suitable polymer carrier which enables drugs to be delivered either via novel routes or in a sustainable fashion or both. By a selection of biocompatible carriers, drugs could be made available at various locations in the body. Targeted delivery of drugs directly to various organs or tissues may be accompanied with an additional benefit of achieving at the same time both the spatial and temporal control of release which is the principle of operation of controlled drug release (CDR) systems. Targeted delivery of drugs directly to the diseased tissues and/or organs and its controlled release have important advantages over the traditional (oral) route: higher local concentration of a drug makes the therapy more effective; improved pharmacokinetics of drug release maintains the required therapy level over an extended period of time; both the duration and unwanted side effects of the therapy are reduced. Last but not least, simplified dosing and the ease of use directly contribute to the improvement of the patients' life quality obviating the need for repeated, potentially uncomfortable, dosing and reduce the risk of incorrect dispensing (Maugh, 2006). Improved versions of patented drugs with pending expiration are also attractive to manufacturers, enabling an extension of the market life cycle of established drugs.

Drugs for parenteral delivery must be sterile and radiation sterilization is a method recognized by many pharmacopoeias to achieve sterility of drugs. Previous reviews of radiation sterilization of drugs dealt mainly with the sterilization of active pharmaceutical ingredients (APIs) alone (Dahlhelm and Boess, 2002; Gopal, 1995; Jacobs, 1995; Marciniec and Dettlaff, 2005). The reviews dealing so

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far with radiation sterilization of drug delivery systems were mainly focused on the sterilization of various polymeric carriers and presented but a few selected examples of loaded systems (Bhattacharya, 2000; Clough, 2001; Edlund and Albertsson, 2002; Jain et al., 2005; Sintzel et al., 1997). In this paper, we summarize the effects of irradiation on CDD/CDR systems in radiation's dual role with respect to these systems: as a sterilizing agent of loaded systems and as an initiator of polymerization and/or crosslinking in polymeric drug carriers before their being loaded with drugs. Only the developments based on the work done since 1990 are included in the text and the following tables. References to earlier work can be found in the previous reviews (Ferguson, 1988; Kabanov, 1998) and in the papers cited herein.

2. The significance of drug delivery systems

A feeling for the dimensions of the field of CDD can be obtained by performing a simple bibliometric count: there are seven journals containing keywords "encapsulation", "controlled release" or "drug delivery" in their titles. The oldest three are about 20 or more years old, while the three most recent ones appeared since 2003. Total annual number of pages of these journals has been growing exponentially and exceeded 10,000 pages in 2005 (Fig. 1), which is no less than about 1000 papers only in that year.

The analysis of US pharmaceutical patent literature of 2005 shows that "drug delivery" as a research term appears 9.5 times per one thousand patents, which lags behind many other contemporary catchwords. However, the frequency of appearance of "drug delivery" increased by 11% from 2004, placing the term in the sixth place by the rate of increase ranking, only behind the terms such as "RNA interference" (RNAi), "HIV" and "stem cell" and well ahead of some other terms which have already been frequently used in the past. For example, 51 out of every 1000 patent specifications refer to "protein", but the term seems to be losing momentum in attracting new attention: the frequency of appearance of "protein" increased in 2005 by only 1% from the previous year. Similar situation exists with patent applications (Lawrence, 2006).

The (inexhaustive) survey of the literature finds 19 sustained and controlled release drugs distributed among five types of carrier systems approved by the FDA by 2000 (Burgess et al., 2002). Eight hydrogel-based products were reported on the market that same year (Gupta et al., 2002). Three additional products in form of implants were approved by the FDA by 2003 (Whittlesey and Shea, 2004). However, this is negligible when compared to 12,708 FDA approved prescription drugs listed in 2006 (Van Arnum et al., 2006). There are far more CDD/CDR systems in the literature than on the pharmacy shelves: the recent estimate that the concept of drug delivery system has been applied to some extent to 10% or more of commercially available drugs (Yasukawa et al., 2004) must be understood as referring to research publications and not to pharmacy stocks.

The growth of CDD systems seen in the context of other successful contemporary developments in the pharmaceutical industry may have not been as fast (and as lucrative) as e.g. biotech-related businesses (Henry, 2004). Nevertheless, the sales of CDD/CDR systems in 2006 were expected to amount to 65 billion dollar (Daniels, 2006), which should be compared with 602 billion dollar of total pharmaceuticals sales in 2005 (Van Arnum, 2006). Major breakthroughs are yet to be expected from the marriage of the CDD concept with the increasing number of the biotech-developed therapeutics. Nevertheless, CDD is already the leading concept in some fields, e.g. in the

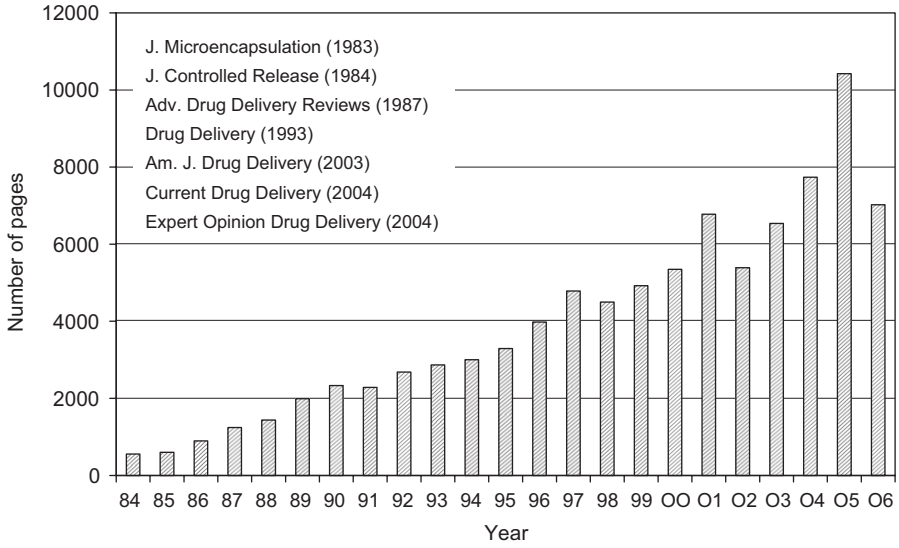

Fig. 1. Total annual number of pages of journals dedicated to CDD/CDR systems. The numbers in parentheses following each journal name denote the year of appearance.

emerging field of nanomedicine, where it is accounting for 55% of companies, 60% of products and 80% of sales (Wagner et al., 2006).

3. The importance of radiation sterilization of drug delivery systems

Just as the research on CDD systems is only a small fraction of the total research effort published in the pharmaceutical literature, so is the work on radiation sterilization of CDD/CDR systems only a small fraction of the total research effort published in that field. Literature search found about 150 journal papers on the subject since 1990, which should be compared with more than 70,000 pages only in dedicated journals in the same period, which are no less than 7000 papers in that type of journals only. The distribution of the 150 papers shows a great dispersion of publication outlets (Fig. 2): specialized journals are obviously not the only possible choices. More than 40 different journals have published work on the subject at least once.

Only one-third of the papers on radiation sterilization were published in specialized journals listed in Fig. 1, so that our subject represents less than 1% of the dedicated literature. Considering the large total volume of pharmaceutical literature, the share of the remaining 100 papers on the subject in the general literature is still much lower.

It is not surprising that Radiation Physics and Chemistry holds a high second rank among the preferred journals, considering that much work has been done by the authors specializing in radiation research and applications. Lessons learned from the related area of food irradiation and the involvement of the nuclear sector in it should not be overlooked. In spite of the massive research effort, food irradiation failed to take root: less-than-enthusiastic acceptance of the industry, the ignorance of the public and the rejection of the authorities have probably been the most decisive key factors (Ehlermann, 2005). However, the nuclear sector's tenacious support to food irradiation might have also eventually proved counterproductive. Therefore, it is reassuring that the majority of papers on radiation sterilization of drug delivery systems have been authored by the pharmaceutical professionals and published in the respective professional journals, which indicates that the pharmaceutical profession recognizes the need for radiation sterilization of CDD/CDR systems.

The choice of drugs selected for the studies on radiation sterilization of CDD/CDR systems reflects not only the unmet needs and the urgency of conditions these drugs are intended to treat, but also the unique adaptability of some therapeutic classes to the concept of targeted delivery. Three leading therapeutic classes accounting for 50% of all radiation sterilizable drugs for controlled delivery are antineoplastic, antibacterial and antiinflammatory agents (Fig. 3).

It is difficult to know whether any of the approved CDD/CDR systems on the market have been sterilized by irradiation, and if so, how much. We know that cross-linking and sterilization by irradiation were successfully applied for the manufacturing of vaginal suppositoria for

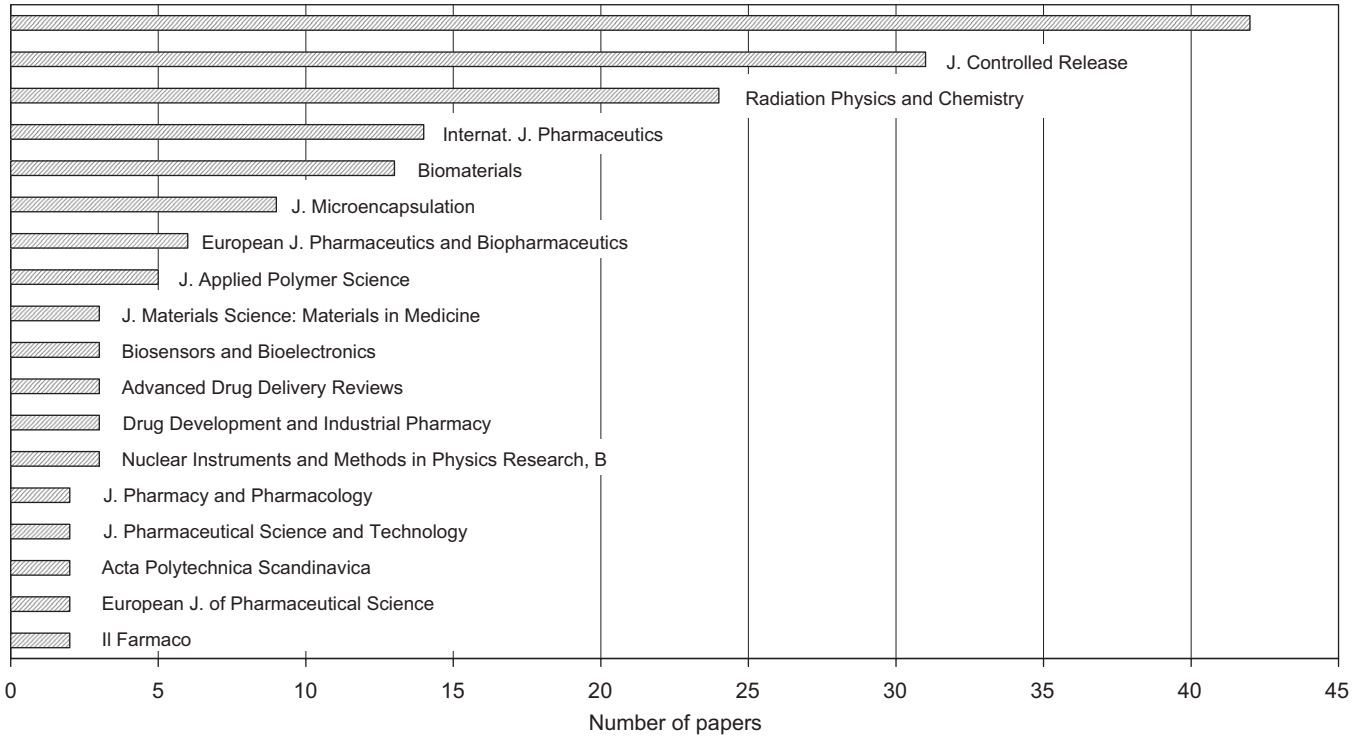

Fig. 2. Distribution of papers on radiation effects on CDD/CDR systems with respect to publication outlets. The uppermost bar represents 42 different journals, each carrying one paper on the subject.

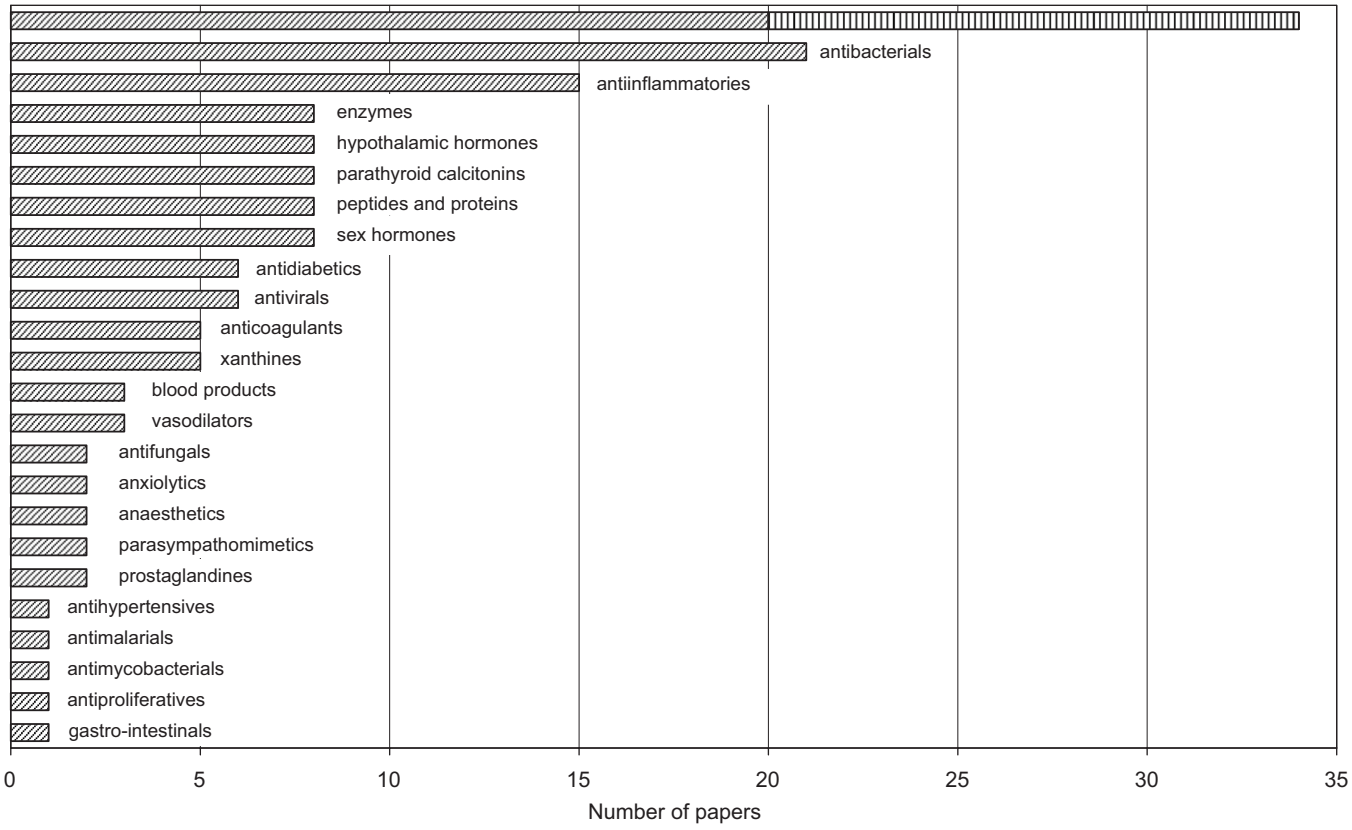

Fig. 3. Distribution of papers on radiation effects on CDD/CDR systems with respect to therapeutic classes of drugs. The uppermost bar represents the most numerous class, antineoplastic agents, 5-fluoro uracil (5-FU) being shown separately.

labor induction and cervical cancer treatment (Rosiak and Olejniczak, 1993) and testicular prostheses for testosterone replacement therapy (Imai et al., 1997). The labor induction system passed complete clinical trials in Poland by 2001 having been involved in more than 300 childbirths (Ulanski et al., 2002), and 12 patients in Japan were treated for hypogonadism by 1997. At least four drug delivery systems sterilized by radiation were commercially available in Switzerland by 1996 (Sintzel et al., 1997). As far as other systems are concerned, due to the paucity of data in the open literature we are in a position not much different than some 20 years ago, when the authors of a review on radiation sterilization of pharmaceuticals concluded that "quite a number of pharmaceutical companies irradiate their products, but for mainly commercial reasons, prefer not to advertise this fact" (Jacobs and Wills, 1988). On the other hand, the fact is that the great majority of published studies on radiation sterilization of CDD/CDR systems have been performed in vitro, while only a small fraction of studies have actually been done in vivo, almost exclusively in animals. In addition to the above-mentioned results of human studies, we were able to identify only two more: gentamicin release from Septacin^{TM} beads assayed in wound drainage (Li et al., 2002) and ciprofloxacin released from ocular minitablets assayed in tear film (Weyenberg et al., 2004).

4. Radiation chemistry aspects of radiation sterilization and crosslinking

Two types of ionizing radiations are used for radiation sterilization and crosslinking: gamma rays emitted from the artificial radioactive isotopes ^{60}Co and ^{137}Cs and beams of energetic electrons from electron accelerators. The absorption of radiation energy from both types of sources occurs on a subatomic level. Electrons injected into matter from an electron accelerator enter into Coulombic interactions with atomic electrons of the medium, which results in numerous electronic excitations and ionizations of atoms along the tracks of energetic electrons. The principal mechanisms of gamma ray interactions also involve the ionization of the interacting atom and the ejection of a high-energy electron in the first step; high-energy electrons ejected in the primary ionization continue to produce numerous electronic excitations and ionizations along their tracks quite in the same way as they would do if they were injected directly from an accelerator. The only difference is that the probability of gamma ray interactions decreases exponentially with depth, while the probability of electron interactions decreases in a much steeper fashion as function of depth. The fraction of gamma ray energy deposited in the primary ionization is negligible in comparison with the energy deposited by the subsequent

generations of secondary electrons. Energy deposition mechanisms of these two types of radiation being the same, the same amount of energy absorbed by matter, irrespectively whether irradiated by gamma rays or fast electrons will produce the same kind and amount of chemical change. This is the rationale for the use of the two types of radiation sources, isotopes and accelerators on an equal footing in practice. Qualitatively different effects observed with gamma ray as compared to electron beam irradiation mainly arise because of the dose-rate effects, particularly in the presence of oxygen or other scavenger molecules. Large dose-rate irradiation of liquids producing high local concentrations of free radicals favors mutual reactions of free radicals (recombination) over their reactions with scavengers in the tracks of the respective impinging radiations.

Because principal interactions involve atomic electrons, the distribution of energy deposited in individual components of irradiated matter depends on the contribution made by that component to the atomic composition. In solution the main contribution to the total mass is made by a solvent. Irradiation of aqueous solutions gives rise to oxidizing (hydroxyl radical $^{\cdot}OH$) and reducing (hydrated electron e^{-}_{aq}) reactive species produced by the radiolysis of water, their relative amounts depending on pH and presence of solutes. These species may disappear through recombination with other reactive species of water radiolysis or they may diffuse some distance away from the site of their original formation, which increases the probability of their reaction with dissolved substances. APIs in irradiated aqueous solutions act as scavengers for the reactive species formed by the radiolysis of water. Scavenging reactions with oxidizing or reducing species result in damage to APIs, the damage being larger than would be expected on the basis of the API mass fraction in the solution alone. This is well illustrated in a survey of irradiation treatment of alkaloids, morphine derivatives and antibiotics (Boess and Bögl, 1996). That review contains comprehensive tables aided by simple graphics in the form of bullets, where each bullet represents a certain amount of decomposition in steps of 0.5%, 1.0%, 1.5%, etc., or 5%, 10%, 15%, etc. or some intermediate steps. While most substances were treated with doses in the range 10–60 kGy, which is unnecessarily high for this type of products, it is also obvious that aqueous solutions exhibited much higher level of decomposition as compared to solid substances. Because of the inherent instability toward irradiation of APIs in aqueous solutions, radiation sterilization of solutions is not recommended for the sterilization of aqueous liquid solutions (EMEA, 2000).

Irradiation of solid substances in the absence of water does not, of course, lead to the formation of diffusible oxidizing and reducing aqueous radiolysis species but, due to the restricted mobility in solids, the consequences of excitation and ionization remain localized on the affected molecules or confined to the immediate vicinity of the site of primary interaction. Intramolecular redistribution of localized charge and excitation energy may then lead to the fragmentation of affected molecules according to the interplay of electron affinities, ionization potentials and bond dissociation energies among the subunits of complex molecules. Large dose-rate (electron) irradiation in a polymeric matrix produces a large steady-state concentration of free radicals which leads to an increased probability of mutual reactions between radicals situated on the same macromolecule (intramolecular crosslinking), as compared to intermolecular crosslinking ensuing at low dose-rate (gamma) irradiation.

5. The effect of irradiation on the principal forms of CDD/CDR formulations

Having excluded solutions due to their inherent instability toward irradiation, the choice of formulations which can be subjected to radiation sterilization remains limited to solids, solids imbibed with liquids (hydrogels) and solids dispersed in liquids (liposomes and nanoparticles).

Irradiation of polymers leads to two main processes simultaneously: chain scission and crosslinking. The structure of the macromolecules, the presence of air and additives and irradiation conditions determine which process will dominate. For example, low dose-rate irradiation of poly(L-lactic acid) fibers in air at dry ice temperature with gamma rays resulted in the decrease of tensile strength because oxygen had time to diffuse to free radicals formed by irradiation and to produce oxidative degradation before the radicals could crosslink with each other producing a network. On the other hand, high dose-rate irradiation with fast electrons under the same conditions resulted in the increase of tensile strength due to crosslinking, which took place at high steady-state concentration of free radicals produced during a short irradiation pulse, before being depleted by oxygen diffusion (Nuutinen et al., 2001).

An intermediate state of matter between a solid polymer and a liquid component is termed gel. Gel formation occurs when a small amount of solid consisting of polymeric gelator molecules, rendered insoluble by the formation of a three-dimensional network, swells by imbibing a large amount of a compatible liquid so that viscosity and the consequential internal friction ultimately increase resulting in a semi-solid state. Gels may be classified according to the liquid phase. The gel that consists of hydrophilic polymer molecules and contains water as a liquid phase is called a hydrogel.

The formation of the three-dimensional polymer network within hydrogel may be achieved by physical and chemical methods. Crosslinking by irradiation randomly introduces crosslinks in space within hydrogels, whereas chemically crosslinked hydrogels exhibit more inhomogeneous distribution of crosslinking points. Crosslinking by irradiation is of a special interest also because it will not only produce a tri-dimensional network without the

addition of chemical initiators, but will also reduce the microbial load of the product at the same time. However, this advantage to kill two birds with one stone was not always exploited: irradiation of some hydrogel forming polymers, such as acrylates, acryloyl-L-proline methyl ester (A-ProOMe) and α,β-poly(*N*-hydroxyethyl)D,L-aspartamide (PHEA), was carried out to produce crosslinking only, the loading with therapeutic agents being done afterwards. Only the release properties in vitro of these hydrogels were subsequently studied, while sterility was not an important issue at that stage of research. Should there had been a need to produce sterile CDD/CDR systems, radiation-sterilized carriers would have had to be subsequently loaded aseptically.

Radiation-induced crosslinking in the presence of therapeutic agents producing sterile loaded hydrogels was described but, as a rule, the principal attention was paid to the release properties rather than to the identification of possible radiation damage to APIs contained therein. Because of the relatively small amount of a loaded API, its damage would not be readily detectable. For example, an aqueous solution containing acryloylated polyaspartamide (PHG), (PHEA derivatized with glycidyl methacrylate, GMA) and 10 mg/ml (0.077 mol/l) of an antineoplastic drug, 5-fluorouracil (5-FU) was irradiated up to 2.5 kGy to obtain a hydrogel (Pitarresi et al., 2001). Assuming that the (i) radiation chemical yield of the hydrated electron in aqueous phase was the same as in water, (ii) complete scavenging of the hydrated electron by 5-FU took place and (iii) subsequent dissociation of the fluorouracil radical anion was quantitative, the calculation shows that less than 1% of the present 5-FU would undergo dissociative electron attachment. However, assumptions (i) and (ii) are overestimates and (iii) is contrary to the observations (Rivera and Schuler, 1983). Consequently, 5-FU within a hydrogel suffers little damage by irradiation, and other APIs are not exception.

Encapsulation within microscopic structures improves drug bioavailability by enhancing drug penetration of capillaries and cells, i.e. their access to tissues. Besides various artificial solid nanoparticles made of polymers, carbon, silicon or metals (Hughes, 2005), one of the most investigated forms of delivery is the liposome. Liposomes are closed vesicular structures formed by layers of lipid membranes enclosing an aqueous interior, which can also be seen as the simplest artificial cells. They can be applied as carriers for both hydrophilic drugs (to be included in their aqueous interior) and hydrophobic drugs (to be entrapped in the lipid bilayer) (Feng and Chien, 2003).

Irradiation of liposomes in the presence of air critically depends on the nature of constituent lipids. Unsaturated fatty acids undergo chain peroxidation (Katušin-Ražem and Ražem, 1999) and the presence of lipid hydroperoxides affects the properties of liposomes as drug carriers by increasing their permeability. Since radiation chemical yields of peroxidation of unsaturated fatty acids are inversely proportional to the square root of the dose-rate electron beam sterilization of unsaturated liposomes would be a better choice than gamma irradiation. Oxidative damage to liposomes could be mitigated by structure modifying factors such as cholesterol, lipophilic antioxidants such as tocopherol and nitroxide compounds Tempo and Tempol, the latter two providing protection to both regions of the lipid bilayer, acyl chains as well as polar headgroups (Samuni et al., 1997).

Irradiation in the absence of oxygen and at a reduced temperature gives rise to crosslinking, which influences the carrier properties of liposomes in the opposite direction than peroxidation, i.e. by hindering the leakage from liposomes. Radiation crosslinking was used in the preparation of artificial red blood cells consisting of radiation crosslinked liposomes loaded with hemoglobin (Akama et al., 1995).

6. The effects of irradiation on carrier materials

Normal reaction of an organism to a foreign substance, including a drug is to distribute it throughout the body via the blood circulation, try to burn it for energy (mainly in the liver) and finally to excrete whatever is left of it. Because of these metabolic processes the concentration of a drug in the body does not remain constant. The time profile of drug concentration at some location in the body is termed pharmacokinetics. To control pharmacokinetics, i.e. to maintain drugs in target tissues within the range of therapeutic concentrations and to accomplish optimized release with respect to space and time, CDD systems consisting of biodegradable carriers loaded with drugs were introduced.

Both natural and synthetic polymers can be used as carriers for CDD/CDR systems. A wide variety of synthetic polymers have been investigated, but as far as radiation sterilization is concerned, a more limited selection of carriers is found in the literature (Fig. 4).

The most frequently used synthetic carriers are aliphatic polyesters the most popular one being based on polylactic acid (PLA) and its copolymers with polyglycolic acid (PGA): PLA-*co*-PGA (PLGA). One-third of radiation-sterilized CDD/CDR systems described in the literature are based on PLA and PLGA.

Polylactic acid exists in two forms: poly(L-lactic acid) (PLLA) is a semi-crystalline material having typically 36% crystallinity, and poly(D,L-lactic acid) (PLA) is an amorphous polymer. Both forms were used for the manufacturing of CDD/CDR systems. PLA was used either alone or copolymerized with PGA, polyvinylpyrrolidone (PVP) or ε-caprolactone (CL). PLA carriers were mostly shaped as injectable microspheres with diameters up to 100 μm, or double-walled microspheres with a larger diameter (430 μm), or implantable rods. PLA with widely varying molecular weight from 6 to 300 kDa was used.

Irradiation of solid PLLA powder in vacuum resulted in approximately equal radiation chemical yields of chain scission and crosslinking, 0.24 and 0.28 μmol/J, respectively.

On the other hand, irradiation of PLA powder in vacuum produced only chain scission and no crosslinking (Babanalbandi et al., 1995). The same material in a compact form, e.g. a thin sheet, was more resistant to radiation-induced degradation in the presence of air as compared to powder, and little change of mechanical properties were noticed up to 30 kGy (Nugroho et al., 2001). With the addition of a crosslinker such as triallyl isocyanurate (TAIC), the gel fraction of PLLA increased with dose, crystallinity and swelling decreased, and tensile strength was not affected by irradiation in vacuum (Jin et al., 2002). By controlling the concentration of crosslinker, dose and annealing time, the gel fraction and degree of swelling could be controlled (Mitomo et al., 2005).

Due to their good initial mechanical properties and ultimate biodegradability PLGA copolymers, besides for CDD/CDR systems, are used for the manufacture of surgical sutures, orthopedic devices (screws, pins, suture anchors), wound closure devices (clips, staples, meshes), cardiovascular stents and scaffolds for guided bone regeneration. Radiation sterilization of drug carriers made of PLGA copolymers and having a varying proportions of PLA:PGA were studied. The composition most often used, PLGA (50:50) copolymer was found suitable for delivering small molecules, as well as large therapeutic proteins. PLGA carriers ranged in size from injectable nanoparticles and microspheres to implantable rods and wafers. Widely varying molecular weight PLGA from 8 to 130 kDa was used.

It is difficult to predict release properties of PLGA carriers based on considerations of the first principles only. The observed rate of drug release is the result of the

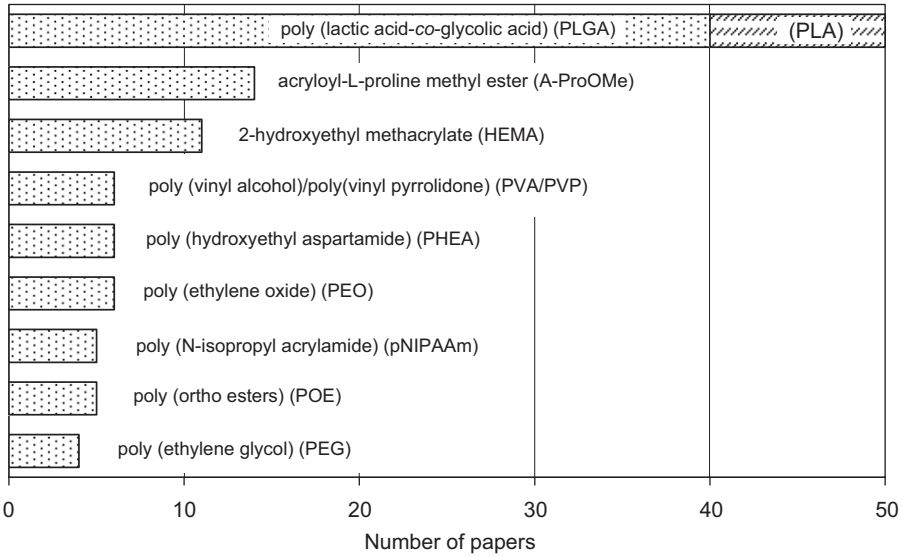

Fig. 4. Distribution of papers on radiation effects on CDD/CDR systems with respect to synthetic polymer carriers.

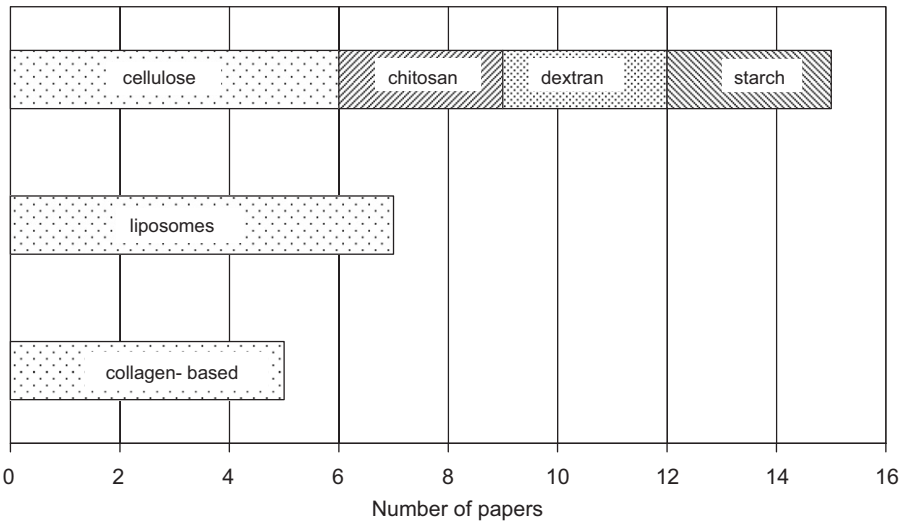

Fig. 5. Distribution of papers on radiation effects on CDD/CDR systems with respect to natural polymer carriers.

Table 1
The effects of irradiation on CDD/CDR systems containing analgesic and antiinflammatory agents

Drug/target	Carrier[a]/dosage form/ dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/conditions	Time span of release	Methods[b]: Effects of irradiation	Reference
Acetaminophen (paracetamol)/ in vitro (H_2O)	A-ProOMe + TMPTMA (X-linker) + DMAA (hydrophilic monomer)/ hydrogel/disks/2.5%	γ/25/r.t., N_2 (before loading)	Complete release from A-ProOMe/TMPTMA (99:1): within 2 d at 10 °C, within 3 d at 30 °C, within 7 d at 37 °C Complete release from A-ProOMe + DMAA + TMPTMA: within 2 d at 0% DMAA, within 1 d at 5% DMAA Complete release from A-ProOMe + CEA + TMPTMA: within 3 d at 0% CEA, within 4 d at 5% CEA Complete release from A-ProOMe + AOA + TMPTMA: within 20 d	Solubility: ● Irradiation of A-ProOMe alone produces polymer soluble in H_2O at $t < 17$ °C (LCST); ● Irradiation of A-ProOMe + TMPTMA produces hydrogel insoluble in H_2O; Gravimetry: Swelling increases with temp.; at temp = const. swelling increases with addition of hydrophilic DMAA; SP: Release rate and released amount increase with swellability (i.e. with decreasing temperature)	Martellini et al. (1998)
Acetaminophen (paracetamol)/ in vitro (H_2O)	A-ProOMe + TMPTMA (X-linker) + DMAA (hydrophilic monomer) + CEA (hydrophobic monomer) + AOA (comonomer) hydrogel/disks/ 5 mm diam. × 1.5 mm/10%	γ/25/r.t., N_2 (before loading)		Solubility: See above; Gravimetry: See above; Irradiation of A-ProOMe + hydrophobic AOA produces hydrogel with swellability and transition temperature decreasing with addition of AOA; SEM: Pore size of p(A-ProOMe-*co*-TMPTMA) decreases with swelling temperature; SP: ● Release rate from A-ProOMe/AOA/TMPTMA determined by hydrolysis; ● Release rate and amount released increase with swellability (i.e. with the addition of hydrophilic DMAA); ● Release rate and transition temperature decrease with the addition of hydrophobic TMPTMA and CEA	Martellini et al. (1999)
Diclofenac Na/ in vitro, pH 7.4, 6.8	PLGA (50:50) $\bar{M}_w$ 4 kDa/ microspheres/50% have 29.4 μm diam./12.7%	γ/5, 15, 25/r.t., vac.	37.7% release within 24 h	SP: ● Drug content not affected by irradiation; ● Release rate increases with dose; LLS: Size increases with dose to 54.6 μm; DSC: Slight increase of T_g with dose;	Çaliş et al. (2002)
Diclofenac Na/ in vitro, pH 7.4, 6.8	PLGA (50:50) $\bar{M}_w$ 88 kDa/ microspheres/50% have 5.77 μm diam./16.1%	γ/5, 15, 25/r.t., vac.	36.4% release within 24 h	SP: ● Drug content not affected by irradiation; ● Release rate increases with dose, decreases with $\bar{M}_w$; LLS: Size increases with dose to 96.6 μm; DSC: Slight increase of T_g with dose; SEM: Deformation of shape and pore size increase with dose	
Diclofenac Na/ in vitro, pH 7.4	Chitosan $\bar{M}_w$ = 1.34 MDa/ microspheres/6.7 μm dia/ 21%	γ/5, 15, 25/r.t., vac.	50% release within 6 h at dose = 0 kGy reduced to 5, 4 and 3 h at doses 5, 15 and 25 kGy, respectively	SP: ● UV spectrum not affected by irradiation; ● Drug release rate increases with dose; FTIR: No new chemical groups appear on irradiation; SEM: No observable surface change; AFM: Surface roughness decreases with dose ESR: Only radicals of chitosan observed; DSC: No change of thermograms with dose; XRD: No change of crystallinity of drug in the carrier; Gravimetry: Swelling slightly decreases with dose	Desai and Park (2006)
Diflunisal/ in vitro, pH 7.4, pH 1/6.8	PHEA $\bar{M}_w$ 56.9 kDa/ hydrogel/microspheres/ 50–60 μm diam./4.76%, 16.7%	γ/604.8/r.t., air (before loading)	90% release within 3 h at pH 7.4, 10% release within 2 h at pH 1, 85% release on pH change from 1 to 6.8	Solubility: 97% crosslinked; Microscopy: Equilibrium swelling ratio 37% after 120 s; SEM: Almost spherical microparticles; XRD: Drug present as molecular dispersion, i.e. in an amorphous state	Pitarresi et al. (1996)

Table 1 (*continued*)

Drug/target	Carrier[a]/dosage form/ dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/conditions	Time span of release	Methods[b]: Effects of irradiation	Reference
Diflunisal/DPPC unilamellar liposomes 100 nm diam.	PHEA $\bar{M}_w$ 56.9 kDa hydrogel/microparticles/ 2.77%	γ/604.8, r.t., air (before loading)	Amount of drug entering from irradiated PHEA into liposome 65–70% immediately on contact	Microscopy: Equilibrium swelling ratio 34%; DSC: ● Rigidity (T_g) increases with dose; ● Entering of drug into liposome not dependent on temperature (contrary to the entry of free drug)	Castelli et al. (2000)
Ibuprofen/ in vitro, pH 7.4, 1	HEMA/MAA + 5% or 10% X-linker (MAOE ester of TPA) hydrogel/powder/25%	40 kV X-rays/r.t., vac.	With 5% X-linker: 80% release within 10 h at pH 7.4; 35% release within 10 h at pH 1; with 10% X-linker: 65% release within 10 h at pH 7.4; 25% release within 10 h at pH 1	Gravimetry: Swelling decreases with X-linker concentration and pH; FTIR: Drug not covalently bound to copolymers; DSC: T_g increases with X-linker, decreases with drug loading; SP: Release rate increases with pH, decreases with X-linker concentration	Mahkam and Allahverdipoor (2004)
Ibuprofen/ in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 13.14 kDa microspheres/ 39.3 μm diam./11.2%	γ/25/dry ice, air	90% release within 9 d	SEM: Size, shape and surface morphology not affected by irradiation; DSC: T_g not affected by irradiation; XRD: No peaks characteristic of crystalline drug (drug is dissolved in matrix); SEC: $\bar{M}_w$ not affected by irradiation; small increase of polydispersity; SP: Relase rate not affected by irradiation; Storage: after 1 year at 4 °C size, shape, surface, T_g, $\bar{M}_w$ and release rate not affected by irradiation	Fernandez-Carballido et al. (2004)
Ketoprofen/ in vitro, pH 3, 6.5, 7.5	A-ProOMe + fatty acid salts: Na laurate (C_{12}) Na myristate, Na palmitate, Na stearate/hydrogel/rods/ 5 mm dia × 10 mm	γ/30/0 °C, N_2 (before loading)	Burst release during the 1st hour; release controlled by pH and number of $-CH_2-$groups in fatty acids	Gravimetry: ● High swelling at temperature < 14 °C; ● Low swelling at temperature > 14 °C; ● Swelling not affected by pH between 3 and 7.5; ● Swelling strongly affected in the presence of Na salts of FA > C_{12} on change from pH 3 to 6.5; SP: Release rate increses with pH and number of $-CH_2-$groups in fatty acids; Drug release: Regulated by surface barrier formation and its destruction by shrinking and swelling	Negishi et al. (1999)
Ketoprofen/ in vitro, pH 3, 5.5, 7.5	A-ProOMe/MA-Gly (40:60 mol%) + 14G (X-linker); A-ProOMe/ MAA (40:60 mol%) + 14 G (X-linker) hydrogel/tablet/ 5 mm diam.	γ/30/0 °C, N_2 (before loading)	100% release within 1.5 h from A-ProOMe/MA-Gly at pH 7.5; 25% release within 6 h from A-ProOMe/ MAA at pH 7.5	Gravimetry: ● Swelling threshold of A-ProOMe/MA-Gly at pH > 3.0 (pK_1(Gly) = 2.34); ● Swelling threshold of A-PrOMe/MAA at pH > 5.5 (pK_a(MAA) = 4.65); ● Swelling of A-ProOMe/MA-Gly > A-ProOMe/MAA, increases with pH; SP: ● Release rate from A-ProOMe/MA-Gly > A-ProOMe/MAA, increases with pH; ● Fickian diffusion from A-ProOMe/MA-Gly at pH > 5.5; ● Non-Fickian (anomalous) diffusion from A-ProOMe/MAA at pH 3.0–7.5	Yoshida et al. (1999)
Ketoprofen/ in vitro, water	A-ProOMe without X-linker; A-ProOMe + 14 G (X-linker) hydrogel/ tablet/5 mm diam.	γ/30/0 °C, N_2 (before loading)	Without X-linker: 85% release within 1 h With X-linker: 60% release within 1 h	Gravimetry: Same temperature-induced swelling rate with and without X-linker, shrinking faster without X-linker; SEM: Same porous structure of swollen gel with and without X-linker, retained in shrunken gels with X-linker; Microscopy: Membrane-like surface in gels without X-linker; SP: Faster release from gels without X-linker	Negishi et al. (2001)

Naproxen Na/ in vitro, pH 6.8, 7.4	PLGA (50:50) $\bar{M}_w$ 34 kDa microspheres/50% have 9 μm diam./12%	γ/5, 15, 25/r.t., vac.	Initial burst up to 60% during the 1st hour; 100% release after 3 d (2 d for 25 kGy-irradiated)	SP: ● Drug content not affected by irradiation; ● Release rate not affected by irradiation up to 15 kGy; ● Release rate increased from 25 kGy—irradiated microspheres; LLS: Size increases with dose to 53 μm; DSC: Slight increase of T_g with dose; SEM: No deformation of shape or change of pore size;	Çaliş et al. (1999)
Naproxen Na/ in vitro, pH 6.8, 7.4 (cont.)	PLGA (50:50) $\bar{M}_w$ 88 kDa/ 50% have 5 μm diam./10.6%	γ/5, 15, 25/r.t., vac.	Initial burst up to 30% during the 1st hour; 100% release after 4 d	SP: ● Drug content not affected by irradiation; ● Release rate not affected by irradiation up to 15 kGy; ● Release rate increased from 25 kGy—irradiated microspheres; ● Release rate decreases with $\bar{M}_w$; LLS: Size increases with dose to 42 μm; DSC: Slight increase of T_g with dose; SEM: No deformation of shape or change of pore size;	Çaliş et al. (1999) (cont.)
Piroxicam/ in vitro, pH 7.4	PLA $\bar{M}_w$ 5.46 kDa + 25% PVP/microspheres/10–40 μm diam./9.17%	γ/15	55% release in 3 d reduced by irradiation to 40% in 3 d; initial burst up to 28% during 6 h	Titration: Acid value increases from 31.13 to 41.50; DSC: T_g decreases from 48.0 to 42.6 °C; Viscosimetry: ● Intrinsic viscosity decreases from 0.1667 to 0.1188 dl/g; ● $\bar{M}_w$ decreases from 5.46 to 3.52 kDa; SP: Differential release becomes more uniform after 36 h (from unirradiated microspheres after 48 h)	Lalla and Sapna (1993)
Suprofen/ in vitro, pH 1/6.8, 7.4	PHEA/hydrogel/ microparticles/ 50–70 μm diam./1.53%	γ/604.8/r.t., air (before loading)	At pH 7.4: initial burst up to 50% followed by complete release within 3 h; At pH 1: initial burst up to 40% followed by additional 40% release after pH change to 6.8	Hemolysis assay: Photosensitizing activity of suprofen in PHEA on red blood cells is about 1/2 of suprofen in PAHy microparticles and significantly lower than of drug alone	Giammona et al. (1998)

[a] *Carriers*: AOA: 4-acryloyloxy acetanilide; A-ProOMe: acryloyl-L-proline methyl ester; CEA: 2-cyanoethyl acrylate; DMAA: *N*,*N*-dimetylacrylamide; DPPC: dipalmitoylphosphatidylcholine; 14G: tetradecaethyleneglycol dimethacrylate; HEMA: 2-hydroxyethyl methacrylate; MAA: methacrylic acid; MAGly: methacryloyl glycine; MAOE: methacryloyloxyethyl ester; PLA: poly(D,L-lactic acid); PHEA: α,β-poly(*N*-hydroxyethyl)-D,L-aspartamide; PLGA: poly(lactic-*co*-glycolic acid); PVP: poly(vinyl pyrrolidone); TPA: terephthalic acid; TMPTMA: trimethylpropane trimethylacrylate.

[b] *Methods:* AFM: atomic force microscopy; DSC: differential scanning calorimetry; ESR: electron spin resonance; FTIR: Fourier transform infrared spectrometry; LLS: laser light scattering; SEC: size exclusion chromatography; SEM: scanning electron microscopy; SP: spectrophotometry; XRD: X-ray diffraction.

Table 2
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antibacterial agents

Drug/target	Carrier[a]/dosage form/ dimensions/loading (%w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Ampicillin trihydrate/ in vitro, pH 6; in vivo (dog plasma)	HEMA + 1% TMPTMA/hydrogel/ beads/3.5 mm diam./ 444 mg/bead (~20%); rods/45.22 mg/cm (~20%)	γ/10, 25/−78 °C	Up to 50% release within 6 h in vitro; up to 85% release within 24 h in vivo	SP: ● Release rate in vitro: ○ 0.454 mg/cm^2(min)$^{1/2}$ from 10 kGy; ○ 0.394 mg/cm^2(min)$^{1/2}$ from 25 kGy; ● Release profile from tablet in vivo: max. conc. 8 μg/ml reached 2 h after administration, released amount 176.6 mg, bioavailability 44.2%; ● Release profile from beads in vivo: max. conc. 4.8 μg/ml reached 6 h after administration, released amount 374.3 mg, bioavailability 84.3%; Biological activity (mg/ml vs. time): Coincident with cumulative release curve (mg/ml vs. time)	Fernandez-Degiorgi et al. (1995)
Cephalosporin (cephem 1 Na salt)/in vitro (veterinary drug)	Peanut oil:wax (95:5) suspension/5.13%	e/5, 10, 15		HPLC: ● More radiolysis products formed in LDPE syringe than in glass; ● Most abundant radiolysis product related to thiodiazolyl; ● Concentration of drug within 45–55 mg/g (90–110%); LC-MS: Radiolysis products increase with dose and storage temp.; Appearance: Colour change from cream to light tan;	Johns et al. (2001)
Chloramphenicol/ in vitro; in vivo: wound dressing (over 50 clinical tests)	PVA or PVA:PVP (1:1) + itaconic diallyl ester hydrogel/films/ 1.4%	e/20–200/r.t. (before loading)	Release rate decreases with dose and time; release rate higher from film with more drug; release rate lower at higher dose	Gravimetry: ● Gel content increases with dose and X-linker; ● Swelling ratio decreases with dose and X-linker; SP: Drug release rate independent of X-linker	Chen et al. (1993)
Ciprofloxacin hydrochloride/in vitro simulated lachrymal fluid pH 7.4	Na alginate + PEG between films of eudragit RL + DEP(plasticizer) and eudragit RS + DEP (C–1); or between films of PVA + DEP (C–2)/ ocular inserts/0.75 mg/ insert	γ/25	Up to 93% release from (C-1) within 5 d; up to 96% release from (C-2) within 5 d	SP: Constant release rate over 120 h; HPLC: Less than 5% degradation after 90 d storage at 40 °C, 75% r.h.;	Charoo et al. (2003)
In vivo/eye (rabbit)	Na alginate + PEG between films of eudragit RL + plasticizer DEP and eudragit RS + DEP (C–1); or between films of PVA + DEP (C–2)/ ocular inserts/0.75 mg/ insert	γ/25	Up to 89% release from (C-1) within 5 d; up to 87% release from (C-2) within 5 d	SP: ● Constant release rate over 120 h; ● High correlation of in vitro and in vivo cumulative release; HPLC: Steady level of drug in aqueous humor above minimum inhibitory concentration (MIC, 0.38 μg/mL) lasting for 4 d; Scores of redness, mucoid discharge, lachrymal secretion, response to ocular stimulus, swelling of eyelids: improvement vs. eye drops starting on day 2	

Ciprofloxacin hydrochloride/in vitro	PLGA (52:48) $\bar{M}_w$ 40 kDa + boric acid/ nanoparticles/ 250–300 nm/1.25%; 2.5%	γ/25	Up to 58% release within 24 h; release increases in the presence of boric acid, decreases with the number of homogenization cycles	PCS: Average size increases from 259 to 293 nm (aggregation); HPLC: Slightly faster release after irradiation; Microbiological assay with *S. aureus* and *P. aeruginosa*: minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) not affected by irradiation	Dillen et al. (2004a)
Ciprofloxacin hydrochloride/in vitro/ isoviscous vehicles for eye drops: mannitol, carbopol (CP), poly(vinyl alcohol)(PVA), hydroxyethyl cellulose(HEC)	PLGA (52:48) $\bar{M}_w$ 40 kDa/nanoparticles/ 210 nm/2.5%	γ/25	Up to 40% release within 24 h into mannitol and PVA; up to 35% release within 24 h into CP 980; up to 33% release within 24 h into HEC, CP 974 and CP 1342; up to 26% release within 24 h into Poloxamer 407	HPLC: Release rate and released amount increase after irradiation; Oscillatory rheometry: • Viscous modulus not affected; • Elastic modulus decreases in PVA, HEC and poloxamer (Newtonian behavior); • CP 974, CP 980 and CP 1342 are mainly elastic and consist of X-linked networks; • Both viscous and elastic modulus decrease in CP 974, CP 980 and CP 1342 (non-Newtonian behavior); • Slower release after irradiation only into Poloxamer 407	Dillen et al. (2004b)
Ciprofloxacin hydrochloride/in vitro simulated lachrymal fluid pH 7.4	Amylopectin (drum dried waxed maize starch) $\bar{M}_w$ 44.3 kDa $\bar{M}_n$ 35.5 kDa powders and minitablets/3%; 4%; 6%; 8%	γ/25, 50	Up to 80% release within 6 h	GPC: $\bar{M}_w$ and $\bar{M}_n$ decrease with dose and temperature; Karl Fischer: H_2O content not affected; ESR: Radicals mainly from starch; Microbiological assay: Not affected by irradiation; Rheometry: • Addition of Carbopol 974 improves consistency and slows down flow rate; • Consistency decreases with irradiation; • Flow rate increases with irradiation; Mechanical properties of minitablets: Crushing strength increases with irradiation, decreases with temperature; Friability: Decreases with irradiation, increases with temperature; SP: Release rate increases more with temperature than with dose;	Weyenberg et al. (2004)
In vivo eye (human)	Amylopectin (drum dried waxed maize starch) $\bar{M}_w$ 44.3 kDa $\bar{M}_n$ 35.5 kDa powders and minitablets/3%; 4%; 6%; 8%	γ/25, 50		SP: Release from irradiated minitablet maintained in tear film for 8 h vs. rapid decrease after application of commercial eye drops	
Ciprofloxacin hydrochloride/in vitro simulated lachrymal fluid	PLGA 52:48 $\bar{M}_w$ 40 kDa nanoparticles/ 220–346 nm/44–54%	γ/25	Up to 35% release within 24 h; release rate constant after irradiation decreased by cryoprotectants mannitol, trehalose and dextran, not affected by glucose	PCS: • Particle size not affected by irradiation; • Polydispersity increases after irradiation; ELS: Zeta potential not affected by irradiation; HPLC: Release rate decreases with irradiation and cryoprotectant; Kinematic viscosity: • Decreases with irradiation (chain scission); • Microbiol. assay with *P aeruginosa*: minimum inhibitory conc. (MIC) and minimum bactericidal conc.(MBC) values not affected by irradiation and cryoprotectants	Bozdag et al. (2005)

Table 2 (*continued*)

Drug/target	Carrier[a]/dosage form/ dimensions/loading (%w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Decamethoxin (DMO)/ in vitro (H_2O)	Polycaproamide suture surgical thread modified with polymeric coatings/ 1.7–2.3%	γ/25	Up to 80% release within 2 weeks	SP: Release rate little affected by irradiation; Mechanical properties: 6.8% strength loss after 12 d storage in 1% DMO solution; Capillarity: Capillary elevation did not exceed 5.8 mm after 12 d storage in 1% DMO solution	Kovtun et al. (2000)
Gentamicin sulphate/ in vitro, pH 7.3	Silicone-based prepolymer PDMS/ocular disks consisting of 2 films, each 0.2 mm thick/10%	γ/25	Complete release within 2 weeks	Mechanical properties: Elastic modulus, tensile strength and elongation at break not affected by irradiation; Gravimetry: Hydrolytic stability better in non-irradiated disks; FPI: • Release rate not affected immediately after irradiation; • Release rate decreases with time and temperature	Bawa and Nandu (1990)
Gentamicin sulphate/ in vivo subcutaneously (mouse)	Poly(fumaric-sebacic acid) (1:1) copolymer/ cylinders/ 0.5 cm diam. × 1 cm/ 20%	γ/25	Close to 100% after 24 h	ESR: • Free radical yield increases in the presence of drugs; • Free radicals derive from drug, not polymer matrix	Mäder et al. (1996)
Gentamicin sulphate/ in vitro	PVA + PG; MC-Eudragit NE30D + glycerol ocular insert/ films/250 μg/insert	γ/25		Microbiolological assay with S. aureus: • One insert after 3 h challenging inhibited the growth for 24 h; • More PVA or larger volume of inoculum required two inserts in 48 h to inhibit the growth; Microbiological. assay with P. aeruginosa: • One insert after 24 h challenging inhibited the growth for 48 h; • No effect of irradiation as compared to unirradiated inserts;	Devarajan et al. (1999)
In vivo, eye (rabbit)	PVA + PG; MC-Eudragit NE30D + glycerol ocular insert/ films/250 μg/insert	γ/25		Microbiological assay: • Fresh insert every 24 h inhibited the growth of *S. Aureus* and *P. aeruginosa* after 48 h; • No effect of irradiation as compared to unirradiated inserts	
Gentamicin sulphate/ in vitro	Poly(EAD:SA) (1:1) copolymer/ (Septacin™)/beads/ 4 mm diam. × 12 mm/ 20%	γ/10–100	Up to 90% release within 4 w	GPC: $\bar{M}_w$ not decreased at $D < 50$ kGy, increases between 50 and 80 kGy, decreases at $D > 90$ kGy; PLM: No visible change of skin-core structure; WAXRD: Crystallinity increases with dose; Gravimetry: No gel formation after irrradiation; ^{1}H-NMR: No crosslinking observable; FTIR: • Carbonyl group formation in the skin; • Loss of H atoms from C–H bonds inversely correlated with the increase of $\bar{M}_w$ between 50 and 80 kGy; MS: No evidence of new C–C bond formation	Deng et al. (2002), Lee et al. (2002)

Gentamicin sulphate/ in vitro, pH 7.4	50/50 blend of RG 502 H (PLGA 50:50) and RG 503 (PLGA 50:50) $\bar{M}_w$ 21.7 kDa, $\bar{M}_n$ 7.7 kDa/microparticles	e/25.3 γ/28.9	Burst release within 4 h (33% after γ, 12% after e) followed by sustained release up to 3rd day (~60%) extented up to 1 w; release profile only slightly increases after storage at 4 °C and 25 °C at 35% and 60% r.h. for 4 and 12 weeks, resp.	SEC: • Electron irradiation reduces $\bar{M}_w$ to 18.4 kDa, $\bar{M}_n$ to 7 kDa; γ irradiation reduces $\bar{M}_w$ to 19 kDa, $\bar{M}_n$ to 6.2 kDa; • Further decrease with temperature and r.h. in storage; (larger decrease than after EtO sterilization); DSC: T_g reduced by 4–6 °C, similar as with EtO, further decrease with temperature and r.h. in storage; ESR: • No long-lived free redicals formed on irradiation of unloaded microparticles; • Free radical lifetime less than 4 w in loaded microparticles; Microscopy: integrity of microparticles better preserved after irradiation than after EtO sterilization; SEM: Microparticles collapsed after EtO sterilization	Friess and Schlapp (2006)
Gentamicin sulphate/ in vitro, pH 7.4	Insoluble collagen/ PLGA microparticle sponge composite	e/25.3 γ/28.9	50% release within the 1st day followed by sustained release of the remaining 50% for over 1 w	AFM: Less deformed fibers after irradiation than after EtO; ESR: Free radical lifetime less than 4 w in loaded composites; Microbiological assay: • Release little accelerated during first 3 d; • Release accelerated by increasing temperature and r.h.; SEM: Porous structure not affected by irradiation	
Pefloxacin mesylate/ in vivo eye (rabbit)	Blends of HPC, HPMC, PVP and PVA with plasticizers PEG or glycerol/ocular films 30–50 μm thick/ 20–100%	γ/5, 10, 15, 20	Nearly constant release rate up to 100% within 8 h	FTIR: No instability caused by irradiation after 2 months storage at temp. < 45 °C; TLC: No instability caused by irradiation after 2 months storage at temperature < 45 °C	Bharath and Hiremath (1999)
Sulpha-methizole/ in vitro, 0.1 N HCl	Deacetylated gellan gum (Gelrite)/beads/ 2–3 mm diam./10%	γ/25	Initial burst reduced by irradiation and transformed into zero-order release extending for 2 h up to 70% release	Gravimetry: Slower swelling after irradiation (crosslinking);	Quigley and Deasy (1992)
Teicoplanin/in vitro	PLGA (75:25) $\bar{M}_w$ 136 kDa/microspheres/ 29 μm diam./10%	γ/25	Initial burst (40% within 1 d), then up to 95% in 35 d; (No comparison made to unirradiated microspheres)	Microbiological assay with *S. aureus*: bioactivity of remaining drug decreased by 99% within 6 months; Release rate: Not affected by irradiation; LS: Particle size not affected by irradiation; SEM: Surface morphology not affected by irradiation; Described effects not compared to unirradiated microspheres;	Yenice et al. (2003)
Teicoplanin/ in vivo, femoral condyle (rabbit)	PLGA (75:25) $\bar{M}_w$ 136 kDa/microspheres/ 29 μm diam./10% and dispersed in chitosan gel	γ/25	Release in synovial fluid lasting for 10 weeks from both microspheres and chitosan gel;	Microbiological assay with *S. aureus* in synovial fluid: Experiment inconclusive because of the wound infection in 86% animals after 2 weeks; Described effects not compared to unirradiated carriers	
Tetracycline base/ in vitro, pH 7.4	Fourth-generation POE:LA (70:30) and (95:5) $\bar{M}_w$ 4.84 kDa, $\bar{M}_n$ 2.8 kDa/liquid or film 0.4 mm thick/5%; 10%; 20%	γ/20/Ar, −70 °C;	3-d lag time eliminated and zero-order release up to 100% from $POE_{95}LA_5$ film reduced from 14 to 9 d by irradiation	HPSEC: $\bar{M}_w$ and $\overline{M}_n$ of $POE_{70}LA_{30}$ not affected by irradiation	Schwach-Abdellaoui et al. (2001)

Table 2 (*continued*)

Drug/target	Carrier[a]/dosage form/ dimensions/loading (%w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Tetracycline hydrochloride/in vitro	PLGA $\bar{M}_w$ 35 kDa, $\bar{M}_n$ 15.7 kDa/microspheres/ (0.7 mm nozzle)/5%; 10%;	γ/27, 55/−80 °C, N_2		ESR: • Signal intensity proportional to drug loading; • Free radicals originating mainly from drug; • Irradiation in the presence of TEMPOL (spin probe) gives diamagnetic species; GPC: $\bar{M}_w$ and $\bar{M}_n$ decrease faster with dose in unloaded microspheres; DSC: T_g decreases with dose, decrease not affected by drug; GC-MS: Absence of hydrophilic spin adducts of free GA and LA to spin probes indicates degradation by random chain scission	Bittner et al. (1999)
Vancomycin hydrochloride/ in vitro, pH 7.4	PLA 17 and 40 kDa + 14 kDa PVA + 1.5, 4 or 10 kDa PEG/microcapsules/ 18–54%	γ/25	Up to 60% release in 60 d; increase with semi-solid PEG up to 85% release in 60 d due to increased burst release	DSC: T_g decreases with irradiation, SP: • After initial burst, very slow release from 40 kDa PLA, little affected by irradiation; faster release from 17 kDa PLA; • Burst release from irradiated 17 kDa PLA + semi-solid PEG larger than from PLA + solid PEG;	Özalp et al. (2001)
	PLGA (90:10) and (70:30), both 12.5 kDa; + 14 kDa PVA + 1.5, 4 or 10 kDa PEG/microcapsules/ 24–53%	γ/25	Burst release from PLGA 40% in 1 d, up to 85% in 60 d, little effect of PEG	DSC: T_g decreases with irradiation; SP: After initial burst, release from PLGA (90:10) little affected by the presence of PEG and its $\bar{M}_w$	
Vancomycin hydrochloride/in vitro pH 7.4	Hydroxyethyl cellulose-trehalose/microspheres/ 85%: 5–20 μm/10%	γ/25, 40	Up to 50% release in 7 h, little increased after irradiation, not dependent of dose and 6 months storage	SP: Chromophore group, drug content not affected by irradiation; DSC: Endotherm peak at 90 °C (loss of H_2O) not affected by irradiation; ESR: Free radicals from matrix proportional to dose up to 25 kGy, signal decays by non-homogeneous kinetics; Microscopy: Shape and size distribution not affected by irradiation; Antimicrobial activity: not reduced by irradiation	Bartolotta et al. (2005)

[a] *Carriers*: DEP, diethyl phthalate; EAD, euricic acid dimer; FAD, fatty acid dimer; HEMA, 2-hydroxyethyl methacrylate; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methyl cellulose; PDMS, poly(dimethyl siloxane); PEG, polyethylene glycol; PG, propylene glycol; PLA, poly(lactic acid); PLGA, poly(lactic acid-*co*-glycolic acid); POE, poly(ortho ester); PVA, poly(vinyl alcohol); PVP, poly(vinyl pyrrolidone); SA, sebacic acid; TMPTMA, trimethylpropane trimethacrylate.

[b] *Methods*: AFM, atomic force microscopy; DSC, differential scanning calorimetry; ELS, electrophoretic light scattering; ESR, electron spin resonance spectroscopy; FPI, fluorescence polarization immunoassay; FTIR, Fourier transform infrared spectroscopy; GC-MS, gas chromatography-mass spectrometry; GPC, gel permeation chromatography; HPLC, high pressure liquid chromatography; HPLC–ESI/MS, high pressure liquid chromatography—electrospray ionization/mass spectrometry; HPSEC, high-pressure size-exclusion chromatography; IR, infrared spectroscopy; LC-MS, liquid chromatography-mass spectrometry; LS, light scattering mass spectrometry; MS, mass spectrometry; NMR, nuclear magnetic resonance; PCS, photon correlation spectroscopy; PLM, polarized light microscopy; SEC, size exclusion chromatography; SEM, scanning electron microscopy; SP, spectrophotometry; TLC, thin layer chromatography; WAXD, wide-angle X-ray diffraction; XRD, X-ray diffraction.

Table 3
The effects of irradiation on controlled drug delivery/controlled drug release systems containing anticoagulants

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)	Time span of release	Methods:[b] Effects of irradiation	Reference
Heparin/in vitro human blood plasma	PUPA + HMDI (X-linker)/film/1 mg/cm^2	γ/25	Complete release within 20 h	SEM: No morphology change of cell organization on the heparinized surface; Toxicity of heparinized film not affected by irradiation; growth of mouse fibroblast cells not affected by extracts of irradiated heparinized film	Albanese et al. (1994)
Heparin 165–190 U/mg	Cuprophan 150M/hemodialysis membrane/80 μg/cm^2	γ/2.3		SP: • Complexation with toluidine blue of non-immobilized heparin reduced to 95% (comparable to EtO and steam sterilization); • Complexation with toluidine blue of immobilized heparin reduced to 97.6% (less than EtO, more than steam sterilization); Thrombin inactivation assay: Anticoagulant activity reduced to 84.8% (comparable to EtO: 86.6%, steam: 80.1%); APTT assay: Anticoagulant activity reduced to 89.7% (comparable to EtO: 91.3%, steam: 91.4%); SP: • Permeability of Cuprophan to Vit B_{12} reduced to 87.1% (EtO: 92.7, steam 18.1%); • Permeability of Cuprophan to sulphobromo phthalein not reduced by irradiation and EtO; reduced to 34.6% by steam; • Permeability of Cuprophan to H_2O reduced to 91.4% (EtO: 104.4, steam: 33.8%)	ten Hoopen et al. (1996)
Heparin 177 U/mg/in vitro pH 7.4	Cuprophan 150M + CDI (coupling agent)/hemodialysis membrane/60–85 μg/cm^2	γ	Release within 1 w: 7.3% release from heparin/CDI = 5; 13.3% release from heparin/CDI = 10; 23.2% release from heparin/CDI = 30; release reduced by radiation sterilization	APTT assay: Release increases with increasing heparin/CDI ratio; release relative to non-sterilized membrane reduced to 83.6%, 92.5% and 94.4% for heparin/CDI ratios 5, 10 and 30, respectively	Hinrichs et al. (1997)
Heparin 139 U/mg/in vitro	PLLA-*co*-CL (50:50)-g-PAA/sheet/98 μg/cm^2	e/(before loading)	50% release within 1 week	Toluidine blue test: 76% of heparin on the surface is biologically active	Säilynoja et al. (1999)
"piyavit" (secretion of salivary glands of leech)/in vivo dog	LDPE-g-PAA surface modified with chloranhydride groups/film/60 μm thick/600 μg/cm^2	γ/0.8, r.t., Ar (before loading)		Clotting time: Increases 3–5 times relative to unmodified samples; Thrombic mass formed after 20 min in modified tubes three times smaller relative to unmodified samples	Kabanov et al. (1997)

[a] *Carriers*: CDI, *N*, *N*′-carbonyldiimidazole; CL, ε-caprolactone; HMDI, hexamethylene diisocyanate; LDPE, low-density polyethylene; PAA, pol(acryl amide); PUPA, poliurethane + poly(amidoamine).
[b] *Methods*: APTT, activated partial thromboplastin time; SEM, scanning electron microscopy; SP, spectrophotometry.

Table 4
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antidiabetic agents

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of realize	Methods:[b] Effects of irradiation	Reference
Insulin/ in vitro, pH 7.4	NIPAAm-*co*-AA + 2G, NIPAAm-*co*-MAA + 2G, NIPAAm-*co*-AA + 14G, NIPAAm-*co*-MAA + 14G, NIPAAm-*co*-AA + MBAAm/ electrically responsive hydrogels/rods 5 mm diam. × 15 mm	γ/30/25 °C, N_2 (before loading)	Up to 60% release within 2 h from hydrogels alkali-treated for 4 h; up to 25% release from non-treated hydrogels	Gravimetry: Shrinks under electric field, expands in the absence of electric field; • Electric response depends on ratio NIPAAm/AA; • At AA or MAA = const. shrinking decreases with temperature and alkali treatment time, increases with voltage; • Alkali treated hydrogels show pulsatile release under electric field, non-alkali treated hydrogels shrink monotonously with time; • Largest oscillations of pulsatile release in NIPAAm/AA/2G, NIPAAm/MAA/2G, NIPAAm/MAA/14G, NIPAAm/AA/14G; • No pulsing of NIPAAm/AA/MBAAm; HPLC: Release increases with alkali treatment, release peaks coincide with the onset of voltage (shrinking)	Morita and Kaetsu (1992)
Insulin/ in vivo, rat serum	A-ProOMe + TMPTMA (X-linker)/ thermosensitive hydrogel/disks/ 5 mm diam. × 1.5 mm/ 3.4% (1% TMPTMA); 1.3% (5% TMPTMA);	γ/25/25 °C, N_2 (before loading)		Gravimetry: Swelling decreases with temperature increase; at $t > 22$ °C swelling increases with TMPTMA; Serum glucose assay: • Glucose level reduced to 60%; • 3.4% insulin disc: returns to the initial value after 80 d; • 1.3% insulin disc: returns to the initial value after 7 d	Carenza et al. (2000)
Insulin/ in vivo, rat serum	A-ProOMe + TMPTMA (X-linker) thermosensitive hydrogel/disks/ 6 mm diam. × 2 mm/ 1.4% (1%TMPTMA) 0.6% (5% TMPTMA)	γ/9.5/r.t., N_2 (before loading)	Release controlled by combination of Fickian diffusion, hydrogel shrinking or swelling and drug dissolution after the first 50 h (from swollen) and subsequent 200 h (from dry matrices)	HPLC: • Release from dry matrices delayed for 7 d (1% TMPTMA) and 8 d (5% TMPTMA) before the onset of Fickian diffusion; • Release from swollen matrices delayed for 4 d (1% TMPTMA) and 2 d (5% TMPTMA) before the onset of Fickian diffusion; • Release slowest from swollen matrices containing 5% TMPTMA Serum glucose assay: Swollen matrices induce a more rapid reduction of glycemia but lyophilized ones induced a larger and a longer lasting reduction	Caliceti et al. (2001)
Insulin/ in vivo, rat serum	PEO-*g*-AA pH sensitive hydrogel/slabs/ $7 \times 3 \times 2.5\ mm^3$	γ/30–100/air/(X-linking of PEO); γ/5–20/ (grafting of AA onto PEO) (before loading)	Blood glucose level decreases to 60% after 4 h but returns to 80% 8 h after oral administration.of hydrogel	Gravimetry: • Gel content increases with dose and PEO concentration; • Degree of grafting increases with time, pH, and concentration of AA; Serum glucose assay: Blood glucose level decreases faster and attains lower values after injection of insulin solution than after oral administration of hydrogel	Nho et al. (2004)
Insulin/ in vitro, pH 1.2/6.8 in vivo, rat serum	PVA-*g*-MAA and PVA-g-AA hydrogels	γ/10–100/r.t., (X-linking of PVA) + γ/5–20/r.t., (grafting of MAA or AA onto PVA) (before loading)	In vitro*:* no release at pH 1.2; optimum release after 5 h using 50% (v/v) EtOH as loading solution	Gravimetry: • Gel content increases with dose; • Swelling degree decreases with dose; • Grafting of MAA increases with dose up to 5 kGy; • At D = const. degree of grafting increases with MAA; • Grafting of AA increases with dose up to 15 kGy; • At D = const. degree of grafting increases with AA up to 20% but is ~6 times smaller than with MAA; • Swelling increases .with time and pH; • At pH = const. swelling increases with degree of grafting;	Park et al. (2004)

				SP: • No release from hydrogels soaked in H_2O or EtOH loading solutions; • Optimum loading solution 50 (v/v%) EtOH;	
				Serum glucose assay: Glucose level decreases to 40% after 2 h, level maintained for at least 6 h	
Glibenclamide/in vitro pH 7.4, 1	HEMA/MAA + 5% or 10% X-linker (MAOE ester of TPA)/hydrogel/ powder/20%	40 kV X-rays/r.t., vac.	5% X-linker: 65% release after 10 h at pH 7.4; 15% release after 10 h at pH 1; 10% X-linker: 45% release after 10 h at pH 7.4; 8% release after 10 h at pH 1	Gravimetry: Swelling decreases with X-linker and pH; FTIR: Drug not covalently bound to copolymers; DSC: T_g increases with X-linker, decreases with drug; SP: Release rate increases with pH, decreases with X-linker	Mahkam and Allahverdipoor (2001)

[a] *Carriers*: AA, acrylic acid; A-ProOMe, acryloyl-L-proline methyl ester; 2G, diethyleneglycol dimethacrylate; 14G, polyethyleneglycol dimethacrylate; HEMA, 2-hydroxyethyl methacrylate; MAA, methacrylic acid; MAOE, methacryloyl oxyethyl; MBAAm, *N,N'*-methylene-bis-acrylamide; NIPAAm, *N*-isopropyl acrylamide; PEO, poly(ethylene oxide); PVA, poly(vinyl alcohol); TMPTMA, trimethylolpropanetrimethacrylate; TPA, terephthalic acid.

[b] *Methods*: DSC, differential scanning calorimetry; FTIR, Fourier-transform infrared spectroscopy; HPLC, high performance liquid chromatography; SP, spectrophotometry.

ultimate interplay of many complexly interrelated factors (Rothen-Weinhold and Gurny, 1997). Nevertheless, some general radiation chemistry regularities were observed. On gamma irradiation of PLGA microspheres in air, two types of radicals, alkyl- and alkylperoxyl radicals were formed (Claybourn et al., 2003); irradiation in vacuum produced only alkyl radicals. Radiation chemical yield of alkyl radicals in gamma irradiated PLGA was higher than in electron beam irradiated PLGA (Bushell et al., 2005), higher at 77 K than at room temperature (Babanalbandi et al., 1996), higher in microspheres than in raw polymer powder (Bushell et al., 2005) and higher in copolymers containing more lactide component (Claybourn et al., 2003). Electron irradiation in air produced chain scission, and the increased chain mobility caused a decrease of gel-transition temperature, melting temperature and crystallization temperature, enabling the formation of crystalline phase in an initially amorphous PLGA. Hindered diffusion of oxygen and enhanced recombination of free radicals in crystalline regions arrested further degradation by balancing chain scission and crosslinking at high radiation dose (Loo et al., 2004). Both number-average and weight-average molecular weights were reduced by irradiation. Faster decrease of the M_n was taken as an indication that random chain scission was not the primary mechanism and that unzipping of the end groups was more probable than chain scission (Athanasiou et al., 1996). This notion was substantiated by measuring the formation of gaseous radiolytic products and NMR identification of new chain ends formed by radiation-induced cleavage of ester bonds in PLA and PGA: radiation chemical yield of ester loss in PLA estimated from $G(CO)+G(CO_2)$ was approximately equal to the radiation chemical yield of chain scission and/or to the radiation chemical yield for the formation of new chain ends (Babanalbandi et al., 1997).

Hydrogels swell in water and are capable of retaining a large volume of water in the swollen state. Together with water they also retain dissolved drugs, which are released when the gels shrink. Swollen hydrogels can be used for drug transport to a selected target whereupon controlled shrinking would cause the load to be delivered on the spot. Dramatic volume transitions in hydrogels can be triggered by a variety of physical, chemical and biochemical stimuli. Physical stimuli include the change of temperature, magnetic field, electric field, solvent composition, light, pressure, sound, etc. Chemical or biochemical stimuli include the change of pH and ions and specific molecular recognition events.

The ability to respond to an external stimulus might with some laxity be termed intelligence. Intelligent polymers that are capable to respond to more than one kind of stimuli can be prepared by radiation polymerization. Their properties depend on the presence of comonomers, cross-linkers, irradiation temperature, dose, etc. For example, irradiation of aqueous solutions of the monomer acryloyl-L-proline methyl ester (A-ProOMe) alone produces a polymer network soluble in water at low temperature;

Table 5
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antifungal agents

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Terbinafine HCl in vitro/pH 7.0, 6.1, 5.5, 4.4	AAm:MA 100:0, 98.8:1.2, 97.6:2.4, 96.5:3.5, 94.8:5.2 hydrogels/tablets/ 4 mm diam. × 2 mm/1–4%	γ/25/r.t., air (before loading)	100% release at pH 4.4 within: 7 h (100:0), 22 h (98.8:1.2), 25 h (94.8:5.2)	Gravimetry: • Swelling increases with increasing pH and MA; • Specific adsorption capacity of hydrogels increases with MA; SP: • Release rate decreases with pH; • Release rate increases with MA; • Cumulative release at pH = const. increases with MA	Şen et al. (2000)
Terbinafine HCl in vitro/pH 7.0, 6.1, 5.2, 4.0	PVP:IA 97.6:2.4, 95.3:4.7, 93.2:6.8, 91.0:9.0 + EGDMA (X-linker) hydrogels/tablets/ 4 mm diam. × 2 mm/0.5–8%	γ/5–25/r.t., air (before loading)	100% release at pH 5.2 within ~30 h little affected by IA	Gravimetry: • Swelling increases with increasing pH and IA; • Specific adsorption capacity of hydrogel increases with IA; SP: • Release rate decreases with pH; • Release rate increases with IA; • Cumulative release at pH = const. increases with IA	Şen and Yakar (2001)

[a] *Carriers*: AAm, acrylamide; EGDMA, ethyleneglycol dimethacrylate; IA, itaconic acid; MA, maleic acid; PVP, poly(vinyl pyrrolidone).
[b] *Methods*: SP, spectrophotometry.

on heating the solution, the polymer precipitates. The temperature at which phase separation occurs is called lower critical solution temperature (LCST). Irradiation in the presence of the crosslinker trimethylpropane trimethylacrylate (TMPTMA) yields thermoresponsive hydrogels, insoluble but swellable in water. Maximum swelling with the change of temperature takes place at LCST. As the concentration of the crosslinker increases, the change of swellability with the change of temperature decreases, as does the release rate of the loaded drug acetaminophen. Release rate and the amount of released drug increase with decreasing temperature. Swelling properties and release rate of crosslinked hydrogel further depend on the nature of comonomers: swellability, transition temperature, release rate and the amount of released drug increase in the presence of a hydrophilic comonomer *N*,*N*-dimethylacrylamide (DMAA) and take the opposite course in the presence of a hydrophobic comonomer 4-acryloyloxy acetanilide (AOA). Scanning electron microscopy reveals that pore size decreased as the temperature increased, thus hindering the diffusion of drug out of the hydrogel (Martellini et al., 1999). Copolymerization of A-ProOMe in the presence of sodium salts of saturated fatty acids (lauric to stearic) gives pH-responsive hydrogels characterized by a burst release of ketoprofen. Both the burst and the subsequent drug release rate increase with pH change from 3 to 6.5 (Negishi et al., 1999).

Radiation polymerization and crosslinking are useful in the synthesis of other acrylate-based thermoreversible superclean hydrogel drug carriers such as copolymers hydroxyethyl acrylate/hydroxypropyl acrylate (HEA/HPA) (Safrany, 1999), 2-hydroxyethyl methacrylate (HEMA) (Mahkam and Allahverdipoor, 2004), *N*-isopropylacrylamide (NIPAAm) (Safrany, 1997) and other acrylic-based copolymers (Lopatin et al., 2005). Some of these polymers can also serve as wound dressing materials, scaffolds for tissue growth, etc. Poor mechanical properties of some polyacrylate hydrogels could be improved by the formation of an interpenetrating polymer network (IPN), which is an intimate combination of two polymers, at least one of which is synthesized or crosslinked in the presence of another. The properties of IPN synthesized by irradiation and consisting of hydrophylic pNIPAAm and hydrophobic PMMA, including swelling and shrinking ratios and release rate, could be tailored by varying the ratio of PMMA to pNIPAAm (Lu et al., 2000). Irradiation in the presence of crosslinkers diethylene glycol dimethacrylate (2G) or polyethylene glycol dimethacrylate (PEGDMA) produced hydrogels responsive to electrical stimuli, which were studied as insulin-delivering vehicles (Morita and Kaetsu, 1992).

Table 6
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antihypertensive agents

Drug/target	Carrier[a]/dosage form/ dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Captopril/*in vivo*, pH 7.2	PLGA (50:50) $\bar{M}_w$ 17, 40, 51 and 67 kDa/ microshperes/ 11–16 μm diam./ (7.4±0.7)%	γ/6.9, 15, 27.7, 34.8/dry ice, vac;r.t., 54.4% r.h.; r.t., 98.5% r.h.	75–85% release from 17, 40, 51 kDa microspheres within 32 d; 100% release from 67 kDa microspheres within 25 d	GPC: • decreases with dose by 6–18%, larger % of decrease in larger $\bar{M}_w$ microspheres; • $\bar{M}_w$ decrease little affected by irrad. conditions (vac., air, r.h.); • $\bar{M}_w\bar{M}_n$ (polydispersity index) not affected by dose; HPLC: • No oxidation or degradation of neat captopril with dose; • Drug content of microspheres decreases with dose, larger decrease in larger $\bar{M}_w$ microspheres; • Oxidation to disulfide increases with dose, larger increase in larger $\bar{M}_w$ microspheres; • Release rate increases with dose from 17 kDa microspheres, decreases with dose from 40 and 51 kDa microspheres; • Sigmoidal release profile from 67 kDa microspheres above 15 kGy, increases with dose (diffusion and erosion); XRD: Drug present in amorphous state; DSC: T_g slightly increases with dose; SEM: • Surface not affected immediately after irradiaton; • After 15 d extraction of 67 kDa microspheres: smooth sphere structure of unirradiated microspheres, porous collapsed structure of microspheres irrad. at 34.8 kGy	Volland et al. (1994)

[a] *Carriers*: PLGA, poly(lactic-*co*-glycolic acid).
[b] *Methods*: DSC, differential scanning calorimetry; GPC, gel permeation chromatography; HPLC, high performance liquid chromatography; SEM, scanning electron microscopy; XRD, X-ray diffraction.

Poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP) are synthetic polymers that have excellent biocompatibility. Radiation-initiated polymerization and crosslinking for the manufacturing of wound dressing hydrogels received more attention than the application for CDD/CDR systems (Rosiak et al., 2003). Nevertheless, several macroscopic drug delivery forms (films, tablets, rods) were prepared and sterilized by irradiation after loading with drugs, including already mentioned PVP vaginal suppositoria containing prostaglandine (Rosiak and Olejniczak, 1993) and PVA tablets containing vasodilator diltiazem hydrochloride (Maggi et al., 2003).

Poly(ethylene oxide) (PEO) is a neutral hydrophilic polymer which swells in water to form hydrogels. Radiation sterilization of PEO plates, rods and tablets for CDD/CDR is described in the literature. The carriers were made of homopolymers of variable molecular mass (0.3–7 MDa) or copolymers with CL, tetraethylene glycol and PVA. Chain scission dominates in the presence of oxygen in solid (Zainuddin et al., 2002), as well as in the solution (Martini et al., 1997), while irradiation of solid in the absence of air produces crosslinking and chain scission simultaneously (Martini et al., 1997). An interesting possibility to control gel properties is offered by the family of star PEO polymer molecules (Griffith Cima and Lopina, 1995) crosslinked by irradiation in solution. Permeability to solutes, elastic modulus and the average length of dangling chain ends are function of the structure of a gel network, which depends on the extent of intramolecular crosslinking (between arms of the same star molecule) and intermolecular crosslinking (between arms of two or more stars), which is in turn determined by the concentration of star molecules in irradiated solutions.

Hydrophilic polymers described so far swell in water to form hydrogels, they get loaded with drugs by swelling in aqueous drug solutions and release their load in contact with water in basically aqueous biological media. On the

Table 7
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antimalarial agents

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Primaquine diphosphate	DSPC 10%–DSPG 33.3%–cholesterol/liposomes/~90 nm/drug:lipid 0.125:1 (mol:mol)	γ/25/r.t.		PCS: Small increase of liposome size after irradiation; HPLC: Drug not affected by irradiation; SP: Drug not affected by irradiation; DSC: Melting temperature reduced by 1.9 °C after irradiation; GC: 5% degradation of cholesterol by irradiation; HPLC: 1.5% degradation of DSPC by irradiation	Stensrud et al. (2000)

[a] *Carriers*: DSPC, distearoyl phosphatidyl choline; DSPG, dimyristoyl phosphatidyl glycerol.
[b] *Methods*: DSC, differential scanning calorimetry; GC, gas chromatography; HPLC, high performance liquid chromatography; PCS, photon correlation spectroscopy; SP, spectrophotometry.

Table 8
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antimycobacterial agents

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)	Time span of release	Methods:[b] Effects of irradiation	Reference
Isoniazid/in vitro, pH 7.2	A-ProOMe + TMPTMA (X-linker) thermosensitive hydrogel/disks/6 mm diam. × 2 mm/1.4% (1% TMPTMA) 0.6% (5% TMPTMA)	γ/9.5/r.t., N_2 (before loading)	Initial (24 h) burst followed by a negligible release	PCS: Slight increase of mean particle size, no evidence of aggregation; HPLC: Drug release not affected by irradiation; retention time not affected by irradiation;	Caliceti et al. (2001)
In vivo mouse serum	A-ProOMe + TMPTMA (X-linker) thermosensitive hydrogel/disks/6 mm diam. × 2 mm/1.4% (1% TMPTMA) 0.6% (5% TMPTMA)	γ/9.5/r.t., N_2 (before loading)	Delivery sustained for over 800 h (unexpected)	HPLC: Nanoparticle uptake by artery slightly increased by irradiation (15.4 μg/10 mg of artery)	

[a] *Carriers*: A-ProOMe, acryloyl-L-proline methyl ester; TMPTMA, trimethylpropane trimethylacrylate.
[b] *Methods*: HPLC, high performance liquid chromatography; PCS, photon correlation spectroscopy.

other hand, viscous consistency of some hydrophobic polymer carriers based on poly(ortho esters) (POE) allows the incorporation of drugs by simple mixing. The use of heat or solvents for loading POE carriers can thus be completely avoided, which is an advantage in the formulation of CDD/CDR systems containing fragile and thermolabile drugs such as peptides, proteins and oligonucleotides. However, the susceptibility of the high molecular weight drugs toward irradiation may be a prohibitive factor with respect to radiation sterilization.

Four generations of POE were synthesized so far, but only the third-generation POE (POE III) and the fourth-generation POE (POE IV) were investigated with respect to radiation sterilization (Einmahl et al., 2001). Gamma irradiation of POE III in the form of a viscous biodegradable fluid lead to a drastic decrease of molecular weight and an inflammatory reaction in vivo (Zignani et al., 1997). High dose-rate (electron beam) irradiation at −78 °C in an inert atmosphere and in the presence of an antioxidant α-tocopherol did not significantly mitigate the damage (Sintzel et al., 1998). It was concluded that irradiation was not a suitable sterilization process for POE III-based CDD/CDR systems and an aseptic preparation was preferred.

While molecular weights of POE IV were somewhat decreased by irradiation, satisfactory post-irradiation stability, lag time reduction, release rates and release periods were obtained with radiation-sterilized POE IV solids made by blending with 30% lactic acid (Schwach-Abdellaoui et al., 2001).

In addition to synthetic polymers, a wide variety of natural materials were investigated as carriers for CDD/CDR systems, but the selection of the materials that were investigated with respect to radiation sterilization was far smaller (Fig. 5).

Here the emphasis has also been on hydrophilic polymers represented by various polysaccharides: cellulose, chitosan, dextran and starch. Albeit polysaccharides have

Table 9
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antineoplastic agents

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Adriamycine/in vitro physiological saline solution	PEGDMA: DEGDMA (20:80 v/v)/ rods/0.8–1.6 mm diam. × 7–10 mm/ 140%	γ/30/–78 °C	Daily dose of drug decreases from 40 μg/ d to 10 ng/d within 35 d	SP: Release rate decreases with time;	Kubo et al. (1992)
In vivo brain (rat)	PEGDMA: DEGDMA (20:80 v/v)/ rods/0.8–1.6 mm diam. × 7–10 mm/ 140%	γ/30/–78 °C		Hystopathological examination: Release limited to tumor;	
Camptothecin in vitro, pH 7.4 In vivo subcutaneous tumor (mice)	Chitosan gel/wafer/5 × 15 × 15 mm^3/ 4.5% (loaded under aseptic conditions) Chitosan gel/wafer/5 × 15 × 15 mm^3/ 4.5% (loaded under aseptic conditions)	γ/25 (only drug was irradiated) γ/25 (only drug was irradiated)	90% release within 30 d	HPLC: No degradation after irradiation and 2 months storage; Time necessary for tumor to reach 500 mm^3: No treatment: 7 d; Intraperitoneal injection: 8 d; Intratumoral implant: 25 d;	Berrada et al. (2005)
Carmustine (BCNU)/ in vitro, pH 7.4	PLGA (50:50) 8, 33 and 110 kDa; PLGA (75:25) 20 and 90 kDa/wafers/3 × 1 mm^2/ 3.85%	γ/25, 50, 75	30% initial burst followed by an almost constant release rate up to 8 d	GPC: $\bar{M}_w$ decreases with dose, % decrease larger for higher $\bar{M}_w$; DSC: T_g decreases with dose; ESR: Free radicals $-^{\bullet}C(CH_3)$ increase with dose, decrease with time; HPLC: Near zero-order release kinetics, rate increases with dose	Lee et al. (2003)
Cisplatin/ in vitro, pH 7.4	PLA(L-LA:D-LA 50:50) $\bar{M}_w$ 54 kDa; PLGA (90:10) (L-LA:D-LA 50:50) $\bar{M}_w$ 58 kDa; PLGA (75:25) (L-LA:D-LA 50:50) $\bar{M}_w$ 58, 72, 100 kDa/ microspheres/40 ± 100 μm/29%	γ/28, 38	From PLGA (75:25) 0 kGy: diffusional release up to 30% within 60 d followed by a final 1 d burst; from PLGA (75:25) 38 kGy: 20 d at a constant rate	GPC: $\bar{M}_w$ reduction after 6 m: • PLA (L-LA:D-LA 50:50) to 70%; • PLGA (90:10) to 66%; • PLGA (75:25) 72 kDa to 50%; • PLGA (75:25) 100 kDa to 40%; SEM: Shape of PLGA (75:25) 100 kDa preserved for 6 w, ruptured within 8 w, alveolar within 12 w; SP: Massive release starts as $\bar{M}_w$ decreases to 25 kDa;	Spenlehauer et al. (1989)
In vivo/liver (rat)	PLLA:PLA (L-LA:D-LA 50:50) $\bar{M}_w$ 54 kDa; PLGA (90:10) (L-LA:D-LA 50:50) $\bar{M}_w$ 58 kDa; PLGA (75:25) (L-LA:D-LA 50:50) $\bar{M}_w$ 58, 72, 100 kDa microspheres/40 ± 100 μm/29%	γ/28, 38		GPC: $\bar{M}_w$ reduction to about 10%: • PLA (L-LA:D-LA 50:50) within 24 w; • PLGA (90:10) within 12 w; • PLGA (75;25) 100 kDa within 8 w; • PLGA (75:25) 72 kDa within 4 w; Histological examination: Mild inflammation at 3 w, second step of inflammation and deformation of microspheres starts as $\bar{M}_w$ decreases to ~20 kDa;	
Cladribine/in vitro, artificial cerebrospinal fluid	PLGA (82:18) $\bar{M}_w$ 30 kDa; PLGA (85:15) $\bar{M}_w$ 30 kDa/films/10 × 10 mm^2, 0.1–0.3 mm thick/1.8%; 4.5%	γ/15, 20, 25	~50% release within 7 w	HPLC: The amount of daily drug release larger from irradiated than from non-irradiated films, larger from 15 kGy than from 20 and 25 kGy irradiated films, larger from non-irradiated than from EtO sterilized films;	Kryczka et al. (2002)
Cladribine/in vitro, artificial cerebrospinal fluid	PLA:CL (70:30) $\bar{M}_w$ 40 kD; PLA:CL (60:40) $\bar{M}_w$ 32 kDa/films/10 × 10 mm^2, 0.1–0.3 mm thick/4.7%; 5.5%	γ/15, 20, 25	~90% release within 7 w from (70:30); ~50% release within 7 w from (60:40)		

Table 9 (*continued*)

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Cladribine/in vitro, artificial cerebrospinal fluid	PLGA (82:18) $\bar{M}_w$ 30 kDa/films/ $10 \times 10\,mm^2$, 0.1–0.3 mm thick/4.5%	γ/15, 20, 25	Daily release decreases from ~30 μmol/mg on the 1st day to 4–5 μmol/ mg by the 48th day	ESR: Formation of $-CH_3$ radical after irradiation in vacuum; IR: No difference after irradiation; DSC: No difference after irradiation; HPLC: The amount of daily drug release larger from irradiated than from non-irradiated films, larger from 15 kGy than from 20 and 25 kGy irradiated films;	Kryczka et al. (2003)
Cladribine/in vitro, artificial cerebrospinal fluid	PLA:CL (70:30) $\bar{M}_w$ 40 kDa/films/5.5%	γ/15, 20, 25	Daily release decreases from 100 to 4–8 μmol/mg in 48 d	ESR: Formation of $-CH_3$ radical after irradiation in vacuum; IR: No difference after irradiation; DSC: No difference after irradiation; HPLC: The amount of daily drug release not affected by irradiation;	
Cytarabine hydrochloride/ in vitro, pH 7	HEMA, MMA, EMA, BMA + 2G (X-linker)/tablets/8 mm diam. × 4 mm/ 0.2%; 1%; 2%, 10%, 20%	γ/15, 18/r.t.		SP: ● Release rate increases with loading and water content; ● Release rate decreases with increasing hydrophobicity (BMA > EMA > MMA), X-linker and dose;	Xie et al. (1993)
Cytarabine/ in vitro, pH 7.4	PHEA $\bar{M}_w$ 57 kDa/microparticles/ 20–100 μm/3.4%	γ/55, 200, 500/r.t./ (before loading)	Fickian diffusion within 4 h	SEM: Irregularly shaped microparticles obtained by irradiation; XRD: Drug dispersed as microcrystallites within microparticles; SP: Release mainly by diffusion;	Spadaro et al. (1996)
Etanidazole/ in vitro, pH 7.2	PLLA $\bar{M}_w$ 85–160 kDa; PLGA (50:50) $\bar{M}_n$ 40–75 kDa; blends PLLA:PLGA (1:1) and (2:1)/double-walled microspheres/430 ± 175 μm/PLLA: 49% drug PLGA: 39% drug PLLA:PLGA blend: (1:1): 55% drug; blend (2:1): 57% drug	γ/25/−78 °C	Diffusion controlled initial release followed by a lag period followed by a burst release; irradiation of 2:1 blend increases initial release from 10% to 15% and reduces lag period from 4 to 2 w	GPC: $\bar{M}_w$ and $\bar{M}_n$ decrease to ~70% at 25 kGy; DSC: Decrease of T_g and T_m with dose; SEM: Degradation increases with dose; HPLC: Release related to degradation;	Lee et al. (2002)
Etanidazole/ in vitro, pH 7.2	Blends: [PLGA (50:50)]: [D,L-PLA] 1:1 (A); [PLGA (50:50)]: [D,L-PLA] 2:1 (B)/ double-walled microparticles/55–80 μm	γ/25, 30/−78 °C	PLGA (50:50): and blend A: release accelerated by irradiation, blend A retains bimodal release profile;	GPC: $\bar{M}_w$ and $\bar{M}_n$ decrease to ~70% in blends, to ~50% in D,L-PLA; DSC: Decrease of T_g with dose; SEM: Complete erosion of core in 3 w; HPLC: Bimodal release from blend A unacceptably accelerated by irradiation;	Yip et al. (2003)
Etoposide/in vitro	Liposome/small even vesicles/0.0574%	γ	96% release within 50 h	SP: Percolation rate higher after moist heat sterilization than after γ irradiation;	Zheng and Zhang (2004)
5-iodo-2′ deoxyuridine	PLGA (50:50) $\bar{M}_w$ 75 kDa/ microspheres/40 ± 5 μm/2–27%	γ/26.7		SP: No detectable drug degradation; IR Raman: No detectable drug degradation;	Geze et al. (1999)
Methotrexate/ in vitro, pH 1.3	HEMA + EGDMA (X-linker) hydrogel/rods/3.5 mm diam. × 1 cm/ 0.6–1.8%	γ/10/−78 °C (before loading)	Diffusion controlled release within 24 h	HPLC: ● Drug release proportional to square root of time; ● Drug release proportional to the amount of loaded drug; ● No effect of irradiation on drug alone; ● Release little affected by the presence of X-linker;	Beyssac et al. (1996)

Mitomycin C/ in vitro, pH 7.0	HEMA + 2G + comonomers HEA and MMA/tablets/7 mm diam. × 2.5 mm/ 1.3–2%	γ/12/−80 °C, N_2 (before loading)	Fraction of the released drug proportional to square root of immersion time		Li et al. (1991)
In vivo, cells of muscle sarcoma (mice)	HEMA + 2G + comonomers HEA and MMA/tablets/7 mm diam. × 2.5 mm/ 1.3–2%	γ/12/−80 °C, N_2 (before loading)		Implanted tablets inhibit tumor growth better than injections of drug. Leukocyte count not affected by implant, reduced to 35% by injection. Necrotization of tumor tissue confirmed by microscopy. Better therapeutic effects of implants with less undesirable effects;	Li et al. (1991) (cont.)
Mitomycin C/in vitro, pH 7.4	Third-generation POE $\bar{M}_w$ 3.5–33 kDa/ viscous biodegradable fluid/1%	γ/1–40/−78 °C		GC: Hydrolysis of POE by exocyclic cleavage;	Zignani et al. (1997)
In vivo, subcutaneous (rat); eye (rabbit)	Third-generation POE $\bar{M}_w$ 3.5–33 kDa/ viscous biodegradable fluid/1%	γ/1–40/−78 °C		Histopathological observation: Increased inflammatory reaction to radiation sterilized POE; aseptic processing prefered; Hyperemia score after subconjuctival injection at least two times larger with irradiated than with aseptically prepared POE, persists longer (7 d);	
Narciclasine/in vitro	pHEMA and pHEMA:TMPTMA (85:15) hydrogels/tablets/2.5 mm diam./ 0.1%	γ/1.8–12.5/−78 °C (before loading)	From pHEMA: 100% release within 140 h; from pHEMA + X-linker: 35% release within 140 h	HPLC: Complete polymerization of pHEMA at 7.2 kGy;	Veronese et al. (1990)
Narciclasine/in vitro, pH 6.2	pHEMA; pHEMA:MPEG (50:50), (75:25) and (90:10); pHEMA:TMPTMA (85:15) and (80:20)/hydrogels/tablets/ 2.5 mm diam./0.1%	γ/3.6–16.2/−78 °C (before loading)	Diffusional drug release increases with hydrophilicity; swelling increases in the same order	HPLC: Complete polymerization of pHEMA at 7.2 kGy; Gravimetry: Swelling not affected by dose above 9 kGy (no additional X-linking) in pHEMA and pHEMA:TMPTMA; pHEMA:MPEG has a maximum in 9 kGy irradiated hydrogels, swelling saturates in 16.2 kGy irradiated hydrogels; SEM: pHEMA and pHEMA:TMPTMA matrices compact and homogeneous; pHEMA:MPEG matrices are sponge-like;	Veronese et al. (1991)
In vivo, subcutaneous (mice)	pHEMA:TMPTMA (85:15) hydrogel/ tablets/2.5 mm diam./0.1%	γ/3.6–16.2/−78 °C (before loading)		Histopathological observation: ● Empty tablets had good biocompatibility; ● Direct injection of drug had deadly effects; ● Loaded hydrogels inhibited animal growth for 10–12 d	
Nimustine HCl/ in vitro, physiological saline solution	PEGDMA: DEGDMA (20:80 v/v)/ rods/0.8–1.6 mm diam. × 7–10 mm/ 125%	γ/30/−78 °C (before loading)	Daily dose of drug release decreases from 2 mg/d to 0.5 μg/d within 35 d	SP: Release rate decreases with time;	Kubo et al. (1992)
In vivo, brain (rat)	PEGDMA: DEGDMA (20:80 v/v)/ rods/0.8–1.6 mm diam. × 7–10 mm/ 125%	γ/30/−78 °C (before loading)		Histopathological examination: Cytotoxic effects of nimustine HCl weaker than those of 5-FU	
Paclitaxel/in vitro, pH 7.2	PLGA (50:50) $\bar{M}_w$ 40–75 kDa + additives: PEG, IPM and TPGS/microparticles 2.8–56 μm formed into disks/5 mm diam./1%	γ/10/−78 °C	Lag time from PLGA reduced from 25 to 16 d; lag time from PLGA + 5% TPGS reduced from more than 35–20 d	GPC: ● No additives: $\bar{M}_w$ reduced to 97% by 10 kGy; ● Addition of TPGS: $\bar{M}_w$ reduced to 88% by 10kGy; SEM: No change of morphology after irradiation; HPLC: Lag time characterized by an almost zero release followed by a constant release rate;	Wang et al. (2003)

Table 9 (*continued*)

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Paclitaxel/ in vitro, pH 7.4	Block copolymers with hard end blocks (MMA, SAN, IBA), soft end blocks (LA, BA) and soft mid blocks (LA, BA)/ coronary stents/0.2–0.5 mg/stent/ 10–25%	e/25, 50, 75	Release from acrylate based copolymers independent of soft mid blocks (PLA and PBA) and of dose; ~70% releasd within 10 d from irradiated p(MMA-BA-MMA)	GPC: ● $\bar{M}_n$ of copolymers of the type p(MMA-LA-MMA) and p(MMA-BA-MMA) decreases with dose; ● $\bar{M}_n$ of copolymers of the type p(IBA-BA-IBA), p(IBA-LA-IBA), p(St-BA-St), p(St-LA-St) and p(SAN-BA-SAN) change little with dose; HPLC: ● Release from p(MMA-BA-MMA) with 62% hard block, p(IBA-LA-IBA) and p(SAN-BA-SAN) little affected by dose; ● Release from p(MMA-LA-MMA) decreases after irradiation; ● Release from p(MMA-BA-MMA) with 41% hard block and p(IBA-LA-IBA) show burst release, not affected by irradiation; ● End blocks of polar monomers (SAN and MMA with high % of hard block) show sustained release, not affected by irradiation; AFM: ● Drug is on the surface of copolymers with non-polar end blocks; ● No drug on the surface of polar copolymers (miscible)	Richard et al. (2005)
Tamoxifen citrate/ in vitro, pH 7.4	β-cyclodextrin (1:1 inclusion complex)/ microspheres/280–300 nm diam.	γ/25/r.t., air	Complete release within 4 d	Gravimetry: Nanoparticles yield 98% (82% after autoclaving); PCS: Size not affected by irradiation, aggregation after autoclaving; LS: ● Zeta potential of unloaded microspheres more negative after irradiation; ● Zeta potential of loaded microspheres more positive after irradiation; SP: ● Drug loading not affected by irradiation, reduced after autoclaving; ● Release not affected by irradiation	Memisoglu-Bilensoy and Hincal (2006)
Tamoxifen citrate/ in vitro, pH 7.4	β-cyclodextrin/nanocapsules/ 280–300 nm diam.	γ/25/r.t., air	90% release within 6 d	Gravimetry: Nanocapsules yield 97% (74% after autoclaving); PCS: Size not affected by irradiation, aggregation occurs after autoclaving; LS: ● Zeta potential of unloaded nanocapsules more negative after irradiation; ● Zeta potential of loaded nanocapsules more positive after irradiation; SP: ● Drug loading not affected by irradiation, reduced after autoclaving; ● Release not affected by irradiation	

[a] *Carriers*: BA, butyl acrylate; BMA, butyl methacrylate; CL, ε-caprolactone; DEGDMA, diethylene glycol dimethacrylate; EMA, ethyl methacrylate; 2G, glycol dimethacrylate; HEA, 2-hydroxyethyl acrylate; HEMA, 2-hydroxyethyl methacrylate; IBA, isobutyl acrylate; IPM, isopropyl myristate; LAc, lauryl acetate; MMA, methyl methacrylate; MPEG, poly(ethylene glycol methyl ether); PBA, poly(*n*-butyl acrylate) PEGDMA, polyethylene glycol dimethacrylate; PHEA, α,β-poly(*N*-hydroxyethyl) D, L-aspartamide; pHEMA, poly(2-hydroxyethyl methacrylate); PIBA, poly(isobornyl acrylate); PLA, poly(lauryl acrylate); PLGA, poly(D,L-lactide-*co*-glycolide); PLLA, poly(L-lactic acid); POE, poly(ortho ester); SAN, styrene-*co*-acrylonitrile; St, styrene; TPGS, tocopheryl polyethylene glycol.

[b] *Methods*: AFM, atomic force microscopy; DSC, differential scanning calorimetry; ESR, electron spin resonance; FTIR, Fourier transform infrared spectrometry; GC, gas chromatography; GPC, gel permeation chromatography; HPLC, high performance liquid chromatography; LS, light scattering; PCS, photon correlation spectroscopy; SEM, scanning electron microscopy; SP, spectrophotometry; XRD, X-ray diffraction.

Table 10
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antineoplastic agent 5-FU

Target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
In vitro, pH 7.0	pHEMA, PHEA or p(HEMA-*co*-MMA) + 2G (X-linker)/ tablets/7 mm diam. × 2.5 mm/ 63–83%	γ/12/−80 °C, N_2	Diffusional release within 1–10 d, depending on hydrophilicity, X-linking and micropores	SP: ● Release decreases with decreasing hydrophilicity (increasing MMA); ● Release decreases with increasing X-linking (increasing 2G); ● Release increases with increasing amount of water added in radiation polymerization process; XRD: 5-FU dispersed in the matrix as microcrystallites	Li et al. (1991)
In vivo, cells of muscle sarcoma (mice)	pHEMA, PHEA or p(HEMA-*co*-MMA) + 2G (X-linker)/ tablets/7 mm diam. × 2.5 mm/ 63–83%	γ/12/−80 °C, N_2		Tumor weight ratio: tumor growth inhibited by 96%; Microscopy: necrotization of tumor tissue; Injection of 5-FU: leukocytes decrease to 53%; Slow release from p(HEMA): No decrease of leukocytes for a bigger therapeutic effect	
In vivo, brain (rat)	PEGDMA: DEGDMA (20:80)/rods/ 0.8–1.6 mm diam. × 7–10 mm/ 1.4%; 1.2%	γ/30/−78 °C	Drug released into the tumor within 30–40 d without entering serum	SP: Concentration of 5-FU in rat brain tumor 0.002–10.8 μg/g 10 d after implantation	Kubo et al. (1992)
In vitro, pH 7.4	Third-generation POE $\bar{M}_w$ 8 kDa/viscous biodegradable fluid/1%	γ/1–40/−78 °C	Up to 100% within 30 h, not affected by Na acetate	^{1}H NMR and ^{13}C NMR: exocyclic cleavage of ortho ester bonds and formation of 1- and 2- isomeric esters of 1,2,6-hexanetriol; GPC: $\bar{M}_w$ = 6.8–7.8 kDa decreases with dose; Viscosimetry: Decrease of viscosity (backbone scission); GC: Formation of acidic radiolysis products; pH-metry: pH decreases from 6.5 to 4.5 in 1–5 d (hydrolysis of POEs); Microbiology: No bacterial growth after 48 h at 37 °C; Gravimetry: Polymer weight loss (backbone scission) up to 20 kGy	Zignani et al. (1997)
In vitro, pH 7.4	Third-generation POE $\bar{M}_w$ 19 kDa, 37 kDa viscous biodegradable fluid/1%	γ/20/–78 °C, Ar, N_2, e/20/−78 °C, Ar, N_2	O kGy: 60 h; 20 kGy γ: 20 h; 20 kGy γ + Ar: 24 h; 20 kGy γ + α-t: 24 h; 20 kGy e: 24 h	ESR: Presence of radical pairs R$^\bullet$—$^\bullet$R and R–$^\bullet$$CH_2$-and radicals R−$^\bullet$CH–, −$^\bullet$$CH_3$ and R-OO$^\bullet$; GPC: ● Drastic decrease of $\bar{M}_w$ with both γ and e irradiation; ● Presence of 0.1% α-tocopheol unable to reduce the damage; ● Post-irradiation decrease of $\bar{M}_w$ faster in γ than in e irradiation; SP: ● Release increases after γ more than after e irradiation; ● Release rate slightly decreases in the presence of α-tocopherol; ● Scission of low $\bar{M}_w$ smaller than that of high $\bar{M}_w$; ● Optimum storage temperature < 4 °C	Sintzel et al. (1998)
In vitro, pH 7.4	NIPAAm + AA + DA + MBAAm (X-linker) xerogel/tablets/ 9 mm diam. × 2 mm/1.25%	γ/5	Irradiation reduced release time from 6 to 2 h	Equilibrium swelling: same in γ-and redox polymerized gels, increases with increasing pH and decreasing temperature; Swelling kinetics: faster in redox polymerized gels, increases with increase of pH and decrease of temperature; HPLC: Slower release from γ-irradiated gel;	Luo et al. (1999)
In vitro, pH 7.4	GMA dextran 40 kDa + gelatin hydrogel/tablets/7 mm × 2 mm	γ/1	100% release within 3 h	HPLC: ● Release rate not affected by temperature decrease from 37 to 15 °C; ● (This hydrogel is not suitable for controlled release of 5-FU)	Aso et al. (1999)

Table 10 (*continued*)

Target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
In vitro, pH 7.4	Fourth-generation POE $\bar{M}_w$ 33–84 kDa + CDM, HD, TEG or TEG-GL/wafers/ $1.2 \times 10 \times 10\,mm^3$/5.5%; 11.6%; 23.6%	X/24/−78 °C (before loading)	2–7 weeks depending on: TEG-GL, or hydrophilicity or CDM/ HD/TEG ratio, or loading %	SEC: $\bar{M}_w$ reduced to 70%, $\bar{M}_n$ to 50% immediately after e—irradiation, thereafter stable in storage for at least 14 weeks; post-irradiation degradation increases slightly with 5-FU; Gravimetry: Erosion of polymers over 5–45 d, depending on concentration of α-hydroxyacid segment (1–15 mol%); SP: Release rates: 0.58 mg/d for 5.5 wt% 5-FU; 1.04 mg/d for 11.6 wt% 5-FU; 1.79 mg/d for 23.6 wt% 5-FU	Ng et al. (2000)
In vivo, colon (rat)	Fourth-generation POE $\overline{M}_n$ 33–84 kDa + CDM, HD, TEG or TEG-GL/wafers/ $1.2 \times 10 \times 10\,mm^3$/5.5%; 11.6%; 23.6%	X/24/−78 °C (before loading)	Complete erosion within 22 d	Pathological examination: no inflammation of surrounding tissues	
In vitro, pH 7.4 (simulated extracellular fluid); pH 6.8 (simulated intestinal fluid); pH 1 (simulated gastric fluid)	PHEA-*co*-GMA (PHG) $\bar{M}_w = 71$ kDa + MBAAm (X-linker)/microparticles/10% (without X-linker), 15% (with X-linker)	γ/2; 2.5/0 °C, N_2	20–60 min at pH 7.4, 20–150 min at pH 1	XRD: 5-FU dispersed in amorphous state; FTIR: Double bonds disappear with dose due to X-linking; HPLC: ● No degradation in 1.2% aqueous solution at 2.5 kGy; ● Release rate decreases with dose, X-linker and pH increase; Gravimetry: Yield of microspheres increases with dose and X-linker, not influenced by the presence of 5-FU; Gravimetry: ● Swelling decreases with dose and X-linker; ● Highest swelling in H_2O, decreases in buffers and at pH 1;	Pitarresi et al. (2001)
pH 7.4, 5.5	PHEA-*co*-GMA (PHG) $\bar{M}_w = 71$ kDa + MBAAm (X-linker)/hydrogels/1.1%	γ/2; 2.5/0 °C, N_2	15–16 h at pH 5.5; 12.5–16 h at pH 7.4	Viscosimetry: ● Viscosity decreases with angular speed (non-Newtonian pseudoplastic behavior); ● Little increase of viscosity with dose, X-linker and pH; HPLC: Release rate decreases with dose, X-linker and pH decrease	
In vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 75 kDa $\bar{M}_n$ 48 kDa microspheres/ 40 ± 35 μm/22%	γ/19.6, 25/r.t., vac.	Initial burst of ~30% followed by nearly diffusional release	SEC: ● $\bar{M}_w$ reduced to 66% (19.6 kGy), 52% (25 kGy); ● $\bar{M}_n$ reduced to 47% (19.6 kGy), 36% (25 kGy); SP: ● 0 kGy: 25% burst release within 1 d, followed by 3%/d within 24 d; ● 19.6 kGy: 35% burst release within 1 d, followed by 3%/d within 21 d; ● 25 kGy: 45% burst release within 1 d, followed by 4%/d within 14 d	Geze et al. (2001)
In vitro, (simulated cerebro-spinal fluid)	PLGA (100:0), (85:15), (75:25) $\bar{M}_w$ ~30 kDa/films/0.1–0.3 mm thick, $10 \times 10\,mm^2$/11.5%, 13.3%, 18.2%	γ/15; 20; 25/	Up to 100 d depending on the carrier	HPLC: ● 0 kGy: released daily amount decreases from 300 to 3 μmol/mg; ● 15, 20, 25, kGy: released daily amount decreases from 10 to 3 μmol/mg; ● Radiation sterilization favored over EtO sterilization	Kryczka et al. (2002)

In vitro, pH 7.4	PLGA (50:50) microparticles/ 20%	γ/4–33	Complete release within 15–18 d	SP: Cumulative release increases with dose and time; Mathematical model: Release described by biphasic curve: initial burst (~30% in1st d) followed by a slower constant release	Faisant et al. (2002)
In vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 104 kDa/ microparticles/30 μm (unloaded), 60 μm (loaded)	γ/4–33/cooling, vac.	Complete release within 14–21 d	SP: Cumulative release increases with dose and time; release described by triphasic curve: initial burst (~50% in 1 d) followed by a slower constant release, then a final rapid release at 14th d and low dose; DSC: $T_g \approx 40$ °C not affected by 5-FU and dose in dry powder; SEC: Linear decrease of $\bar{M}_w$ to 70 kDa at 28 kGy not affected by 5-FU; SEM of unloaded microparticles: smooth surface, not affected by dose; SEM of loaded microparticles: smooth surface, not affected by dose; Mathematical model: diffusion coefficient of 5-FU exponentially increases with dose; simple model does not account for increased release at long time, low dose; comprehensive model better accounts for increased release at long time, low dose	Faisant et al. (2003)
In vitro, pH 6.8 (simulated intestinal fluid, SIF); pH 1.2 (simulated gastric fluid, SGF)	AA:chitosan (99.9:0.1) (99.5:0.5) (99.0:1.0) (98.5:1.5) hydrogel/strips/ $10 \times 10 \times 2$ mm^3/1.5–11%	γ/30, 50, 70 (before loading)	Biphasic release; in SIF: initial burst (90% within 1 h); in SGF: slow release (90% within 50 h)	Gravimetry: • Gel content increases with dose, chitosan concentration; • Equilibrium swelling reached after 120 h (400–1000%); • Equilibrium swelling decreases with increasing chitosan concentration; • Equilibrium swelling increases with increasing pH; FTIR: Presence of COO^- groups of PAA which complex with NH_2 groups of chitosan forming polyelectrolyte complex; SEM: Swollen gels have a volcano-like surface; SP: • Release rate increases with H_2O, decreases with chitosan concentration; • Release slower in SGF than in SIF	Shim and Nho (2003)
In vitro, pH 7.4	Poly(methylidene malonate) (PMM) $\bar{M}_w$ 31.5 kDa/ microspheres/40–50 μm/ 10–25%	γ/25	Before optimization: 90% release within 24 h; after optimization: 65% release within 24 h	SEC: • Decrease of $\bar{M}_w$ to 27 kDa by 25 kGy; • Decrease of $\bar{M}_n$ to 16 kDa by 25 kGy; SEM: • 5-FU microcrystallites inside microspheres; • Irradiated microspheres (25 kGy) not degraded in vitro, after 43 d release still going on	Fournier et al. (2004)

[a] *Carriers*: AA, acrylic acid; CDM, *trans*-cyclohexene dimethanol; DA, dodecyl acrylamide; DEGDMA, diethyleneglycol dimethacrylate; 2G, glycol dimethacrylate; GMA, glycidyl dimethacrylate; HD, 1,6-hexanediol; HEA, 2-hydroxyethyl acrylate; MBAAm, *N,N'*-methylene-*bis*-acrylamide; MMA, methyl methacrylate; NIPAAm, *N*-isopropyl acrylamide; PAA, poly(acrylic cid); PEGDMA, poly(ethyleneglycol dimethacrylate); PHG, acryloylated polyaspartamide; pHEMA, poly(hydroxyethyl methacrylate); PLGA, poly(D,L-lactide-*co*-glycolide); POE, poly(ortho ester); TEG-GL, triethylene glycol monoglycolide.

[b] *Methods*: DSC, differential scanning calorimetry; ESR, electron spin resonance; FTIR, Fourier transfom infrared spectrometry; GC, gas chromatography; GPC, gel permeation chromatography; HPLC, high performance liquid chromatography; NMR, nuclear magnetic resonance; SEC, size exclusion chromatography; SEM, scanning electron microscopy; SP, spectrophotometry; XRD, X-ray diffraction spectrometry.

been known as degradable-type polymers under the action of ionizing radiation, it was recently demonstrated that chemically pure cellulose hydrogels could be obtained by electron beam irradiation-induced intermolecular crosslinking of the highly concentrated aqueous solutions in the absence of both crosslinking agents and oxygen (Wach et al., 2003). However, the doses necessary to reach maximum gel fraction and swelling ratio were well in excess of 50 kGy which might be damaging to any API loaded before irradiation. Irradiated solid forms of polysaccharide CDD/CDR systems: powder, film, beads and microspheres exhibited little instability after irradiation: in some instances, release rate was slightly increased, or initial burst was reduced and zero-order release period extended (Bartolotta et al., 2005).

The effects of radiation sterilization on carrier properties of liposomes were less pronounced than the effects of heat sterilization: release rate of the antineoplastic agent etoposide from liposomes was higher after moist heat sterilization than after gamma irradiation (Zheng and Zhang, 2004). Gamma irradiation was found suitable for the sterilization of solid lyophilized liposomes composed of saturated lipids: distearoyl phosphatidyl glycerol (Na salt) (DSPG), distearoyl phosphatidyl choline (DSPC), dimyristoyl phosphatidyl choline (DMPC) and mixed liposomes (DSPG/DSPC 25:75 mol%) (Stensrud et al., 1999). Irradiation of liposomes composed of an unsaturated lipid, egg phosphatidyl choline (egg PC) in oxygen atmosphere led to peroxidation (Zuidam et al., 1995). The same occured in soya phosphatidyl choline (soya PC), which contains even more unsaturation than egg PC. However, soya PC had toxic effects on murine macrophage RAW 264 line, irrespectively of whether it had previously been irradiated or merely kept in contact with oxygen (Stensrud et al., 1999). It must be concluded that highly unsaturated lipids are not suitable as drug carriers unless special precautions to prevent peroxidation had been taken, irrespective of irradiation.

Unlike the vesicular structure of liposomes, where lipidic bilayer encloses the drug containing interior, drugs contained in solid lipid nanoparticles (SLN) are dispersed as solid solution, either throughout the volume of SLN or preferentially located in drug-enriched core or in the outer shell (Wissing et al., 2004). An interesting concept of high drug-loaded nanoparticles for CDD/CDR, consisting nearly entirely of amphiphilic prodrugs which self-assemble into ordered nano-sized aggregates has been recently described: sterilization by irradiation of stearoyl glycerosuccinyl acyclovir reportedly induced two unacceptable changes: the aggregation of particles and radiation chemical damage, but none of the two was quantified (Jin et al., 2006). The literature is mostly silent about radiation sterilization of SLN. Some SLN are sensitive toward autoclaving and radiation has been mentioned as an alternative along with filtration (Schwarz et al., 1994), but aseptic preparation remains the least damaging although the most complex and expensive alternative.

The most successful and stimulating applications of collagen are shields in ophthalmology, injectable dispersions for local tumor treatment and sponge and minipellet carriers of various drugs (Friess, 1998). All mentioned applications require sterility, but one sterilization method is definitely out of question: moist heat sterilization, because it denatures the hydrated protein.

Osteogenic proteins cannot simply be poured or sprinkled into the site of a bone defect. For osteogenic proteins to effectively induce bone healing, a carrier material may be needed. In addition to binding the protein, a carrier should provide a temporary scaffold until replaced by a new bone and should ensure the release of the protein so as to maintain the therapeutic concentration appropriate for healing. The collageneous extracellular matrix of bone is considered an optimal delivery system for osteogenic proteins. Radiation sterilization of collagen pellets loaded with bovine bone morphogenetic protein (BMP) resulted in a comparable to (Ijiri et al., 1994) or a

Table 11
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antiproliferative agents

Drug/target	Carrier/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[a] Effects of irradiation	Reference
U-86983 (2-(4-morpholinyl)-8-(3-pyridinyl-methoxy)-4H-1-benzopyran-4-one)/in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 102 kDa/ nanoparticles/ 123 nm diam./ 5.4–20.4%	γ/25	Initial burst (70%) followed by slow release; complete release (90%) within 16 d	PCS: Slight increase of mean particle size, no evidence of aggregation; HPLC: Drug release not affected by irradiation; retention time not affected by irradiation;	Song et al. (1997)
Ex vivo, carotid artery (dog)	PLGA (50:50) $\bar{M}_w$ 102 kDa/ nanoparticles/ 123 nm diam./ 5.4–20.4%	γ/25		HPLC: Nanoparticle uptake by artery slightly increased by irradiation (15.4 μg/ 10 mg artery)	

[a] *Methods*: HPLC, high performance liquid chromatography; PCS, photon correlation spectroscopy.

Table 12
The effects of irradiation on controlled drug delivery/controlled drug release systems containing antiviral agents

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Acyclovir/in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 20 kDa $\bar{M}_n$ 12 kDa/ microspheres/0.5–150 μm, mean diam. 46 μm	γ/25/dry ice	Zero-order release from 1 to 63 d, 100% within 70 d	SEM: No change of surface morphology and size; FTIR: No IR spectral change; DSC: T_g increases from 44.67 to 46.52 °C; new exothermic peak at 204.17 °C; XRD: Acyclovir incorporated within the matrix in the crystalline state; SP: Release rate constant $k = 1.73$ μg/d mg (sterilized microspheres); GPC: Slight decrease of $\bar{M}_w$ and $\bar{M}_n$	Martínez-Sancho et al. (2004)
Stearyl-glycero-succinyl-acyclovir (SGSA)/in vitro	Self-assembled nanoparticles in aq. suspension/1.5%	γ/15/r.t.		Turbidimetry: aggregation of nanoparticles; HPLC: Drug content decreases on irradiation; Autoclave or 100 °C bath sterilization prefered over irradiation	Jin et al. (2006)
9-β-D-arabino-furanosyl adenine (Ara-A)/in vitro	A-ProOMe-*co*-HEMA + PEGDMA (X-linker) hydrogel/rods/ 8 mm diam. × 5 mm/1.8%	γ/30/25 °C, N_2 (before loading)	Initial burst within 24 h followed by 11 ng/h for 9 d	Gravimetry: • Swelling decreases with temperature, HEMA and number of $[-(CH_2CH_2O)_n]$ units in PEGDMA; • Swelling—deswelling kinetics at 24 h intervals reversible throughout 30 d; SP: Pulsatile release when cycled between 10 and 37 °C; SEM: At 0 °C gel contains large pores	Miyajima et al. (1993)
9-β-D-arabino-furanosyl adenine (Ara-A)/in vitro	A-ProOMe-*co*-HEMA + 9G (X-linker); A-ProOMe-*co*-St + 9G (X-linker)/hydrogel/rods/ 8 mm diam. × 5 mm/1.8%	γ/30/25 °C, N_2 (before loading)	Initial burst within 48 h	Gravimetry: • Swelling decreases with temperature, HEMA and St (stronger decrease with hydrophobic St); • Rate constants for deswelling increase with temperature; • Rate constants for swelling decrease with temperature; • Deswelling much faster than swelling; SP: Pulsatile release of 11 ng/h at 10 °C (due to slow diffusion of H_2O) and 33 ng/h at 37 °C (“matrix pumping” due to the shrinking of gel)	Miyajima et al. (1995)
Ganciclovir/ in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 34 kDa/microspheres/ 300–500 μm diam./8.6%	γ/25/dry ice, air	100% within 42 d	SP: Zero-order release 32.8 μg/d during 21 d, followed by 2 μg/d for the next 21 d, not affected by irradiation	Herrero-Vanrell et al. (2000)
Zidovudine/ in vitro, pH 1; pH 7.4	PHEA $\bar{M}_w$ 56.9 kDa hydrogel/microspheres/ 50–60 μm diam./4.76%, 16.7%	γ/604.8/r.t., air (before loading)	100% within 1.5 h at pH 7.4; 100% within 0.5 h at pH 1 (H_2O soluble)	Solubility: 97% polymer crosslinked by irradiation; Microscopy: Swelling gives microparticles with 137% larger diam. in 2 m; SEM: Almost spherical shape of microparticles; XRD: Drug present in the matrix as molecular dispersion, i.e. in an amorphous state	Pitarresi et al. (1996)

[a]A-ProOMe, acryloyl-L-proline methyl ester; HEMA, 2-hydroxyethyl methacrylate; 9G, nonaethyleneglycol dimethacrylate; PEGDMA, poly(ethylene glycol dimethacrylate); PHEA, α,β-poly(*N*-hydroxyethyl)-D,L-aspartamide; PLGA, poly(D,L-lactic-*co*-glycolic acid); St, styrene.

[b]*Methods*: DSC, differential scanning calorimetry; FTIR, Fourier transform infrared spectrometry; GPC, gel permeation chromatography; SEM, scanning electron microscopy; SP, spectrophotometry; XRD, X-ray diffraction spectrometry.

Table 13
The effects of irradiation on controlled drug delivery/controlled drug release systems containing anxiolytic agents

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Clonazepam/in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 34 kDa/microspheres/ 2–10 μm diam./15%	γ/25/r.t., vac., air	64% within 24 h from irradiated in air and stored for 6 months; 61% within 24 h from irradiated in vac. and stored for 6 months	SEM: Size distribution of microspheres shifted to larger sizes after loading, little affected by irradiation; DSC: Exothermic peak shifted to lower temperature after irradiation, not affected by air; SP: Release rate constant increases with irradiation, presence of air during irradiation and post-irradiation storage; ESR: • G(radicals) in neat drug at 77 K: 0.0030 μmol/J; • G(radicals) in unloaded microspheres at 77 K: 0.26 μmol/J; • G(radicals) in loaded microspheres at 77 K: 0.12 μmol/J; • G(clonazepam radicals) in loaded microspheres: 0.065 μmol/J; • G(polymer radicals) in loaded microspheres: 0.055 μmol/J; • G(total radicals) (calculated): 0.22 μmol/J	Montanari et al. (2001)
Clonazepam	PLGA (50:50) $\bar{M}_w$ 34 kDa/microspheres/ 5–15 μm diam./15%	γ/25/77 K, vac.		ESR (PLGA): • G(–$CH_2^{\bullet}$) = 0.071 μmol/J (chain scission); • G(–$CH^{\bullet}(CH_3)$) = 0.087 μmol/J (H abstraction); • G(–$C^{\bullet}(CH_3)O$–) = 0.060 μmol/J (H abstraction); • G(–$CH^{\bullet}O$–) = 0.042 μmol/J (H abstraction); ESR (clonazepam): Nitrobenzene-like radical anion transformed into nitroxyl on heating from 77 to 298 K; ESR (loaded microspheres): PLGA radicals decay, clonazepam radicals increase on heating from 77 to 298 K (spin transfer) leading to a deviation from additivity rule and to dominant nitroxide radical	Faucitano et al. (2003)

[a] *Carriers*: PLGA, poly(D,L-lactic-*co*-glycolic acid).
[b] Methods: DSC, differential scanning calorimetry; ESR, electron spin resonance; SEM, scanning elecron microscopy; SP, spectrophotometry.

Table 14
The effects of irradiation on controlled drug delivery/controlled drug release systems containing blood products

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Hemoglobin (artificial red blood cells) (ARC)/in vitro	DODPC + 2,4-octadienoic acid + cholesterol (7:2:7)/bilayer lipid vesicles/280 nm diam.	γ/25		SP: • 20% leakage reduced below 5% by the addition of more than 50 mM trehalose and sucrose to the external H_2O phase; • Low oxidative damage and low conversion to met-Hb within 20 w of storage; same when stored in dry state at 4 °C in the presence of 250 mM saccharide; LS: Increase of size after freeze-drying and rehydration due to aggregation and fusion inhibited by the addition of more than 50 mM trehalose or sucrose	Wang et al. (1992).
Hemoglobin (artificial red blood cells) (ARC)/in vivo (rat)	DODPC/liposomes/ 200 nm diam./2, 4, 6 and 8 g/kg	γ/5/4 °C, Ar; dose rates: 1.65, 3.3, 5 and 10 kGy/h	ARCs disapear from bloodstream within 2 w	SP: Polymerization conversion increases with increasing dose rate; GPC: $\bar{M}_n$ decreases with dose and dose rate; SP: No leakage of Hb from irradiated ARCs after 10 freeze-thaw cycles; LS: No size change of irradiated ARCs after 10 freeze–thaw cycles followed by a 1 year storage at −86 °C; Hematological tests: WBC, RBC, Hb, Hct, PLT recovered to control values 2 weeks after administration; Biochemical tests: ALP, T-CHO, PL increase, TG decreases up to 2 m after administration of ARCs; LDH, GOT, GPT, TP, BUN, CRE, T-BIL, ALB, GLU, A/G not changed for up to 4 months	Akama et al. (1995)
Hemoglobin	PEO $\bar{M}_w$ 0.6 and 1.5 MDa/hydrogel/ plates/100 mm diam. × 2–3 mm	3 MeV e/40/r.t., air		Calculation: Average molecular weight between X-links, $\bar{M}_c$ increases with volume fraction of polymer in gel after irradiation; At a const. vol. fraction of polymer in gel, $\bar{M}_c$ decreases with $\bar{M}_w$; Distance of diffusion: Diffusion coefficient decreases with $\bar{M}_w$ and volume fraction of polymer in gel	Kofinas et al. (1996)
Hemoglobin (artificial red blood cells) (ARC)/in vitro	DODPC or AODPC + cholesterol + Na palmitate (7:7:2)/ bilayer vesicles/200 nm diam.	γ/4 °C, Ar/dose rate 1–10 kGy/h		SP: Polymerization conversion increases with increasing dose rate (faster in DODPC than in AODPC); GPC: $\bar{M}_w$ decreases with dose and dose rate; initiation rate constant in AODPC ≈ 1/2 that in DODPC; Surface pressure: • Surface area of AODPC smaller than of DODPC; • Monolayer of DODPC breaks at 10 mN, AODPC at 23 mN;	Hosoi et al. (1997)

Table 14 (*continued*)

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
				SP: • No leakage of Hb from irradiated ARCs after 10 freeze-thaw cycles followed by a 1 y storage at −85 °C; • After 24 h storage at 37 °C more than 60% Hb oxidized to met-Hb, oxidation increases with dose; • Presence of Hb outside the vesicles prevents the formation of met-Hb inside the vesicles by irradiation	

[a] *Carriers*: AODPC, 1-stearoyl-2-(2,4-octadecadienoyl)-phosphatidylcholine; DODPC, 1,2-*bis*-(2,4-octadecadienoyl)-phosphatidylcholine; PEO, poly(ethylene oxide).
[b] *Methods*: GPC, gel permeation chromatography; LS, light scattering; SP, spectrophotometry.

higher bone formation than sterilization with ethylene oxide (Pekkarinen et al., 2005a). Collagen matrix is significantly more radiation sensitive than BMP: almost no bone formation was observed with pellets composed of unirradiated BMP and irradiated collagen (Ca yield 1.1% of control), while pellets prepared with irradiated BMP and unirradiated collagen had calcium yield 76% of control (Ijiri et al., 1994). Radiation damage to collagen could be mitigated by the addition of carboxymethyl cellulose (CMC) and the resulting putty-like implants also improved the histological picture of the fracture (Cook et al., 2005).

At least 15 BMPs were recognized by 2003 (Geiger et al., 2003). A commercial product consisting of 3.5 mg of recombinant human osteogenic protein-1 (rhOP-1) which is also known as BMP-7, and 1 g of bovine Type I collagen has been marketed under the tradename Osigraft. Osigraft is terminally sterilized by gamma irradiation (EMEA, 2004).

7. The effects of irradiation on drug release

CDD/CDR systems undergoing radiation sterilization have usually been manufactured in one of the two formats, microparticles or macroscopic objects. Microparticles can be administered by injection and may range in size from nano- to microspheres while macroscopic objects in the form of rods, disks, beads, plugs, sheets and wafers must be administered by surgical implantation to the target tissue or, exceptionally, by simple insertion. To be effective, drugs contained inside their microscopic or macroscopic carriers must reach the target tissue or systemic circulation (become bioavailable). The first step, the penetration either through the membrane (if the drug has been encapsulated within one) or through the monolithic matrix of the carrier material (if the drug has been embedded within one) can be affected by irradiation.

Theoretical treatment of release kinetics shows that the rate of drug release from both capsule- and matrix-type CDD/CDR systems depends on many factors such as the solubility of drug in the polymeric membrane/matrix material, drug solubility in environmental (aqueous) solution, drug diffusivity in the polymeric membrane/matrix material, drug diffusivity in environmental (aqueous) solution, thickness of the membrane/thickness of the drug dispersion zone, diffusion coefficient of solvent in the polymer and thickness of the hydrodynamic boundary diffusion layer (Kanjickal and Lopina, 2004). The effect of radiation sterilization on the release kinetics would be determined by the complex interplay of the relevant factors before and after irradiation.

The largest radiation-induced changes in irradiated CDD/CDR systems are associated with the largest molecules, i.e. with molecules of the polymeric carrier material and involve simultaneous chain scission and crosslinking. Because of these changes, irradiation has the largest effect on drug diffusivity in the membrane/matrix polymer material. Indeed, drug diffusion in the polymeric

Table 15
The effects of irradiation on controlled drug delivery/controlled drug release systems containing enzymes

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
β-galactosidase/ in vitro, pH 7.4	GMA dextran, (GMA dextran):(gelatin)/ temp. sensitive hydrogel/tablets/ 7 mm diam. × 2 mm	γ/1	14% within 3.5 h from GMA dextran, unaffected by temperature; 20% within 1.5 h from GMA dextran:gelatine at 37 °C	^{17}O-NMR: • Enzyme release from GMA dextran unaffected by temperature; • Enzyme release from (GMA dextran):(gelatine) increses after-temperature increase from 15 to 37 °C; • Release rate decreases with X-linking; • The ratio (release rate at 37 °C):(release rate at 15 °C) increases to 35 at 32% X-linking; • Release rate increases with gelatin %; • The ratio (release rate at 37 °C):(release rate at 15 °C) increases to 28 at 20% gelatin	Aso et al. (1999)
Glucoamylase/ 10,000 U/g	2G, 4G, 9G, 14G, HEA:14G (1:1) films/ 6 or 60 mm diam./ 0.5%	300 keV e/10/25 °C, air		Enzyme activity: • Peaks at optimum thickness of irradiated solution with respect to beam energy; • Peaks at 30% monomer (14 G) concentration, decreases with increasing temperature (due to the increase of porosity, i.e. increase of the surface); • Increases with increasing number of oxyethylene units (due to the increase of hydrophilicity); • Peaks at HEA:14 G (1:1); • Increases with the addition of filter paper and copolymerization with HEA	Kumakura et al. (1992)
Glucose oxidase	Sepharase 6B/ microspheres	γ/1–25		Amperometry: • Sensitivity not affected by 25 kGy immediately after irradiation but mechanical damage appears after 6 w; • Sensitivity decreases by more than 50% after 7 kGy + 4-d treatment with 0.6% H_2O_2	Von Woedtke et al. (2002)
Horseradish peroxidase	NIPAAm:NASI (93.1:6.9) hydrogel/ rods/15 mm diam.	γ/0.2–15/r.t., N_2 (before loading)		SP: • Immobilized enzyme activity decreases with time and storage temperature; • Immobilized enzyme activity has an optimum at 30 °C, pH 7; • Free enzyme activity increases with temperature; • Free enzyme activity has an optimum at pH 5	Zhai et al. (1993)
RNase $\bar{M}_w$ 5.9 kDa	A-ProOMe + TMPTMA (X-linker)/ thermosensitive hydrogel/disks/ 6 mm diam. × 2 mm/ 1.4% (1% X-linker) 0.6% (5% X-linker)	γ/9.5/r.t., N_2; (before loading)		SP protein assay: loading inversely proportional to $\bar{M}_w$ of protein and % of X-linker;	Caliceti et al. (2001)

Table 15 (*continued*)

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Superoxide dismutase $\bar{M}_w$ 33 kDa	A-ProOMe + TMPTMA (X-linker)/ thermosensitive hydrogel/disks/ 6 mm diam. × 2 mm/ 1% (1% X-linker); 0% (5%.X-linker)	γ/9.5/r.t., N_2; (before loading)		SP protein assay: No loading of protein $\bar{M}_w$ >30 kDa in matrices with 5% X-linker due to small pore size	
Urease/in vitro, pH 7	MEEP $\bar{M}_w$ 2.45 MDa hydrogel/films/7.3%	γ/2, 5/vac.	The final pH is reached 2 h after addition of urea	pH increase on addition of urea: • $\Delta pH = 3.5\times$ larger than with free unirradiated urease; • $\Delta pH = 2.75\times$ larger than with free 5 kGy irradiated urease; • $\Delta pH = 1.75\times$ larger than with immobilized 5 kGy irradiated urease; • Little difference between 2 and 5 kGy irradiation; • Stepwise addition of urea causes a stepwise increase of pH; • Each subsequent ΔpH smaller than the previous one	Allcock et al. (1994)
Urease/5.600 U/g	Starch-*g*-AAm/ hydrogel/10%	γ/2.5, 5, 7.5, 10, 15/N_2 (before loading)		Gravimetry: • Grafting yield increases with dose and monomer concentration; • Swelling capacity first increases with dose, than decreases; • Swelling little affected by monomer concentration; • Immobilization of urease increases with dose; • Enzyme residual activity decreases with repeated use; • There are optimum monomer concentration and dose	Dung et al. (1995)

[a] *Carriers*: A-ProOMe, acryloyl-L-proline methyl ester; GMA dextran, glycidyl methacrylated dextran; 2G, ethyleneglycol dimethacrylate; 4G, tetraethyleneglycol dimethacrylate; 9G, nonaethyleneglycol dimethacrylate; 14G, tetradecaethyleneglycol dimethacrylate; HEA, hydroxyethyl acrylate; MEEP, poly(di(methoxyethoxyethoxy)phosphazene); NASI, *N*-acryloxy succinimide; NIPAAm, *N*-isopropylacrylamide; TMPTMA, trimethylolpropane trimethacrylate.

[b] *Methods*: ^{17}O-NMR, ^{17}O nuclear magnetic resonance; SP, spectrophotometry.

membrane/matrix material has been recognized as the critical release rate-controlling factor and the majority of theoretical models for drug release have been based on diffusion equations (Peppas et al., 2000). The simple exponential relation,

$$M_t/M_\infty = kt^n, \quad (1)$$

has been introduced to describe the general drug release behavior of controlled release polymeric systems, where M_t and M_∞ are the amounts of drug released at time t and at equilibrium, respectively, k is the proportionality constant, and n the diffusional exponent related to the release mechanism (Ritger and Peppas, 1987). For $n = \frac{1}{2}$ the equation describes Fickian diffusion in planar geometry, while at $n = 1$ the released fraction is proportional to time, i.e. the release rate is constant and independent of time (zero order). Initial drug release from surfaces in real systems often occurs with an initial burst and sometimes the burst may also occur toward the end of the release process.

Relation (1) is a simple semi-empirical expression which describes the overall process but which is, nevertheless, indicative of the actual mechanism of drug release. As far as rate controlling mechanisms are concerned, three mechanisms have been identified: diffusion of drug through the matrix or the membrane, swelling of the carrier in a compatible liquid accompanied by the drug release (because carriers are made to be water compatible we speak of hydrogel carriers) and erosion of the carrier (Peppas et al., 2000).

The example of the release controlled by diffusion through a matrix is the release of the vasodilator drug diltiazem hydrochloride from polyvinylalcohol (PVA) tablets (Maggi et al., 2004). Both unirradiated and irradiated PVA tablets swell in water and a gel layer is formed on the surface which controls the drug release by diffusion. The release from unirradiated PVA tablet is described by Eq. (1) with n close to $\frac{1}{2}$. The integrity of the tablets did not change on irradiation because radiation-induced crosslinking of PVA was dominant, even after 50 kGy. Moreover, crosslinking did not hinder two-way diffusion through the matrix: both swellability in water and the release profile of the drug practically did not change after irradiation (i.e. the value of n remained close to $\frac{1}{2}$).

Double-walled microspheres act as reservoir systems. PLLA shells and more hydrophilic PLGA cores were fabricated with crystalline highly water-soluble antineoplastic drug etanidazole entrapped within the core (Lee et al., 2002). The release profile consisted of a lag phase during which a slow diffusion of the drug occurred for about 3 weeks, and the main release phase during which most of the drug was released over the next 3 weeks. Irradiation accelerated the release in the lag phase and reduced it to 1 week; release rate in the lag phase remained diffusion controlled, with n close to $\frac{1}{2}$, k increased by a factor of 2. Scanning electron microscope photographs revealed that irradiation enhanced the erosion and drug release from the more hydrophilic core faster than enhancing the development of porosity in the more hydrophobic and more radiation-resistant shell.

Table 16
The effects of irradiation on controlled drug delivery/controlled drug release systems containing gastrointestinial agents

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Mesalazine prodrug (3,3′-azobis(6-hydroxy benzoic acid)) (ABHB)/in vitro, pH 1, pH 7.4	HEMA-*co*-MAA + 5% or 10% of MAOE of TPA (X-linker) hydrogel/powder/30%	40 kV X-rays/r.t., vac.	15–20% release within 10 h at pH 1; near zero-order release at pH 7.4	Gravimetry: • 10% X-linker: equilibrium swelling (90%) at pH 7.4 reached after 3 h, 50% at pH 1 reached after 1.5 h; • 5% X-linker: equilibrium swelling (240%) at pH 7.4 reached after 2 h, 100% at pH 1 reached after 1 h; FTIR: Drug not covalently bound to matrix; DSC: T_g increases with concentration of X-linker; SP: ● Release from copolymer + 10% X-linker: o 15% (saturated) within 10 h at pH 1; o 55% (saturated) within 10 h at pH 7.4; ● Release from copolymer + 5% X-linker: o 20% (saturated) within 10 h at pH 1; o 80% (no saturation) within 10 h at pH 7.4	Mahkam (2004)

[a] *Carriers*: HEMA, 2-hydroxyethyl methacrylate; MAA, metacrylic acid; MAOE, methacryloyl oxyethyl ester; TPA, terephthalic acid.
[b] *Methods*: DSC, differential scanning calorimetry; FTIR, Fourier transform infrared spectrometry; SP, spectrophotometry.

Table 17
The effects of irradiation on controlled drug delivery/controlled drug release systems containing hypothalamic and pituitary hormones

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Recombinant human insulin-like growth factor I (rhIGF-I)/in vitro, pH 7.4	PLGA (50:50)/microspheres/1.5 ± 0.13 μm diam./5.4%	γ/25/r.t.	Initial burst increases from 26% to 36% by irradiation; amount released within 28 d increases from 67% to 71%	SEM: Spherical shape, relatively rough surface and pore distribution not affected by irradiation; LLD: Mean particle size increases to 1.88 ± 0.22 μm; DSC: T_g decreases by a few degrees; CD: Molar ellipticity decreases after irradiation (hydrolysis or dimerization of rhIGF-I?); SDS-PAGE: Additional band (14 kDa) indicates dimerization of drug; SP: After the initial burst release rate not affected by irradiation;	Carrascosa et al. (2003)
Leuprolide (LHRH analog) (nonapeptide Mw 1209.5 Da) in vitro, pH 7.0	PLGA (50:50) $\bar{M}_w$ 8.6 kDa/microspheres/10–125 μm diam./formulated with CMC and mannitol	γ/10, 15, 25/dry ice;	Higher release from irradiated microspheres during first 20 d, subsequently no difference; 100% release within 42 d	HPLC: • Loss of peptide, impurity peaks increase with dose, largest loss in formulated microspheres; • Initial burst release increases with dose; release after 20 d due to erosion, not affected by formulation or irradiation; SEC: $\bar{M}_w$ and $\bar{M}_n$ decrease with dose, enhanced by excipients; DSC: • T_g decreases with dose in unloaded microspheres • T_g = const. in loaded microspheres	Shameem et al. (1999)
In vivo (rat serum)	PLGA (50:50) $\bar{M}_w$ 8.6 kDa/microspheres/10–125 μm diam./formulated with CMC and mannitol	γ/10, 15, 25/dry ice;		RIA: Serum testosterone suppression profile (chemical castration) not affected by irradiation	
Leuprolide acetate/in vivo (dog serum)	[PLGA (75:25)]:[NMP (45:55)] polimer solution ATRIGEL® (injected soluton forms implant as NMP dissipates)/3%, 4.5%, 6%	γ/25/N_2 (before loading)	Serum testosterone level peaks after 3 d, then for about 100 d remains below castration level (0.5 ng/ml)	GPS: $\bar{M}_w$ decreases from 17 to 15 kDa; RIA: Longer residence of drug in implants with higher loading; LC/MC/MS: Initial burst release of drug as dissipating NMP leaves; after 30 d the release is comparable to the one from a commercial LUPRON® microspheres	Ravivarapu et al. (2000)

RS-49947 (LHRH analog) (decapeptide)/ in vitro, pH 7.4	Silicon elastomer macroporous matrix/ hardened non-erodible implants/ $1 \times 3 \times 1\,mm^3$/42%	γ/12.5/dry ice; γ/25/ r.t.	80% within 100 d	HPLC: Cumulative release decreases with irradiation (observed only in one batch)–no differences in drug release characteristics observed as a function of irradiation in other batches	Burns et al. (1990)
Melanotan I (tridecapeptide with melanotropic activity)/ in vitro, pH 7.4	PLGA (50:50)/rods/ 2 mm diam. × 1 cm/ 2–10%	γ/15, 25, 35/dry ice	Triphasic release profile: initial burst (<3%) + slow release for 3 w + zero-order rapid release	HPLC: • Onset of rapid release reduced from 18 to 16 d in irradiated implants (all doses); • 100% release within 5 w accelerated to 4 w in 25 and 35 kGy irradiated implants; • 15 kGy irradiated implants deviate from zero-order kinetics and reach 100% release within 6 w	Bhardwaj and Blanchard (1997)
Triptoreline (LHRH agonist)/in vivo (rat plasma)	PLGA (50:50) $\bar{M}_w$ 49.8 kDa, $\bar{M}_n$ 22.5 kDa/microspheres	γ/25	Biphasic release profile: initial burst folowed by a zero-order release	SEC: • $\bar{M}_w$ decreases from 52.9 to 43.2 kDa; • $\bar{M}_n$ decreases from 28.9 to 20 kDa; RIA: • Triptoreline serum level from irradiated microspheres higher than from non-irradiated, burst release on day 5, constant level up to 1 m; • Testosterone serum level maintained between 0.2 and 0.8 ng/ml for 1 m	Ruiz and Benoit (1991)
Vapreotide (somatostatin analog)/ in vivo (rat plasma)	PLGA (75:25), PLGA (50:50)/rods/ 1.5 mm diam. × 0.5 or 1.5 cm/2.5, 7.5% (core)	γ/25/−78 °C, air	Triphasic release profile: initial burst + latent period + release for 3 m	GPC: • $\bar{M}_w$ reduced by irradiation; • Extrusion before irradiation inhibits $\bar{M}_w$ degradation; RIA: Onset time for the release increases with $\bar{M}_w$	Rothen-Weinhold et al. (1997); Rothen-Weinhold and Gurny (1997)
Vapreotide (somatostatin analog) (cyclic octapeptide)	PLA $\bar{M}_w$ 6 kDa/rods/ 1.5 mm diam. × 1.5 cm/ 18.5% (core)	γ/5–50/−78 °C, air, N_2, Ar		HPLC: • Purity of drug above 98.5% at all doses immediately after irradiation; • Purity reduced below 85% 10 m after storage in air; • Storage in N_2 or Ar after irradiation protects purity above 95% within 6 m, 88% within 10 m; • Number of impurity peaks increases from 14 to 27 after 9 m storage at 4 and 40 °C, respectively; • No degradation product larger than 0.5%	Rothen-Weinhold et al. (1999)

[a] *Carriers*: CMC, carboxymethyl cellulose; NMP, *N*-methyl-2-pyrrolidone; PLA, poly(L-lactic acid); PLGA, poly(D,L-lactic-*co*-glycolic acid).

[b] *Methods*: CD, circular dichroism; DSC, differential scanning calorimetry; GPC, gel permeation chromatography; HPLC, high performance liquid chromatography; LC/MS/MS, liquid chromatography-mass spectrometry-mass spectrometry; LLD, laser light diffractometry; RIA, radioimmuno assay; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEC, size exclusion chromatography; SEM, scanning electron microscopy; SP, spectrophotometry.

Table 18
The effects of irradiation on controlled drug delivery/controlled drug release systems containing local anesthetic agents

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Bupivacaine/in vitro, pH 2	PLGA (50:50), $\bar{M}_w$ 34 kDa/microspheres/ 2–5 μm diam./40%	γ/25/25 °C, air; 25 °C, vac.; 77 K, vac.		SEM: Size and shape not affected by irradiation; HPLC: Drug content of microspheres decreases by 4% after irradiation; SP: Release rate constant ($0.04\,h^{-0.5}$ (0–2 m), increases with storage to $0.05\,h^{-0.5}$ (after 6 m) to $0.057\,h^{-0.5}$ (after 1 y); ESR: • Irradiation at 77 K in vacuum creates $-^{\bullet}CH_2-$, $-^{\bullet}CH-$, $-^{\bullet}C(CH_3)-$, $-CH(CH_3)-$ and radicals of the drug; • On heating to 298 K after 2 d: $-^{\bullet}CH-$, $-^{\bullet}C(CH_3)-$ and radicals of the drug remain; • Irradiation at 25 °C in vacuum creates the same radicals as above (after heating); • Irradiation at 25 °C in air creates nitroxyl and peroxyl radicals; • No evidence of spin transfer between drug and carrier	Montanari et al. (2002)
Bupivacaine/in vitro, pH 7.4	PLGA (50:50), $\bar{M}_w$ 34 kDa/ microspheres/ 10% < 0.4 μm 50% < 0.6 μm 90% < 1 μm/ formulation 1:10%; formulation 2:25%; formulation 3:40% drug	e/25/25 °C, air; γ/25/25 °C, air	Diffusion controlled release during the first 6 d; 90% release from 10%, and 25% within 2 w; 75% release from 40% within 2 w	AFM: Surface roughness (35 nm) increases with irradiation to 72.5 nm (e) and 84 nm (γ); LLD: Size not affected by loading and irradiation; FTIR: No evidence of drug-carrier interaction; DSC: T_g decreases after irradiation, more in γ than electron irradiation; T_g not affected by loading; HPLC: • Drug content decreases by 9% after γ, 2% after e irradiation; • Release rate constant ($0.045\,h^{-1}$) increases after irradiation to $0.06\,h^{-1}$ (e) and $0.07\,h^{-1}$ (γ); • Release rate constant from formulation 3 (40% drug) lower by 25%	Montanari et al. (2003)

[a] *Carriers*: PLGA, poly(D,L-lactic-*co*-glycolic acid).
[b] *Methods*: AFM, atomic force microscopy; DSC, differential scanning calorimetry; ESR, electron spin resonance; FTIR, Fourier transform infrared spectrometry; HPLC, high performance liquid chromatography; LLD, laser light diffractometry; SEM, scanning electron microscopy; SP, spectrophotometry.

Swelling-CDR is also described by Eq. (1): when the rate of water diffusion into hydrophilic polymer is greater than the rate of the relaxation of polymer chains, a sharp boundary between the glassy core and the swollen shell is established. Drug release can occur from the swollen shell only, and if swelling is advancing at a constant velocity the overall drug release rate will also be constant ($n = 1$). Because of this property, oral drug delivery systems are usually based on hydrophilic swellable matrices made of complex carbohydrate polymers (polysaccharides) such as starch and hydroxypropylmethyl cellulose, but oral administration does not concern us here because it does not command sterility. On the other hand, some swellable polysaccharide matrices show burst release profile which may be improved by irradiation: radiation-induced crosslinking of gellan gum (Gelrite) beads loaded with sulphamethizole eliminated the burst and reduced the release kinetics to zero order process (Quigley and Deasy, 1992). The opposite effect is also possible: in vitro release of ciprofloxacin from irradiated intraocular minitablets made of pure amylopectin was slightly accelerated with respect to the untreated minitablets. Moreover, the release profile after radiation was more acceptable than after heat sterilization (Weyenberg et al., 2004).

Contrary to the acceleration of drug release generally obtained from radiation-sterilized CDD/CDR systems due to radiation-induced degradation of most polymers, the irradiation of liposomes composed of unsaturated lipids yielded polymerized lipid membranes capable of containing hemoglobin and acting as artificial red blood cells (Akama et al., 1995).

Drug release from erodible polymers may occur concomitantly with the surface erosion or bulk erosion. The factor determining the ultimate degradation behavior and therefore the release mechanism, is determined by the relative movement of two fronts, a hydration front and an erosion front. For example, hydrolysis of the ortho ester bonds in the surface layers of the hydrophilic POE III polymers produces acetic acid which further accelerates hydrolysis. If hydration is faster than erosion, which is the case in hydrophilic matrices, the matrix will eventually become completely permeated with water. At that point, hydrolysis occurs at comparable rates throughout the volume and bulk erosion takes place (Einmahl et al., 2001). The release of embedded drug is described by a sigmoidal curve. Irradiation greatly reduced molecular weight of POE III polymers, hence the viscosity and the lag period of the sigmoidal release curve of 5-FU were also significantly reduced, with the concomitant increase of the release rate (Sintzel et al., 1998). Because of the instability against irradiation and the formation of radiation-induced degradation products, which may be responsible for the inflammatory reaction (Zignani et al., 1997), irradiation was not recommended as a sterilization treatment for POE III.

POE IV contains lactic acid units in the polymer backbone (POE_xLA_y) that control the degradation rate of ester linkages. The hydrolysis takes place predominantly in the surface layers of the polymer matrix. Weight loss, the release of hydrolysis products and drug release are described by a curve showing a lag period followed by an approximately constant (zero-order) rate. The constant release rate is a consequence of the equilibrium established between water penetration and surface hydrolysis (erosion front) controlling polymer erosion and drug release. Radiation sterilization of $POE_{95}LA_5$ films loaded with tetracycline did not affect molecular weight of the polymer

Table 19
The effects of irradiation on controlled drug delivery/controlled drug release systems containing parasympathomimetic agents

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods: Effects of irradiation	Reference
Pilocarpine nitrate (PN)/in vivo, eye (albino rabbit)	NaCMC/4% gel; HPMC/4% gel; LFC–127/20% gel; C-940/1–6% gel; C-941/6% gel/all gels contain 2% drug	γ/25	Mean reduction of pupil diam. achieved within 30 min, returns to normal within 4–6 h	Miotic response: ● Increases with PN concentration up to 2% w/v; ○ Time required to achieve 1 mm reduction of pupil diam. not affected by irradiation; ○ Time required to achieve peak response not affected by irradiation; ○ Peak miotic response not affected by irradiation; ○ Duration of significant miotic response not affected by irradiation; Viscosimetry: Viscosity of C-940 4% gel almost doubled by irradiation; Mechanical properties: Irradiation gives a brittle gel	Deshpande and Shirolkar (1989)
Pilocarpine/in vivo, eye (rabbit, human)	Acrylic plastic/rod applicators/55 mm/0.5 mg/rod	γ/32.9		Miotic response: rabbit eye returns to normal a little faster after eyedrops than after the application with a rod; maximum miosis of human eye 20% higher with rod, returns to normal 1 h later than after the application of eyedrops;	Alani (1990)

[a] *Carriers*: C-940, Carbopol-940; C-941, Carbopol-941; HPMC, hydroxypropyl methyl cellulose; LFC-127, Lutrol FC-127; NaCMC, Na carboxymethyl cellulose.

Table 20
The effects of irradiation on controlled drug delivery/controlled drug release systems containing parathyroid calcitonin and biphosphonates

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods[b]: Effects of irradiation	Reference
Calcitonin (salmon)/ in vivo, rat serum	PLGA (50:50) $\bar{M}_w$ 29 kDa, $\bar{M}_n$ 15.9 kDa/ microspheres/ 109 μm diam./3.5% entrapped + 1% adsorbed on the surface	γ/25	Burst release of adsorbed drug followed by sustained release of entrapped drug within 5–9 d	Radioimmunoassay: No data reported relative to unirradiated microspheres; PCS: No size change after irradiation	Mehta et al. (1994)
Clodronate Na	DMPC, DSPC, DSPG, 20% DSPG/DSPC, soya PC, egg PC/ liposomes/92–103 nm diam.	γ/25/r.t., O_2, N_2		DELS: Zeta potential of all liposomes becomes more negative with irradiation; Coulter cell counting: Growth inhibition increases with unsaturation and irradiation; Toxicity test: Cytotoxicity produced only by soya PC irradiated in O_2	Stensrud et al. (1999b)
Bovine bone morphogenetic protein (BMP)/in vivo, (rat thorax)	Collagen/pellet/104%	γ/25		● Irradiated BMP/irradiated collagen pellet: o Densitometry: produced photodensity 4% of control; o SP: Alkaline phosphatase 1.8% of control; (both comparable to EtO sterilization at 55 °C/1 h or 37 °C/4 h); ● Irradiated BMP/non-irradiated collagen pellet: o Densitometry: produced photodensity 72% of control; o SP: Alkaline phosphatase 70.5% of control; ● Non-irradiated BMP/irradiated collagen pellet: o Densitometry: no production of photodensity; o SP: No alkaline phosphatase activity; Conclusion: Only EtO sterilization at 29 °C/5 h is acceptable	Ijiri et al. (1994)
Bovine bone morphogenetic protein (BMP)/in vivo, calvarial deffect (rat)	PLGA (50:50)/putty-like matrix/0.25%	γ/18/r.t., air (before loading)		Histomorphometry: ● Largest area of bone formation produced by irradiated polymer formulation + BMP; ● No residual polymer with 18 kGy irradiated PLGA; ● Fibrous tissue formation with 18 kGy irradiated PLGA + BMP only slightly lower than with non-irradiated unloaded PLGA; ● Inflammation of the site with irradiated PLGA + BMP lower than with control or PLGA alone, but higher than with non-irradiated PLGA + BMP	Andriano et al. (2000)
Bovine bone morphogenetic protein (BMP)/skull onlay (rat)	PLGA (50:50)/putty like matrix/0.25%	γ/15, 25/r.t., air		Histomorphometry: No statistical difference in implant area, new bone area and % of new bone formation between 15 and 25 kGy irradiated and control (non-irradiated) PLGA + BMP systems	

Recombinant human osteogenic protein-1 (rhOP-1) (36 kDa 139 amino acids protein)/in vitro (osteosarcoma cells of rat)	Bovine collageneous matrix; baboon + rat collageneous matrix/ pellets/0.1 mg/pellet, 0.5 mg/pellet, 2.5 mg/ pellet	γ/25–30/r.t., vac.	Bone % by 90th day reduced by irradiation to 84%; bone % by 365th day enhanced to 120% by irradiation	HPLC: Recovery of rhOP-1 from irradiated pellets 67% (85% from non-irradiated pellets); SDS/PAGE: • Electrophoretic mobility not affected by irradiation; • Immunoblot assay: immunoreactivity not affected by irradiation; Cell culture: • Biological activity not affected by irradiation; • Alkaline phosphatase activity in vitro not affected by irradiation; SP: Ca content in vivo reduced by irradiation, % reduction smaller in matrices loaded with more rhOP-1;	Ripamonti et al. (2000)
In vivo (rat, baboon)				Histomorphometry: Generated cartilage and bone tissue reduced by irradiation, % reduction smaller in matrices loaded with more rhOP-1; Cell culture: Alkaline phosphatase activity in vivo not affected by irradiation	
Recombinant human osteogenic protein-1/ in vivo, ulna (dog)	Bovine bone derived Type I collagen + CMC/putty/ implants/3.5%, 1.75%	γ		Radiography: Greater and earlier bone formation with larger amount of rhOP-1 (94 vs. 65% for 3.5% and 1.75% loaded, respectively); Mechanical properties: No difference between particulate and putty-like formulations; Histology: Improved by the addition of CMC	Cook et al. (2005)
Reindeer bone morphogenetic protein (BMP)/in vivo (mouse)	Collagen/sponge/ $8 \times 8\,mm^2$/33.3%, 66.6%	γ/31.5		Radiography: • Incorporation of ^{45}Ca from radiation sterilized implants containing 33.3% and 66.6% BMP is 30% and 60% higher respectively than from EtO sterilized implants; • Area of new bone 45% higher in radiation sterilized groups; • Mean optical density of new bone 70–75% higher in radiation sterilized groups	Pekkarinen et al. (2005a)
Reindeer bone morphogenetic protein (BMP)/in vivo (mouse)	Gelatin/implants or capsule/5 mg/implant and soluble gelatin injection/5%	γ/41		Radiography: • Bone area and optical density of new bone (osteoinductivity) of gelatine capsules implants not affected by irradiation; • Optical density of new bone not affected by irradiation of gelatin injection; • Bone area reduced to 50% by irradiation of gelatin injections; • Incorporation of ^{45}Ca from implants not affected by irradiation; • Incorporation of ^{45}Ca from injection reduced by irradiation	Pekkarinen et al. (2005b)

[a] *Carriers*: CMC, carboxymethyl cellulose; DMPC, dimyristoyl phosphatidyl choline; DSPC, distearoyl phosphatidyl choline; DSPG, distearoyl phosphatidyl glycerol; PLGA, poly(D,L-lactic-*co*-glycolic acid).

[b] *Methods*: DELS, Doppler electrophoretic light scattering; HPLC, high performance liquid chromatography; PCS, photon correlation spectroscopy; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SP, spectrophotometry.

Table 21
The effects of irradiation on controlled drug delivery/controlled drug release systems containing peptides and proteins

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Bovine serum albumin (BSA) $\bar{M}_w$ 66 kDa/ in vitro, pH 7.4	HEMA:PEG (90:10) + TMPTMA (X-linker) hydrogel/rods/ 2.5 mm diam. × 50 mm/1%	γ/25/dry ice	55% release within 140 d	SP: No release from p(HEMA:PEG) for PEG $\bar{M}_w < 15$ kDa SEM: Porosity and swellability increase with $\bar{M}_w$ of PEG;	Carenza et al. (1993)
Bovine serum albumin (BSA)	NIPAAm:NASI (93.1:6.9) hydrogel/rods/15 mm diam.	γ/0.2–15/r.t., N_2 (before loading)		SP: Conjugation of BSA to (NIPAAm-*co*-NASI) decreases with dose: • 10% decrease by 5 kGy; • 70% decrease by 7 kGy;	Zhai et al. (1993)
Bovine serum albumin (BSA)/in vitro, pH 7.4	GMA dextran:gelatin temperature sensitive hydrogel/tablets/ 7 mm diam. × 2 mm	γ/1	20% release within 1.5 h from GMA dextran: gelatin at 37 °C	HPLC: Pulsatile release on temperature increase from 15 to 37 °C due to sol-gel transition of gelatin	Aso et al. (1999)
Bovine serum albumin (BSA) $\bar{M}_w$ 66 kDa	A-ProOMe + TMPTMA thermosensitive hydrogel/ disks/6 mm diam. × 2 mm/ 0.5% (1% X-linker), 0% (5% X-linker)	γ/9.5/r.t., N_2 (before loading)		SP: Protein assay: no loading of protein $\bar{M}_w < 30$ kDa in matrices with 5% X-linker due to small pore size	Caliceti et al. (2001)
Cytochrome *c*	PEO M_w 0.6, 1 and 5 MDa hydrogel plates/ 100 mm diam. × 2–3 mm/	3 MeV e/40/r.t., air		Calculation: • Average molecular weight between X-links, $\bar{M}_c$, after irradiation increases with volume fraction of polymer in gel; • At a constant volume fraction of polymer in gel M_c decreases with M_w; Distance of diffusion: Diffusion coefficient decreases with M_w and volume fraction of polymer in gel	Kofinas et al. (1996)
Ovalbumin $\bar{M}_w$ 44.3 kDa/ in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 13 kDa microspheres/no NaCl: diam.$_{50\%}$/diam.$_{90\%}$ 14–32 μm	γ/25; r.t., air	100% burst release from unirradiated microspheres within 6 h	SEM: Size change to diam.$_{50\%}$/diam.$_{90\%}$ 15/45 μm (+aggregation); SP: The completion of burst release to 100% postponed to 30 h; ESR: • Radicals formed at low temp.: $-^{\bullet}CH(CH_3)$, $-^{\bullet}CH_2$, $-^{\bullet}CH-$ and $-^{\bullet}C(CH_3)-$ reduced by heating to $-^{\bullet}CH-$ and $-^{\bullet}C(CH_3)-$; • Perthiyl radicals RS-S$^{\bullet}$ detected after annealing to r.t.;	Dorati et al. (2005)
	PLGA (50:50) M_w 13 kDa + 0.36% PEG M_w 0.4 kDa/microspheres/ + 10%NaCl: diam.$_{50\%}$/ diam.$_{90\%}$ 19–30 μm		10% burst release within 6 h followed by 50% within 7 d	SEM: Size change to diam.$_{50\%}$/diam.$_{90\%}$ 21/31 μm (insignificant increase); SP: No burst release; 20% release (to saturation) within 2 d;	

Ovalbumin $\bar{M}_w$ 44.3 kDa/ in vitro, pH 7.4 (cont.)	PLGA (50:50) M_w 13 kDa + 0.36% PEG M_w 0.4 kDa/microspheres/no NaCl: diam.$_{50\%}$/diam.$_{90\%}$ 25–43	γ/25; r.t., air	60% burst release from unirradiated microspheres within 24 h (saturated)	SEM: Size change to diam.$_{50\%}$/diam.$_{90\%}$ 26/47 μm (insignificant incr.); SP: Burst release enhanced by irradiation to 70% (saturated); ESR: All radicals derived from PLGA, PEG radicals not detected;	Dorati et al. (2005) (cont.)
	PLGA (50:50) $\bar{M}_w$ 13 kDa + 0.048% PEG M_w 0.4 kDa/microspheres/ + 10% NaCl: diam.$_{50\%}$/diam.$_{90\%}$ 21–33 μm		6% release within 24 h followed by 50% within 4 w	SEM: No size change (diam.$_{50\%}$/diam.$_{90\%}$ 22/33 μm); SP: Release not affected by irradiation; ESR: All radicals derived from PLGA, PEG radicals not detected	
	PLGA (50:50) $\bar{M}_w$ 13 kDa + 30.73% PEG M_w 4 kDa/microspheres/no NaCl: diam.$_{50\%}$/diam.$_{90\%}$ 34–69 μm		100% burst release from unirradiated microspheres within 24 h	NMR: • 2% fragmentation of irradiated 4 kDa PEG; • PEG loading of microspheres not affected by irradiation; SEM: Size decrease to diam.$_{50\%}$/diam.$_{90\%}$ 30/50 μm (+ aggregation); SP: Burst release reduced to 40% within 6 h followed by slow release up to 90% within 7 d;	
	PLGA (50:50) $\bar{M}_w$ 13 kDa/ + 14.3% PEG M_w 4 kDa microspheres/ + 10% NaCl: diam.$_{50\%}$/diam.$_{90\%}$ 29–56 μm		100% burst release within 24 h	NMR: PEG loading decreases to 12% by irradiation; SEM: Size decrease to diam.$_{50\%}$/diam$_{90\%}$ 29/48 μm (insignificant); SP: Burst release reduced to 70% within 6 h followed by slow release up to 90% within 7 d	
Soybean protein isolate	Chitosan:soybean protein isolate blends (100:0, 75:25, 50:50, 25:75)/membrane/ 45–65 μm thick	10 MeV e/25, 50, 100		FTIR: No chemical modifications of blend components; Contact angle: Surface energy increases with dose; SEM: No change of morphology after irradiation; Gravimetry: Equilibrium degree of hydration not affected; Mechanical properties: Strength, stiffness and brittleness of 100:0, 75:25 and 50:50 blends not affected by irradiation; Density: No X-linking between chitosan and protein by irradiation.	Silva et al. (2004)
Transforming growth factor-β1/in vitro, pH 7.4	(L-LA):(CL-*co*-D,L-LA 60:40) 85:15/polymer paste/2 mm diam. × 3 mm drill/50 μg/rat	γ/25	In vitro release detectable after 6 h, sustained release extended for 7 d;		Tielinen et al. (2001)
In vivo, distal femur (rat)	(L-LA):(CL-*co*-D,L-LA 60:40) 85:15/polymer paste/2 mm diam. × 3 mm drill/50 μg/rat	γ/25		Microradiography: The failure of TGF-β1 to enhance healing of the bone defect not influenced by irradiation	

[a] *Carriers*: A-ProOMe, acryloyl-L-proline methyl ester; CL, ε-caprolactone; GMA, glycidyl methacrylate; HEMA, poly(2-hydroxyethyl methacrylate); LA, lactic acid; NASI, *N*-acryloxysuccinimide; NIPAAm, *N*-isopropylacrylamide; PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PLGA, poly(D,L-lactic-co-glycolic acid); TMPTMA, trimethylolpropane trimethacrylate.

[b] *Methods*: ESR, electron spin resonance; FTIR, Fourier transform infrared spectrometry; HPLC, high performance liquid chromatography; NMR, nuclear magnetic resonance; SEM, scanning electron microscopy; SP, spectrophotometry.

Table 22
The Effects of irradiation on controlled drug delivery/controlled drug release systems containing prostaglandines

Drug/target	Carrier[a]/dosage form/ dimensions/ loading (% w/w)	Radiation type/dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
17β-estradiol semi-hydrate (17 βE2)/ in vitro, pH 7.4	PLGA (50:50) $\bar{M}_w$ 33.7 kDa, $\bar{M}_n$ 16.5 kDa/ microspheres/ 26–31 μm diam./ 7.9%, 18.4%	γ/5.1, 15.2, 26.6/−78.5 °C, Ar	From 7.9% loaded: 50% release within 28 d (0 kGy), 23 d (5.1 kGy), 22 d (15.2 kGy), 20 d (26.6 kGy); 20 d (26.6 kGy); from 18.4% loaded: 50% release within 34 d (0 kGy), 28 d (26.6 kGy)	SEM: Surface morphology not affected by irradiation; GPC: • $\bar{M}_w$ reduced linearly with dose to 85% at 26.6 kGy, reduction not affected by loading; • Polydispersity not affected by dose and loading; HPLC: • 17βE2 loss from 7.9% loaded: 5.4% at 15 and 26 kGy, from 18.4% loaded: 3.5% at 15 and 26 kGy; • 9,11-dehydro E2 formation: 5% from 7.9% loaded at 15 and 26 kGy 3% from 18.4 loaded at 15 and 26 kGy; 17βE2–PLGA conjugates formation from 7.9% loaded: 5% at 15 and 26 kGy; from 18.4% loaded: 3% at 15 and 26 kGy	Mohr et al. (1999)
17β-estradiol semi-hydrate (17 βE2)/ in vitro, pH 7.4	PLGA (75:25) $\bar{M}_w$ 17.3 kDa, $\bar{M}_n$ 12.2 kDa/ microspheres/ 18–22 μm diam./ 18.4%, 44.4%	γ/26, 34.1/ 77 K, vac.;−78.5 °C, Ar	Not determined	HPLC: Release increases with dose, release rate becomes closer to zero order with loading and dose; DSC: T_g reduced by loading, not affected by dose at a given loading; Microbiological assay: D_{10} of *B. pumilus* ATCC 27142 in PLGA: 2.4 kGy; (Our calculation of data on the more radiation-resistant spores in placebo microspheres gives $D_{10} = 20$ kGy); SEM: Surface morphology not affected by irradiation; GPC: $\bar{M}_w$ reduced linearly with dose to 94% at 25 kGy, reduction not affected by loading; Polydispersity not affected by dose and loading	
Prostaglandin $F_{2\alpha}$/in vitro, Ringer solution	PVP/rods/8 mm diam. × 35 mm/ 5 mg/rod	γ/10–93	85% release within 3 h	Gravimetry: Degree of equilibrium swelling decreases with dose (inversely proportional to dose); Calculation: • $\bar{M}_c$ decreases linearly with dose; • Size of polymer net mesh decreases with dose	Rosiak and Olejniczak (1993)

[a] *Carriers*: PLGA, poly(D,L-lactic-*co*-glycolic acid; PVP, poly(vinyl pyrrolidone).
[b] *Methods*: DSC, differential scanning calorimetry; GPC, gel permeation chromatography; HPLC, high performance liquid chromatography; SEM, scanning electron microscopy.

but eliminated the 3-d lag period and slightly increased the release rate. Release rates from irradiated POE IV polymers could be modulated by many parameters such as composition, polymer molecular weight and additives (Schwach-Abdellaoui et al., 2001).

8. Regulatory aspects of radiation sterilization of drugs

As a rule, early guidelines did not differentiate between drugs and medical devices. The fundamental difference between the two is that the drug has a defined chemical structure which, once the drug has been formulated, remains the same. On the other hand, a device undergoes an incremental development throughout its market lifetime (Phillips and Phillips, 2005). CDD/CDR systems can be understood as drug–device combinations: while the API remains the same, the composition and design of the carrier may change in response to changing needs and/or new research results.

The use of a minimum dose lower than 25 kGy for sterilization has its commercial and economic attractions: it can lower general sterilization costs and make a wider range of products available for patient care while at the same time jeopardizing neither the integrity of a product nor the patients' safety. It is of a special interest in radiation sterilization of pharmaceuticals because a possibly deleterious

Table 23
The effects of irradiation on controlled drug delivery/controlled drug release systems containing sex hormones

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Medroxy progesterone acetate/in vitro	PEO $\bar{M}_w$ 300 kDa + PEG/latex covered rods/4.5 mm diam. × 30–35 mm/ 350 mg/rod	γ/25/Ar	100% release within 5 d	SP: • 2.5 d lag phase followed by zero-order release; • Release rate modifiable by the number of latex layers;	Rosiak et al. (1998)
In vivo, humans	PEO $\bar{M}_w$ 300 kDa + PEG/latex covered rod/4.5 mm diam. × 30–35 mm/ 350 mg/rod	γ/25/Ar		SP: 1 d lag phase followed by zero-order release	
Progesterone/in vitro	NIPAAm:VTPDMS (50:50) copolymer + 1% MBAAm (X-linker)/ thermally reversibile hydrogel with hydrophobic microdomains/disks/ 15 mm diam. × 1.5 mm	γ/5–15/N_2	20% release from pure NIPPAAm; 40% within 12 d from 50:50; 13% from 85:15 copolymer	DSC: Two values of T_g are evidence of microdomains; Elemental microanalysis: More NIPAAm enters the gel than there is in the feed mixture; GPC: Copolymer 50:50 exhibits a single elution peak as contrasted with a physical mixture of two homopolymers showing two peaks; Gravimetry: • Swelling temperature and H_2O content not affected by copolymer composition; • Copolymers containing >50% NIPAAm exhibit slow deswelling, copolymer 50:50 exhibits rapid deswelling; Calculation: M_c between X-links decreases with dose and X-linker; SP: Higher zero-order release rate from (50:50) copolymer than from p(NIPAAm) hydrogel	Dong and Hoffman (1990)
Progesterone/in vitro, pH 7.4	D,L-PLA $\bar{M}_w$ 120 and 300 kDa/microspheres/ 45–90 μm/10%	γ/5–1000	Initial diffusional release (10–200 h) followed by a zero-order release (50–240 d) followed by a final burst release	GPC: $\bar{M}_w$ reduced by 50 kGy from 311 to 88 and from 120 to 60 kDa; Titration: • –COOH content increases with dose; • Observed $\bar{M}_w$ larger than $\bar{M}_w$ calculated from COOH content; DSC: T_g decreases linearly with dose; HPLC: • Diffusional release increases with dose, release rate constant linearly decreases with T_g; • Zero-order release from 120 kDa PLA reduced by irradiation from 240 d to 140 d (25 kGy), to 100 d (50 kGy) to 60 d (100 kGy); • Final burst release starts at $T_g < 37$ °C	Yoshioka et al. (1995a)

Table 23 (*continued*)

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Progesterone/in vitro, pH 7.4	D,L-PLA $\bar{M}_w$ 10, 50, 140, 160 and 300 kDa/ microspheres/ 45–90 μm/10%	γ/5–100	Initial diffusional release (50 h) followed by a zero-order release (60 d) followed by a final burst release up to 85%	HPLC: • Diffusional release rate constant from 10 kDa PLA not affected by H_2O content and dose at $D<25$ kGy, decreases with $\bar{M}_w$; • No diffusional release from amorphous 160 kDa microspheres; • Diffusional release from crystalline 160 kDa microspheres not affected by $D<50$ kGy; • Final burst release starts at $T_g<37$ °C; • Zero-order release from 140 kDa PLA little increases with dose up to 50 kGy, at 100 kGy abrupt release sets in after 60 d; • Decomposition of progesterone: <15% at 100 kGy; GPC: $\bar{M}_w$ decreases with dose; Titration: –COOH content increases with dose; DSC: T_g not affected by $D<25$ kGy.	Yoshioka et al. (1995b)
Progesterone/in vitro	PDMS/sheets/2 mm thick/10%	γ/50, 75, 100	Diffusional release within 1.5 d; Cumulative release 4 mg/cm^2	Mechanical properties: hardness modulus increases with dose; GPC: Extracts of sol fraction have $\bar{M}_w$ 8.7 kDa; FTIR: Increase of $–CH_3$, Si–C and Si–O–Si signals due to chain scission; Microscopy: Porosity formed by gas evolution; STA (TGA + DSC): No decomposition of progesterone with irradiation; SP: Release profile not affected by dose;	Mashak and Taghizadeh (2006)
Testosterone/in vivo, rat	A-PrOMe-*co*-HPMA (80:20) gel/tablets/ 8 mm diam./12%	γ/30/25 °C, N_2	Constant release rate 38 μg/d over 54 w	Gravimetry: • Fast swelling (2 h) to 1000% at 10 °C, shrinkage to 30% at 37 °C; • Weight of ventral prostate of castrated rats restored to normal weight in several days; DSC: Lower critical solution temperature (LCST) is 14 °C; Microscopy: • Deswollen gel consists of a transparent layer on the surface and an opaque core; • Shrinking leads to rigid membrane formation on the surface which inhibits passage of H_2O;	Yoshida et al. (1995)
Testosterone/in vitro	PLGA (80:20)microspheres/ (~75% have diam. 16–50 μm)/15.8%	γ/25	90% release within 3 d	Viscosimetry: Viscosity of unloaded PLGA reduced to 71% by irradiation; SP: • Initial release slightly faster from irradiated microspheres; • Release during the first 24 h not affected by irradiation	Shen et al. (2000)

Testosterone/ex vivo, porcine mucosa	Potato, corn or rice starch-*g*-PAA (1:5) or maltodextrin-*g*-PAA (1:5) hydrogel/tablets/ 7 mm diam.	γ/18 (before loading)	Bioadhesion: detachment force and work of adhesion higher in irradiated than in reference formulation (physical mixture of 5% Carbopol 974P, 94% DDWM starch and 1% Na stearyl fumarate); Bioadhesion increases upon neutralization of AA with Ca^{2+} ions	Ameye et al. (2002)
In vivo, gingiva (dog)	Tablets/9 mm diam./ 30%	γ/18 (before loading)	CLIA: In vivo adhesion time (22 h) and time during which plasma testosterone concentration was above the target 3 ng/ml (13.5 h) are larger in lyophilized and partially netralized irradiated grafted starch than the values in reference formulation, 15.7 h and 11.3 h, respectively;	

[a] *Carriers*: PAA, poly(acrylic acid); A-ProOMe, acryloyl-L-proline methyl ester; HPMA, 2-hydroxypropyl methacrylate; MBAAm, methylene-*bis*-acrylamide; NIPAAm, *N*-isopropyl acrylamide; PDMS, poly(dimethyl siloxane); PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PLA, poly(D,L-lactic acid); PLGA, poly(D,L-lactic-*co*-glycolic acid); VTPDMS, *bis*-vinyl terminated poly(dimethyl siloxane).

[b] *Methods*: CLIA, chemiluminescent immunoassay; DSC, differential scanning calorimetry; GPC, gel permeation chromatography; FTIR, Fourier transform infrared spectrometry; HPLC, high performance liquid chromatography; SP, spectrophotometry; STA, simultaneous thermal analysis (DSC+TGA); TGA, thermogravimetric analysis.

effect of 25 kGy sterilization dose on the API may be prohibitive.

The first guideline specifically focused on radiation sterilization of drugs for parenteral delivery was issued by the Radiation Sterilization Task Force of the Parenteral Drug Association (PDA, 1988). It did not specify sterilization dose but dose setting procedures developed earlier for medical devices and accepted by the Association for the Advancement of Medical Instrumentation (AAMI, 1984) were suggested. The European Guideline 3AQ4a (EEC, 1991), while admitting that 25 kGy dose may be regarded as adequate for sterilization of pharmaceuticals which have a low initial bioburden and no radioresistant spores, had also permitted the use of other doses subject to previous validation. Since the first appearance of the ISO Standard 11137 in 1995 encompassing medical devices, pharmaceuticals, biologics and in vitro diagnostics, all subsequent European, American and international documents will treat dose setting, irrespective of the material to be treated, in accordance with the ISO Standard (ISO, 2006; CFR, 2006).

Several recent important guidelines specifically pertaining to radiation sterilization of pharmaceuticals should be mentioned here:

- Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products was prepared by the Sterility Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee of the Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA, 1994);
- Manufacture of Sterile Active Pharmaceutical Ingredients was prepared by the task group from the Active Pharmaceutical Ingredients Committee (APIC) of the European Chemical Industry Council (CEFIC, 1999);
- Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) supplied its Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96) with an annex comprising Decision Trees for the Selection of Sterilization Methods (CPMP/QWP/054/98). Decision tree for sterilization choices for non-aqueous liquid, semi-solid or dry powder products recommends radiation sterilization as a method of choice second only to thermal sterilization. (EMEA, 2000);
- Guidance document Process Validation: Irradiation Sterilization of Pharmaceuticals was developed by the Health Products and Food Branch of Health Canada (Health Canada, 2001);
- World Health Organization considers sterile pharmaceutical products in a chapter on Quality Assurance of Pharmaceuticals in its Volume 2 of Good Manufacturing Practices (WHO, 2001).

Table 24
The effects of irradiation on controlled drug delivery/controlled drug release systems containing stimulants

Drug/target	Carrier[a]/dosage form/dimensions/ loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Fenethylline hydrochloride/in vitro, pH 7.4	HEMA-co-IA (100:0, 98:2, 96.5:3.5, 95:5) + 0.5 EGDMA (X-linker) hydrogel/ disks/5 mm diam. × 1 mm/ 10%	γ/25/degassed (before loading)	10% burst release within 5 m followed by diffusional release	Gravimetry: • Swelling without IA not pH sensitive; • pHEMA (without IA) not swellable; • Swelling increases more than 3 × with IA and pH increase; • Swelling at pH 7.4 is by Fickian diffusion at all conc. of IA; SP: Release rate increases with IA; Calculation: • Diffusion coefficient of H_2O in the matrix increases with IA; • Diffusion coefficient of drug in the matrix increases with IA	Tomić et al. (2007)

[a] *Carriers*: EGDMA, ethylene glycol dimethacrylate; HEMA, 2-hydroxyethyl methacrylate; IA, itaconic acid.
[b] *Methods*: SP, spectrophotometry.

9. Tabular presentation of radiation effects on CDD/CDR systems containing various therapeutic classes

Comprehensive information on the effects of radiation sterilization on CDD/CDR systems published since 1990 can be found in the tables. The tables are organized according to the therapeutic classes of drugs. Twenty-six therapeutic classes have been the subjects of studies of radiation effects on CDD/CDR systems. Generic (non-proprietary) names of drugs are used, and within a given therapeutic class drugs are organized in alphabetic order. Eighty-five different drugs have been studied. The total number of entries (153) shows that some drugs have been the subject of research more than once. Multiple entries of a drug are ordered chronologically. The nature of the target delivery into which and release from which have been studied is designated by the inscriptions in vivo and in vitro below the name of the drug. In most cases, in vitro release into phosphate buffer solution pH 7.4 or water has been studied (Tables 1–26).

The characteristics of carriers appear in the second column. Ninety-two monomers, polymers, crosslinkers and surface active agents have been used to produce homo- or co-polymers, crosslinked polymers, polymer mixtures or lipidic vesicles for CDD and release. Most often-used dosage form is the hydrogel which has been manufactured as nano- or microparticles or shaped into rods, films, wafers, etc.

Gamma radiation was most extensively used type of radiation; some use was made of electron beam irradiation while only a few studies used X-ray irradiation. Studies with polymeric carriers prepared by radiation polymerization and/or crosslinking before the loading of a drug are marked by "(before loading)". Depending on the applied dose and their bioburden, these carriers would in many cases yield a sterile system if loaded aseptically after irradiation.

The column describing time span of release contains mostly the description of the release profile of unirradiated CDD/CDR systems or the background information on the basic release properties before the changes of the composition, temperature, pH, etc. have been produced by irradiation.

More than 30 physicochemical methods have been employed for the study of the effects of irradiation. Only several studies addressed the effect of radiation on the decomposition of the drug itself. Some of these studies reported no degradation of the drug, whether irradiated within the carrier (Berrada et al., 2005; Stensrud et al., 2000) or in neat form (*in substantia*) (Beyssac et al., 1996). Measurable degradation products only of large polypeptide hormones leuprolide (Shameem et al., 1999) and vapreotide (Rothen-Weinhold et al., 1999) were observed, where the impurities were found to increase with dose, and storage time and temperature, respectively. Almost exclusively the effects on the properties of irradiated integral systems and their influence on drug release have been reported. Very little undesirable effects have been found, so that it might be concluded that, generally speaking, irradiation is a promising means to both sterilize and/or manufacture most of the studied CDD/CDR systems.

10. Concluding remarks

The value of any new drug is determined by the unmet needs and the urgency of the condition it treats. The list of the top 46 pharmaceuticals ("Drugs that changed our world") (Baum, 2005) lists the drugs whose success

Table 25
The effects of irradiation on controlled drug delivery/controlled drug release systems containing vasodilators

Drug/target	Carrier[a]/dosage form/dimensions/loading (% w/w)	Radiation type/dose (kGy)/conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Diltiazem hydrochloride/in vitro (dissolution test)	HPMC $\bar{M}_w$ 70 and 280 kDa/tablets/9.5 mm diam./63.5%	γ/7.5–50/25 °C, air γ/18/77 K, vac.	Time neded for drug release decreases with dose; at constant dose, time is longer at higher $\bar{M}_w$ (higher viscosity)	ESR of powdered drug: ● C–H bond ruptures lead to the formation of benzyl-type radicals, while the addition of H^+ and $H^\bullet$ leads to cyclohexadienyl-type radicals; ● On admission of air peroxyl radicals are formed leading to ring opening and breaking of S–C bonds and formation of perthiyl, sulphonyl and sulphynyl radicals; ESR of HPMC: On annealing from 77 K a sequence of radicals is observed including α-ether type, aldehydic and acyl radicals; HPLC: No degradation observed at 50 kGy; Viscosimetry: ● Viscosity decreases with dose; ● G(chain scission) = 1.2 μmol/J (70 kDa); ● G(chain scission) = 1.4 μmol/J (280 kDa); SP: ● Release profile typical of diffusion; ● Release rate increases with dose, decreases with viscosity; Photomicrography: Erosion of tablets increases with dose, decreases with $\bar{M}_w$	Maggi et al. (2003)
Diltiazem hydrochloride/in vitro (dissolution test)	PEO 2 MDa and 7 MDa/tablets/9.5 mm diam.	γ/7.5, 25, 50/25 °C, air; γ/15/77 K, vac.	Time needed for drug release decreases with dose and $\bar{M}_w$	SP: ● Release from unirradiated tablets controlled by both diffusion and swelling; ● Irradiated tablets dissolve rapidly; Photomicrography: No gel layer formed in irradiated tablets, size rapidly reduced by erosion; Viscosimetry: Viscosity rapidly reduced by dose, larger initial decrease in 7 MDa PEO, common dose dependence of viscosity above 2 kGy; ESR: ● Heating from 77 K to 173 K reveals the presence of $–CH_2CH^\bullet O–$ and $–OCH_2\bullet$ radicals; ● Warming to 298 K reveals the presence of aldehydic radical –O–H–CH(=O)	Maggi et al. (2004)
Diltiazem hydrochloride/in vitro (dissolution test)	PVA (degree of hydrolysis 88.7%)/tablets/9.5 mm diam.	γ/7.5, 25, 50/r.t., air	Complete release within 20 h	SP: Release controlled by diffusion, not affected by irradiation; Photomicrography: ● Outside gel layer formed by swelling; ● No difference between irradiated and unirradiated tablets	

[a] *Carriers*: HPMC, hydroxypropyl methyl cellulose; PEO, poly(ethylene oxide); PVA, poly(vinyl alcohol).
[b] *Methods*: ESR, electron spin resonance; HPLC, high performance liquid chromatography; SP, spectrophotometry.

Table 26
The effects of irradiation on controlled drug delivery/controlled drug release systems containing xanthines

Drug/target	Carrier[a]/dosage form/ dimensions/loading (% w/w)	Radiation type/ dose (kGy)/ conditions	Time span of release	Methods:[b] Effects of irradiation	Reference
Theophylline/in vitro	PEO, $\bar{M}_n$ 35 and 900 kDa and 5 MDa/ hydrogel/membranes/ $1 \times 1\,cm^2$	γ/30, 50, 80, 100/(membrane synthesis)	Linear permeation at 5 ng/s within 4 h	Volumetry: Equilibrium volume swelling ratio increases with PEO concentration in irradiated H_2O solution, decreases with $\bar{M}_n$ and dose; Calculation: Interjunction molecular weight $\bar{M}_c$ decreases with $\bar{M}_n$ and dose; Diffusion: • Partition coefficient 1.03 ± 0.22, decreases with PEO concentration in irradiated H_2O solution; • Diffusion coefficient increases with mesh size, decreases with dose; • However, diffusion of theophylline not affected by irradiation (molecular radius 0.3 nm smaller than mesh size)	Stringer and Peppas (1996)
Theophylline/in vitro and ex vivo (porcine mucosa)	Potato, corn or rice starch-*g*-PAA + 3% PVP (binder) hydrogel/ tablets/9 mm diam. × 4 mm/10%	γ/3.12, 6.24, 18.72 (before loading)	Complete release within 9 h from potato starch-*g*-AA (1:2.5) irradiated with 18.72 kGy	SP: • Complete release from rice starch-*g*-PAA (1:5) within 5 h; • 65% release from (1:12.5) and pure PAA within 10 h (zero-order); • Complete release from corn starch-*g*-PAA (1:5) within 5 h, retarded by cations: $Na^+ < Mg^{2+} < Ca^{2+}$ (Fickian diffusion up to 60% release); • Release kinetics not affected by amylose and amylopectin content of starches and by pH; Gravimetry: Erosion and swelling decreased by ions: $Na^+ < Mg^{2+} < Ca^{2+}$; In vitro bioadhesion: detachment force and work of adhesion increase in potato starch-*g*-PAA (1:5) in the presence of cations: $Na^+ < Mg^{2+} < Ca^{2+}$	Geresh et al. (2004)
In vivo, gingiva (dog)	Potato, corn or rice starch-*g*-PAA + 3% PVP (binder) hydrogel/ tablets/9 mm diam. × 4 mm/10%			Bioadhesion: Adhesion time increases in potato starch-*g*-PAA (1:5) in the presence of cations: $Na^+ < Mg^{2+} < Ca^{2+}$	
Theophylline/in vitro, pH 7.4	HEMA-*co*-IA (100:0, 98:2, 96.5:3.5, 95:5) + 0.5 EGDMA (X-linker) hydrogel/ disks/5 mm diam. × 1 mm/10%	γ/25/degassed (before loading)	10% burst release within 5 min followed by diffusional release	Gravimetry: • Swelling without IA not pH sensitive; • pHEMA (without IA) not swellable; • Swelling increases more than 3 × with IA and pH increase; • Swelling at pH 7.4 is by Fickian diffusion at all concentrations of IA; SP: Release rate increases with IA; Calculation: • Diffusion coefficient of H_2O in the matrix increases with IA; • Diffusion coefficient of drug in the matrix increases with IA	Tomić et al. (2007)

[a] *Carriers*: EGDMA, ethylene glycol dimethacrylate; HEMA, 2-hydroxyethyl methacrylate; IA, itaconic acid; PAA, poly(acrylic acid); PEO, poly(ethylene oxide); PVP, poly(vinyl pyrrolidone).
[b] *Methods*: SP, spectrophotometry.

apparently did not depend on the concept of controlled or targeted administration. This is not surprising given the fact that the success of most listed drugs was already established before the concepts of CDD/CDR were even developed. It should be noted that most drugs today are used by patients with chronic conditions for long periods of time, a situation conducive to the application of CDD/CDR concepts. We may wonder how the list will look after a number of CDD/CDR systems enter into practice. Bearing in mind that the society is willing to pay "the price which is never as high as the cost of managing the same diseases during the earlier stages of no-technology or halfway technology" (Thomas, 1978), we may safely assume that various CDD/CDR systems will certainly figure in some future list. As the needs arise, the increased use of CDD/CDR systems will bring along the increased need for sterile systems, and radiation sterilization shall have its share among the sterilization methods of choice. Extant legal regulations of sterilization of pharmaceuticals are not inhibitory and present no hurdle for the development and application of radiation sterilization. Moreover, the guiding literature is well developed and user friendly. The industry is eager to compensate for the apparent decline of new blockbuster drugs and extend the commercial lifetime of the established drugs with expiring patent protection. The stage is set for radiation manufacturing and sterilization of CDD/CDR systems on an industrial scale.

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