# 21. Smart medical textiles based on cyclodextrins for curative or preventive patient care

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**Abstract.** This chapter deals with smart textiles based on cyclodextrins (CDs) for curative or preventive patient care. CDs are topologically represented as toroids in which the openings expose the hydroxyl groups. As consequence, hydroxyl residues can be easily modified in order to introduce reactive groups and to perform their grafting onto fibers. Moreover, the interior of the toroid is sufficiently "hydrophobic" to host nonpolar medications (*e.g.* antibiotics, anti-inflammatory, insecticides, insect repellents, essential oils, phlebotonics, *etc*.). Upon complexation, the drug bioavailability is modified and a sustainable controlled release can be obtained for dermal or transdermal treatments. In this chapter, the general features of CDs and their attachment techniques to the fabric's surface have been reviewed. Finally, their applications and some future directions of investigation for the development of new functionalized textile products with advanced properties have been presented.

**Keywords.** Cyclodextrin, Host-Guest Chemistry, Antipathogen, Anti-inflammatory, Insecticide, Cosmetotextile, Phlebotonic Molecule, Bandage, Drug Delivery, Textile Functionalization.

## 21.1 Introduction

Cyclodextrins (CDs), also called Schardinger dextrins, are non-reducing cyclic oligomers of 1,4-linked α-D-glucopyranose. The most important native CDs are six, seven or eight-membered oligomers, named, respectively, α-, β- and γ-CD (Szejtli, 1998). These cyclic oligosaccharides have a shallow truncated cone shape with hydrophilic annulus due to the primary and the secondary hydroxyl groups of the glucoses that face the exterior ends of the molecule. In contrast, the cavity has a "hydrophobic" character due to carbons and ethereal oxygen atoms and allows the formation of reversible inclusion complexes with polar compounds (amines, acids, esters, *etc.*), aliphatic or aromatic hydrocarbons, *etc.* (Szejtli, 1998). At more than one century after their discovery by the French chemist Villiers (Villiers, 1891), the CDs are among the most used host molecules in the supramolecular chemistry domain (Dietrich, 1991). They are widely applied in agriculture (Campos *et al.* 2014), food technology (Szente & Szejtli, 2004), pharmacy (Funasaki *et al.* 2008), biotechnology (Singh *et al.* 2002), chemical and biological analysis (van de Manakker *et al.* 2009), chemical synthesis (Bjerre *et al.* 2008), catalysis (Leclercq *et al.* 2007, 2009), cosmetic industry (Buschmann & Schollmeyer, 2002), environmental protection technologies (Baudin *et al.* 2000), textile industry (Szejtli, 2003), and many other industrial applications (Hedges *et al.* 1998). The main reasons why CDs are so popular are the following: (*i*) they are produced from a renewable raw material (*i.e.* starch), (*ii*) their preparation applies only enzymatic environmental-friendly technologies, (*iii*) they are relatively cheap and are produced in amounts of thousands of tons per year, (*iv*) their numerous chemical modification is relatively easy, (*v*) they are biocompatible in consumable concentrations, and (*vi*) they are biodegradable (Nardello-Rataj & Leclercq, 2014). Taking into account the increasing demand on the world textile market and the need of highly smart performing materials, the amelioration of textile materials remains still an open gate for new applications. In this

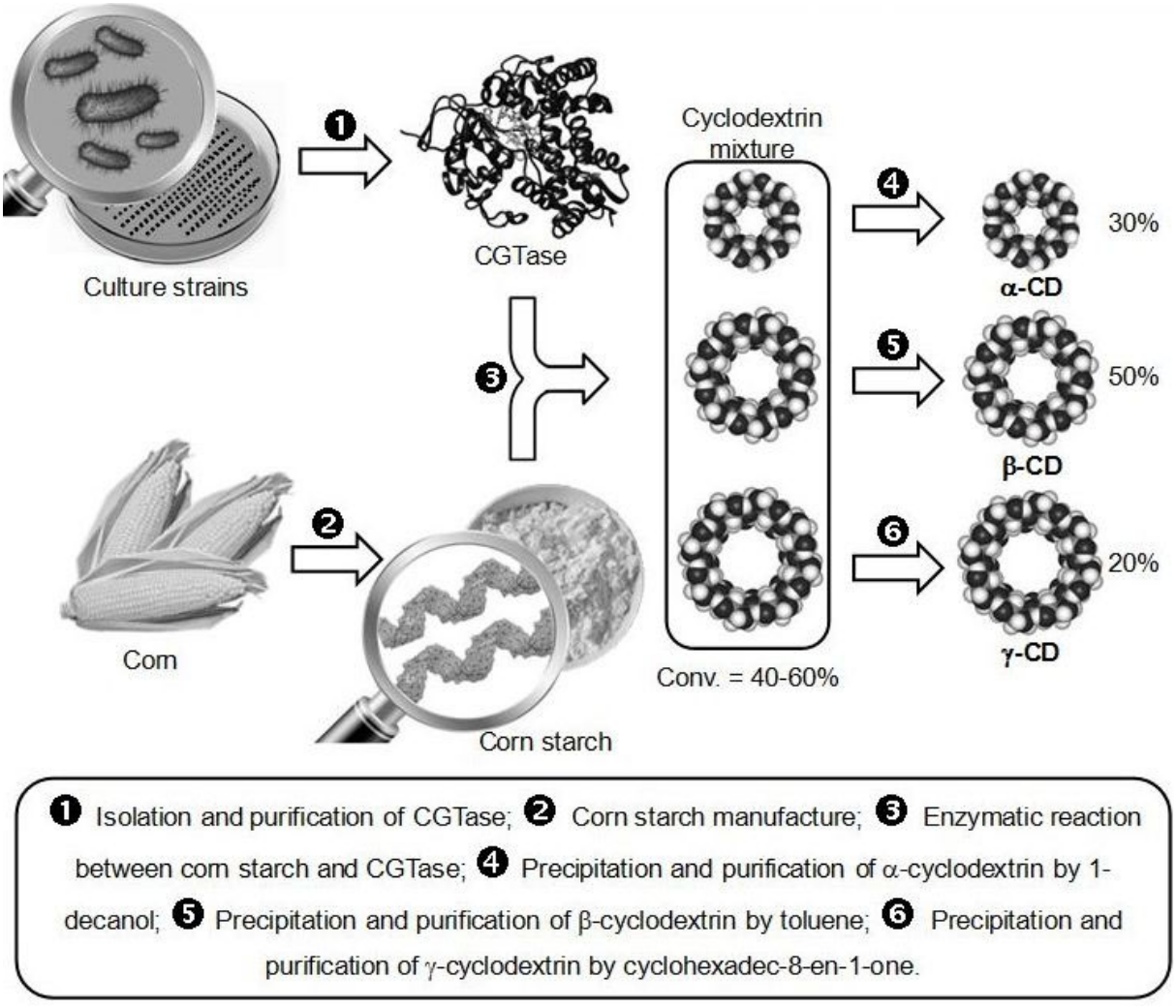
context, the use of CD inclusion complexes is particularly interesting to improve the performances and to obtain new functionalities of medical textiles (Bhaskara-Amrit *et al.* 2011). One of the most important and well documented uses of CDs is the encapsulation of biocides (*e.g.* bactericides, fungicides, virucides). For instance, the grafting of CDs on the fabrics can be used to achieve antiseptic textiles in order to avoid skin disease with superinfection hazard. In appropriated conditions, the complexation of medications by the CD improves (*i*) their physicochemical properties (*e.g.* reduced vapor pressure, *etc.*), (*ii*) their controlled release and bioavailability, (*iii*) their shelf-life, (*iv*) their storage conditions and their environmental toxicity, and (*v*) their resistance to repeated washing (Nardello-Rataj & Leclercq, 2014). The second well documented use of CDs in the literature is probably the loading of insecticides in order to diminish the hazard of infections transmitted by the biting of insects. The third application is the cosmetotextiles on the borderline between cosmetic and medicine. Finally, some promising future directions of applications are still in development to obtain new functionalized textile products with advanced properties. In the following sections, all these applications are illustrated by some references taken from the literature after a general presentation of CDs.

## 21.2. Cyclodextrins Production, Binding Properties and Applications

### 21.2.1. Synthesis and Characteristics

The starch degradation by enzymes gives rise to dextrin (a mixture of low-molecular-weight polysaccharides), to oligosaccharides containing a small number of glucose units (typically three to nine) and finally to glucose. For instance, the α-amylase, found in human saliva, is responsible for this degradation. The production of CDs, which are cyclic oligosaccharides, is relatively simple and involves the treatment of ordinary starch (*e.g.* corn starch) by enzymatic degradation in the presence of cyclodextrin glycosyl transferase

(CGTase, EC 2.4.1.19). This enzyme is produced by numerous microorganisms: *Bacillus macerans*, *Klebsiella oxytoca*, *Alkalophylic bacillus*, *Bacillus circulans*, *etc.* (Figure 21.1, Szejtli, 1998). In addition to the CGTase, the industrial production of CDs requires large quantities of corn starch. In this context, Wacker Chemie AG, which producing CDs since the 1980s, has implanted its latest production plant in Eddyville, Iowa (USA) next to the cornfields in 1999. In the whole, Wacker produces up to 7,500 metric tons/year of CDs and it is the world's largest producer (Wacker website).

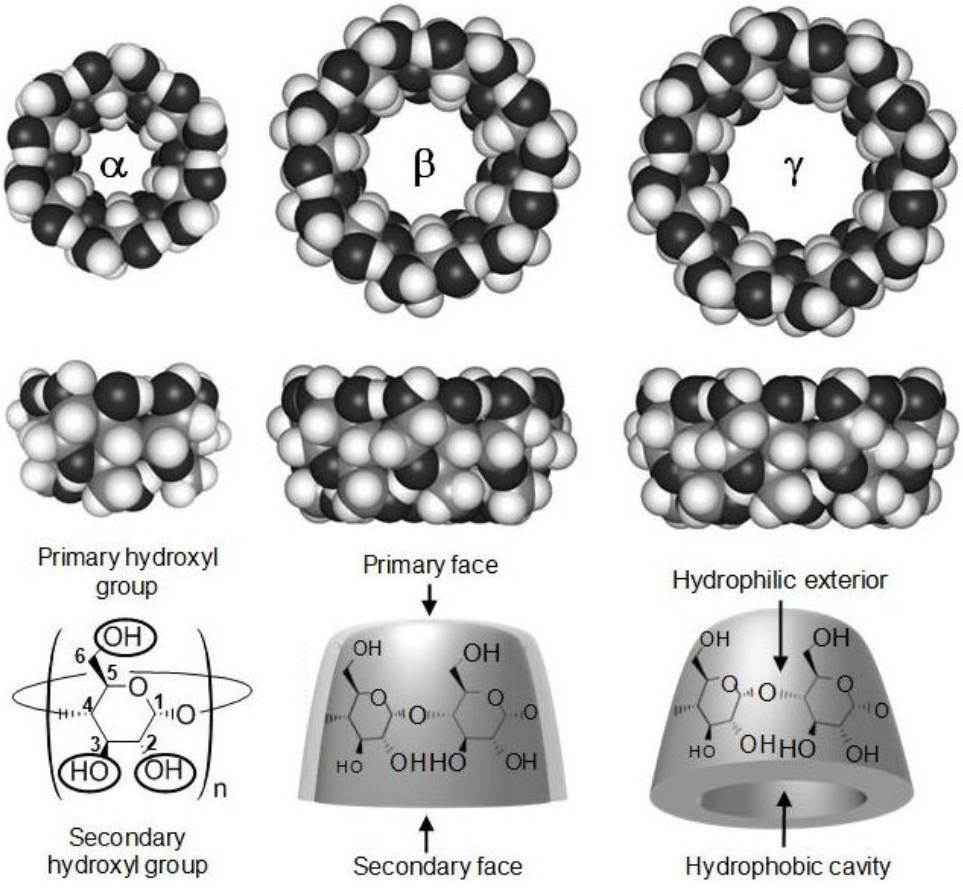



*21.1* Enzymatic production of native cyclodextrins from corn starch.

From an historical point of view, the CDs synthesis occurs in two steps: the starch hydrolysis by the CGTase, resulting in a mixture of α-, β- and γ-CD with six, seven and eight

glucose units per molecule due to the helical structure of the starch, and the separation and purification of the three natural CDs. The simplest method to separate α-, β- and γ-CD from the reaction mixture is the selective precipitation by forming inclusion complexes with an adequate guest molecule (for example, α-, β- and γ-CD crystallize with 1-decanol, toluene and cyclohexadec-8-en-1-one, respectively). However, this kind of production was associated with considerable cost due to the separation process. Nowadays, the elucidation of the DNA sequence involved in the production of the CGTase allows to isolate selective α-, β- and γ-CGTase, which further increases the yield while decreasing the production cost (Toth, 2005).

From a structural point of view, the glucopyranosyl residues of the three common CDs are linked in a ring by α-1,4 glycosidic bonds. All glucose residues are in a $^4C_1$ (chair) conformation (Figure 21.2, Szejtli, 1998).



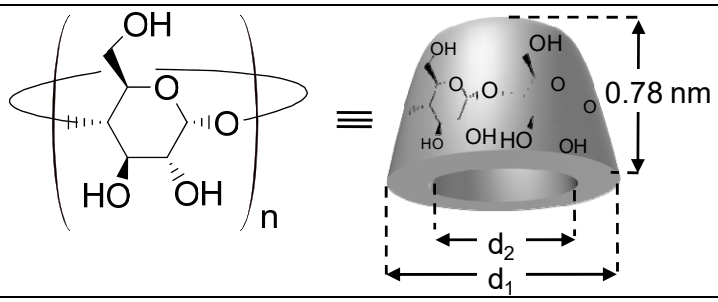

*21.2* Molecular structure and schematic representation of native cyclodextrins.

These three CDs have similar structures (in terms of bond lengths and orientations) apart from the structural necessities of accommodating a different number of glucose residues. CDs can be topologically represented as truncated cone (*e.g.* a bottomless bowl-shaped) stiffened by H-bonds between the secondary hydroxyl groups (*e.g.* 3-OH and 2-OH) around the outer rim. The H-bond strengths are α-CD < β-CD < γ-CD. The flexible primary hydroxyl groups are also capable of forming linking H-bonds around the bottom rim but these are destabilized by dipolar effects, easily dissociated in aqueous solution and not normally found in crystalline structures. In α-CD, the 3-OH groups play the role of H-bonds donor whereas the 2-OH groups are acceptor. In contrast, an inversion is observed for β- and γ-CD (Saenger *et al.* 1998).

In solution, the larger and the smaller openings of the cone expose to the solvent the secondary and the primary hydroxyl groups, respectively. This arrangement allows a variation of the polarity between the exterior and the interior of the truncated cone: CD rings are amphipathic. Indeed, the primary and the secondary hydroxyl groups, oriented to the narrow and the wider edge of the cone, allow a hydrophilic exterior. In contrast, the cavity has a "hydrophobic" character due to carbons (*e.g.* $C_3$-H and $C_5$-H) and ethereal anomeric oxygen atoms. Therefore, CDs present a good aqueous solubility with the possibility to complex hydrophobic residues of molecules with remarkably sensitivity and selectivity depending of the cavity size (Table 21.1). Indeed, in aqueous solution, the hydrophobic cavity of α-, β- and γ-CD contains about 2, 6 or 9 poorly held water molecules which can be easily displaced to accommodate hydrophobic molecules (*e.g.* aroma compounds or lipophilic drugs, Uekama *et al.* 1998, Loftsson & Brewster, 2013). For instance, α-CD forms inclusion complexes with aliphatic residues (*e.g.* decanoic acid) whereas β-CD prefers small aromatic, bicyclic or tricyclic compounds (*e.g.* adamantane) and γ-CD accommodates easily larger hydrophobic

molecules (*e.g.* the partial inclusion of fullerene $C_{60}$). The most commonly reported host:guest ratios are 1:1, 2:1 and 1:2 (Rekharsky & Inoue, 1998). The binding is an exothermic process (*i.e.* $\Delta H < 0$). However, the binding is also entropy driven due to the reduction of the hydrophobic surface in contact with water and the release of water molecules from the cavity to the bulk phase (see below).

**Table 21.1.** Main properties of the native cyclodextrins.

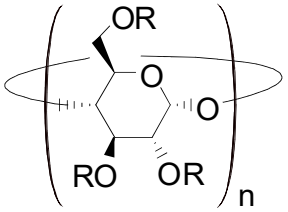
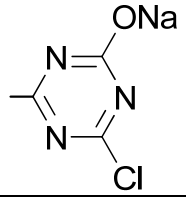



| | n | Mass | $d_1$ (nm) | $d_2$ (nm) | Cavity volume ($nm^3$) | Aqueous solubility (g/L)[a] | Hydrate $H_2O$ (cavity)[a] | Indicative price (€/g)[b] |
|---|---|---|---|---|---|---|---|---|
| α-CD | 6 | 972 | 1.37 | 0.50 | 0.174 | 129.5 | 6.4 (2.0) | 0.73 |
| β-CD | 7 | 1134 | 1.53 | 0.65 | 0.262 | 18.4 | 9.6 (6.0) | 0.48 |
| γ-CD | 8 | 1296 | 1.69 | 0.85 | 0.472 | 249.2 | 14.2 (8.8) | 4.76 |

[a] Taken from Sabadini *et al.* 2006. [b] Fine chemical grade price obtained from CycloLab Cyclodextrin Research and Development Laboratory Ltd., Budapest, Hungary. It is noteworthy that the price will depend on purity and technological grade of the CD.

The formation of the inclusion compounds allows CDs to be used to greatly improve the water solubility of hydrophobic compounds. This is the reason why CDs have attracted much interest for pharmaceutical applications (see below). Since the water-solubility of native CDs ranges from 18 to 232 g/L, a variety of modified CDs has been developed to improve the formation of inclusion complexes and their solubility. Indeed, the hydroxyl groups allow the introduction of various functional groups (Khan *et al.* 1998). For instance, some native and chemically modified CDs are presented in Table 21.2.

**Table 21.2.** Structures and acronyms of some modified cyclodextrins.[a]

| | Abbreviation | Substituent |
|---|---|---|
|  | **ME** | –H or –$CH_3$ |
| | **HP** | –H or –$CH_2CH(OH)CH_3$ |
| | **S** | –H or -$SO_3Na$ |
| | **SBE** | –H or –$(CH_2)_4SO_3Na$ |
| | **CM** | –H or –$CH_2CO_2Na$ |
| | **MCT** | –H or  |

[a] ME: methyl; HP: 2-hydroxypropyl; S: sulfo; SBE: sulfobutyl ether; CM: carboxymethyl; MCT: monochlorotriazinyl.

## 21.2.2. Toxicological properties

In the literature, detailed studies of toxicology, mutagenicity, teratogenicity and carcinogenicity were carried out for the native CDs (Stella & He, 2008). The cellular toxicity is directly correlated to their ability to complex the membrane phospholipids and the cholesterol. In consequence, CDs have an *in vitro* hemolytic activity in the order β-CD > α-CD > γ-CD (Irie & Uekama, 1997). However, the toxicological implication *in vivo* is considered negligible. The general toxicity on laboratory animals has been also reported in the literature (Saenger, 1980). The results support no acute intoxications (*i.e.* no inflammatory response, no cell death and no cell degeneration). The effect on human gastrointestinal tract is also minimal (Stella & He, 2008). However, α- and β-CD present renal damage and dysfunction but only at high concentrations (Thompson, 1997). A standard battery of reproductive and developmental tests has been performed indicating that none of the tested CDs are genotoxic, embryotoxic, teratogenic or mutagenic (Stella & He, 2008). All the human

clinical experiences indicate that the CDs can affect the human organism only at extremely high concentrations. Finally, it is noteworthy that various products using CDs are approved or undergo evaluation by regulatory agencies for use in food and pharmaceuticals. Indeed, β-CD was admitted in some countries as food additives (E 459) in the form of pellets and pills, with the restriction "*only as necessary*" (Buschmann *et al.* 2001).

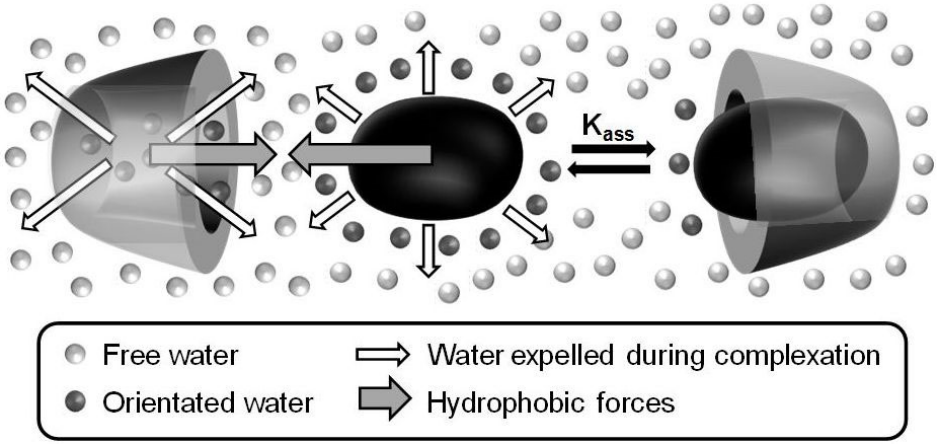
For textile finishing, the CDs modified with reactive groups are used. The most used anchor-group is the monochlorotriazinyl residue (MCT, Reuscher & Hirsenkorn, 1996) which reacts with the cellulose hydroxyl groups leading to permanent covalent bonds between the fibers and the CDs (see below). For these MCT-β-CD, the toxicological properties are very important because most of times the human skin is in permanent contact with textiles during the various activities of everyday life when touching or wearing fabrics. According to the Organization for Economic Co-operation and Development (OECD) tests, the MCT-β-CD derivatives have a neutral effect on the human body. Indeed, the median lethal dose (LD50) is greater than 2 g/kg (Reuscher & Hirsenkorn, 1996). Moreover, the MCT-β-CD derivatives have no effect on skin (*i.e.* the OECD tests No 404 and No 406 indicate no dermal irritation/corrosion and no skin sensibilization, respectively). No mutagenic evidence was found in studies carried out on bacteria for the MCT-β-CD (OCDE test No 471). Comparable results were also obtained for the textile products finished with this type of derivatives, these results being backed up by the first clinical tests with T-shirts, which detected no human skin irritations (Buschmann *et al.* 2001). Finally, α-, β-, and γ-CD are also all generally recognized as safe by the Food and Drug Administration (Stella & He, 2008).

### 21.2.2. Binding Properties

As mentioned above, CDs are typical host molecules which can form inclusion complexes with various hydrophobic molecules. These guest molecules can be completely or partly

accommodated inside the cavity. The inclusion complexes exist in solid state as well as in solution. In aqueous solution, the solubilized CDs accommodate some water molecules inside the cavity with energetically unfavorable interactions (Szejtli, 1998). On the other hand, these water molecules are expelled outside and favorable interactions take place between the host and the guest molecule (Figure 21.3). In other words, the well-known hydrophobic effect is the driving force of complexation process: the complexation is entropy-driven (Junquera *et al.* 1999). Indeed, pure water molecules adopt a structure that maximizes the entropy due to the formation of a highly dynamic 3-D hydrogen bonding network. In the presence of hydrophobic molecules (or apolar residues), the H-bonds are partially disrupted around the nonpolar solute. Indeed, the nonpolar molecules are unable of forming H-bonds with water. As consequence, a cavity is created in which water molecules form a "cage" around the solute (*i.e.* the hydrophobic molecule is locked in a clathrate-like basket shape). In this clathrate, the H-bonds are reoriented tangentially to such surface to minimize the number of disrupted H-bonds. The same behavior can be invoked for the water molecules inside the CD cavity. In this case, there are fewer mobile water molecules in the system. In order to maximize the entropy of the system, the water molecules are expelled from the CD cavity whereas the hydrophobic molecule shifts inside the CD cavity to form the inclusion complex. Upon complexation, the surface area exposed to water is reduced and the disruptive effect is minimized: a smaller surface area is obtained for the inclusion complex than the total surface area created by the hydrophobic cavity and the nonpolar molecule. Some water molecules are now available to recreate the dynamic 3-D hydrogen bonding network thus the final entropy of the system is higher than the initial one (*i.e.* $\Delta S > 0$, Junquera *et al.* 1999). Therefore, the complexation was found to be entropy-driven at room temperature because of the reduced mobility of water molecules in the solvation shell of the non-polar solute. However, it is

noteworthy that at higher temperature, when water molecules become more mobile, this energy gain decreases along with the entropic component (Rekharsky & Inoue, 1998).



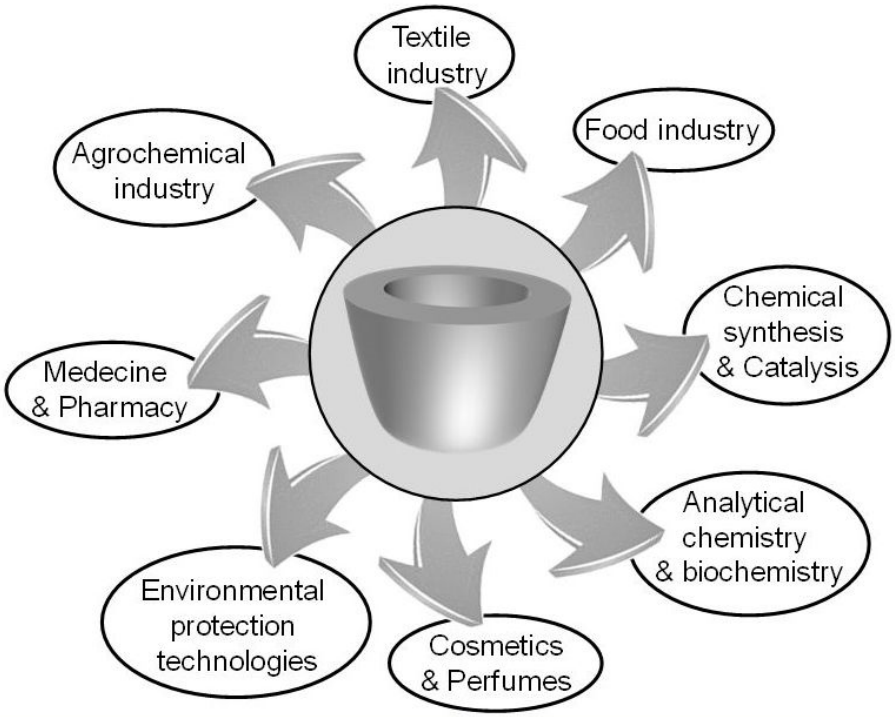

*21.3* Cyclodextrin/guest inclusion complex formation upon hydrophobic effect.

Moreover, some complementary interactions (*i.e.* van der Waals forces and H-bonds) appear between the guest and the CD molecule. In addition, the cycle stress decreases leading to a low energy steady state. All these non-covalent interactions ensure the complex cohesion. It is noteworthy that the presence of substituent can be used to maximize the recognition between the guest and the CD. For instance, the introduction of ionic residues on the CD can be used to create ionic interaction between complementary ionic regions. In other words, the number of binding sites of the CD host can be adjusted as function of the guest structure. It is noteworthy that binding constants and stoichiometries can be easily determined by various methods such as NMR, phase solubility, UV-visible, potentiometry, surface tension measurements, *etc*. (Rekharsky & Inoue, 1998, Leclercq *et al.* 2013b). Classically, the CD:Guest molar ratio is of 1:1. However, various stoichiometries can also be obtained (see above). The mechanism for higher stoichiometries involves a sequential stepwise complexation process depending on various factors: (*i*) the CD used (*i.e.* the macrocycle size and the nature of substituent), (*ii*) the variations of temperature, concentration and pH, (*iii*) the solvent polarity, and (*iv*) the presence of other compounds (*e.g.* competition between various

guest). Based on the Le Chatelier's principle, which state that a system always acts to oppose changes in chemical equilibrium, the inclusion complexes can be easily separated by preferential complexing, by ultrasounds or by heating (see below, Hirsch *et al.* 1985).

### 21.2.3. Applications in Free Form

The binding properties of the CDs are very useful for numerous applications. Some of them are presented in Figure 21.4 (Del Valle, 2004).




*21.4* Principal applications of cyclodextrins.

From an academic point of view, CDs have a potential interest to perform chemical and catalytic reactions. Indeed, they can control the regioselectivity of reactions while improving performance (Leclercq *et al.* 2005). They act as carriers or emulsifiers of hydrophobic substrates in aqueous phase (Leclercq *et al.* 2013a). They are often used for development of artificial enzymes (Breslow & Dong, 1998). CDs are also increasingly used in analytical chemistry and biochemistry, including HPLC (High Performance Liquid Chromatography).

Indeed, CDs change the affinity of the injected molecules for the stationary phase, and thus alter their retention time (Xiao *et al.* 2012). Moreover, CDs allow the separation of enantiomers because of their chirality. The exaltation of the responsiveness of photosensitive molecules upon complexion is used in fluorimetry (Hamasaki *et al.* 1993).

From an industrial point of view, there are three factors that have longtime prevented their industrial use: *i*) the cost of production, *ii*) the incomplete toxicological studies and *iii*) the lack of knowledge pharmaceutically (Del Valle 2004). As these information are now available (see above), CDs in their free form (*i.e.* in solid or in solution) are now commonly used on an industrial scale. Thus, in the agrochemical field, the CDs are used to improve the efficiency of fertilizers, herbicides, insecticides, repellents, *etc*., and to solidify liquid biocides in order to achieve a better stability during their storage (Nardello-Rataj & Leclercq, 2014). The industrial applications of CDs are also very important in cosmetic. Indeed, they improve the solubility of vitamins A and E, they stabilize the taste and colors of toothpastes, they play also the role of anti-plaque compounds, they reduce the irritation caused by shampoo formulations, they protect perfumes and allow a long-lasting fragrance release (Buschmann & Schollmeyer, 2002). In environmental protection technologies, CDs are used to soil remediation or to reduce oxidizer requirements in paper production (Boyle, 2006). CDs are also commonly used in food industry to: (*i*) preserve aromas, (*ii*) extend the duration of chewing gum taste, (*iii*) trap odor molecules, (*iv*) protect molecules against oxidation or thermal decomposition, (*v*) prepare cholesterol free products (from milk, butter, eggs, *etc*.), and (*vi*) emulsify mayonnaise, desserts and sweets (Szente & Szejtli, 2004). In paint industry, CDs improve the compatibility of ingredients, the stability of the paint as well as the range of colors and the quality of dyes (Szejtli, 2004).

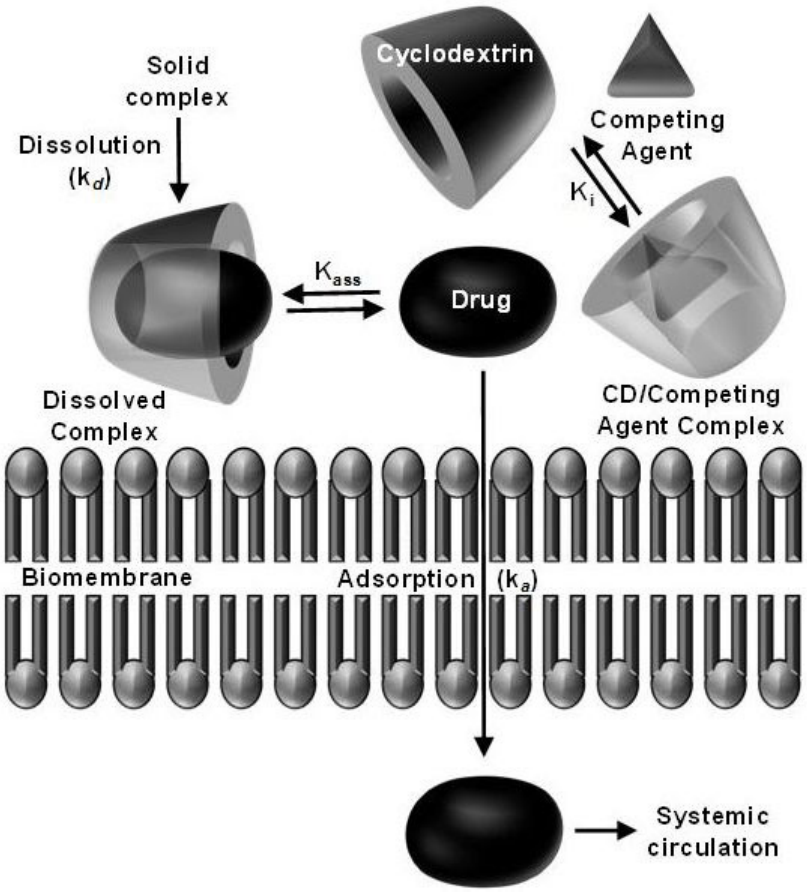
However, the first global consumer of CDs is undoubtedly the pharmaceutical industry (Loftsson & Brewster, 2011). Indeed, due to their hydrophobic cavity and hydrophilic outside,

they can form inclusion complexes with a wide range of hydrophobic drugs. Upon complexation, the biologically active molecules solubility is improved. Moreover, CDs act as carriers in which hydrophobic drugs can be released under specific conditions on a specific target. In most cases the mechanism of controlled-degradation of such complexes is based on pH change, leading to the loss of hydrogen between the host and the guest molecules (Zhang & Ma, 2013). Alternative means for the disruption of the complexes take advantage of heating or enzymatic cleavage of α-1,4 links between glucoses (see above). In consequence, the complexation enhances the bioavailability of medications. For instance, the controlled release of nicotine in the smoking cessation treatment occurs by the use of β-CD/nicotine (Nicorette® sublingual tablets). Numerous formulations that used CDs are commercialized worldwide to complex fungicides, bactericides, anti-inflammatories, *etc*. For instance, the β-CD/piroxicam, a non-steroidal anti-inflammatory drug (NSAID), is also used in various formulations distributed under various commercial names (*e.g.* Brexin®, Flogene® and Cicladon®, Loftsson & Duchêne, 2007). In addition, side effects of the active ingredients may also be reduced (*e.g.* irritation intestinal mucosa). For instance, they can used to decrease by 6-fold the propylene glycol, responsible for the greasy and sticky effects, of anti-alopecia formulation (Alopexy® 2%, Delaunois & Navarro, 1997). They also reduce the sensitivity of the active ingredients to light, heat, hydrolysis and oxidation. Moreover, aqueous CD solutions can generate aerosols suitable for pulmonary deposition. The α-CD has been authorized for use as "*a novel food ingredient*" (*e.g.* dietary fiber, Furune *et al.* 2014) in the European Union since 2008 to reduce blood sugar peaks following a high-starch meal (Decision 258/97/EC of the European Parliament and of Council of the 26 May 2008). α-CD is also used in weight loss supplements and anti-obesity medications to bind the fat (Buckley *et al.* 2006). They can also transform liquid compounds in solids (powder or tablets) by precipitation of inclusion complexes. For instance, CDs are used to encapsulate ethanol and to

produce alcoholic beverages when mixed with water. The other applications of CDs are the treatment of inflammation or throat infection (with iodine), the coronary dilatation (with nitroglycerin), the anti-ulcerate (with benexate), the complexation (*e.g.* vectors) for vitamins or hormones, the reduction of side-effects and the increase in efficiency of anti-cancer drugs (Calleja *et al.* 2012).

The wide use of CDs for pharmaceutical purposes can be explained by the reversibility of the host/guest binding. However, when the complexes are dissociated, the reverse process occurs according to the binding constant value ($K_{ass}$). For solid complexes, the dissociation occurs quickly when water is added. Despite the initial dissociation energetic barrier due to the interactions between guest and host molecules, it is the concentration gradient which prevails, and the guest drugs leave the host molecules. Given the small concentration in solution, the complex reformation is impossible, the released molecule remains in solution and can interact with the biological target with a controlled release (Challa *et al.* 2005). For solutions, the complexes act as a reservoir of drugs which are readily available for adsorption onto the biological target. Indeed, as the free drug concentration is in equilibrium with the drug adsorbed onto the target and with CD/drug complexes, the decrease of free drug concentration, due to the drug adsorption by the target, alters the equilibrium between free and complexed drug: the drug is progressively released in solution (Figure 21.5).

The last, but one of the main fields of application of CD complexes, is the obtaining of smart textiles. Indeed, the applications presented above can be transposed to the textile technology where the CDs are used to fix on the textile fibers various active compounds; *e.g.* antipathogens, anti-inflammatories, insecticides, essential oils, venotonic molecules, *etc*. (Szejtli, 2003). Before we move on to look at CD/drug complexes and their applications, the first step to obtain these new and smart textiles is the binding of CDs on the fabrics.




*21.5* Mechanism of controlled release of drug from free cyclodextrin inclusion complex to a given biological target.

## 21.2.4. Interaction with Textile Support

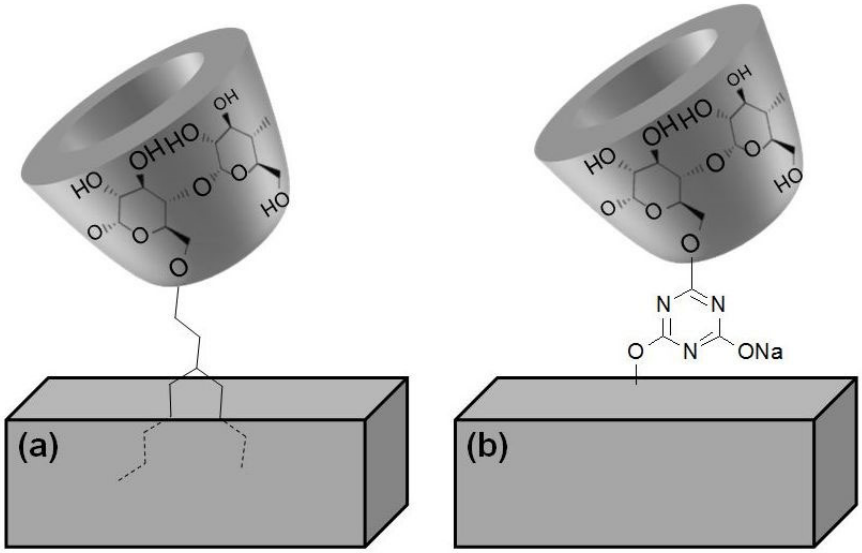
From a general point of view, CDs can be "fixed" on textile materials by means of various methods including spraying, printing, padding, grafting, surface coating, impregnation, ink jet printing, *etc*. (Table 21.3, Bhaskara-Amrit *et al.* 2011). These methods can be divided in two: physisorption and chemisorption. In comparison with chemisorption, in which the electronic structure of bonding molecules is changed and covalent or ionic bonds are formed, physisorption can only be observed in the environment of low temperature (at room temperature) and in the absence of strong chemisorptions. For instance, the physical

adsorption is based on the use of hydrophobic groups which “penetrate” the polymer surface (see Figure 21.6a).

**Table 21.3.** Possible interactions between cyclodextrins and some textile fibers (PES: polyester, PA: polyamide, PAN: polyacrylonitrile).[a]

| | Natural fibers | | Synthetic fibers | | |
|---|---|---|---|---|---|
| Interactions | Cotton | Wool | PES | PA | PAN |
| van der Waal forces | × | × | ✓ | ✓ | ✓ |
| Ionic interactions | × | ✓ | × | ✓ | ✓ |
| Covalent bonds | ✓ | ✓ | × | ✓ | × |
| Cross-linking agents | ✓ | ✓ | ✓ | × | × |
| Graft polymerization | ✓ | ✓ | ✓ | ✓ | ✓ |

[a] Adapted from Andreaus *et al.* 2010.

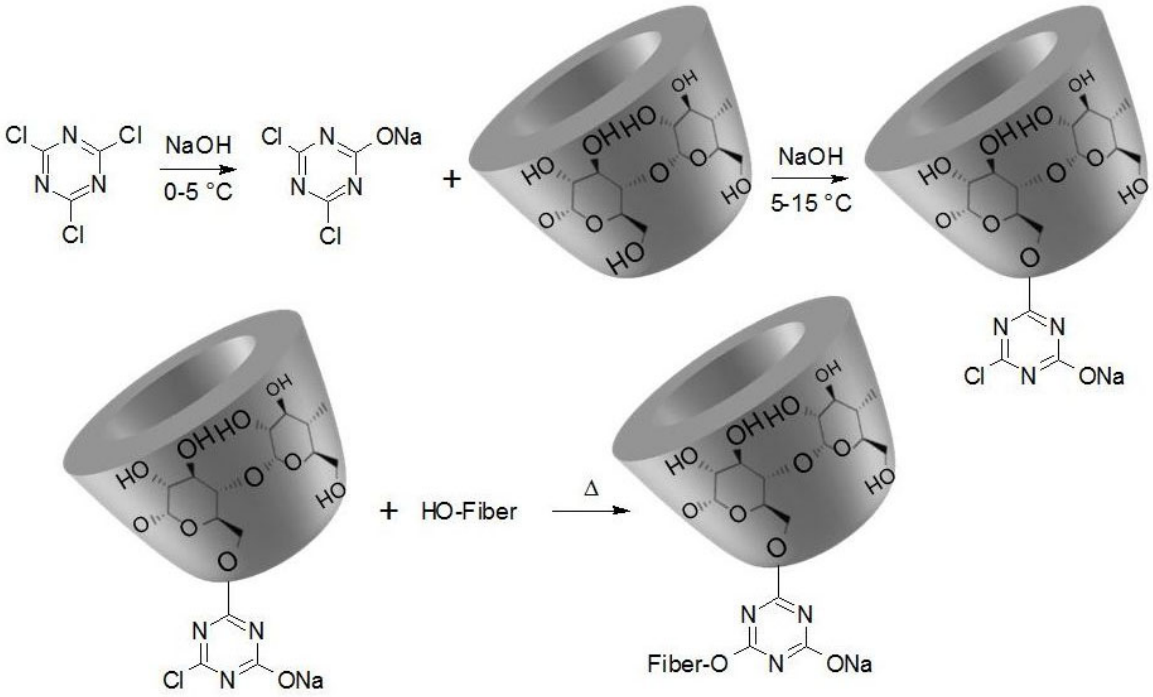



*21.6* Schematic representation of physisorption (a) and chemisorption (b) of modified cyclodextrins at the polymer surface.

This method is particularly useful for hydrophobic nonionic CDs that can be fixed to hydrophobic textiles (*e.g.* polyamide, polyester and polyacrylonitrile) through apolar

interactions. This physisorption can be very useful for removing unpleasant smells. Indeed, the textile is treated by spraying with a solution of CD. As CDs are no binding to the fibers, the undesirable complexes can be removed by washing (Trinh *et al.* 1997). In this case, CDs are not reused and the application of this system is limited to "deodorization". In contrast, the permanently fixation of CDs on the fabrics can be achieved by chemisorption. Here, the fixation which involves a chemical reaction between the surface and the adsorbate allows the generation of chemical bonds at the adsorbent surface (see Figure 21.6b).

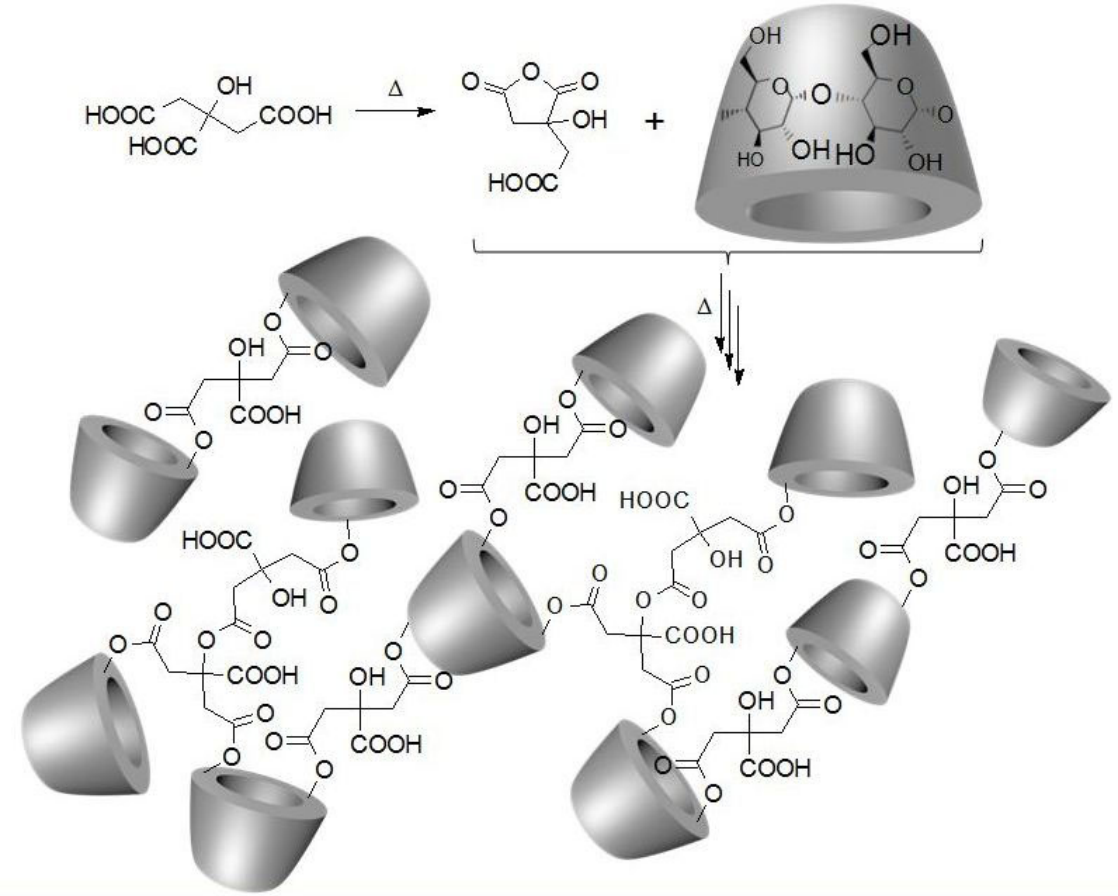
In a more detailed way, the grafting of CDs on cellulose fibers is common and generally easy to perform. The first cellulose-CD copolymer has been described in 1980 (Szejtli *et al.* 1980). This method involves the use of epichlorohydrin as cross-linking reagent to fix CD to alkali-swollen cellulose fibers. However, the majority of chemical adsorption prior requires the addition of reactive residues on the native CDs. Since 1996, one of the most used residues is probably the monochlorotriazinyl binding to CD (*e.g.* MCT-β-CD, Reuscher & Hirsenkorn, 1996). This kind of CDs is obtained by: (*i*) the treatment of 2,4,6-trichloro-1,3,5-triazine in the presence of sodium hydroxide to obtain 2,4-dichloro-6-hydroxytriazine sodium salt, and (*ii*) the addition of native CDs to this derivate in the presence of sodium hydroxide allows the formation of MCT-CD. Finally, the CD grafted fibers are obtained easily by the immersion of the textile material in a bath containing the MCT-CD through a simple nucleophilic substitution (Figure 21.7). The fixed CDs can be used to complex smells or perfumes. In contrast to the textiles spraying with a solution of CD, CDs can be reused and new substances can be reloaded inside the CD cavities. For instance, odor can be controlled by applying an antimicrobial finish (see below). Upon humidity, the biocide is progressively released and the odor molecules can be trapped in the cavities of the CDs and can be removed during laundering. This system can be used on T-shirts and other sports apparel.




*21.7* Synthesis of monochlorotriazinyl-cyclodextrin (MCT-CD) and its grafting on the fabric.

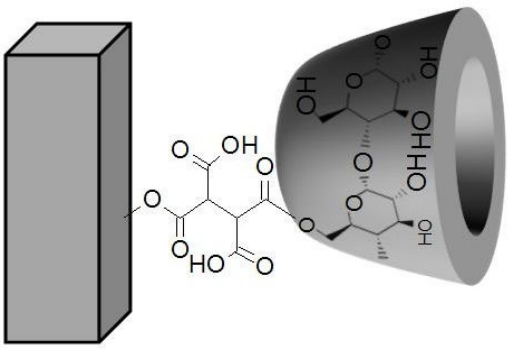
The grafting of CDs on synthetic fibers (*e.g.* polyester, polyamide, *etc*.) is also common and generally easy to perform. For instance, polyamide fibers, used in the medical field for different prostheses, can be modified by the incorporation of CDs which complex antibiotic molecules. In this case, a controlled release of the antibiotic is obtained in order to avoid hazardous infections (see below). From a synthetic point of view, the CDs are attached by the use of citric acid (CTR) as reticulating agents (Figure 21.8, Martel *et al.* 2002). It is noteworthy that the reaction occurs between CDs and citric acid to form polyester (*i.e.* poly(CTR-CD)). Finally, this polyester interacts with the polyamide fabric to form a continuous film. Another similar method of grafting uses the 1,2,3,4-butanetetracarboxylic acid (BTCA) as cross-linking agent (Martel *et al.* 2002). This method can be used with cotton, wool, polyester, polyamide, polyethylene terephthalate, *etc*. In this method, the fibers are treated with β-CD and BTCA in aqueous solution. BTCA molecules react *via* anhydride formation with hydroxyl groups of β-CD and form nano-assembly which can be physically

attached to the fibers surface at the elevated temperature. Such assembly could be schematically presented as shown in Figure 21.9.



*21.8* Reaction of cyclodextrins with citric acid to form poly(CRT-CD).

Finally, newer methods are also reported in the literature. For instance, 6-monodeoxy-6-mono(*N*-tyrosinyl)-β-cyclodextrin can be fixed on cotton surface by enzymatic reactions (Agrawal *et al.* 2010). In conclusion, a large variety of modified fabrics can be easily obtained and the number of binding sites on textile can be easily controlled by the number of CDs incorporated.




*21.9* Nano-assembly of β-cyclodextrin *via* 1,2,3,4-butanetetracarboxylic acid onto cotton textile.

## 21.2.5. General applications of cyclodextrins in textile industry

From a general point of view, CDs are used in textile industry, as in free form, to improve: (*i*) the physicochemical properties of the various guest molecules (*e.g.* wettability, reduced vapor pressure, *etc.*), (*ii*) the controlled release and bioavailability, (*iii*) the shelf-life, (*iv*) the storage conditions, and (*v*) the biodegradability (Nardello-Rataj & Leclercq, 2014). In such conditions, four mains fields can be highlighted: (*i*) their use as auxiliary substances in laundering, (*ii*) their use in fibers dyeing, (*iii*) their use in textile finishing, and (*iv*) their use in medication delivery. In this section, these key advantages are illustrated by some typical examples. However, it is noteworthy that the separation of the CDs applications is purely fictive as the combination of advantages is often reported.

CDs can be used in washing liquids for various reasons. Indeed, in the literature it is known that CDs form inclusion complexes with detergent molecules. As surfactants have potential drawbacks on the human body or on the environment (*e.g.* skin irritation, hemolysis, protein denaturation, *etc*.), the addition of CDs to the final rinse water reduces the residual surfactant content on the laundered fabric from 209 to 134 ppm (Dehmer *et al.* 1998). In other words, CDs reduce the potential harmful interaction of detergent molecules with the human

skin. In addition, CDs can act as defoaming agents and may be used to reduce water consumption. Moreover, CDs may be used to prevent colors from running in textiles during washing or rinsing (Weiss *et al.* 1998). Finally, CDs can be used to avoid the fragrances evaporation during the storage of washing powders. Indeed, perfumes complexed by CDs are more stable and are easily displaced by the detergent molecules during the washing process.

CDs can be also used in the textile dyeing. Indeed, CDs increase the affinity of the dyestuff to the textile, but decrease the diffusion coefficient into the fabric. For instance, disperse dye-printed cotton and cotton-polyester fabrics, with improved dye absorption, were prepared by treating the fabric with α- or β-CD and printing the fabric with pastes containing a disperse dye (Okano, 1978). Moreover, the light stability of the textiles was improved by using UV-filter/ME-β-CD complexes and textile dyes (Remi *et al.* 1996).

CDs, physically adsorbed, are used to remove sweat or sweat degradation from the textile by preventing their penetration into the fiber interior (see above, Poulakis *et al.* 2002). In these formulations, complexes can be easily removed by simple washing. CDs can be also used to incorporate fragrance in synthetic fiber polymers. In appropriate conditions, wash resistant fragrant fabrics can be obtained (Fujimura, 1985). Indeed, in the presence of CDs, the vapor pressures of perfumes are reduced. As consequence, the properties of fragrant textiles are clearly improved.

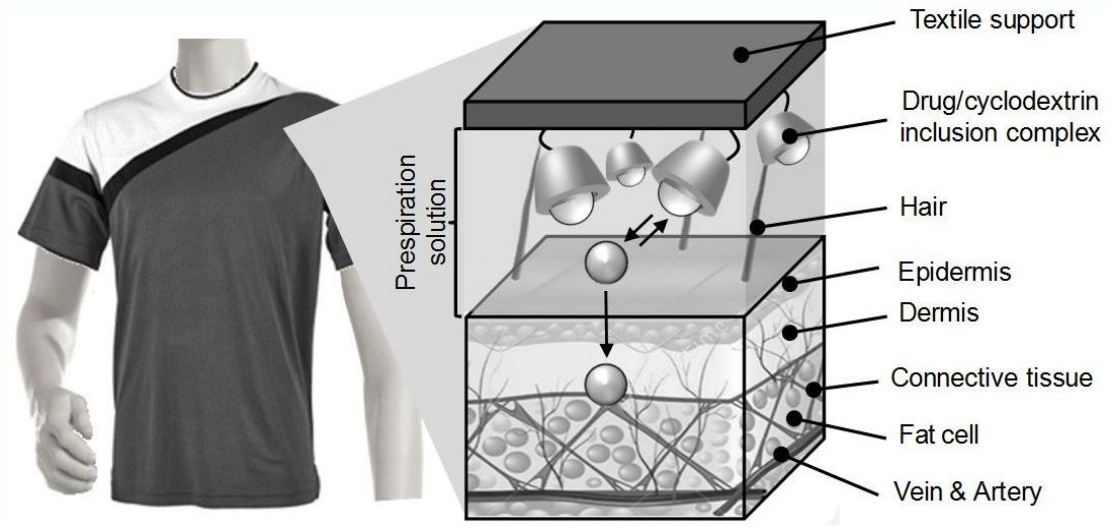
CDs and their inclusion complexes can be also very useful for some miscellaneous uses: (*i*) the reinforcement of rubbers, (*ii*) the removal of harmful organic pollutant substances from textile finishing process by the formation of inclusion complexes, and (*iii*) the prevention of starch depositing on the iron (Szejtli, 2003).

However, the most important application of CDs on textiles industry is to obtain textiles with pharmacological properties. Indeed, the chemically bound CD retains its complex

forming ability and can be “loaded” with biologically active guests (drugs, insect repellents, antimicrobial agents, *etc*.). The fabrics made from such fibers ensure drug release upon contact with skin. The following section is devoted to this topic.

## 21.3. Cyclodextrins Grafted on Textiles for Medical Purposes

As presented in the previous section, upon CD encapsulation, the physicochemical properties of the guest molecules are changed (*e.g.* the solubility of drugs increases, the vapor pressure is reduced, the stability against light and oxygen increases, *etc*.). When CDs are anchored to textile fibers, we obtained new smart medical products which allows the simply and controllably administration of various medication molecules *via* complexation (see above). Indeed, the sustained drug delivery is due to the equilibrium between the drug complexed by CDs and the drug released in perspiration prior to the diffusion in dermis (Cezar-Doru *et al.* 2014). A scheme of this diffusion process is illustrated in Figure 21.10.



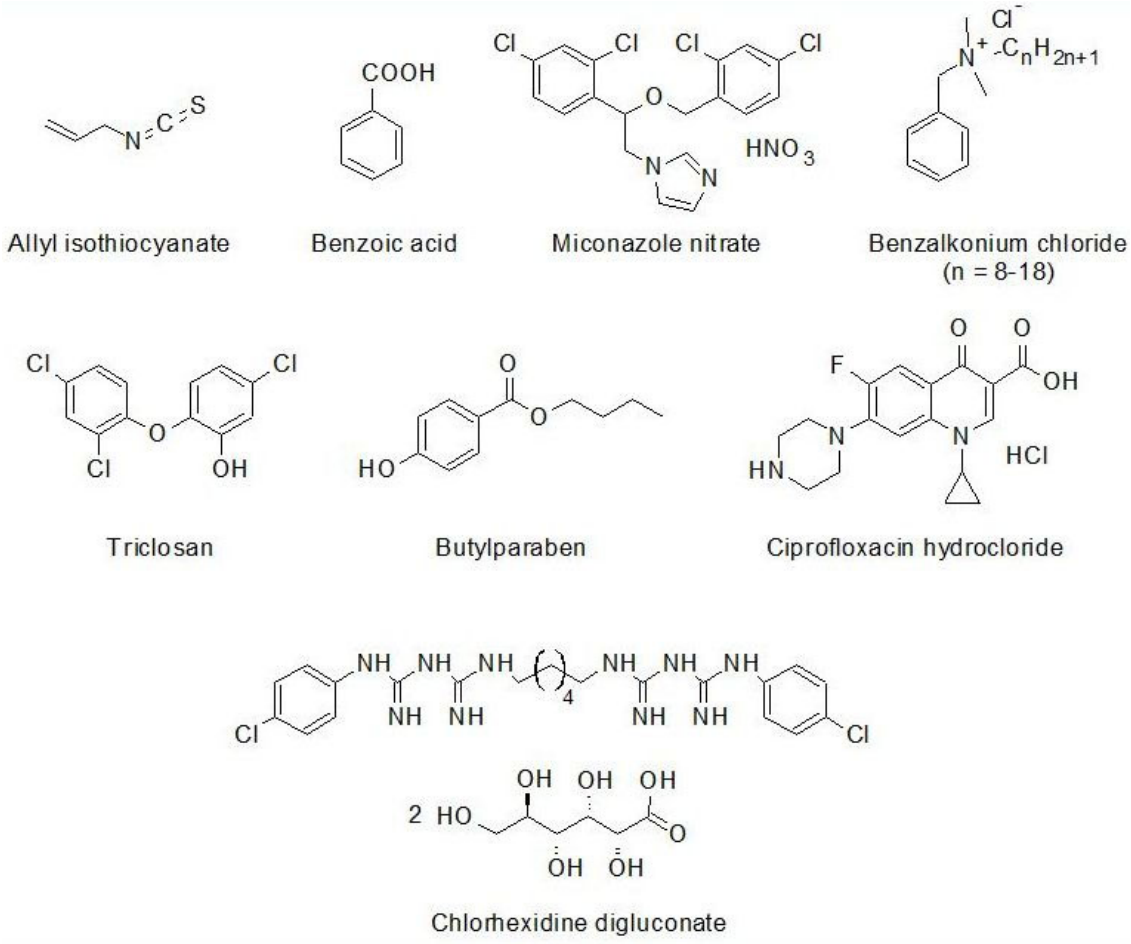

*21.10* Diffusion principle of drug from cyclodextrin inclusion complexes grafted onto textile to dermis.

### 21.3.1. Antipathogen Textiles

Pathogen is used to mean an infectious agent, including bacteria, virus, prion, fungus or protozoan. The host may be an organism: vertebrate, insect, plant, fungus or bacterium. To prevent and to treat these infections, antipathogen agents, defined as "*active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means*" (Directive 98/8/EC of the European Parliament and Council of the 16 February 1998, Article 2.1.a), are commonly used. In the last decades, the antipathogen agents in textile industry for health care and hygiene applications received a lot of attention. Indeed, to prepare medical bandages, the complexation of antipathogen agents is very useful to achieve a sustained drug release from the fabrics upon contact with skin. However, for sake of clarity, only some typical examples of CD/biocide inclusion complexes on textile are reported. It is noteworthy that the chemical structures of the active biocides mentioned in this section are presented in Figure 21.11.

Antipathogen medications based on iodine, in various forms (*e.g.* elemental iodine or water-soluble triiodide), are very active to treat superficial skin infections. It is noteworthy that the water-soluble triiodide anion, $I^{3-}$, is generated *in situ* by adding iodide to poorly water-soluble elemental iodine. In this case, the reverse chemical reaction releases free elemental iodine available for antisepsis. Various topical solutions have been developed including: (*i*) tincture of iodine (e.g. iodine in ethanol, or iodine and sodium iodide in a mixture of ethanol and water), (*ii*) Lugol's iodine (iodine and iodide in water, forming mostly triiodide), and (*iii*) povidone-iodine (a stable chemical complex of polyvinylpyrrolidone). As CDs are known to complex iodine, a cellulose fabric containing chemically-bound β-CD (0.27 equivalent of β-CD/g) using epichlorhydrin has been patented in 1991. In order to

obtain a smart medicated bandage, this fabric was treated with 50 mL solution of 1% $I_2$ and 0.7% KI in 75% ethanol (Szejtli *et al.* 1991).

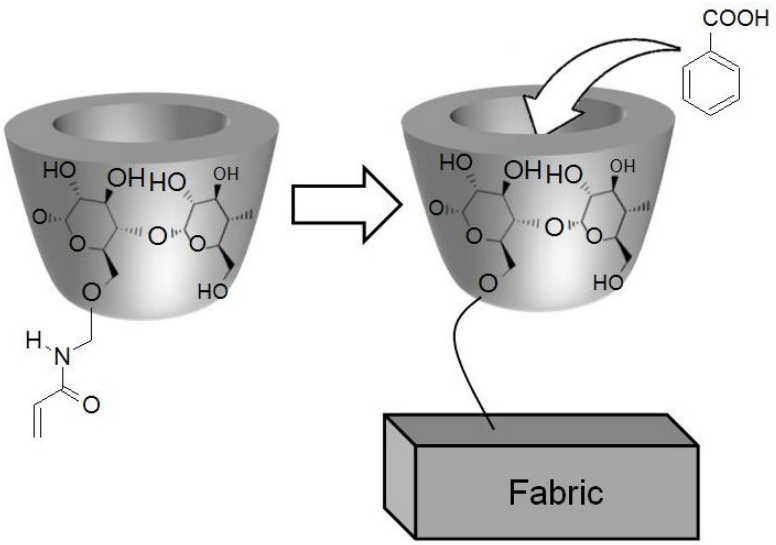



*21.11* Chemical structures of active biocides mentioned in this section.

In 1997, Yamamoto and Saeki published on anti-infective bed sheets containing CD inclusion compounds of antimicrobial agents for controlling infections in hospitals, old-age home, *etc*. As the allyl isothiocyanate (bactericide) is particularly volatile, its encapsulation by CDs is a smart solution in order to obtain anti-infective sheets (see Figure 21.11, Yamamoto & Saeki, 1997). The anti-infective sheets were easily prepared by mixing the inclusion complex particles with thermoplastic resin, followed by molding so that average particle size of the particles is larger than average thickness of the sheets. Particles of allyl isothiocyanate/β-CD inclusion complex (≈ 25 μm) showed antimicrobial activity against

various common pathogen strains (*e.g. Candida albicans*, *Salmonella enteritidis*, *Staphylococcus aureus*, *Escherichia coli*) while control particles of inclusion complex was not effective on *E. coli*. The antimicrobial particles were mixed with low-density polyethylene and the mixture was extrusion-molded, followed by stretching to give a 20 μm-thick anti-infective sheet. The same authors published in 1998, bed sheets containing non-crystalline calcium phosphate and CD inclusion compounds of allyl isothiocyanate as antimicrobial agents active against *C. albicans* and *S. aureus* (Yamamoto & Saeki, 1998).

In 2000, the grafting onto cotton fiber with acrylamidomethylated-β-CD (AAM-β-CD) has been reported in the literature (see Figure 21.12, Lee *et al.* 2000).




*21.12* Structure of acrylamidomethylated-β-cyclodextrin (AAM-β-CD) and schematic representation of an inclusion compound formed on the fabric's surface.

Firstly, the authors synthesized the chemically modified CD by the reaction of *N*-methylolacrylamide (NMA) with β-CD in the presence of formic acid as catalyst. After purification and initiation of the cotton cellulose backbone with ceric ion, the modified β-CD was grafted. The amount of grafted CD was determined by fluorescence measurements. The possibility of textile finishing of CD containing cotton fibers was investigated using an

archetypal antibacterial agent (*e.g.* benzoic acid, see Figure 21.11). Antibacterial activity against *S. aureus* of benzoic acid-treated samples were retained even after 10 laundering cycles, suggesting that utilization of CD in functional textile finishing is very promising.

The previous results have been used for the modification of cellulosic fabric (Tencel®) with β-CD to obtain biocidal textiles (P. Lo Nostro *et al.* 2002). The authors used two β-CD derivatives: the well-known MCT-β-CD and the AAM-β-CD. After the grafting, benzoic acid and iodine were included in the β-CD cavities at the textile's surface. The untreated and treated fabrics were evaluated through scanning electron microscope (SEM), differential scanning calorimetry (DSC), UV-visible spectra, X-ray diffractometry, water absorbency, breaking load loss. The results prove the inclusion of the biocidal compounds in the CD cavities. Moreover, the fabric's surface properties were not significantly modified by the chemical treatments. Finally, the biocidal properties of finishing fabrics were evaluated. The best activity is observed for benzoic acid included in AAM-β-CD-Tencel®, particularly against *S. aureus* and *C. albicans*. This cellulose fabric may be suitable for medicinal bandages.

In this context, the encapsulation of miconazole nitrate salt into the cavity of MCT-β-CD covalently bound onto textile fibers has been reported in 2008 (see Figure 21.11, Wang *et al.* 2008). The miconazole salt is an imidazole antifungal agent used topically to the skin or to mucous membranes to cure fungal infections. It is noteworthy that additional antibacterial and antiparasitic actions are also reported due to the inhibition of the ergosterol synthesis, a critical component of cell membranes. A grafting yield of about 5% was obtained when MCT-β-CD (60-100 g/L) and $Na_2CO_3$ (50-60 g/L) react at 150-160 °C during 5-8 min. In order to know the quantity of miconazole nitrate entrapped in the functionalized textile with MCT-β-CD, UV spectrophotometry, on modified and unmodified fabrics, have been performed. The

functionalized textile with MCT-β-CD was richer than the unmodified one (up to 8.2-fold). As expected, the biocidal activity against *C. albicans* was enhanced for the MCT-β-CD modified textile impregnated with the antifungal drug. The finished fabric retains its antifungal property after ten washes unlike the unmodified textile.

The immobilization of butylparaben and triclosan with the use of a cationic-β-CD polymer has been developed more recently (see Figure 21.11, Qian *et al.* 2009). The butylparaben is known to be an antimicrobial agents used in pharmaceutical suspensions whereas the triclosan is an antibacterial and antifungal molecule. The butylparaben is known to act by inhibiting DNA, RNA and enzymes (*e.g.* ATPase and phosphotransferase) synthesis. The biocidal mechanism of triclosan is greatly influenced by its concentration. Indeed, at high concentrations, triclosan acts as a biocide with multiple cytoplasmic and membrane targets, whereas, at the lower concentrations, triclosan is essentially bacteriostatic (Russel, 2004). In the last case, the cell membrane fatty acid synthesis of bacteria is inhibited due to the formation of a stable complex between enoyl-acyl carrier protein reductase, nicotinamide adenine dinucleotide and triclosan. One-step condensation of β-CD, epichlorohydrin and choline chloride (1/5/2) was used for the synthesis of the cationic-β-CD polymer (CP-β-CD). The aqueous solubility of butylparaben and triclosan encapsulated in the CP-β-CD polymer were improved from 0.001 to 2.80 and to 1.64 g/L, respectively. It is noteworthy that the aqueous solubility of butylparaben is greatly improved into the CP-β-CD cavities due to its smaller volume. The CP-β-CD polymers, loaded with triclosan and butylparaben, were adsorbed on cellulose fibers and the antimicrobial activities against *E. coli* and *Salmonella* were reported. The best activity is obtained for the triclosan loaded inside the CP-β-CD cavities. The biocidal mechanism of the CP-β-CD polymers was investigated by observing the morphology of *E. coli*. with atomic force microscopy (AFM). As the cell membrane was not affected by the CP-β-CD polymer loaded with butylparaben or triclosan, the authors proposed

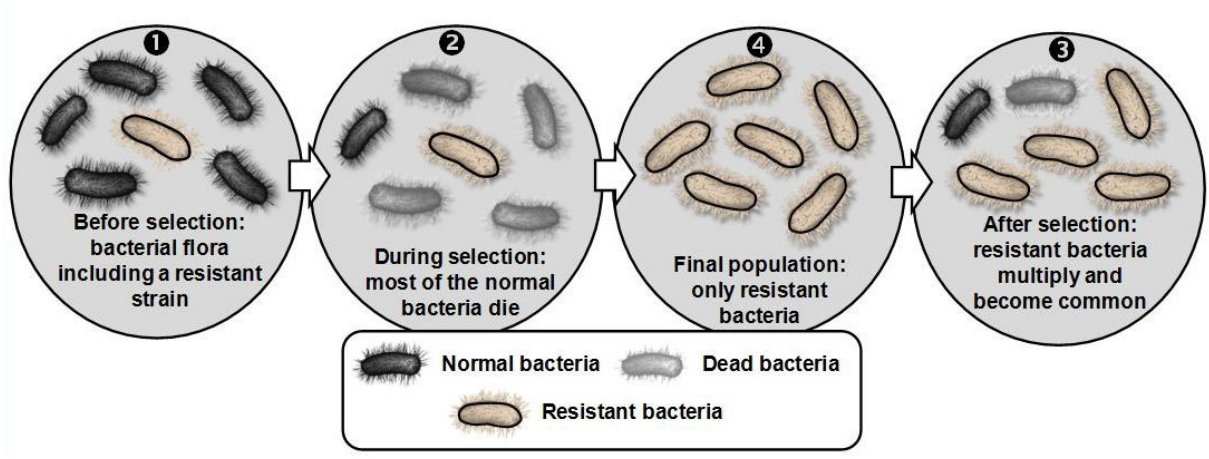
that the biocide/CP-β-CD complexes inhibit only the cell metabolism. The authors concluded that the cationic groups of the CP-β-CD polymer facilitate the biocide delivery due to the binding of polymer on the negatively charged cell membrane.

In 2013, cellulosic medical bandages functionalized with CDs have been reported for prolonged release of chlorhexidine digluconate (see Figure 21.11, Cusola *et al.* 2013). The surface-functionalization has been performed using citric acid as a cross-linker agent. SEM and Fourier transform infrared spectroscopy (FTIR) analyses were used to characterize the bandage. The drug-delivery kinetics of the encapsulated antibacterial agent was carried out by immersing the medical bandage into an aqueous medium, and the quantity of the released biocide was measured, as a function of time, by UV spectroscopy. The retention of the biocide, after 12 h, was around 30% and 10% for the grafted and non-grafted samples, respectively. After 2 days, non-grafted samples did not release the biocide anymore, whereas for grafted samples this delay was extended to 4 days. These results support the potential use of this cellulosic bandage in medical domain.

Ciprofloxacin is an antibiotic that can treat a number of respiratory, urinary tract, gastrointestinal and abdominal infections. It presents an excellent human tissue penetration and it is classified as broad-spectrum antibiotic. Indeed, it is active against Gram-negative (*E. coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *etc*.), and Gram-positive (*S. aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *etc*.) bacterial pathogens. Therefore, scientists drew attention to its inclusion inside β-CD grafted on cellulose fabrics (see Figure 21.11, Dong *et al.* 2014). The β-CD-grafted cellulose was prepared by the formation of CTR-β-CD (see above). The CTR-β-CDs were covalently bound to the hydroxyl groups of cellulose. In the best conditions ([CTR-β-CD] = 300 g/L, pH 3.4, 15 min, 160 °C), the grafted ratio of β-CD onto cellulose

fibers was 9.7 %. The ciprofloxacin hydrochloride was encapsulated and the release behavior from cellulose fibers was also studied. A prolonged release of the biocide from the cellulose was clearly observed. Indeed, the cumulative release from the virgin fibers was 90 % within the first 30 min, while the modified ones reached the same level after 240 min due to the formation of inclusion complexes. However, the presence of β-CD and its inclusion complexes modified the cellulose microstructure and its mechanical properties. As expected, the activity against *E. coli* and *S. aureus* was excellent for grafted fibers loading ciprofloxacin compared to virgin ones: the virgin fibers loading biocide were active for 4 days whereas the grafted fibers were active for 15 days.

As a response to pressures imposed, resistance of microorganisms to classical organic biocides increases (Figure 21.13).




*21.13* Principle of resistance mechanisms through selection of the most resistant pathogens.

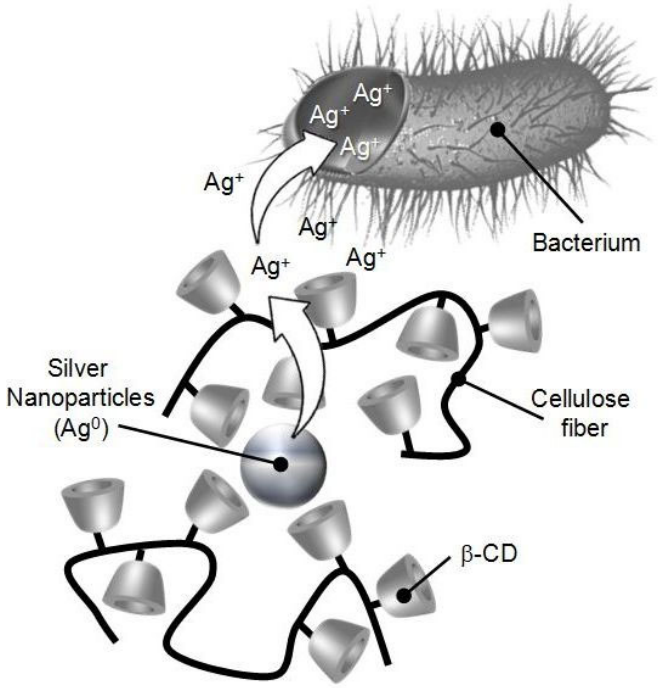
As consequence, the use of metal nanoparticles as alternative biocidal agents has emerged in the last decade (Maillard, 2005). Metal nanoparticles have high thermal stability, low toxicity to human cells and effective broad-spectrum activity, making them good candidates to inhibit the bacterial growth. Their antibacterial activity is due to their rapid breakdown which releases ionic metal that interact with the thiol or *N*-end amine residues of bacterial enzymes

leading to the inhibition of the DNA replication (Stobie *et al.* 2008). Moreover, the bacterial cytoplasmic membranes can also be damaged leading to cell lysis (Feng *et al.* 2000).

In this context, silver ions ($Ag^{+}$) have been loaded on CD-grafted onto cotton fabrics (Bajpai *et al.* 2010). Due to the prolonged release of silver ions for a period of seven days, a correct antibacterial activity was obtained against *E. coli*. The antibacterial action of silver applied on cellulose fibers grafted with MCT-β-CD has been reported in the literature (Popescu *et al.* 2013). Through a completely ecological process, without dispersants, the authors could "link" the silver nanoparticles ($Ag^{0}$) or silver ions ($Ag^{+}$) due to the interactions between the hydroxyl groups of the grafted CD and the silver ions or the nanoparticles. These interactions are supported by FTIR spectra and by the value of the binding constants (360 and $3.07\times10^{6}$ $M^{-1}$ for $Ag^{0}$ and $Ag^{+}$, respectively). The antibacterial activities against *E. coli* and *S. aureus* were very similar for the two fabrics grafted with CD and treated with $Ag^{0}$ or $Ag^{+}$. This suggests that the silver nanoparticles ($Ag^{0}$) were dissociated into silver (I) cations which act as active species (Figure 21.14). Finally, the authors established a relationship between the binding constants of the CD with $Ag^{0}$ and $Ag^{+}$ and the antibacterial activity as well as the resistance to washing. Indeed, the antibacterial effect of grafted fabrics, washed 10 times, was equal to the unwashed original fabric.

In 2011, the use of carbon nanotubes with copper or silver nanoparticles embedded on water-insoluble CD polyurethane polymers have been explored (Lukhele *et al.* 2011). After the characterization, the resulting material was tested for water disinfection. Indeed, the authors have performed the determination of the antibacterial properties of the material against *Salmonella typhi* and *E. coli* using water samples containing an organic pollutant (*e.g. p*-nitrophenol) in addition to bacteria. The material based on polyurethanes adsorbed up to 55% of *p*-nitrophenol pollutant and reduced up to 3 logs the bacteria titers. The mechanism is due to a synergism between the metal nanoparticles and the carbon nanotubes. Indeed, carbon

nanotubes exhibit a strong antimicrobial activity because of the piercing of the bacterial cell membranes (Liu *et al.* 2009). This type of material may be very suitable to avoid water-related diseases (*e.g.* leptospirosis, malaria, dengue, typhoid fever, *etc*.).




*21.14* Proposed antibacterial mechanism of silver nanoparticles capped by β-CD grafted on cellulose fibers.

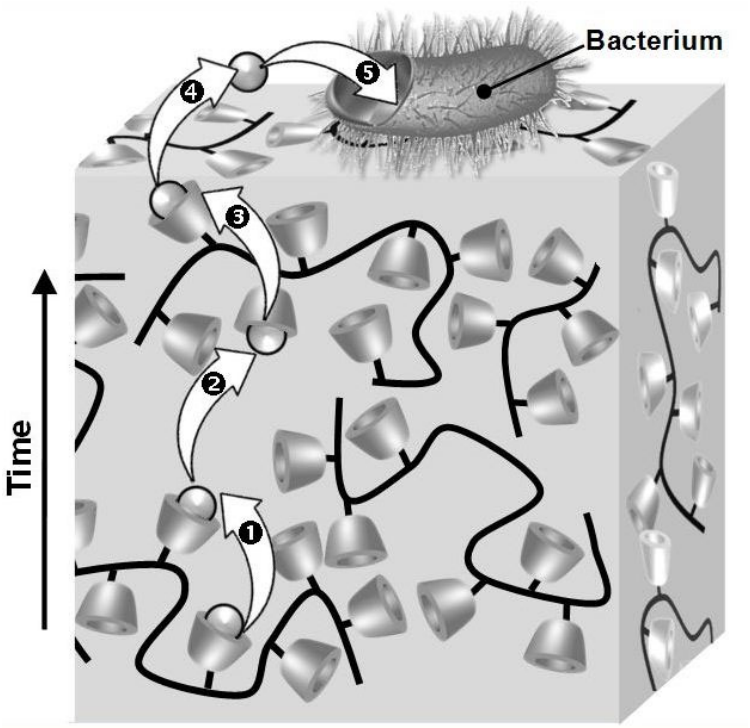
In 2013, the synthesis of sulfated-β-CD/cotton/ZnO nano composite has been reported (Sundrarajan *et al.* 2013). The sulfo-β-cyclodextrin (S-β-CD) was cross-linked with cotton fabric using ethylenediaminetetraacetic acid (EDTA). Next, the fabric surface was padded with ZnO nanoparticles. The synthesized β-CD/ZnO cotton fabrics were fully characterized using FTIR, X-ray diffraction (XRD), granulometric analysis and transmission electron microscopy (TEM). The antibacterial efficiencies were very high (99% and 97% against *S. aureus* and *E coli*). Following the same protocol, the authors have extended the coating of S-β-CD polymer cross-linked with cotton fabric by $TiO_2$ and Ag nanoparticles (Selvam *et al.* 2012). The biocidal efficiency against *S. aureus* and *E. coli* decreases in the following order:

ZnO > Ag > $TiO_2$. As the best biocidal activity, obtained for the S-β-CD/ZnO cotton fabric, presents also the low production cost, this type of cellulose fabric may be suitable for medicinal bandages, *etc.*

In 2014, the synthesis of β-CDs/polyacrylonitrile/copper nanorods composite fibers has been performed to obtain antibacterial textile (Li *et al.* 2014). The synthesis requests the preparation of the β-CDs/polyacrylonitrile composite fibers by electrospining follow by the preparation of the β-CDs/polyacrylonitrile/copper nanorods composite fibers by adsorption and reduction. The composite fibers were fully characterized by FTIR, SEM, TEM, energy dispersive spectroscopy and X-ray photoelectron spectroscopy. The results indicated that the copper nanorods were not only successfully synthesized on the surface of the composite fibers but also the copper nanorods were distributed without aggregation on the composite fibers. The antibacterial efficacy of the composite fibers against *E. coli* indicated that they have bactericidal effects only in the presence of copper nanorods. Based on the literature, the authors mentioned than the loaded copper ions interact with bacterial cell membranes which induced structural change and leading to cell death. The proposed system can be useful to perform water purification systems by its use as filtration membrane.

It is noteworthy that a more sustained release can be obtained when CDs are trapped inside a matrix networks. In this context, hydrogels based on CDs can be useful to create robust networks with switchable mechanical properties will capable of serving as device coatings. As expected for affinity-based mechanisms, the release of drugs from the CD-based hydrogels was slower than classical diffusion-based release from dextran gels due to the complexation of the drug inside the CD cavity (Thatiparti *et al.* 2010). Indeed, in affinity-controlled release kinetics, the guest drug released from one CD may become available to form new complexes with other free CDs during the diffusion through the hydrogel matrix (Figure 21.15,

Concheiro & Alavarez-Lorenzo, 2013). The slow, sustained, affinity-based release of antibiotics from the CD-based hydrogels is of potential interest as delivery platform.



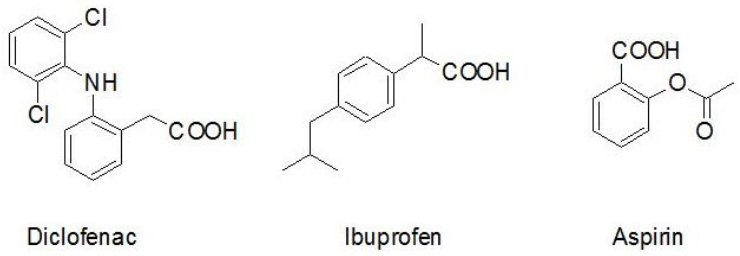

*21.15* Proposed mechanism of biocide release from a CD-based hydrogel.

For the prevention and the management of wound infections, the use of HP-β-CDs as main components of hydrogels and gauzes has been proposed for the prolonged release of benzalkonium chloride (Garcia-Fernandez *et al.* 2013). It is noteworthy that the benzalkonium chloride (see Figure 21.11) is a classical antiseptic used in many consumer products such as eye, ear and nasal drops or sprays, skin antiseptics (Bactine® and Dettol®), throat lozenges and mouthwashes, treatment of fever blisters (Viroxyn®), burns and ulcers treatment, and in cleaners for hard surfaces (Lysol®). As benzalkonium chloride is known to form easily inclusion complexes with various CDs, the authors have grafted CDs to cotton gauzes using citric acid as cross-linker (190 °C, 15 min). In parallel, authors formed hydrogels based on HP-β-CD and hydroxypropyl methylcellulose. The biocidal activity against *S. epidermidis* and *E. coli* revealed that the benzalkonium chloride in hydrogels and gauzes inhibited the

growth and reduced the number of living bacterial cells. The results, as well as the slow and sustained affinity-based release of benzalkonium from the CD-based networks, highlight the role of CDs as main components of hydrogels and gauzes for the efficient delivery of antiseptics.

### 21.3.2. Anti-inflammatory Textiles

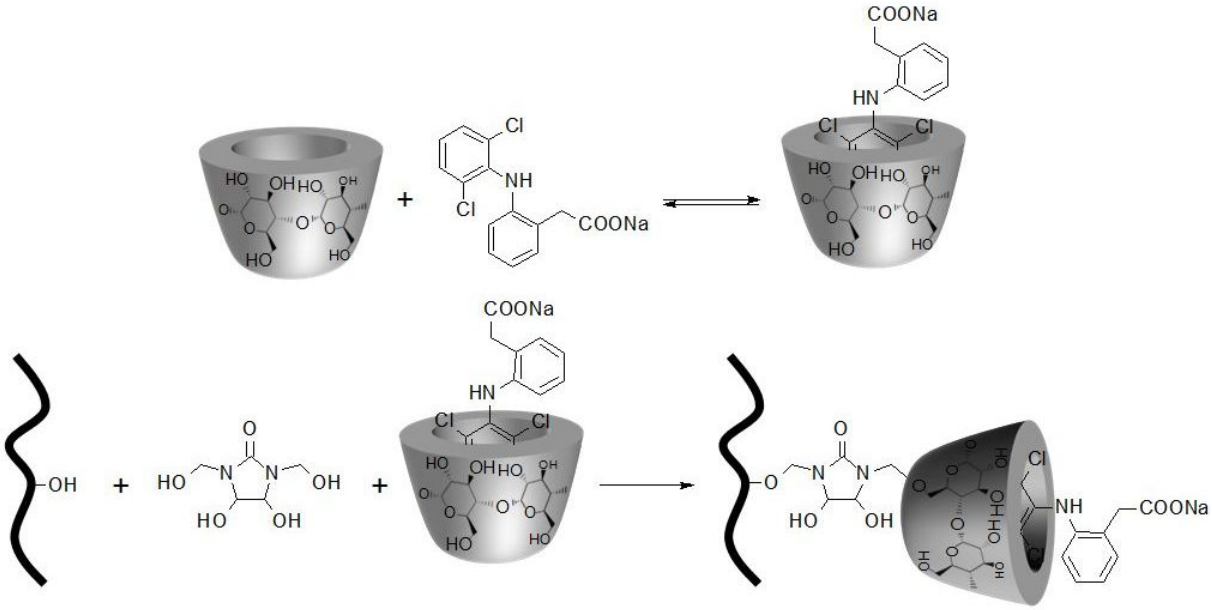
As seen in the previous section, CDs grafted onto textile fibers are very useful to deliver antibiotics. Therefore, if the antiseptic is replaced by an anti-inflammatory, we obtain an anti-inflammatory textile. The advantages of these fabrics are similar to those based on antiseptics. However, for inflammation treatment, the textiles based on CDs offer favorable solutions to: (*i*) the sensitivity of certain patients to the oral administration, (*ii*) the possible omission for children and old people, and (*iii*) the frequent change of bandages in the case of conventional bandages. Indeed to help stop swelling, a bandage able to gradually release the medication (*e.g.* diclofenac, ibuprofen or aspirin, see Figure 21.16) directly to the inflamed region avoids all these difficulties. As consequence, in the present section, only some typical examples of "textiles" based on CDs are reported.




*21.16* Chemical structure of diclofenac, ibuprofen and aspirin.

In 2010, a bandage capable of releasing diclofenac sodium has been developed (NSAID, see Figure 21.16, Montazer & Mehr, 2010). The bandage was executed in two steps: the complexation of diclofenac sodium by β-CD, followed by complex grafting onto cotton

wound dressing using a cross-linking agent (*e.g.* dimethyldihydroxylethylene urea, see Figure 21.17).




*21.17* Synthesis of the cotton bandage impregnated with CD/diclophenac complex by means of dimethyldihydroxylethylene urea (DMDHEU).

The complexion of β-CD and diclofenac sodium was proved by UV spectrophotometry and NMR spectroscopy. The surface morphology and drug release were studied by SEM and dissolution kinetic measurements, respectively. The results revealed that the cross-linking agent prolongs the drug release time. The authors have proved that the increase of the medicine release rate is not proportional to its initial concentration. Moreover, if the textile is impregnated in a vat containing ethanol, the drug release was increased during the initial hours. However, if the bandage was not treated with ethanol, the initial release of medication was slow. Therefore, the bandage containing ethanol can be very useful when the inflammation is severe. In other words, the drug release of these bandages is switchable according to the ethanol concentration.

Another method is also possible to obtain indirectly a prolonged release of anti-inflammatory agents. Indeed, as gels or hydrogels can be impregnated in gauzes for medical bandage, the work of Pose-Vilarnovo *et al*. can be very fruitful in this field. In this paper, the authors reported on the effect of β- and HP-β-CD on the diffusion and the release behavior of diclofenac sodium from hydroxypropyl methylcellulose gels (Pose-Vilarnovo *et al.* 2004). These gels were prepared with 0.5-2.0% polymer and different drug/CD mole ratios. The viscosity of the gels strongly depended on hydroxypropyl methylcellulose proportions (from 0.7 to 100 mPa.s), which affected to a lesser extent the resistance to the diffusion of the drugs (D from 60 to $5 \times 10^{-6}$ $cm^2/s$). The influence of CD on diffusion was particularly evident in gels prepared with polymer proportions above its entanglement concentration, 2.0% hydroxypropyl methylcellulose. In these systems, while high drug/CD proportions enhanced the diffusivity preventing polymer/drug hydrophobic interactions, low drug/CD ratios hindered it. This system may be particularly useful to modulate drug release from gels. Indeed, the influence of CDs dependents on the nature of the drug and on the molecular size and hydrophilic character of the CD used.

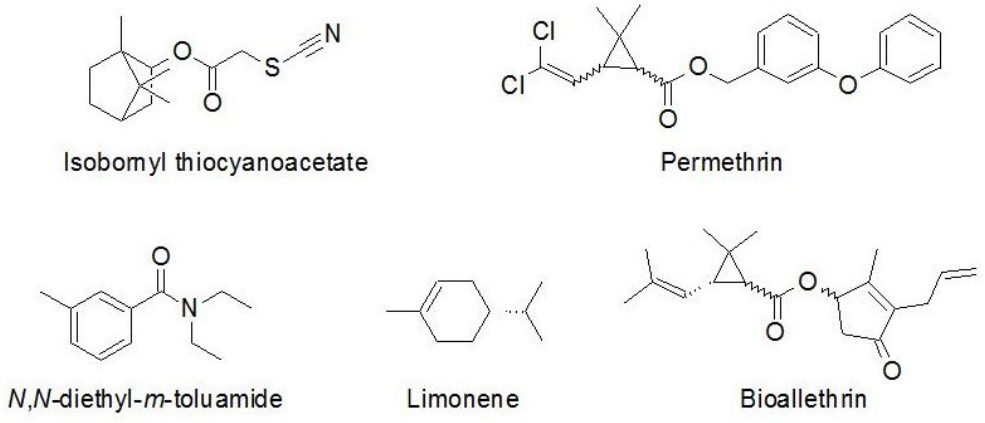
On the other hand, as ibuprofen (IBU) and aspirin (see Figure 21.16) are also widely used NSAIDs to treat fever, mild-to-moderate pain, painful menstruation, osteoarthritis, dental pain, headaches and arthritis and as these two drugs are known to form inclusion complexes with various CDs, their inclusions in CDs grafted onto cotton fabric is very promising. In this context, fabric functionalized with MCT-β-CD has been developed for their controlled release (Agrawal *et al.* 2010). The maximum amount of MCT-β-CD on the cotton fabric sample achieved was 2.585 $g/m^2$ out of 3.2 $g/m^2$ delivered on the surface by drop-on-demand inkjet print head. The release kinetics of aspirin and IBU with these textiles is switchable depending on several external stimuli (*e.g.* pH, electrolyte, *etc*.).

Similarly to diclofenac sodium, it is also possible to obtain sustained IBU release by the incorporation of CDs inside polyvinylpyrrolidone/poly(ethylene glycol) dimethacrylate (PVP/PEG-DMA) hydrogels (Nielsen *et al.* 2009). To retard the release of water-soluble sodium ibuprofenate, the three native CDs (4-5 w/w%) were covalently grafted to the vinylpyrrolidone/ethyleneglycol dimethacrylate copolymer matrix in the presence of *N*-methylolacrylamide (NMA) and under UV radiation (see above). The IBU salt was loaded by swelling in various IBU/CD ratios. As the release rate and the release profile of ibuprofen can be modified by the CD used, the best compromise for sustained drug release was obtained with the β-CD hydrogel. These hydrogels show promising wound care properties when they are applied on a textile surface for medical bandages.

### 21.3.3. Insect Repellent and Insecticide Textiles

Insects are very common vectors of various diseases. Indeed, insects spread pathogens (*e.g.* bacterial, viral and protozoan) from one host to another. Two main mechanisms can be highlighted: *via* their bite (*e.g.* malaria spread by mosquitoes) *or* via their faeces (*e.g.* Chagas' disease spread by *Triatoma* bugs). Mosquitoes are perhaps the best known vector. Indeed, they transmit a wide range of tropical diseases including yellow fever, dengue fever and malaria. For instance, malaria is caused by parasitic protozoans belonging to the genus *Plasmodium*. The common symptoms include fever, fatigue, vomiting and headaches. However, in severe cases, seizures, coma or death are possible. Although this disease poses a particular threat on the continents of Africa, Asia and South America, the malaria can be controlled with the use of mosquito nets, insect repellents or insecticides. The malaria prevention is more cost-effective than treatment of the disease in the long run by chloroquine or mefloquine. In such conditions, the use of textile with insect repellent properties comprising a natural or synthetic fabric and an encapsulated active ingredient having

insecticide or insect repellent properties can be very useful. Therefore, the capability of CDs to include various hydrophobic molecules can be exploited to produce new grafted textiles with insecticidal or insect repelling performances. These are particularly promising and not only for malaria. In this section, only few typical examples taken from the literature have been developed. The chemical structures of the insecticides or insect repellents mentioned in this section are presented in Figure 21.18.




*21.18* Chemical structures of insecticides or insect repellents mentioned in this section.

In 1992, wash-resistant and insecticidal fibers have been developed (Agrawal *et al.* 1992). These fibers were prepared by treating fibers with an organic insect proofing agent, a molecular CD or an oligomer ($M_w \leq 3000$), and a siloxane. For instance, acrylic fibers were treated with a solution containing 0.34% β-CD, 0.14% isobornyl thiocyanoacetate (see Figure 21.18) and 0.5 g/L aminosiloxane (based on the fiber mass). After 45 min at 90 °C in a package dyeing machine and a heat treated for 10 min at 100 °C, the mixture was blended with untreated fibers and a woven fabric was produced which even after 20 washings showed insecticidal properties.

In 2005, the use of MCT-β-CD grafted onto cellulosic textiles through covalent bonds have been proposed for entrapping hydrophobic insecticides on the surface of the fabric and

releasing them progressively (Romi *et al.* 2005). In this work, the authors used the permethrin (insecticide) and the *N*,*N*-diethyl-*m*-toluamide (insect repellent, see Figure 21.18). UV-visible spectrophotometry and thermal analysis have confirmed the presence of the guest molecules in the β-CD molecules grafted on cotton fabric surface. Bioassays, against *Aedes aegypti* and *Anopheles stephensi* (two mosquito species of medical importance), repellency and irritancy were performed. The *N*,*N*-diethyl-*m*-toluamide appears to be unsuitable for a direct treatment of cotton fabrics: its activity was kept only in a short time after the treatment. In contrast, fabrics grafted with MCT-β-CD and loaded with permethrin kept the insecticidal/irritant efficacy even for a long time after the treatment. In other words, the permethrin treatment of bed nets or curtains made with this textile can be very useful to avoid malaria disease.

In 2008, Hebeish *et al.* have used an insecticide against anopheles (*e.g.* limonene, see Figure 21.18) applied to cotton fabrics with the conventional impregnation and coating methods in addition to the functionalized fabric obtained *via* grafting with MCT-β-CD. For, the conventional methods, emulsion of limonene and polymeric binder were used whereas limonene inclusion inside the MCT-β-CD cavities was used with the functionalized fabric (Hebeish *et al.* 2008). Bioassay test results expressed as repellency, knockdown and mortality were very good. Moreover, good washing and storage results have been also reported.

In 2014, a new textiles consisting in cotton/poly(glycidyl methacrylate) copolymer containing β-CD allowed the introduction of two insecticides (permethrin and bioallethrin, see Figure 21.18) against blood sucking insects (Hebeish *et al.* 2014). The chemical functionalization of cotton was realized by grafting glycidyl methacrylate alone or in combination with β-CD by irradiation using fasting electron beam. It is noteworthy that the retreatment of the obtained modified cotton was also made to increase the amount of CDs. The inclusion of the two insecticides was performed and gas chromatography was used to

quantify the insecticides in finished fabrics. The untreated and treated fabrics were fully characterized through FTIR, SEM and physical testing. The toxic activity properties were directly correlated to the amount of loaded insecticide and the bioassay test has revealed a fast acting against mosquitoes.

### 21.3.4. Cosmetotextiles

By definition, cosmetotextile is a technology merging cosmetics and textiles through the process of encapsulation. These textiles are consumer articles containing cosmetic products for a controlled release of these last. These textiles are sometimes border medical applications. Indeed, most of them use essential oils, herbal oils, oils from flower seeds which have skin care benefits in that they provide an occlusive layer that lubricates the epidermis, together with a moisturizing effect. Most of them contain bioactive molecules and have been used medicinally in history. However, essential oils have declined because of modern medicine is based on molecules rather than refer to “essential oils” as a class of medication. However, essential oils are able to have pharmaceutical effects such as sedation, anti-depressant, insect repellent, *etc*. (Voncina & Vivod, 2013). Some of them are fungicide, bactericide and insecticide. In contrast to the previous sections that use molecular drugs, essential oils (*i.e.* mixtures of molecules) are directly used to obtain cosmetotextiles. Here, only border case between cosmetic and medicine have been presented.

Essential oils have been used as insect repellent in order to discourages insects from landing or climbing on that surface. Some synthetic repellents have been presented above. It is noteworthy that these synthetic repellents tend to be more effective than natural repellents. However, synthetic insect repellents are highly toxics. Indeed, some of them result in dermatitis and other skin problems. In this context, cedar oil is often used as a natural insect repellent because of its low toxic. As essential oil repellents tend to be short-lived due to their

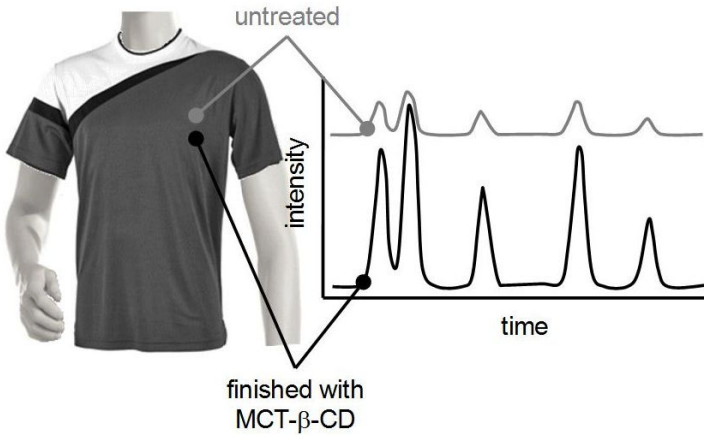
volatile nature, their encapsulation with β-CD is a smart solution. In 2013, the encapsulation of cedar oil in wool and PET/wool blend fibers with β-CD have been reported in the literature (Voncina & Vivod, 2013). The complex formation between cedar oil and β-CD was determined by FTIR spectroscopy. This textile fabric showed, after being treated with β-CD/cedar oil complexes, a prolonged moth's oppression compared to the textile materials treated only with cedar oil. After β-CD/cedar oil treated wool was exposed to a moth's colony during two months no visible damage was observed to the naked eye. In contrast, the wool samples treated only with cedar oil was only protected during the first days due to the cedar oil evaporation. In this example, the cedar oil encapsulated in the β-CD cavity avoids the oil evaporation and improves its gradual release.

In 2011, Cravotto and co-workers used cosmetotextiles in the treatment of chronic venous insufficiency in legs by means of elastic bandages loaded with natural products which possess phlebotonic properties (Cravotto *et al.* 2011). One of these compounds is aescin, the main active principle of the horse chestnut tree (*Aesculus hippocastanum* L.), which has shown marked anti-inflammatory, vasoprotecting and circulation boosting properties. The efficient synthetic procedure developed by the authors for the preparation of β-CD-grafted viscose uses 2-step ultrasound-assisted reaction. Indeed, viscose fabric soaked in a mixture of DMF and hexamethylene diisocyanate was sonicated at 80 °C. Then, the viscose fabric, soaked in a solution of β-CD in DMF, was sonicated for 2 h at 70 °C. The fabric was washed and dried before to perform aescin complexation. The grafted fabric has been characterized by FTIR and cross polarization magic angle spinning NMR (CPMAS) spectra and by an empiric colorimetric method which used phenolphthalein as the CD guest. The efficacy of the new cosmetotextile has been corroborated by *in vitro* studies of diffusion through membranes, cutaneous permeation and accumulation in porcine skin. Aescin in the cosmetotextile showed

excellent application compliance and was easily recharged. The authors mentioned the possibility to perform an industrial production of this grafted-textile.

### 21.3.5. Other Smart Opportunities

In this section, miscellaneous applications of grafted textiles have been presented. In 2001, the use of CDs grafted onto fabrics can be used to collect the perspiration in order to establish medical diagnostics (Buschmann *et al.* 2001). Indeed, up to now blood or urine tests are normally used due to the problems of taking a sweat probe from a patient. This becomes easy when MCT-β-CDs are grafted on textiles. Indeed, CDs are able to complex various organic molecules from the perspiration. The gas chromatography can be easily performed after extraction of substances from the textile functionalized with CDs. In such conditions, as the organic substances are pre-concentrated due to the presence of CDs in comparison with untreated textile, the identification becomes easier (Figure 21.19).




*21.19* T-shirt partially finished with and without cyclodextrins and schemes of the corresponding gas chromatograms obtained after extraction.

In 2008, polyethylene terephthalate vascular prostheses coated with a CD polymer have been proposed to replace damaged arteries (Blanchemain *et al.* 2008). The prostheses involve the complexation of antibiotics (*e.g.* ciprofloxacin, vancomycin and rifampicin) to minimize

the risk of infection during and after surgical interventions *via* their controlled release. The epithelial cell was used to determine the antibiotics viability, whereas human pulmonary microvascular endothelial cells were used for cell proliferation. Some pathogen strains (*e.g. S. aureus*, *E. coli*, *etc*.) were used to determine the antimicrobial activity of the antibiotic loaded in prostheses coated with CD polymer and compare to the virgin one. A larger amount of antibiotics was adsorbed onto prostheses coated with CD polymer compared to the virgin one (26.7 *vs.* 35.3 mg/g, 51.1 *vs*. 72.4 mg/g and 4.1 *vs*. 21.0 mg/g for rifampicin, vancomycin and ciprofloxacin, respectively). Therefore, a better microbiological activity was showed for prostheses coated with CD polymer and loaded with antibiotics. The rifampicin and ciprofloxacin were toxic (22 mg/L and 35 mg/L, respectively), but the vancomycin is nontoxic. The poor viability and proliferation of the human microvascular endothelial pulmonary cells when the prostheses coated with CD polymer containing antibiotic were due to the cytotoxicity of the antibiotic itself. This kind of property can be exploited in order to fight the intracellular bacteria without compromising the *in vivo* applications of the functionalized prostheses. Moreover, as polyethylene terephthalate is used in fibers for clothing, some fruitful developments are expected for other textile applications.

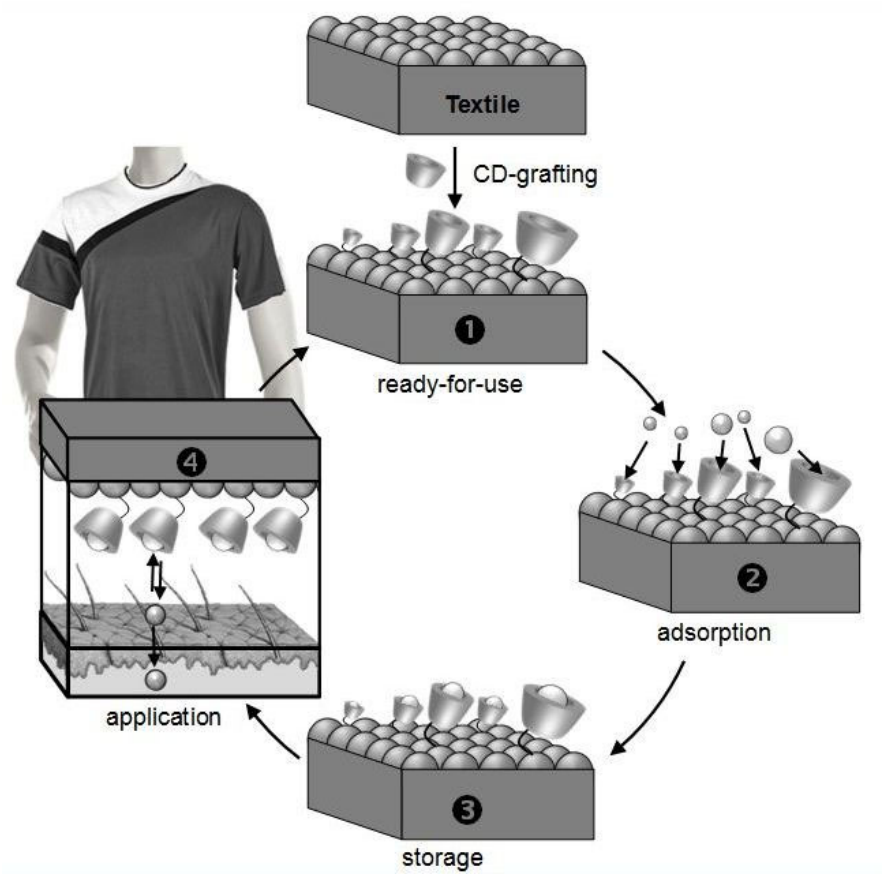
In 2013, the use of cellulose supports has been proposed to obtain anti-allergic pajamas (Hritcu *et al.* 2013, Radua *et al.* 2013). The cotton was grafted with MCT-β-CD as a support of an inclusion compound with natural anti-allergic active principles: extract of *Viola tricolor*, solution of propolis and of menthol, as well as the pharmacologic products: methylprednisolone aceponate, hydrocortisone and pimecrolimus. The fabric was characterized by FTIR and SEM analyses. The anti-microbial of the textile material grafted with MCT-β-CD and with *Viola tricolor*, propolis and menthol absorbed onto the cotton was tested. The results prove that these modified textiles inhibit the microbial development of *Rhizopus* and *Trichoderma* and avoid the encouragement of allergic reaction. These textiles

can be very useful to improve the curative properties and the comfort of pajamas for patients with contact and atopic dermatitis.

## 21.4. Conclusion and Perspectives

This chapter presents an analysis of current and potential applications of smart textile based on cyclodextrins for curative or preventive patient care. Due to their molecular structure, cyclodextrins are topologically represented as toroids in which the openings expose the hydroxyl groups. As consequence, hydroxyl residues can be easily modified in order to introduce reactive groups and to perform their grafting onto natural or synthetic fibers. Moreover, the interior of the toroid is sufficiently "hydrophobic" to host nonpolar medications. Indeed, cyclodextrins allow to encapsulate antibiotics, anti-inflammatory, insecticides, insect repellents, essential oils, antihistaminics, phlebotonics, *etc*. on the fabric surfaces. As the formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of delivery kinetic rate, the drug bioavailability is clearly modified. This modification offers the possibility of controlled release which is one of the most important advantages for textile industry in addition to their reused (Figure 21.20). As host-guest systems are reversible, the textiles with grafted cyclodextrins behave as kinetic retardants. Indeed, for most of inclusion complexes, the complexation kinetics is extremely fast. Accordingly, the delayed release which is generally observed in the presence of cyclodextrins is not linked to kinetics of inclusion but is rather induced by the thermodynamic control. Indeed, at a given time, only a small percentage of drug is free and really bioavailable. Thus, the prolonged release comes from displacement of the inclusion equilibrium. However, the releasing kinetics of guest substances from cyclodextrin cavities as well as the study of the key parameters that influence this phenomenon must be rationalized. This rationalization combined with their capacity to form

inclusion complexes with numerous drugs offers unrestricted possibilities and we can suppose that in the near future new smart medical textiles will emerge and open up a new approach for designing novel drug delivery systems.




*21.20* Preparation and life cycle of CD-grafted medical textile.

## 21.5. Acknowledgements

This chapter is dedicated to the memory of my father Gérard Leclercq (1948-2015).

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