Health Care-Associated Infections: Controlled Delivery of Cationic Antiseptics from Polymeric Excipients

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Abstract

Nowadays, the treatment of health care-associated infections represents a serious issue, due to the increasing number of bacterial strains resistant to traditional antibiotics. The use of antiseptics like quaternary ammonium salts and biguanides is a viable alternative to face these life-threatening infections. However, their inherent toxicity as well as the necessity of providing a sustained release to avoid the formation of pathogen biofilms are compelling obstacles towards their assessment in the hospitals. Within this framework, the role of polymeric drug delivery systems is fundamental to overcome the aforementioned problems. Biocompatibility, biodegradability and excipient-drug interactions are crucial properties determining the efficacy of the formulation. In this work, we provide an in-depth analysis of the polymer drug delivery systems that have been developed or are under development for the sustained release of positively charged antiseptics, highlighting the crucial characteristics that allowed to achieve the most relevant therapeutic effects. We reported and compared natural occurring polymers and synthetic carriers to show their pros and cons and applicability in the treatment of health care-associated infections. Then, the discussion is focused on a particularly relevant class of materials adopted for the scope, represented by polyesters, which gave rise, due to their biodegradability, to the field of resorbable drug delivery devices. Finally, a specific analysis on the effect of the polymer functionalization over the formulation performances for the different types of polymeric carriers is presented.

Keywords: Health care-associated infections; Cationic antiseptics; Polymeric drug delivery systems; Controlled delivery; Sustained release.

1. Introduction

In the recent years, biocompatible polymers attracted an increasing interest for the production of drug delivery devices, stimulated by the wide range of thermomechanical and physico-chemical properties accessible with these materials. Biodegradability, tunable mechanical properties and easiness of functionalization are attractive characteristics for the application of these materials to various clinical treatments[1–3]. Among them, an emerging field of application is represented by the sustained release of antiseptic compounds for the treatment of health care-associated infections (HCAIs)[4].

HCAIs are pathologies that cause long hospital stays, high morbidity and mortality risk, development of antibacterial resistant microorganisms and additional costs for the health system, specifically for intensive health care units[5,6].

The systemic literature review of national and multicenter studies in high-income countries published by the Word Health Organization (WHO) presents a HCAI prevalence value, which refers to the hospitalized patients who acquired at least one HCAI, ranging from 3.5% to 12%[7]. In order to clarify the implications of those values, according to the European Centre for Disease Prevention and Control (ECDC), every year in Europe more than 4 million people are affected by HCAI, accounting for direct costs of approximately € 7 billion[8]. Among these, surgical site infections (SSIs), the category in which the pathogen is acquired during the surgical procedure, deserve significant attention being the second most reported HCAIs in Europe and in United States, as well as the most frequent in low- and middle-income countries[5,9–13].

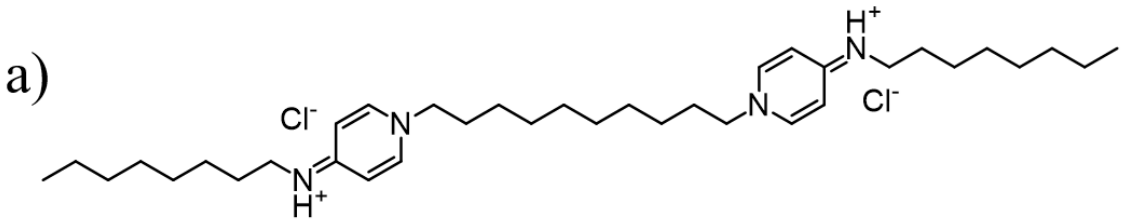
The main cause of this phenomenon is the abuse and misuse of antibiotics done by the society in the past decades. Indeed, these are among the most prescribed medicines in human history, with an estimation of 50% of unneeded prescriptions[14]. Consequently, this pushed the microbial evolution towards the spreading of resistant strains[15]. As a matter of fact, in the last decades, *Staphylococcus aureus* developed the resistance against methicillin (MRSA) first and then against vancomycin (VRSA)[16,17]. *Staphylococcus epidermidis* also showed an increased number of strains resistant to riphampicin[18]. It is then evident that antibiotics are progressively losing their reliability in the fight against these strains[19]. The situation is worsened by the fact that the total amount of antibiotics intended for human use is outnumbered by that used by food industries, which contribute significantly to antibiotic resistance, as animals serve as carriers for the development of drug-resistant strains[14,20].

In this context, the choice of antiseptics as therapeutics for topical application is gaining an increasing interest in order to reduce the use of antibiotics and promote an efficient treatment of resistant strains. The positive outcome of the antiseptic-based treatments relies on the careful control of the dosage. In fact, the antiseptics, unlike antibiotics, do not work on specific cellular pathways but rather exert their toxicity on membrane efflux pumps, intracellular and nuclear functions, thus presenting a broader spectrum of activity[21–23]. A wide range of active chemical agents, known as biocides, including biguanides, bisphenols, halogen-releasing agents, heavy metal derivatives and quaternary ammonium compounds may be present in antiseptic products[24]. Among them, this review is focused on the formulation of two interesting classes of positively charged compounds, namely quaternary ammonium compounds (QAC) and biguanides[25–28].

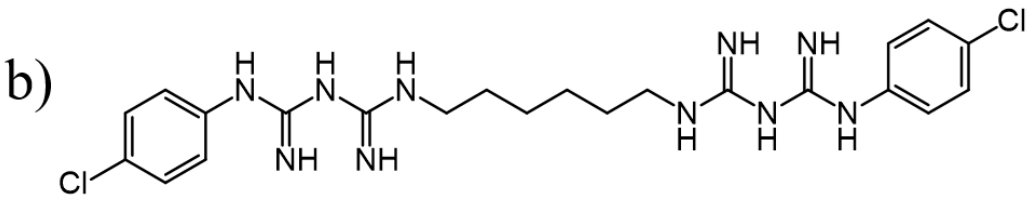
Their efficacy against a specific bacterium is expressed in terms of Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC), which represent the minimal concentration required to inhibit bacterial growth or to kill bacteria, under *in vitro* conditions, respectively[29].

In particular, QACs are broad-spectrum antibacterial agents applied in medical, industrial and household contexts. Their general structure comprises a positively charged nitrogen “head”, linked to alkyl chains of different lenght[24]. QACs tend to be quite stable and water-soluble compounds. In solution, ionization results in the production of a cation, the substituted nitrogen part, which provides surface activity. They are characterized by an amphiphilic behavior provided by a polar head group and hydrophobic hydrocarbon chains, resulting in a detergent-like mechanism against microbes[24]. Being the electrostatic interaction the driving force for non-specific binding, QACs present an inherent toxicity also to mammalian cells. Indeed, their toxic effects are hampering their use for systemic applications, which would necessitate a careful control on the amount of drug administered. However, they are widely accepted for topical applications[30]. Among them, octenidine dihydrochloride (OCT) is one of the most used in the treatments for skin, mucous membrane and wound management decolonization[31]. It is a cationic surfactant bearing two cationic centres separated by a long aliphatic C10 chain, as shown in **Figure 1a**. OCT is effective against both Gram-positive and Gram-negative bacteria (e.g. *S. aureus*, *E. coli*), fungi, yeasts, dermatophytes, enveloped viruses and echinococcal cysts and no resistance is known yet[31,32].

Regarding biguanides, these are naturally occurring cations that generally exhibit antibacterial activity against Gram-positive and Gram-negative microorganisms[33]. Among these, chlorhexidine (CHX) is a widely applied therapeutic due to its broad-spectrum efficacy, substantivity properties and low irritation. It is present in a wide range of products to prevent infections, such as preoperative skin cleansing, surgical site preparation and personal hand antiseptic products. Specifically, CHX is a chlorinated biguanide that is present as bis-cation at physiological pH, as shown in **Figure 1b**[34]. CHX positive charge is capable of interacting via non-specific binding with the phospholipid membrane of the negatively charged bacteria, causing a damage in the outer layers of the cell[35,36]. Despite advantages such as a wide antimicrobial spectrum and substantivity, CHX activity is pH dependent. Moreover, *in vitro* studies have demonstrated that CHX, as many commonly used antiseptics such as OCT and povidone-iodine, presents specific dose-dependent and time-dependent cytotoxicity profiles on fibroblasts, myoblasts, and osteoblasts[37–40].



Octenidine dihydrochloride



Chlorhexidine

Figure 1: *Chemical structure of (a) octenidine dihydrochloride and (b) chlorhexidine.*

In this frame, it is worth mentioning also that for the antiseptics used in postoperative wound management, generally the treatment is considered successful if it is able to provide antimicrobial activity in a time window within 2 to 6 weeks[41]. In order to pursue this prolonged effect as well as to avoid potentially dangerous drug concentration peaks, drug delivery systems able to slowly release the antiseptic during time are extensively researched. Among these systems, those based on polymeric materials are the most appreciated in terms of tunable properties and versatility. Different antiseptic formulations based on polymer excipients have been developed, with some of them already applied in the clinics. Given their importance in favoring the applicability and diffusion of the antiseptics among the patient population, a systematic analysis of the requisites and characteristics for a successful polymeric drug carrier able to modulate the release of biocides is urgently required.

This review is intended to specifically describe the polymeric drug delivery systems able to efficiently encapsulate and release CHX and OCT as positively charged antiseptic compounds, focusing on the critical attributes enabling to maximize the therapeutic index of these antiseptics. A review and critical comparison of natural and synthetic polymers used as drug carriers is performed, with particular emphasis to polyesters, which due to their biocompatibility and biodegradability gave rise to the important family of resorbable devices. Finally, the most studied and efficient polymer

functionalization strategies able to enhance the therapeutic index of the drug by slowing down its release and to minimize the number of repeated administrations as well as concentration-related side effects are described.

2. Sustained Release of OCT and CHX

The pharmacological treatment of diseases is traditionally based on multiple dosing of a therapeutic agent specifically formulated (i.e., tablets, capsules, and injections) in order to maintain the drug concentration in the addressed site within a given therapeutic window. Regarding antiseptics, following the traditional administration approaches, which consist typically in saline or water and alcohol solutions and lotions, a large amount of drug is released in a short period as shown in **Figure 2** (blue curve)[42]. This determines a significant fluctuation in the drug concentration, leading to the necessity for repeated administrations as well as to difficult control over the instantaneous drug concentration, which may cause adverse reactions for the patient[43].

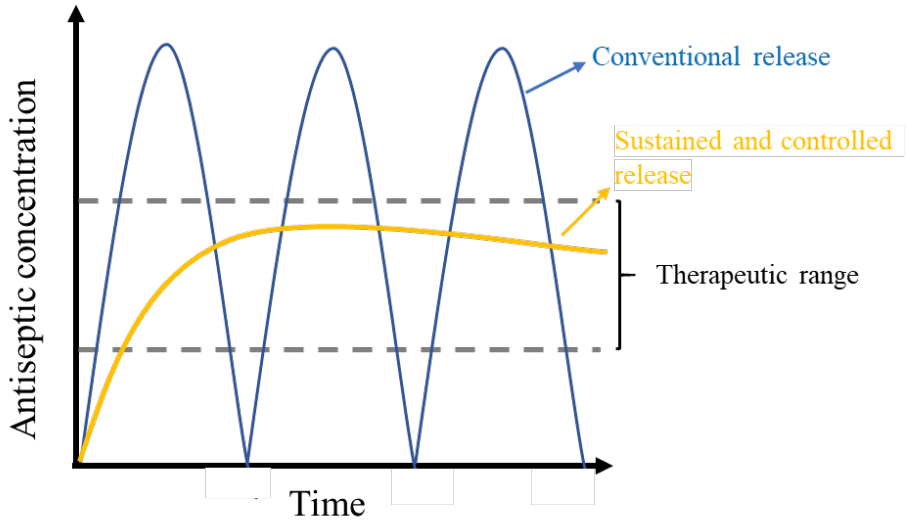


Figure 2: General antiseptic concentration profile in the targeted area for a conventional drug administration, consisting in a in situ antiseptic administration after the surgery, with respect to a sustained and controlled delivery.

These problems may be effectively overcome by the use of controlled drug delivery systems, releasing the active principle slowly during time, thus allowing a better predictability and reproducibility of its concentration in the targeted area. Due to this higher control, an overall reduced amount of active principle in the final formulation is often required, together with less administrations, leading to an improved compliance for the patient[44,45]. This represents the goal motivating the development of delivery systems acting as antiseptic excipients for topical treatment, such as wound management. Indeed, sustained and local antimicrobial agent release may overcome not only high dosage-related side effects but also infection recurrence due to the premature suspension of the treatments and low compliances due to frequent administration required[4]. There is not a standard therapeutic window in surgical wound management [41]. However, the time scales of the different wound healing phases, namely hemostasis, inflammation, proliferation, matrix formation and remodeling, were rationalized[46]. In this context, prolonged drug release (over a window of at least two weeks) able to guarantee the sterility until the matrix formation phase is desirable in order to avoid bacterial burden renewal as well as frequent dress change[47]. Moreover, an ideal release profile is represented by an initial controlled burst release followed by a zero-order kinetic able to maintain an effective and safe drug concentration (i.e. between the minimum effective concentration (MEC) and the maximum toxic concentration (MTC))[48]. Indeed,

the initial burst release is aimed at providing immediate and strong antibacterial activity, while the subsequent milder and prolonged release promotes healing, as shown in **Figure 3**[49].

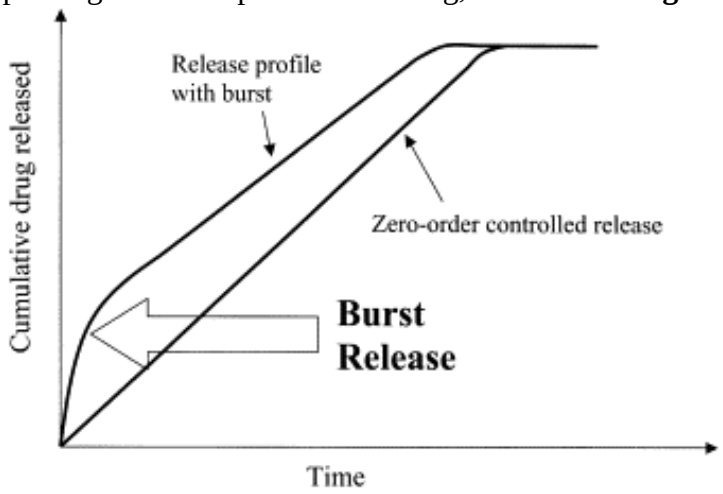


Figure 3: Trend of the ideal profile in the release of the antiseptics with respect to a typical zero-order release. Reproduced with permission from [49]. Copyright Elsevier 2001.

Being CHX and OCT the most studied and commonly used representatives of biguanides and quaternary ammonium compounds, respectively, hereinafter drug delivery systems able to provide long lasting release of those antimicrobial agents will be reported.

There are two main categories in which polymer excipients for sustained drug release could be divided, namely natural and synthetic drug delivery systems. The following sections will provide an overview of the polymeric drug delivery systems developed for CHX and OCT in both categories and pros and cons will be analyzed in detail.

2.1. Natural Drug Delivery Systems

Natural drug delivery systems have been widely researched for the sustained release of antiseptic compounds, due to their high biocompatibility to the human body. Indeed, different CHX and OCT delivery systems based on cellulose[50–53], polysaccharides[54–60], collagen[61] can be found in the literature, as described in **Table 1**.

Among polysaccharides, chitosan is widely appreciated in the medical and pharmaceutical fields, due to its appealing properties, such as biodegradability, biocompatibility and ability to form films and gels[62]. Moreover, it provides an acceleration in the granulation phase during the wound healing process while having a bacteriostatic effect and bio-adhesive properties due to its positive charges[63,64]. Currently, it represents one of the most exploited excipient for wound dressing, since it is already present in the market with various products, namely ChitoSam™, ChitoFlex, ChitoGauze XR pro and Axiostat®.Therefore, chitosan-based delivery systems in the forms of film[60], hydrogel[56], micro-[58] and nano-[59] particles have been widely investigated as CHX excipients.

Drug release kinetics from chitosan hydrogels, resulting from both drug diffusion and matrix degradation, proved to be dependent and consequently controllable by the crosslinking density of chitosan network thus allowing an adjustable therapeutic window[56].

However, since both chitosan and the antiseptic are positively charged at physiological pH, polymer-drug interactions and in turn the loading efficiency are hampered by electrostatic repulsion. To overcome this problem, functionalization with negatively charged groups increasing the complexity of the system are required to enhance the drug loading and to improve the characteristics of the formulation[59]. In this context, CHX loaded hexametaphosphate (HMP) nanoparticles have been exploited to provide antimicrobial properties to the commercially known Savlon® Alginate

Dressings[65]. HMP NPs gained attention due to synthesis process easiness and the NP ability to form a stable colloidal suspension exploitable in dip coating. Colloidal stability as well as capability of fast adherence to different surfaces are both obtained thanks to NP surface charges. As a matter of fact Barbour *et al.*[65] successfully dip coated medical grade titanium with HMP NPs. The colloidal coating showed a long-lasting antimicrobial effect with a sustained CHX release over a period of 99 days. Overall, the use of chitosan may be particularly advantageous in wound dressing because of the many beneficial properties that this compound provides for the application.

However, the intrinsic solubility of this polymer prevents *in vivo* long-term exposure to the exudating wounds, since their biological fluids may hamper the integrity of the device. At the same time, the polymer-drug electrostatic attraction needs to be carefully controlled in order to efficiently encapsulate and release the drug. As a matter of fact, in the case of pectin, a widely used anionic polysaccharide, strong drug-polymer interactions result in an inefficient antimicrobial activity, due to undesired drug retention. Indeed, pectin microparticle synthesis involving CHX as cross-linking agent as well as encapsulated active ingredient resulted in a drug release kinetic reaching its plateau after 20 minutes and releasing only 7% of the total drug after 6 hours. This could be solved by the simultaneous presence of another di-cation (*i.e.* zinc) able to compete with CHX as gelation agent and providing a less tight microparticle network[57]. A possible solution, in order to reduce the drawbacks in the clinical application and to pave the way to a long term wound dressing device is represented by films made of a network of alginate and pectin (SA-PC) crosslinked with calcium chloride, in order to improve the physicochemical and mechanical properties of the formulation[66]. In this context, promising tests performed both *in vitro* and *in vivo* validated this approach for wound dressings encapsulating antidiabetic compounds[66,67].

Table 1: Advantages, drawbacks and possible functionalization to improve the formulation performances for the different natural polymers used as excipients for positively charged antiseptics.

Polymeric excipient	Formulation form	Advantages	Drawbacks	Functionalization
Chitosan[54,56,58–60]	Hydrogel, microspheres and nanoparticles	Biodegradability, bioadhesive properties, granulation phase acceleration	Hampered polymer-drug interactions, low loading efficiency, fast drug release	Peptidomimetic derivative glutathione (GSH)[59], tripolyphosphate or a,b-glycerophosphate cross-linking[56,60]
Pectin[57,68,69]	Hydrogel, microparticles	Biodegradability, easiness of gelation	Excessive drug retention	Divalent cations (Zn^{2+} Ca^{2+}) as gelation agents[57,68]
Collagen [47,61,70–72]	Film composed by a collagen matrix	Biodegradability, stimulation of healing process, polymer-drug affinity	Batch safety and reproducibility for bovine or porcine derived	Glutaraldehyde crosslinking[72]
Cellulose[73–76]	Matrix for wound dressing	Efficient drug loading, high stability, prevention of wound drying	Fast drug release	Addition of ciclodextrins or poloxamers[73,74]

Another natural polymer commonly applied in the medical formulation of antiseptics is collagen, since it is not only biocompatible and biodegradable, but also stimulates wound healing enhancing

fibroblast synthesis and endothelial cell migration[47,70]. Denatured collagen (gelatin) matrices containing 2.5 mg of chlorhexidine gluconate (CHG), commercially known as PerioChip™, are widely used in the treatment of periodontal environment bacterial colonization. This delivery system is able to maintain high CHG concentration for 72 h, due to both diffusion mechanism and initial matrix degradation which occurs typically in a range between 7-10 days[61].

Nonetheless, issues regarding batch safety and reproducibility of collagen needs to be overcome for this type of formulations. In fact, bovine or porcine derived collagen poses transgenic transmission risks besides its fast degradation that hinder the possibility of providing a long lasting release[77]. Towards this direction, fish-derived or denaturated collagen preventing transgenic risks may represent safe alternatives to conventional collagen formulations[72,77].

In this context, cellulose represents the most studied natural polymer. In fact, the highly porous nature of this organic macromolecule may result in a high drug loading capacity[76]. In the past, cellulose-based delivery systems such as bacterial nanocellulose (BNC), gained attention owing to their unique properties. BNC fulfills the requirements for usage as wound dressing, among them biocompatibility, mechanical and thermal stability, softness, exudate absorbance preventing wound drying and proper gaseous exchange[73].

The addition of antimicrobial properties to nanocellulose through the encapsulation of an antiseptic compound leads to an active wound dressing able to improve acute and chronic wound treatment outcomes.

As a matter of fact, Moritz *et al.*[75] successfully loaded OCT into a BCN fleece thanks to capillary and diffusional forces, obtaining an 8 hours initial burst effect and 96 hours lasting sustained release. Specifically, it is worth mentioning that after 24 hours, more than 80% of the loaded drug was released, which may result in a frequent wound dressing change and in turn, lower patient compliance. For this reason, in order to improve the capacity to sustain the release of the formulation, other excipients need to be added. Specifically, different studies investigated nanocellulose formulations comprising cyclodextrins (CD), which are cyclic structures of D-glucose oligosaccharides [51,52,74]. CD has a 3D truncated cone structure featuring a hydrophilic external surface and a hydrophobic inner cavity. Hydrophobic or Van der Waals weak interactions allow CD to entrap guest molecules as CHX[55], resulting in inclusion complexes able to delay the drug release kinetics[78,79].

Interestingly, in the study by Lavoine *et al.*[74] a combination of micro-fibrillated cellulose and CDs coating successfully resulted in cellulosic substrates-based drug delivery systems of CHG as shown in **Figure 4**.

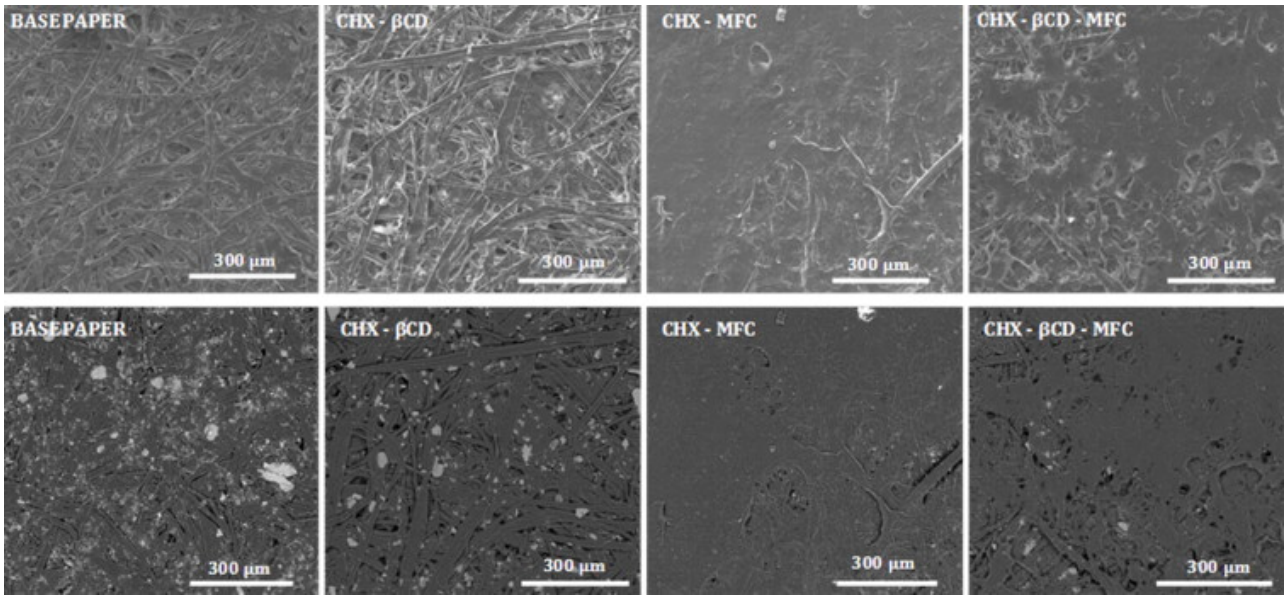


Figure 4: Scanning electron microscopy (SEM) images of the different surfaces on the cellulosic substrate varying the wound dressing formulation (from left to right): cellulosic substrate, CHX and CD, CHX and micro-fibrillated cellulose (MFC), CHX, MFC and CD. The upper panels show the topography of the samples measured with Everhart–Thornley detector (ETD) while the bottom ones provide information about the homogeneity of the coating through the back-scatter electron (BSE) mode in order to highlight the distribution of both the cellulosic parts and the fillers. Reproduced with permission from [74]. Copyright Elsevier 2014.

Particularly, the coupling of these two excipients produced a synergistic combination of effects: the micro-fibrillated cellulose reduced the initial burst effect, while the presence of a CD drug reservoir resulted in prolonged release. In this case, the results were observed for over 50 hours.

Overall, the main advantages of natural drug delivery systems include their biocompatibility and biodegradability ensuring patient safety. In addition, concerning the wound dressing application, their capacity to absorb the wound exudate guaranteeing a sufficient air permeability while promoting the healing process represents characteristics of paramount importance in the clinical application. Moreover, being produced from renewable sources, natural drug carriers may reduce the carbon footprint in the medical and pharmaceutical economy. However, their low stability, batch-to-batch variability, possibility of transgenic transmission and the difficulty in reaching a long-lasting release make them less versatile drug carriers compared to their synthetic counterparts. This is even more so considering the poor control over their chemical and mechanical properties during the synthesis. The lack of control during the production process and the drop in the physicochemical characteristics of the formulation during time hinder the possibility to provide a long-term sterility of the wound, fundamental in the future in the fight against HCAIs infections.

In order to overcome these issues, synthetic materials often represent the solution, owing to their versatility and high reproducible as well as tunable properties.

2.2. Synthetic Drug Delivery Systems

Concerning CHX and OCT releasing systems based on synthetic polymers, in this chapter the focus will be mainly on the non-biodegradable excipients while the biodegradable ones will be treated separately in the next sections.

Among synthetic polymers, the most studied delivery systems are represented by methacrylates[80–85], polyurethanes[86–89], silicon[90,91], alkoxysilanes[92], ethylene-vinyl acetate copolymers[93–95], self-assembled polyelectrolytes[96–98].

These synthetic polymers, differently from the natural-derived ones, are mainly applied as long-lasting antimicrobial releasing carriers in order to respond to the rising demand of HCAIs from dental as well as orthopedic surgery. In this field, an important aspect is related to the mechanical properties of the formulation, which should be kept for the whole duration of the release. As matter of fact, CHX and OCT are widely applied in dental restorative formulations, oral fungal infections and in surgical procedures as active ingredients inside bone cements.

Poly(methyl methacrylate) (PMMA) for example has been widely used as antibiotic releasing bone cement since 1960[84]. Addressing the threat of antibiotic-resistant bacteria, OCT loaded PMMA bone cements were investigated as an effective solution in the treatment and prevention of infections due to orthopedic surgical procedures. As a matter of fact, Weckbach *et al.* mixed together cement and OCT powder to obtain the commercially known bone cement Palacos®, achieving a low but sustained release up to 6 weeks with a prolonged antimicrobial efficacy against *S. Aureus*[85].

Methacrylate-based systems in different formulations have been further investigated as CHX loading systems[80–85]. Specifically, in dental applications, the drug delivery system may be produced via *in situ* polymerization exploiting a photo-initiator, where the drug is entrapped in the matrix during the radical-driven polymerization process. However, the main problem found in the application of cationic antiseptics as biguanide and QACs as active principles for methacrylate-based formulations is the protonation of the amine groups of the drug that is thought to consume free radicals, interfering with the radical polymerization[81]. This could result in the lack of desired properties as well as side effects due to an uncontrolled drug release, making this type of polymers not particularly suitable for the application.

As an alternative, polyurethane-based CHX carriers under different forms such as films or three-layer systems[86,87], antimicrobial patches[88] and nanoporous webs[89] have been investigated.

Since polyurethanes (PU) are a class of polymers synthesized from the polymerization of di-isocyanates and diols (or polyols), they can be obtained from a wide range of available building blocks, paving the way to the fine tuning of their mechanical and physico-chemical properties[99].

Polyurethane-based releasing systems are widely appreciated in biomedical industry: BIOPATCH®, a polyurethane-based patch for the release of CHX, replaced every week, is proved to be more effective in reducing pin-tract infection than topical antibiotic treatment performed twice a day with three different antibiotics, owing to its 7 days sustained release[88].

In the study of Huynh *et al.*[86], a medical grade polyurethane under different forms (e.g. film and three layer system) was studied *in vitro* as chlorhexidine diacetate (CDA) long lasting delivery system. The drug release rate and tunability were demonstrated to be dependent from the structure of the drug carrier. Indeed, the simplest formulation consisting in the PU film showed an initial burst directly dependent on the drug loading and a kinetic of release strongly dependent on the salt concentration in aqueous phase. These limitations, which prevent a long-term release of the compound may be overcome by using a three-layer system.

In fact, a three-layer delivery system featuring two outer unloaded PU layer serving as rate-controllers provided a 29 days lasting release following zero-order kinetics in distilled water as well as in physiological saline solution.

Indeed, PU multilayer system attracted the interest from researchers as coating material for their controlled release and higher drug loading capacity compared to the single layer reservoir.

As a matter of fact, the release kinetics of two different CHX salts loaded in a three-layer polyurethane drug carrier proved to last 42 days with an initial 24 hours burst effect[87]. The authors reported the

delaying effect of the two unloaded layers and the different CHX salt solubility as key factors influencing the diffusion-driven drug release[100].

Among the different efforts towards infection prevention and management, the synthesis of polyelectrolyte films proved to be particularly interesting as antimicrobial agent releasing wound dressing[96,97]. A step forward in this direction is attempted by Agarwal *et al.*[96] who provided sustained antimicrobial activity to a biological wound dressing by stamping a polyelectrolyte multilayer film incorporating CDA on top of it.

Layer-by-layer ultrathin nanostructures serving as matrices for localized drug release proved to last for 8 days *in vitro*. However, the stamping process may undermine the local stability of CDA loaded thin film, resulting in more rapid elution of CDA.

Following this discussion, it should be clear that the achievement of localized, controlled and sustained antiseptic release able to reduce the bacterial colonization and increase the treatment compliance poses many constraints to be satisfied. Biocompatibility, process reproducibility and mechanical properties tunability are the fundamental performances to be provided by the formulation for these applications. However, even if the synthetic polymers aforementioned are able to guarantee these properties, a further important point of discussion is the fate of the drug carrier after the complete release of the drug. In order to avoid accumulation of plastic in the environment and, even worse, in the human body, the biodegradability of the carrier represents a key characteristic. This is the rationale behind the wide research and investigation towards polyester-based drug carriers, which will be discussed in the following section.

3. Polyester-Based Drug Delivery Systems

Synthetic polyesters as polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) and their copolymers gained increasing interest in the development of drug delivery systems for their biocompatibility, tunable properties, and degradability into non-toxic and well resorbed molecules, which avoids further surgery for the removal of the implants[101,102]. In those devices, the release of the drug is often achieved by diffusion, whose rate is strongly influenced by the progressive degradation of the polymer matrix, in which the therapeutic is incorporated. At the same time, the high control over the synthesis processes enables reproducibility in the final product as well as tunable degradation rates and customizable mechanical characteristics for a good control over the drug release[103,104]. Compared to natural polymers that undergo enzymatic degradation only, polyesters degrade through both enzymatic or hydrolytic cleavage of the labile ester bonds, leading to a progressive reduction in the molecular weight [102]. Specifically, the degradation of insoluble polyester particles in water may occur via bulk or surface erosion[105]. The former consists in a roughly homogeneous decay of the molecular weight and density involving the whole polymer volume, with the produced fragments that diffuse outside the polymer matrix. On the other hand, the surface erosion is described by a progressive degradation occurring mainly on the surface and causing a progressive shrinking in the polymer volume[106]. Normally the surface erosion rate is constant until the complete dissolution of the polymer, while the bulk erosion one depends on different factors and may vary during time[107]. The occurrence of one or the other mechanism is mainly influenced by two processes, namely the water diffusion into the polymeric matrix, the subsequent chain cleavage and the retro diffusion of the fragments from the bulk[108]. Indeed, if the water and fragment diffusion inside and from the bulk is faster that the chain cleavage, the material is characterized by bulk erosion degradation, otherwise the surface erosion is predominant[108]. It is also worth mentioning that these phenomena depend also on the polymer size. Each polymer is characterized by a critical size above which the bulk erosion is

lost. In this context, aliphatic polyesters typically show a bulk erosion behavior consisting in 10^{-1} m as characteristic size and their characteristic degradation time can be easily controlled. Furthermore, another factor that plays a key role in the aliphatic polyester degradation process is represented by the autocatalysis. Indeed, the breakage of the ester bonds inside the polymer matrix leads to the formation of acidic products that lowers the microenvironment pH, thus catalyzing the further hydrolysis of the ester bonds in the polymer backbone[109,110]. This phenomenon, in the drug delivery application may be triggered not only by the polymer fragments but also by certain type of drugs that are loaded inside the carrier. In fact, the local increase or decrease of the pH inside the polymeric matrix caused by the active principle molecules represents a common effect measured in the polymeric carrier[111–113]. However, this should not represent an issue when dealing with quaternary ammonium salts. In fact, their pKa is above the pH of both the water and the human body, therefore their protonation state is negligible during the production and the application of the formulation, not influencing the microenvironmental pH of the matrix. Finally, the other important parameters involved in the polymer degradation consist in the copolymer composition, molecular weight, crystallinity and stereochemistry of the monomers, whose tuning makes it is possible to adapt the formulation characteristics and degradation rates to the different applications[104,114]. Indeed, the slow degradation rate of PLA makes it one of the most common choices for the production of long-term orthopedic implants such as plates and screws. Whereas, PGA and its copolymers with lactic acid (PLGA) present faster degradation, thus making it particularly suitable for the fabrication of sutures and drug delivery devices[115]. The timespan of PLGA hydrolytic degradation is dependent on glycolide to lactide (G/L) ratio. Since glycolide is less hydrophobic than lactide, by increasing its proportion in the PLGA it is possible to significantly speed up the degradation. As an example, increasing the G/L weight ratio from 25:75 to 50:50 can accelerate the degradation by two-fold from 100 to 50 days[103,115,116].

Another advantage in using polyesters is the possibility of providing a broad range of mechanical properties. Indeed, it is possible to obtain polyesters with a relatively brittle structure like PGA as well as highly flexible ones as PCL, despite this is typically characterized by a low tensile modulus, which may hamper its application in several fields[117].

Following the aforementioned promising features, the research is increasing its efforts in the application of these compounds as excipients to achieve a sustained and controlled release of antibiotics and antiseptics[115,118,119]. Specifically, in this section, a focus on the role played by the different polyester-based delivery devices as fibers and films for wound dressing, patch, micro- and nanoparticles is reported in the delivery of antiseptics.

Young *et al*. investigated the use of injectable adhesives made of lactic acid (LA) and propylene glycol (PG) dimethacrylates for the sustained release of CHX during bone repair. The drug release study from polymeric disks reported a direct correlation between the LA and PG block molecular weights and the CHX release, due to a reduction in cross-linking and to the interaction between the degradation product of the polymer and the drug[119]. However, the low affinity between the polymeric excipient and the drug caused a significant early release of the active principle due to its low encapsulation efficiency inside the polymeric matrix. Moreover, the possible dependency of the antiseptic release from the disc size may create problems in the final application of the formulation.

For these reasons, a more extensive investigation focused on the application of different types of polyesters, namely PCL and PLA as fiber-based delivery systems was performed. Indeed, PCL sutures endowing CDA were realized by Scaffaro *et al.* to prevent infections on sutured wounds. The polymer monofilaments were spun thanks to a capillary rheometer and showed a sustained drug release up to one week with a burst release that increased with the drug concentration[120]. Instead, PLA fibers were mainly used to encapsulate antiseptics through electrospinning. Different works

investigated the characteristics of PLA fibers containing CHX used either alone or to reinforce PCL films[121,122]. Specifically, Luo *et al*. showed a fast drug diffusion from the fibers in the first day, with a prolonged release evaluated for up to 650 hours. When the same drug particles were encapsulated with a layer-by-layer strategy, the release rate significantly decreased. On the other hand, when the PLA fibers were used as a reinforcement to PCL films, a significantly faster drug release and lower infection rate was observed when both the fibers and the film were loaded, with complete bacterial growth inhibition[121]. Therefore, the use of the electrospinning technique provided a versatile tool able to tailor the suture fibers drug release and initial burst for the application. Moreover, the possibility to electrospin different materials together may be particularly advantageous for the wound dressing application. Indeed, the use of this technique with PLA or PLGA coupled with natural polymers as collagen and chitosan may guarantee at the same time the mechanical properties and the strict control over the drug release provided by biodegradable polyesters and the promotion of the wound healing of these natural polymers[123,124]. In this context, another promising formulation is that of thermogelling polymers. In fact, triblock polymers made of PLGA-PEG-PLGA are able to provide the correct exudate absorption and air permeability, beside the tunable release of the drug and the easiness of application[125]. In this way, by exploiting the physicochemical characteristics of the formulation (*e.g.* hydrogel or fibers) it is possible to achieve the set of properties required by the application.

Despite these raising applications of polyesters, they are mostly used in the production of micro- and nanoparticles for drug delivery. Indeed, biodegradable particles are already a well-established method to efficiently deliver therapeutics for the treatment of various pathologies like diabetes and cancer and for vaccine delivery due to their interesting properties[126–128].

In fact, polymeric microparticles (MPs) are extensively employed as biomaterial because of their favorable characteristics in terms of simple production and design, good biocompatibility and broad structure variety[129–131].

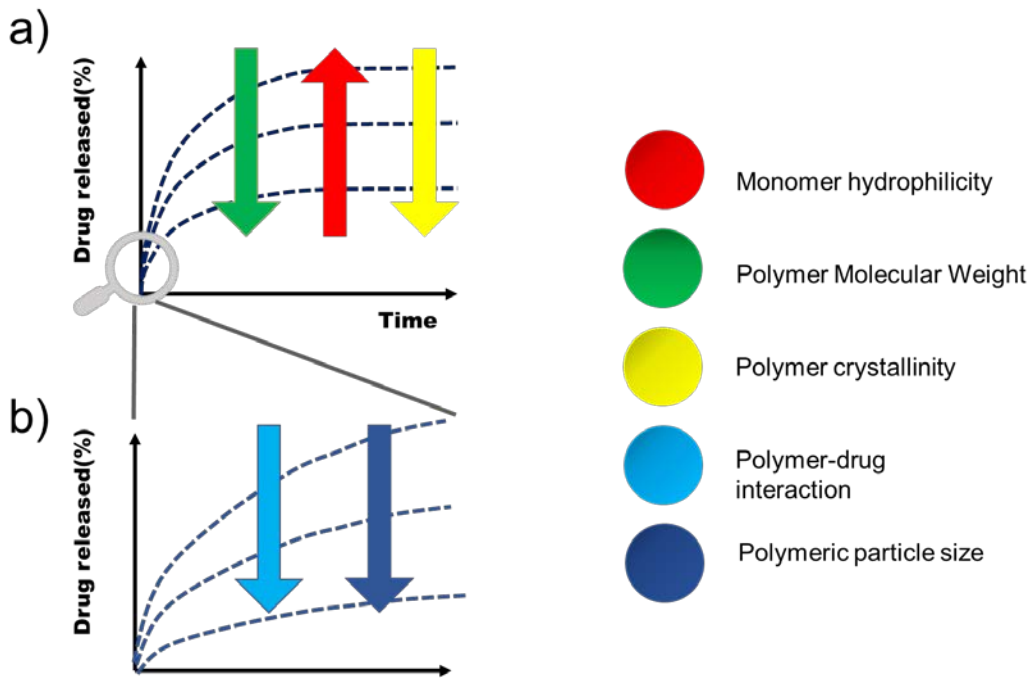


Figure 5: Schematic representation on the effect of the polyester characteristics on the release of the active principle. a) Influence of the most significant polymer and monomer characteristics on the kinetic of release of the antiseptic from the formulation; b) Effect of the formulation characteristics as the polymeric particle size and polymer-drug interaction on the drug encapsulation and initial burst.

"Microparticle" is the term used for spherical particles with diameters in the micrometer range (typically from 1 μm to 1000 μm)[126,132].There are different interesting features of MPs that make them particularly suitable for antiseptic release: (i) controlled release of encapsulated materials, (ii) protection of the encapsulated materials against degradative reactions (e.g., oxidation, dehydration, UV, heat, acids and bases) in the external environment (iii) improved shelf life, (iv) delivery of therapeutics into the target location with high efficiency and for long time periods, (v) enhancement of solubility profile of poorly soluble active agents, (vi) enhancement of bioavailability of the loaded drug and reduced side effects[127,128,131]. MPs are usually formed by a polymer matrix in which an active compound can be immobilized, either on the surface or entrapped inside the bulk. With respect to the distribution of the active compound, two different categories of MPs can be distinguished: microspheres and microcapsules. Microspheres refer to MPs composed of a homogeneous mixture comprising the active principle and the excipient, while in microcapsules the core is either empty or liquid (e.g. vesicles) in order to efficiently encapsulate and tune the release of hydrophilic compounds. Furthermore, one or more discrete domains of active compound may be found in the microcapsule core[133].

Drug molecules can be released from polymeric MPs through water filled pores, following two different processes: convection produced by the osmotic pressure and the diffusion caused by random movements due to the concentration gradient. In addition to diffusion, the drug molecules can be released from the polymer matrix by erosion[134]. As such, the drug release can be influenced by morphological properties of the polymer selected, such as molecular weight, molecular weight distribution, copolymer composition, presence of end functional groups, crystallinity and solubility, as described in **Figure 5**[135–141].

In the recent years, a significant effort was done in order to apply these delivery systems to compounds as QACs and biguanides.

Specifically, in order to efficiently encapsulate antiseptics in MPs, the polymer-drug interaction has to be enhanced. In fact, PLGA MPs providing a sustained release of the antiseptic were investigated in a formulation of povidone-iodine, as an intramammary disinfectant delivery system[142]. Despite the sustained diffusion of the antiseptic compound over 28 days, the moderate drug encapsulation and the significant initial burst lowered the formulation efficacy. Furthermore, in this case, the method of production of the formulation (i.e. solvent evaporation method) provoked a low process yield complicating an eventual subsequent scale-up.

Instead, the presence of molecules able to improve the affinity between the polymeric carrier and the antiseptic may significantly increase the drug retention and encapsulation. As an example, Yue *et al.* produced a CHX delivery system composed by PLGA MPs able to provide the sustained release of the active principle. Specifically, the prolonged drug retention was obtained through the interaction of CHX with cyclodextrins characterized by a different lipophilicity. It was proved also that increasing the hydrophilicity of the cyclodextrin (e.g. *hydroxypropyl beta-cyclodextrin*) a better encapsulation and a faster release were obtained[143]. In this context, the biocompatibility of the polyester formulation can be also further improved through the addition of natural polymers in a blend[144,145]. Indeed, PLGA-based MPs with a shell of glycol-chitosan were synthesized by Chen *et al.* Specifically, CHX was released together with different growth factors in order to promote wound regeneration together with antibacterial activity. In these systems, the rate of the drug was proved to be dependent on the copolymer composition. In fact, 85:15 PLGA formulations showed a sustained release up to one week with efficient antibacterial activity, while worse results were found for 50:50 PLGA MPs[145].

However, depending on the final application, particles characterized by a smaller size, as nanoparticles (NPs) may be preferred. Indeed, NPs generally range from 10 nm to 1000 nm in

size[126,146]. Exploiting their size at the nanoscale, these nanostructures can circulate in the blood for prolonged periods of time, with a controlled release that causes lower drug level fluctuations in the plasma[147]. Moreover, similarly to microparticles, they offer a wide variety of advantages compared to conventional therapies, such as targeted drug delivery, sustained release, protection of labile groups from degradation, low toxicity and increased drug specificity[148].

It is worth mentioning that, as the size of the nanoparticles is reduced, the maximum drug loading per particle decreases. However, since the surface to volume ratio increases, the diffusion of the drug out of the particles is favored as shown in **Figure 5.** Consequently, the burst release in polymer nanoparticles is higher and overall, the release of the drug is mainly driven by diffusive phenomena.

In this context, biodegradable polyester-based NPs, using a core of PLA and its copolymers, represent and interesting tool to achieve a sustained release of antiseptics compounds for oral or topical applications and different studies are focusing on this aspect in the recent years.

Indeed, Baier *et al.* studied the enzyme-triggered release of OCT from PLA-based nanoparticles stabilized by different surfactants. In this type of drug delivery systems, the release of the drug was triggered only by the action of specific enzymes, which caused the degradation of the polymer matrix, allowing a sustained antimicrobial activity of the formulation[149]. However, the use of a significant amount of surfactant may negatively influence the biocompatibility of the formulation. Furthermore, the use of preformed polymers decreases the tunability of the particle characteristics.

In order to improve the different properties of the formulation as drug encapsulation efficiency and degradation time of the polymeric matrix, copolymers of PLA with different monomers have been investigated[150]. In this context, the choice of the co-monomer is crucial in the characteristics of the final formlation.

In fact, the possibility to copolymerize PLA with a hydrophilic compound (*e.g.* PEG) leads to an increase of the drug loading efficiency and a higher control to the release of the active principle due to the higher porosity of the colloidal system. Two studies report the use of self-assembled bi- and tri-layered nanoparticles made of poly(ethylene glycol)-b-poly(lactic acid) (PEG-b-PLA) block copolymers. Due to the presence of both hydrophilic and hydrophobic moieties, the particles could effectively entrap CHX in the interior, showing higher degradation rates. Overall, through these strategies, sustained antimicrobial activity up to 21 days were obtained [34,151].

Copolymers of PLA and PGA are also commonly studied as carriers for antiseptic delivery. Indeed, PLGA was employed in different studies for the nanoencapsulation of CHX in restorative dentistry[152]. Priyadarshini *et al.* prepared nanoparticles *via* emulsion/evaporation, with high drug entrapment efficiency (up to 88%). The *in vitro* CHX release showed a bi-phasic trend, with an initial burst in the first 3 hours followed by a slow progressive escape of the drug via a combination of diffusion and polymer degradation up to 28 days. Moreover, exploiting the feature of the PLGA copolymer it is possible to tune the release of the drug by varying the copolymer composition.

Nonetheless, other polyesters, e.g. PCL may be used in the synthesis of polymeric NPs. Indeed, Lboutounne *et al.* developed a drug delivery system consisting of CHX encapsulated in PCL NPs for the treatment of nosocomial infections. This drug delivery system was proposed as a substitute to antiseptic topical formulations (hand-washing agents) that could lead to skin problems such as dermatitis or allergies. The authors investigated the effect of the drug carrier on the porcine skin compared with the traditional CDA solution. It was proved that CDA absorption in the skin was three times higher from nanocapsules than from the corresponding solution. Thanks to their size, the particles could adhere to bacterial surface, inhibiting the bacterial growth[153]. However, the formulation achieved a maximum encapsulation efficiency of 60 %, due to a low affinity between the polymer and the drug.

Indeed, one of the main drawbacks that is limiting the application of polyester-based formulations is the poor affinity to the cationic antiseptic, with its amphiphilic and electrostatic character. Due to

their molecular structure, the drug molecules tend to locate at the interface between the formulation and the aqueous environment, leading to a fast release. Consequently, polymer functionalization able to increase the affinity between the polymer and the charged antiseptic may significantly enhance the drug loading in the formulation.

4. Current Trends for the Control of the Antiseptic Concentration within a Therapeutic Window

One of the major issues of polyester devices in the controlled delivery of therapeutics is the so-called "burst release", where a large amount of drug is released in the first 24 hours[154,155]. This fast delivery of therapeutics results in possible toxicity for the patient, due to high drug concentrations and short release profiles[134]. While a strong antibacterial activity is required in the first hours after the surgery, also a sustained antiseptic release over the targeted timeframe of sterility is necessary[49]. In this context, a variety of possible functionalizations can be carried out in order to enhance the interaction between the polymer matrix and the drug, thus lowering the initial burst depending on the specific application[156].

Biodegradable polyesters can be functionalized following post-polymerization or copolymerization routes. In the former case the polymer is first synthetized and then enriched with functional groups devoted to the retention of the drug. However, the possibility of racemization or scission of the ester bonds as side reaction represent the main limit of this strategy. Therefore, a more frequently used method involves the copolymerization of functional monomers with commercially available ones. The moieties bearing functional groups are protected during the polymerization to avoid side reactions, so a deprotection step is usually required to obtain functional polymers[157].

In this context, an efficient strategy employed to enhance the active ingredient loading and to slow down the drug release is the conjugation between the therapeutic molecule and the pendant groups of the polymer backbone[134,158]. By changing the strength of the chemical bond it is possible to tune the release rate depending on the application[159]. Specifically, the presence of a covalent bond may allow to achieve linear release kinetics. Indeed, Yoo *et al.* showed how the release of Doxorubicin-PLGA conjugated nanoparticles was independent from drug diffusion but relied only on polymer degradation, with a zero-order profile[160]. A similar strategy may be envisioned for the controlled delivery of antiseptics. However, a potential drawback of covalently binding the drug to the polymer chain is the loss of biological activity[161]. Moreover, a further limitation of the technique is the need for active groups both in the drug molecule and the polymer chains.

Starting from this strategy, modified antibacterial agents usually presenting functional groups such as carboxy-, hydroxy- and amino- moieties may be functionalized through the covalent linkage to a polymerizable monomer, mainly acrylic[144,162–164]. In this way the final monomer is composed by a ionizable end group, providing the desired therapeutic effect (*e.g.* ammonium, pyridinium), a polymerizable group (*e.g.* methacrylate) and an alkyl chain spacer[165]. For example, Beyth *et al.* realized dental composites in which a quaternary ammonium compound was attached to a polymerizable monomer. As the polymerization was carried out, the bacterial agent was incorporated in the resin, thus avoiding its fast release. However, even if the antibacterial activity was sustained for 3 months, antiproliferative effects were shown only against bacteria in contact with the antibacterial molecules[165].

In order to overcome the issue related to the loss of biological activity, many groups, instead of covalently binding the antiseptic to the polymer, exploited their electrostatic interaction relying on

oppositely charged species to obtain polymeric devices with the possibility of entrapping a large quantity of drug[137,166]. Indeed, the electrostatic interaction between the therapeutic and the polymer allows the formation of complexes that can significantly reduce the release rate[166–168]. Most of the times, because many polymers are neutral under physiological conditions, the functionalization with ionic species is required to obtain charged polymeric chains. In this case, the drug release depends not only on the electrostatic interaction with the polymer, but also on the strength of the bond introduced by the charged functionality[169]**.** Specifically, this type of functionalization proved to be particularly efficient in the encapsulation and release of cationic amphiphilic compounds as QACs and biguanides. For example, two groups reported the use of cyclodextrin as a functionalizing agent to increase the affinity with the released antiseptic drugs, particularly benzalkonium chloride and chlorhexidine. In the first study, CD is immobilized on cotton gauzes by using citric acid as a linker. High encapsulation efficiencies of benzalkonium chloride could be obtained, due to the formation of inclusion complexes with CDs. Moreover, being the drug positively charged, an ionic interaction with free carboxylic groups of citric acid was observed, thus increasing the loading values. The release of benzalkonium chloride was sustained for 2 weeks, with higher antibacterial properties with respect to commercial products[170]. The second study instead, employs the same strategy to prolong the release of chlorhexidine from cellulosic substrates[171]. Finally, it is worth mentioning that the presence of the electrostatic interaction is able to significantly improve the drug loading also for synthetic polyester-based formulations containing cationic antiseptics. For example, some studies on PLGA microparticles reported the influence of polymer end groups on OCT release[172]. Indeed, deprotonated carboxylic groups are able to establish an electrostatic interaction with the drug once in an aqueous environment, which prevents the fast diffusion of the amphiphilic active principle outside the polymeric carrier. Moreover, the application of this functionalization to NPs composed of complex polyester architectures (*e.g.* star-shaped and brush-like structures) allowing to modulate the number of carboxylate groups in the carrier, univocally showed that there is a linear correlation between the drug encapsulation efficiency and the number of anionic groups, as shown in **Figure 5**[173].

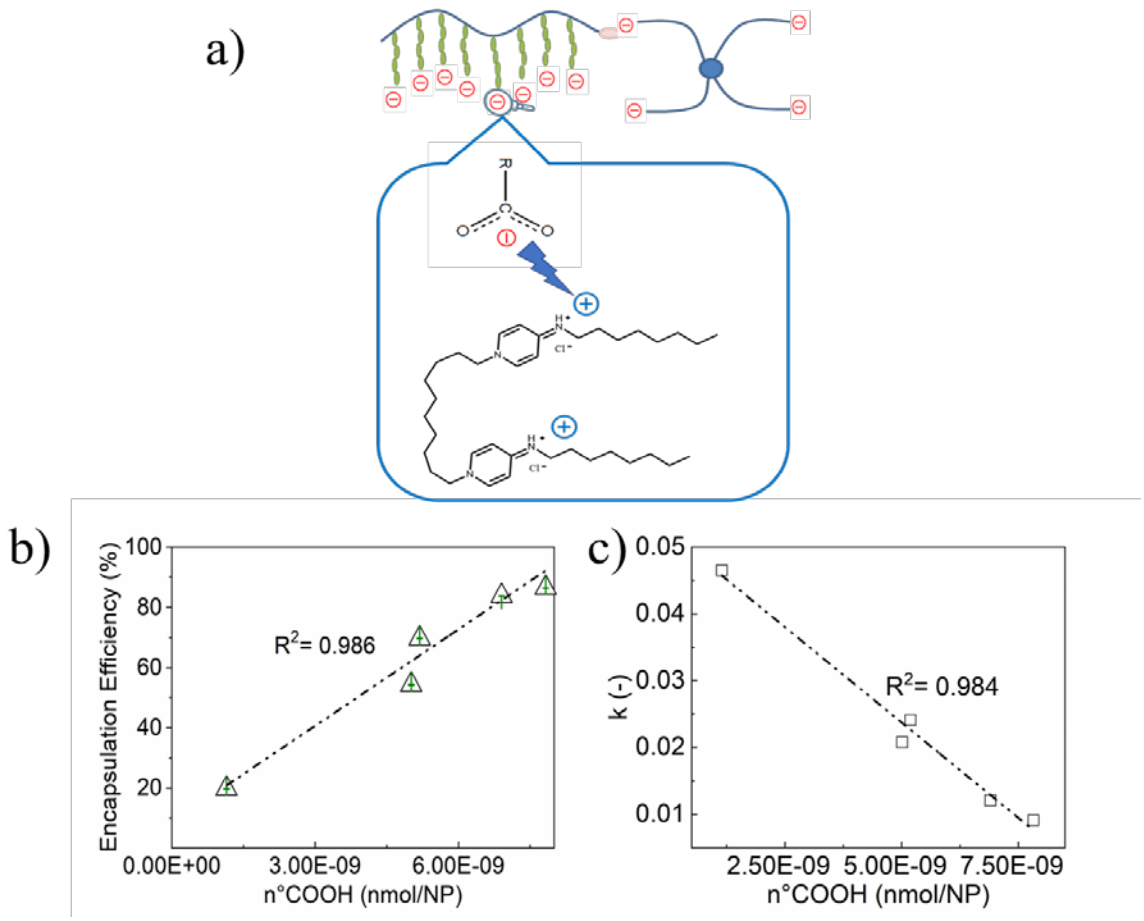


Figure 6: Mechanism of electrostatic interaction between negatively charged polyesters of different structure and the positively charged octenidine dihydrochloride (a); dependency of encapsulation efficiency (b) and kinetic constant (c) from the number of ionizable groups per particle. Reproduced with permission from [173].

This is counterbalanced by the enhanced release rate of the drug for these types of systems. In fact, PLGA with free carboxyl termini is more hydrophilic at physiological pH and it can absorb more water compared to capped species with esterified termini[103,141,174,175].

Overall, the polymer-drug electrostatic interaction showed to be a promising route to the encapsulation and release of QACs and biguanides since it allows at the same time a higher encapsulation efficacy and a controlled release due to the degradation of the polymeric matrix that occurs in the timespan required for the application. Moreover, the presence of an acidic end group in the polymeric chain should not influence the polymer toxicity. In fact, from different tests performed both *in vivo* and *in vitro* the comparison between the polymers functionalized with acidic end groups and their ester counterparts (i.e. RESOMER RG H and S) shows the absence of a significant difference in the cellular toxicity between these polymers[176,177] Since, the ester PLA and PLGA-based formulations are already present in the market, these preliminary results may pave the way to the clinical application of these functionalized materials also for the release of positively charged antiseptics. In this context, the use of these polymers as excipients for biguanides and quaternary ammonium salts allows their application for a wide range of HCAIs. Among these, they may be particularly beneficial in the case of wound dressing. In fact, the possibility to use them in synergy with the aforementioned natural polymers could promote wound healing and exudate adsorption while maintaining the tunability and mechanical properties of polyesters. Finally, the carboxylic functionalization could provide a sustained drug release over time, thus addressing the issue regarding the dressing change frequency. Indeed, the possibility to reduce the number of medical treatments

through a sustained and control release of the drug from the polymeric excipients may decrease the pressure and the costs on the national health systems while reducing the risks of complications for the patient[178].

5. Conclusions

Surgical site infections represent one of the most urgent problems to be solved in healthcare. At the same time, the increase in the number of bacterial strains resistant to antibiotics led to the consideration of antiseptics to fight against this type of infections. However, the use of antiseptics, most of them charged at physiological conditions, brings about the necessity of providing an efficient encapsulation in polymer excipients and their long-lasting release in order to avoid the bacterial colonization of the site even after hospitalization. Based on this, polymeric carriers are promising tools thanks to their versatile characteristics provided by the polymer structure. Specifically, in this review the most promising natural and synthetic polymers were discussed as drug delivery systems. While the formers are characterized by an enhanced biocompatibility, the versatility provided by the synthetic polymers, especially polyesters, able to couple it with their biodegradability proved to be a key point in the production of efficient formulations. Moreover, the combination of the advantages given by the synthesis of polyesters with specific functionalities able to enhance the affinity between the excipient and the drug may represent a crucial aspect to significantly increase the performances of the final formulations. Among these, regarding the categories of quaternary ammonium compounds and biguanides analyzed in this review, the electrostatic interaction between the positively charged drug and the polymer showed to be a promising feature to be exploited in the future in order to improve the treatment of these infections.

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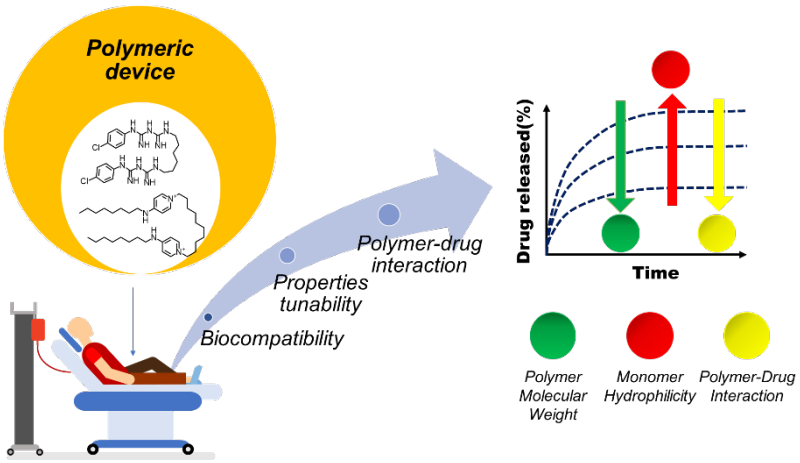

This review provides the guidelines to efficiently produce a polymeric formulation able to guarantee a sustained release of positively charged antiseptic for the long-term sterility in the treatment of health care-associated infections.