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Medical devices modified at the surface by γ-ray grafting for drug loading and delivery

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Importance of the field: Medical devices with the capability of hosting drugs are being sought for prophylaxis and treatment of inflammatory response and microbial colonization and proliferation that are associated with their use.
Areas covered in this review: This review analyzes the interest of γ-ray irradiation for providing medical devices with surfaces able to load drugs and to deliver them in a controlled way. The papers published in the last 20 years on the subject of γ-ray irradiation methods for surface functionalization of polymers and their application for developing medicated medical devices are discussed.
What the reader will gain: The information reported may help to gain insight to the state-of-the-art of γ-ray irradiation approaches and their current advantages/limitations for tailoring the surface of medical devices to fit preventive and curative demands.
Take home message: Grafting of polymer chains able to establish specific interactions with the drug, grafting of stimuli-responsive networks that regulate drug diffusion through the hydrogel-type surface as a function of the surrounding conditions, and grafting of cyclodextrins that control uptake and delivery through the affinity constant of inclusion complexes have been revealed as efficient approaches for endowing medical devices with the capability of also acting as drug delivery systems.

Keywords: anti-inflammatory drug, antimicrobial surface, drug delivery, gamma-ray grafting, grafted cyclodextrin, medical device, stimuli-responsive polymer

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1. Introduction

Temporary or permanent insertion of medical devices has become an essential part of modern medical care, playing an important role in common diagnostic and therapeutic procedures and in management of critically ill patients [1]. Medical devices should possess properties that match the needs of the intended use. Mechanical behavior, optical properties, conductivity, degradability or chemical stability, which are mainly given by the bulk structure of the material, have to be combined with surfaces capable of dealing with the host body environment. The medical device should elicit the least foreign-body reactions or, if intended to be integrated into the host tissues, induce selective bonding of cells and tissues [2]. Both surface and bulk properties should ensure good performance and biocompatibility (**Figure 1**).

Knowledge of the events occurring at the solid–liquid interface when a medical device is placed in the biological environment is critical for the proper design regarding biocompatibility, functionality and durability [3]. The implantation event itself and the foreign-body nature of the medical devices usually lead to injury,

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Article highlights.

- Medical devices play a key role in common diagnostic and therapeutic procedures.
- Strategies for improving the biocompatibility of medical devices and for preventing inflammatory response and microbial colonization and proliferation are attracting much attention.
- Incorporation of bioactive compounds capable of eliciting or catalyzing a specific response in the host body provides extra therapeutic features.
- Radiation-induced graft polymerization is a convenient and powerful technique for providing materials with three-dimensional polymer networks at their surface, capable of imbibing drugs and delivering them in a controlled way.
- Three main types of γ-ray-induced surface modification have been developed and evaluated for drug delivery: grafting of polymer chains, grafting of stimuli-responsive networks and grafting of cyclodextrins.
- Advanced medical devices with properties carefully tailored for drug delivery can provide remarkable benefits in medical care, minimizing the foreign-body reactions and the risk of infections.

This box summarises key points contained in the article.

inflammation and wound healing response [4]. Local inflammation of the tissues results in redness, swelling and pain on pressure at the insertion site and discomfort of the patient [5]. The dimensions of the medical device, the physical and chemical properties mainly at the surface, and the release of leachable substances determine the intensity and time duration of the (acute and/or chronic) inflammatory and healing processes [6]. As soon as a medical device is inserted or implanted, a race for colonizing its surface starts. In such a race, proteins adsorb onto the material within seconds [7]. Host cells, which include platelets, endothelial cells, fibroblasts and macrophages, and microorganisms also participate in such a race and interact with the adsorbed protein layer as well as the biomaterial, the winner cells hindering the adhesion of those that arrive behind. The initial protein adsorption onto a biomaterial surface plays a key role in which cells colonize the surface and how the body responds to an implanted biomaterial [8]. The adhesion of macrophages and foreign-body giant cells reduces the bactericidal capability of these cells and induces their apoptosis, which contributes to the persistence of infections associated with the use of medical devices [9]. The deleterious effects of adherent inflammatory cells constitute a potential risk for the degradation of the biomaterial and the clinical failure of the medical device [6].

The use of implants and medical devices has become a leading cause of healthcare-related bloodstream infections, which are associated with considerable morbidity and mortality [10-13]. The infections are caused by microorganisms that remain on the medical device after sterilization and/or come from contact with the skin or mucosa of the patient at the moment of insertion [14]. Most nosocomial infections related to the use of intravascular devices are due to coagulase negative staphylococci (40%), *Staphylococcus aureus* (20%) and fungi, particularly *Candida albicans* (10%) [15,16]. If the inocula exceed threshold levels or if the host defenses are impaired, the microorganisms can attach to the surface of the medical device and subsequently form a biofilm [17]. Microbial cells residing in a biofilm (sessile cells) show marked genotypic and phenotypic differences when compared with their planktonic counterparts, including increased antimicrobial resistance [11,18]. The proliferation of microorganisms can result in dissemination to other regions of the host body, provoking bloodstream infections that are particularly dangerous in patients with a compromised immune system [17-19]. If host defense mechanisms and systemic antibacterial chemotherapy are not able to stop the infection, the removal of the device may be required. Nevertheless, in some cases the removal/replacement of the implanted device is associated with significant costs, in both economic and quality of life terms [1,10,11].

Strategies for improving the biocompatibility of medical devices and for preventing inflammatory response and microbial colonization and proliferation are attracting much attention. Biocompatible materials, mainly polymers, should provide a surface that minimizes adverse tissue reactions or, preferably, that mimics a biologic substrate that can guide the healing in a favorable pattern [20]. Incorporation of bioactive compounds capable of eliciting or catalyzing a specific response in the host body provides extra therapeutic features. An example of the benefits of this approach can be found in the already commercialized drug-eluting stents (metal cores coated with a polymeric dispersion of anti-inflammatory or immunosuppressive drugs), which stay open longer and reduce the risk of restenose [20-23]. However, most commercial polymers used for prostheses, meshes, sutures or catheters (e.g., polyethylene [PE], polypropylene [PP], poly(styrene), poly(tetrafluoroethylene) [PTFE], or poly(ethylene terephthalate) [PET]) show poor affinity for bioactive compounds. Therefore, direct soaking inside drug solution does not lead to significant loading. Antiseptics, antibiotics or anti-inflammatory drugs have been physically incorporated in coatings, chemically bonded on the surface or integrally compounded into the material of the device, with the aim of achieving sustained delivery of sufficient amounts of drug [24]. The first two approaches have already been clinically tested, with satisfactory results [25], although coating may undergo premature delamination due to the moisture of the biological environment [2]. Compounding into the matrix may alter the mechanical properties if the amount of drug is high, or may require the use of coadjuvants to regulate the release rate [26].

Alternatives to physical coating or compounding require previous surface functionalization of the polymeric medical device. The nature of the functional groups and their density should be carefully fitted to the characteristics and the amount

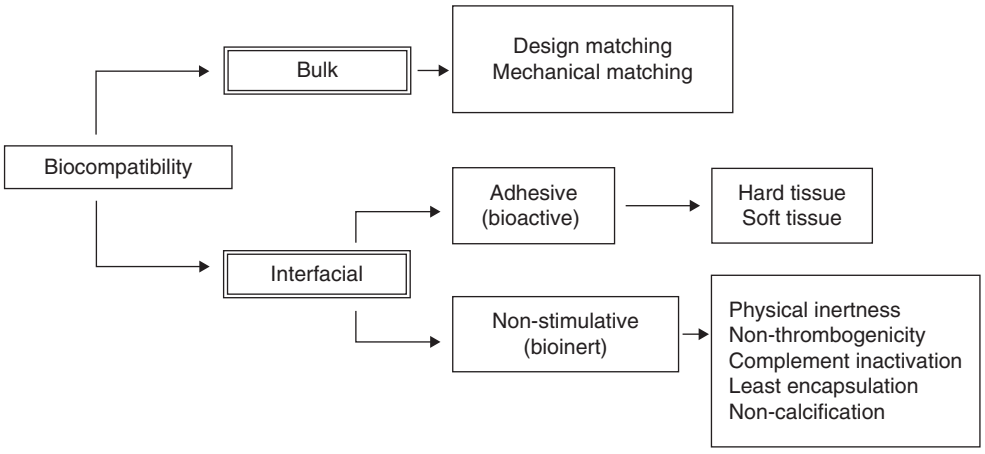

Figure 1. Material biocompatibility depends on the bulk properties (mainly the mechanical ones) and on the capability of the surface to stimulate a physiological response.
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of the bioactive substance to be incorporated. Bioactive compounds can be covalently conjugated to polymeric surfaces or chemically interacting through reversible bonds with the modified surfaces. In the first case, the bioactive is expected to exert its function while attached to the surface; for example, regulating adhesion of cells, bacteria or proteins. In the second case, the bioactive is trapped in a three-dimensional polymer network from which it should be delivered in a controlled way, with the aim of preventing adverse foreign-body reactions or minimizing the risk of infection during insertion. **Table 1** summarizes the most frequently used techniques for functionalizing surfaces [27]. Dry processes using ionizing or UV radiation, low-temperature plasma or ozone gas are effective for almost all polymer substrates because they generate non-selective free radicals or peroxides on the treated surface. The density of active species depends markedly on the substrate polymer and the treatment conditions.

An excellent review of the state-of-the-art of covalent conjugation of bioactive compounds to modified surfaces has been published elsewhere [27]. Next sections focus on recent achievements related to the non-covalent incorporation of bioactive molecules, mainly drugs, on the surface of γ-ray radiation functionalized polymeric medical devices.

2. γ-Ray radiation-induced surface modification

Radiation-induced graft polymerization is a convenient and powerful technique for providing materials with desirable properties for specific applications. This technique does not require the use of catalysts or additives to initiate the reaction [28,29]. Comparative studies have pointed out that modification by gamma irradiation is one of the preferred methods for surface functionalization of polymeric materials because of the uniform and rapid creation of active radical sites, rendering high values of grafting in a clean and rapid way [30,31]. The sterilizing efficiency of the gamma irradiation may also be an extra point to take into account when a medical device is designed. Nevertheless, the downregulation of the dose to avoid polymer damage and the manipulation of the device after the irradiation may mean terminal sterilization of the medical device still needed.

The grafting can be achieved by applying pre-irradiation, pre-irradiation oxidative, or direct grafting methods. In the pre-irradiation method, the polymer substrate is first exposed to ionizing radiation in vacuum or under an inert atmosphere to generate radicals before being exposed to a monomer. Grafting is initiated by macroradicals trapped in the irradiated polymer, and homopolymerization does not occur. The disadvantages of this method are: i) the polymer matrix may degrade because the dose is high; ii) the grafting yield depends strongly on the reaction temperature and on the crystallinity of the polymer; and iii) the degree of grafting is lower compared with the two other approaches. The pre-irradiation oxidative grafting method consists of first irradiating the polymer in the presence of air or oxygen, which leads to either hydroperoxides or diperoxides. In a second step the polymer enters in contact with the monomer to initiate the grafting reaction. The irradiated polymer is heated (in the absence of air) and the peroxides decompose to give macroradicals that are the active sites for graft polymerization (**Figure 2**) [32].

In the direct or simultaneous method, the polymer substrate is immersed in a monomer-solvent mixture, which may be liquid or vapor and may contain additives. Irradiation produces active sites in the polymer matrix, mainly macroradicals, which can initiate the graft polymerization but also the homopolymerization of the monomer (**Figure 3**). This last event is an untoward side reaction. As polymer

Table 1. Relevant techniques used for modifying polymer surfaces with chemical groups that reversibly interact with drug molecules or that serve as precursors for the conjugation of drug molecules.

Technique	Procedure	Advantages	Disadvantages	Ref.
Wet chemical	The material is treated with liquid reagents to generate reactive functional groups (mainly oxygen-containing moieties) on the surface	Does not require specialized equipment Better penetration into pores than plasma and other techniques	Nonspecific. A range of oxygen-containing functional groups is generated. Extended treatment in concentrated corrosive solution. Hazardous waste	[82-84]
Silane monolayers	Treatment of surfaces with oxygen plasma, followed by chemical vapor deposition of the silane Different end functionalities can be obtained	Enables the coupling of an organic polymer to inorganic substrates or to hydroxylated polymer surfaces	The siloxane linkage can be hydrolyzed at high temperatures or alkaline pH	[85-87]
Plasma	A gas is partially ionized into charged particles and electrons. Provides modification of the top nanometer of the surface, generating hydroxyl, carboxyl or amine groups	No solvents. No chemical waste. Less degradation and roughening of the material	Many parameters (time, temperature, power, gas composition/flow/ pressure, distance to plasma source) affect the yield. High inter-lab variability	[88-95]
Corona discharge/ flame treatment	A stream of ionized air bombards the polymer surface and generates oxidation products	Low cost. Continuous process	Unstable surface polar groups	[96,97]
UV irradiation	Reactive sites generated by radiation can become functional groups on exposure to gas or can initiate graft polymerization	The penetration of the functionalization can be tuned by varying wavelength	Risk of modifying the optical properties of the polymer	[98-102]
γ-Ray irradiation	Direct irradiation of the polymer in contact with a monomer or pre-irradiation in an inert atmosphere or in the presence of air or oxygen, followed by immersion in a monomer solution	Versatile grafted structure. No high temperature. Useful in large-scale processes	Homopolymerization	[103,104]

degradation requires higher absorbed doses than the grafting process, it is possible to perform direct grafting under controlled conditions without significant damage of the substrate.

3. Non-covalently loaded drugs on radiation-functionalized materials

Non-covalent incorporation of drugs requires the previous formation of a sponge-like or a hydrogel-type layer on the surface of the device, where the drug molecules can be effectively hosted and retained and from where they are released in a controlled way once in contact with the biological fluids. Grafting of polymers with functional groups capable of interacting with the target drug molecules is being explored intensively for this purpose. Depending on the chemical structure of the polymer that serves as a substrate and the monomers that are going to be grafted, different performances can be achieved.

3.1 Surface functionalization with polymers

As early as in 1986 the vascular prosthesis of PET yarn was modified with acrylamide by deposition of a monomer solution followed by γ-ray irradiation, increasing surface hydrophilicity and thus making it non-thrombogenic. The aim was to combine the good biocompatibility of polyacrylamide hydrogels with the high mechanical properties of PET [33]. This approach was later used to make medical devices more lubricating and less thrombogenic [34].

Gamma radiation has progressively attracted interest as a way to create adequate surfaces for the loading of antimicrobials. Medical grade black braided silk suture and pure mulberry silk twisted yarn have been grafted with methacrylic acid (MAA) by immersion in 20 vol.% monomer solution and γ-ray irradiation for several hours. Irradiation generates free radical sites along the protein chain (fibroin) of silk by the abstraction of hydrogen from secondary carbon atoms, that is, from α-alanine. The grafting of MAA is initiated from these sites. Silk-*g*-MAAs were immersed in 0.5% aqueous sodium

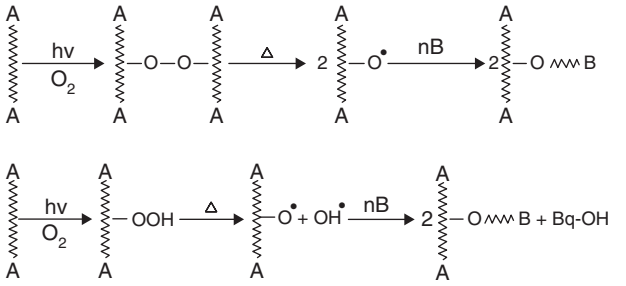

Figure 2. Scheme of a radiation grafting using the pre-irradiation method.

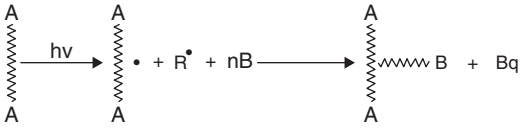

Figure 3. Scheme of a radiation grafting using the direct method.

hydroxide solution for 4 h to convert the carboxylic acid groups to sodium carboxylate, in order to facilitate the loading of 8-hydroxy quinoline (8-HQ) hydrochloride by immersion in a 15% drug aqueous solution. The percentage of 8-HQ immobilized increased from 2.5%, for unmodified silk to 25.2% for silk-*g*-MAA with a grafting degree of 88%. The release of the drug in water was sustained for 32 days (**Figure 4**). These silk-*g*-MAA materials loaded with 8-HQ were found to be active against *Escherichia coli*, *S. aureus* and *Pseudomonas aeruginosa* [35]. 8-HQ has also been successfully incorporated to 2-hydroxyethyl methacrylate (HEMA)-grafted PP monofilaments (7.5% drug in 65% grafted pHEMA); the sutures showing sustained delivery in water for 4 days [36]. Nevertheless, it should be noted that the grafting notably deteriorates the strength of the sutures. Thus, an adequate balance between drug loading and maintenance of mechanical properties should be achieved for the suture to be of practical interest.

The graft polymerization of 1-vinylimidazole (VIm) and of acrylonitrile onto PP monofilaments using the simultaneous radiation grafting method (dose rate 0.27 kGy/h) has been explored for preparing sutures medicated with ciprofloxacin or tetracycline hydrochloride, respectively. PP-g-VIm sutures were more hydrophilic but also more brittle than PP because, as the grafting increases, the chains in the amorphous region are pushed apart [37]. PP-*g*-VIm was immersed in 15% ciprofloxacin hydrochloride solution. This drug has broad antimicrobial spectrum and is capable of binding with the protonated nitrogen atoms of the modified suture. Ciprofloxacin release from 12% grafted PP sutures (containing 60 mg/g) was sustained in phosphate buffer pH 7.4 for at least 90 h [38]. Grafting of acrylonitrile on PP sutures followed by hydrolysis rendered carboxylic groups available for interacting with tetracycline hydrochloride [39,40]. The maximum conversion of nitrile groups into carboxyl groups was limited to 62% and led to sutures with carboxyl content ranging from 0.042 to 0.25 mmol/g [41]. Tetracycline loadings of 0.5 – 3% were achieved for sutures with a degree of grafting ranging from 2 to 8%. Once immersed in water, the sutures delivered most drug in the first 24 h, and an exponential decrease in the release rate was observed in the following days [42]. *In vitro* microbiological tests using *E. coli*, *K. pneumoniae* and *S. aureus* did not give evidence of an inhibited zone around the unmodified suture, which was completely surrounded by the colonies of bacteria. By contrast, clear inhibition zones were observed around the tetracycline-loaded sutures (**Figure 5**). The resistance of sutures to infection was also tested *in vivo* on albino rats. The sutures were stitched near vertebral column and *S. aureus* (10^4 – 10^6 bacteria) was injected at the implantation site. Those sutures loaded with 8-HQ or tetracycline were capable of inhibiting the bacterial growth even after the fourth postoperative day. Tissue compatibility was not altered by the surface modification of the sutures.

Antimicrobial surfaces have been also prepared by immobilization of silver ions on PP fabrics previously grafted with acrylic acid (AAc) by a pre-irradiation method (5.9 kGy/h). The silver ions provided biocidal features to the fabric for being used as an air filter. Compared with other ions (Fe^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+} or Co^{2+}), silver was the only one capable of inhibiting the growth of *E. coli*, *P. aeruginosa* and *S. aureus* (**Figure 6**) [43].

3.2 Surface functionalization with multistimuli-responsive networks

In the field of drug delivery there is long experience of preparing smart hydrogels for achieving controlled release [44,45]. On the other hand, grafting of stimuli-responsive polymer chains has been studied for many years as a way to regulate the hydrophilicity of the surface and the adhesion of cells to polymeric surfaces as a function of environmental variables [46]. Implementation of surface functionalization with stimuli-responsiveness has been explored recently for preparing drug-eluting medical devices with already promising results.

PP and PE endowed with temperature and pH-responsive swelling by grafting sensitive components [47-49] have been developed recently for improving vancomycine loading and release behavior [50]. Vancomycin is one of the most frequently chosen antibiotics for the treatment of methicillin-resistant *S. aureus* (MRSA) infections associated with the use of catheters [51]. For a rational surface functionalization, monomers for interacting with the drug were screened by isothermal titration calorimetry (ITC), AAc sodium salt being the most successful [52,53]. Three sets of surface-functionalized PP films were prepared: i) one having crosslinked poly(acrylic acid) (PP-*g*-PAAc) to achieve specific binding; ii) another with crosslinked poly(*N*-isopropyl acrylamide) (PP-*g*-PNIPAAm) to test the effect of the volume phase transition on drug loading and release; and iii) the third set having

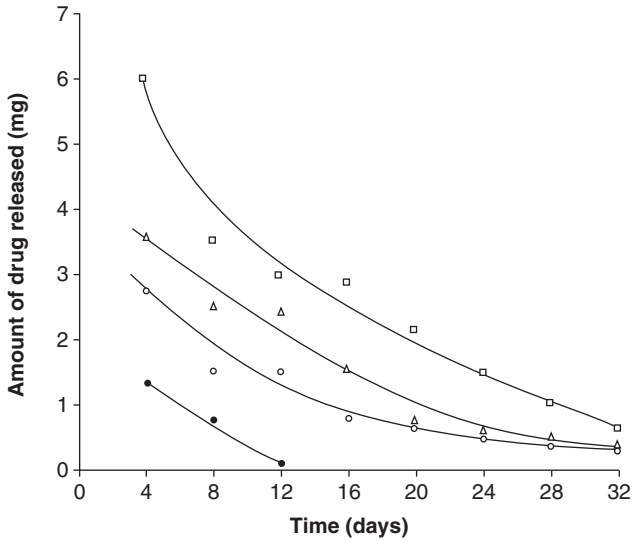

Figure 4. 8-HQ release profiles from ungrafted silk loaded with 2.5% drug (●), silk with 42% degree of grafting and 10.3% drug (○), silk with 63% degree of grafting and 15.2% drug (△), and silk with 88% degree of grafting and 25.2% drug (□).
Reproduced with permission from [35].

Figure 5. Zone of inhibition against *K. pneumoniae* (a) control PP suture and (b) drug-loaded PP suture (acrylonitrile degree of grafting (5%).
Reproduced with permission from [42].

interpenetrating networks (IPNs) *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc for combining the two mechanisms of action. The IPNs were synthesized by first pre-irradiating PP with a ^{60}Co γ-source, followed by immersion in a NIPAAm solution to lead to grafting and crosslinking of NIPAAm onto PP, and then interpenetration of the second network by redox polymerization and crosslinking of AAc. The *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc was dually responsive (**Figure 7**).

Immersion of the surface-functionalized PP films in vancomycin aqueous solutions (0.4 mg/ml) revealed that grafting with crosslinked PNIPAAm leads to 1 – 2 mg vancomycin loaded per gram, mainly hosted in the aqueous phase of the network. The drug loading increased remarkably (ranging from 25 to 75 mg/g) with the content in PAAc on surface. It is important to note that the PP-*g*-PAAc films were previously swollen in pH 7.4 phosphate buffer to enable the ionization of the AAc groups. PP-*g*-PAAc films were able to take up almost all drug present in the loading solution, avoiding any waste of non-sorbed drug. The *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc showed a synergistic loading. At the loading conditions (20ºC), the PNIPAAm network is completely swollen and forces the PAAc network to expand. This facilitates the contact of the drug with the acrylic acid groups and also enhances the volume of aqueous phase entrapped in the IPN. Vancomycin release was sustained for 8 h in pH 7.4 phosphate buffer owing to the strength of the drug–PAAc interactions, which are at maximum when the acrylic acid groups are ionized. The *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc maintained their ability to uptake and to sustain the release after four cycles of loading/release. From the point of view of the efficiency of the vancomycin-loaded PP films to kill bacteria attempting to adhere to a catheter-type device surface, the 'instantaneous' release rate per surface area (ARR) is a critical parameter [54]. The minimum required flux of vancomycin that must be delivered to the near-wall zone of PP films to kill *Staphylococcus* spp. (N_{kill}) is $3.5 \cdot \times 10^{-3}$ μg/(cm^2·s). The films that combine a high loading with sufficient ability to sustain the release at pH 7.4 provided ARR values above the N_{kill} for at least 6 h. The eradication of bacteria during the early period following implantation is critical to prevent the development of biofilm on catheters and implants [55,56].

The effectiveness of the vancomycin-loaded PP disks at inhibiting MRSA biofilm formation was demonstrated using the Modified Robbins Device (MRD) [57]. Disks were subjected to 1 h of adhesion and 24 h of biofilm formation under a continuous flow of fresh growth medium. This not only creates ideal conditions for microbial growth (as nutrients are constantly provided to the bacteria and waste products are removed) but also prevents accumulation of vancomycin in the reactor because any drug released from the disks is immediately washed away, effectively reducing the contact time between the sessile bacteria and the vancomycin. This is in contrast to static biofilm model systems (e.g., microtiter plates) in which the released vancomycin could accumulate. The vancomycin-loaded PP films showed a much reduced likelihood of biofilm formation by MRSA, even under the unfavorable conditions of the test.

The surface functionalization with *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc was later optimized by applying γ-ray irradiation in every step of the synthesis: i) graft copolymerization of PNIPAAm onto PP films using the pre-irradiation oxidative method; ii) crosslinking of PP-*g*-PNIPAAm by

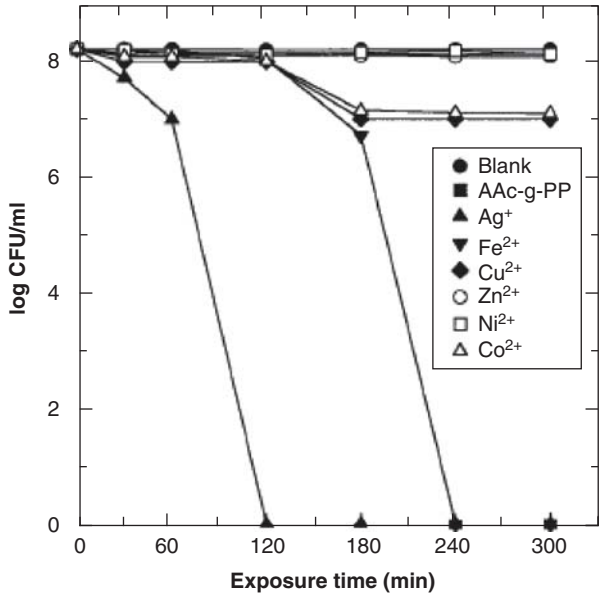

Figure 6. Evolution of viable cell number of *P. aeruginosa* in fabrics of PP grafted with acrylic acid and loaded with different ions, after being immersed in a solution with 10^8 cells/ml.

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irradiation in water to form the first network, with or without *N*,*N*′-methylenebis(acrylamide); and iii) formation of the second network through the polymerization and crosslinking of AAc inside crosslinked PP-*g*-PNIPAAm using a low radiation dose of 2.5 kGy [58]. These *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc films were more lubricating than pristine material, loaded up to 94 mg/g of IPN and sustained the delivery for several hours at pH 7.4 phosphate buffer. Therefore, grafting of PP with AAc or IPNs of PAAc and PNIPAAm enables the tuning of the amount of vancomycin loaded as well as the drug release rate and may have a great potential to prevent infections associated with the use of biomedical devices.

3.3 Surface functionalization with cyclodextrins

Functionalization with cyclodextrins (CDs) provides polymeric materials with the capability of loading at their surface any drug capable of forming inclusion complexes. CDs are non-toxic cyclic oligosaccharides composed of 6 – 12 D-(+)-glucopyranose units linked by α-(1 – 4) bonds, which can host molecules able to fit completely or partially into the cavity [59,60]. The relatively weak interaction forces involved in the complex formation enable hosted molecules within the CDs to be in rapid equilibrium with free molecules in solution [61-64]. CD–drug complex formation in aqueous media is commonly used to increase the apparent solubility of hydrophobic drugs up to many orders of magnitude above the solubility coefficient of the guest alone in water [65]. A high local proportion of CDs on the surface of the medical device can create a favorable microenvironment for the uptake of the drug. The drug–CD affinity constant may determine the amount loaded as well as the delivery rate when entering into contact with the physiological medium, as observed for hydrogels made with CDs [66-69].

Several approaches to functionalize the surface of medical devices with CDs have been developed: i) thermofixation of CD units on the surface of vascular polyester prostheses by impregnation with an aqueous solution of CDs, catalyst and citric acid, roll-squeezing and curing at 140 – 190ºC for a variable time [70]; ii) polymer blending by melting of mill rolls containing CDs and poly(vinyl chloride) and compression at 150ºC for 5 min [71]; and iii) pulsed plasma polymerization for the grafting of GMA onto inorganic substrates or textiles in order to load them with odorizants or antifungal agents or to be used as reactive filters [72,73]. The first two approaches have been shown to be useful to enable the loading of vancomycin and to reduce adhesion of epithelial cells and proteins, but have the drawback of requiring high temperatures to proceed, which may alter the bulk properties of many materials. At present, pulsed plasma polymerization allows only low-scale functionalization.

Recently, γ-ray irradiation has been applied for this purpose. PE and PP were surface-functionalized with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) according to a two-step procedure: grafting of glycidyl methacrylate (GMA) onto pre-irradiated substrates; and reaction of epoxy groups of GMA with hydroxyl groups of β-CD and HP-β-CD forming ether bonds (**Figure 8**) [74]. The greater the yield of GMA grafting, the higher the amount of CD attached to PE and PP (ranging from 0.013 to 0.734 μmol/cm^2). CD-functionalization did not modify wettability and friction coefficient. Both pristine and CD-functionalized films withstood autoclaving without prejudice of their features and were highly cytocompatible, with cell viability > 95% [75].

A low degree of functionalization was sufficient to enhance the capability of PE and PP films to take up diclofenac and to sustain its delivery for 1 h in pH 7.4 phosphate buffer, which could be useful for management of initial pain and inflammation at the insertion site as well as for preventing adhesion of certain microorganisms (as observed for diclofenac-loaded contact lenses [76]) if these materials are used as medicated medical devices [75].

Miconazole is a quite hydrophobic drug endowed with a powerful activity against dermatophytes and *Candida albicans* [77]. The fact that fungal biofilm formation was only recently described [78] notably hindered the development of approaches for preventing fungal colonization of medical devices [79]. Surface functionalization with β-CD or HP-β-CD led to remarkable loadings of miconazole when immersed in saturated aqueous solutions of miconazole nitrate, providing PE and PP with an antifungal surface while maintaining their favorable mechanical properties. The capability of the miconazole-loaded device to prevent *C. albicans* biofilm formation, tested using the MRD biofilm model system, was very remarkable, that is, PE-*g*-GMA-βCD, PE-*g*-GMA-HPβCD

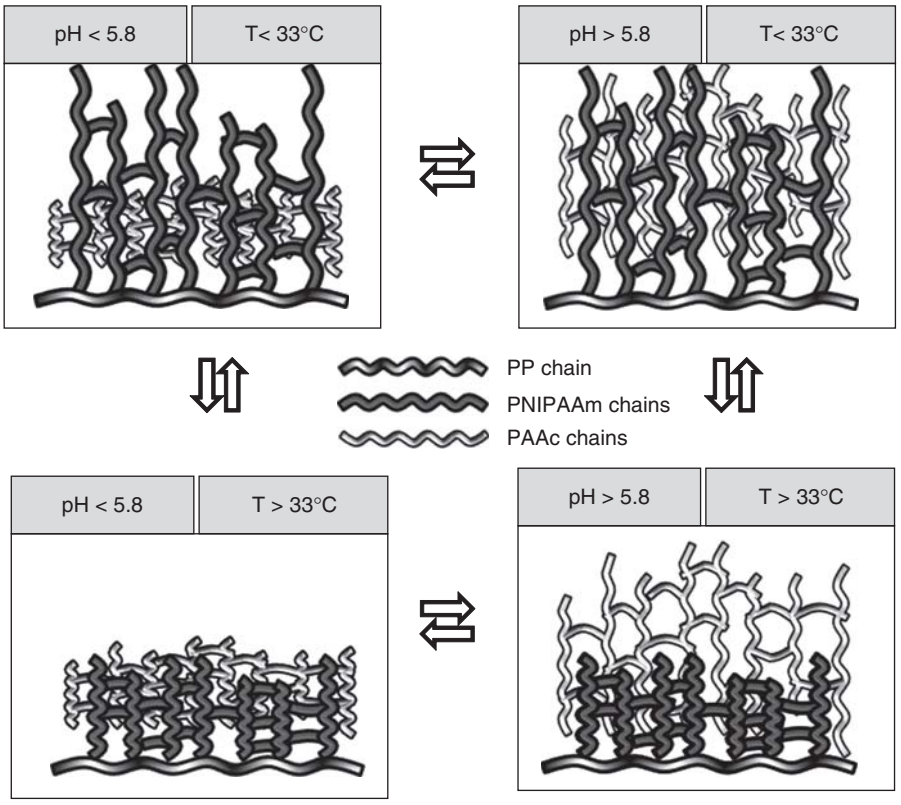

Figure 7. Scheme of the dual temperature- and pH-responsiveness of *net*-PP-*g*-PNIPAAm-*inter-net*-PAAc.
Reproduced with permission from [58].

or PP-*g*-GMA-HPβCD contained 96, 97 and 87% less sessile cells than the silicone controls. These findings indicate that miconazole is released from the CD cavities in the active form, resulting in a significant reduction in *C. albicans* biofilm formation [80].

Surface functionalization with β-CD or HP-β-CD may also inhibit specific and nonspecific interactions responsible for the initial adherence of the microorganisms [81]. In contrast to unmodified PE and PP, which adsorb significant amounts of fibrinogen (~ 0.047 mg/cm^2) but not albumin, the CD-modified polyethers promoted the adsorption of albumin (between 0.015 and 0.155 mg/cm^2) and completely prevented the adsorption of fibrinogen [80]. Thus, the strategy of functionalization with CDs may be suitable to fight against microorganisms on two different fronts: (i) prevention of colonization through a modified adsorption profile of host proteins; and (ii) inhibition of proliferation through the loading and release of miconazole.

4. Expert opinion

Advanced medical devices with properties carefully tailored for drug delivery can provide remarkable benefits in medical care, minimizing the foreign-body reactions and the risk of infections. Despite progress in this field, the development of materials suitable for the production of sutures, catheters and implants able to take up sufficient amount of drug and to provide a local delivery at the appropriate rate is still a challenging task. Surface functionalization of preformed medical devices may endow the devices with affinity to the drug while keeping the original bulk properties. The surfaces should be tailored to the features of each drug. Identification of functional groups or chemical structures able to interact with a specific drug and elucidation of the effect of environmental variables on the strength of the binding are key points for the correct design of the functionalized surface. Isothermal titration calorimetry is particularly useful for evaluating ionic and hydrophobic interactions and inclusion complex formation, which are mechanisms involved in the permanence of the drug on the device surface. Although so far tools for rational design have seldom been applied, it is foreseeable that in the near future they may contribute to optimizing grafted materials and to widening the use of the medicated medical devices, leading to a decrease in health complications.

γ-Ray irradiation is a versatile technique from the point of view of both the substrates to be functionalized and the nature and structure of the components to be grafted on the surfaces. This technique does not require the use of any initiator, catalyzer or other additives, minimizing the presence of residual substances after grafting. Three main types of

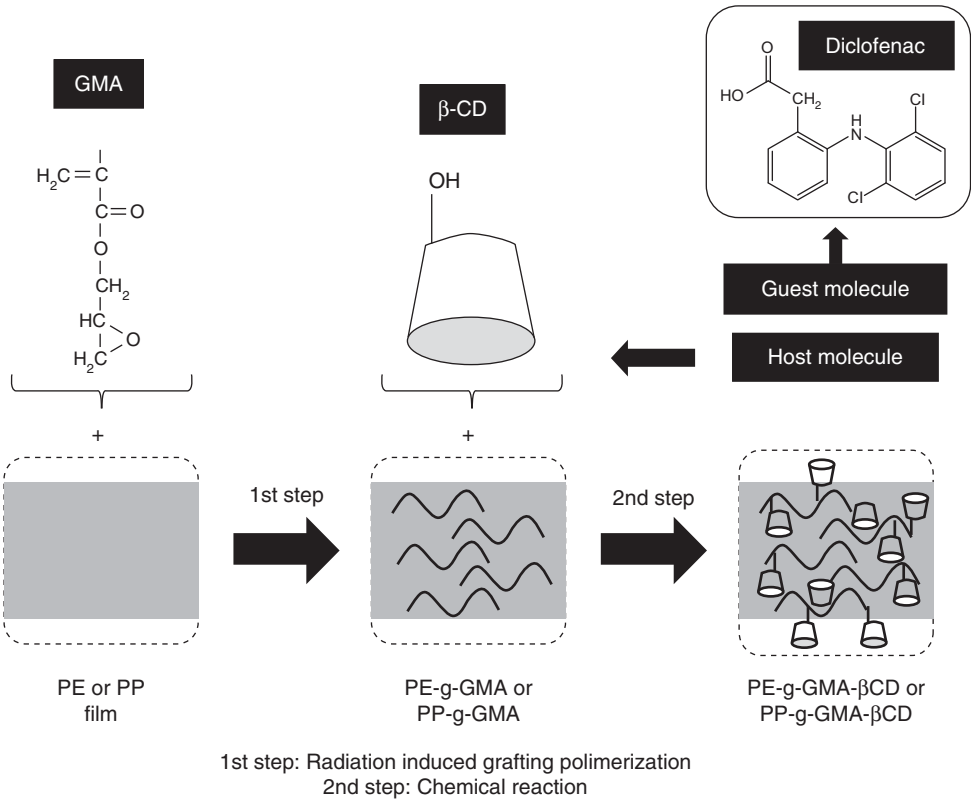

Figure 8. Steps followed to functionalize PE and PP surfaces with cyclodextrins.
Reproduced with permission from [75].

γ-ray-induced surface modification have been developed and evaluated for drug delivery: grafting of polymer chains, grafting of stimuli-responsive networks and grafting of CDs. Functionalization with polymers containing groups capable of interacting with specific drugs, mainly through electrostatic interactions, is useful for creating antimicrobial sutures and fabrics. Grafting of networks sensitive to temperature and pH maximizes the loading of the drug at laboratory conditions and enables a precise delivery once inserted in the body. The structure of the network resembles that of a hydrogel in which the drug can be hosted not only physically dispersed in the mesh, but also specifically interacting with chemical groups of certain monomers (e.g., vancomycin and acrylic acid sodium salt). Temperature-sensitive polymers that shrink at physiological temperature provide slow release, leading to sustainedly efficient drug levels in the surroundings of the medical device. pH-sensitiveness may endow the material with the possibility of selective delivery as requested by the conditions of the environment, for example, the growth of microorganisms. Grafting of CDs enables the hosting of quite hydrophobic drugs, which are loaded and released as a function of the affinity constant of the complexes. CD-grafted materials have been shown to be adequate for loading therapeutic doses of anti-inflammatory drugs, such as diclofenac, and antimicrobial agents, such as miconazole. Medical devices with antimicrobials non-covalently loaded at their surfaces have already proved capable of preventing the development of biofilm-related infections, avoiding the systemic collateral effects of high doses of antibiotics and overcoming concerns on bacterial resistance. Furthermore, most of these functionalizations provide extra benefits in terms of biocompatibility, lubricity and protein adsorption.

In sum, grafting by γ-ray irradiation is a suitable technique for providing polymeric medical devices with the capability of acting as drug delivery systems.

Declaration of Interest

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