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Textile-based drug release systems

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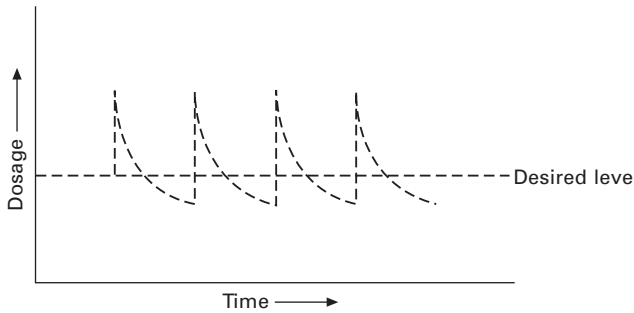
3.1 Introduction

Since the dawn of mankind textile materials have been produced and used to protect people from the surrounding environment. Over the years, textile properties like quality and wearing comfort have improved, and it is true to say that textile materials are an important aspect of our everyday lives. Logically, textile materials have found their way in the medical field as well, e.g., artificial aortas and bandages. However, advanced functional textile drug delivery systems were not developed until the end of the last millennium.

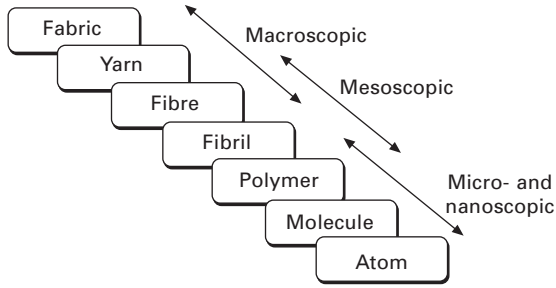
Why explore and develop textile materials in drug delivery systems? In many cases, drug delivery methods like pills and injections will give no problems, nevertheless, situations can be thought of where other systems would be more preferable. For example, in oral delivery systems like tablets, pills, capsules, the drug is absorbed in the stomach or intestinal tract. As some drugs are metabolised, they might lose their activity before being able to fulfil their purpose. Consequently, relatively high doses are necessary to achieve the desired effect (Fig. 3.1), which might give rise to adverse or toxic effects. Delivery through the skin bypasses the liver, making it possible to lower drug doses. Moreover, one can imagine situations where oral administration is less applicable or impractical, e.g., with children, people with swallowing difficulties or in the case of dementia. Transdermal and *in-vivo* drug delivery systems can be a good alternative in these situations. Furthermore, in cases of necessity for prolonged drug treatment, such a delivery system can possibly be preferred above daily injections or intake of pills. Advanced drug delivery systems can have many advantages in safety and effectiveness over conventional drug delivery systems by reducing dosage and frequency of dosing. However, when designing drug delivery systems one needs to be aware that not all drugs are applicable in prolonged drug dosage systems, and that such systems need to be developed taking into consideration drug properties, pharmacological demands and reliability.



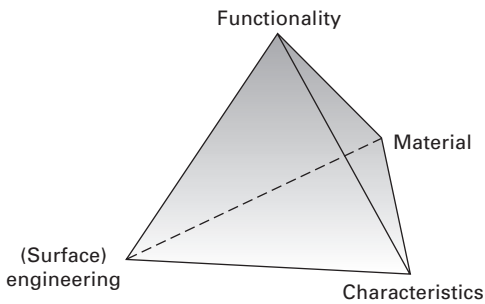
3.1 Drug dosage in time in a conventional drug delivery system.

Textile materials are extremely versatile materials, combining different materials and structures. Properties and functionalities of textiles are affected by chemical, physical and physical-chemical characteristics on micro-, nano-, meso- and macroscopic length scales (see Figs 3.2 and 3.3). On a macroscopic scale, although dependent on the actual fabrication process, textile materials are relatively 'open' and 'loose', permeable structures, with absorptive capacities as well. Especially the open permeable structure and large surface area makes textile materials a useful basis for *in-* and *ex-vivo* drug delivery applications. Moreover, people are used to wearing and using textile materials, making it a logical choice to use textile materials as a basis for *ex-vivo* drug delivery systems in professional and private situations. Textile drug delivery systems can thus contribute to a better quality of life.

Over the years, various delivery methods have been developed. A well-known category consists of so-called transdermal patches. They are mostly based upon multi-layer systems in which, besides an ointment or other drug-containing substance, a regulatory system like a membrane is used. In many cases the textile material in these transdermal patches is simply forming a support layer in the delivery system. Usually, no specific advanced treatments are required to gain useful patches. These kinds of slow release or delivery systems will not be the topic of this chapter. Owing to the enormous progress over the years in supramolecular chemistry, nanotechnology, nanobiotechnology, and polymer science and technology, high-performance textile drug delivery technologies have been developed (Breteler *et al.*, 2002). This chapter will essentially focus on aspects of more advanced and promising functional textile drug delivery systems or slow release systems like textile bearing cyclodextrins (e.g. Lee *et al.*, 2000; Lu *et al.*, 2001; Buschmann *et al.*, 2001; Martel *et al.*, 2002a,b; Szejtli, 2003; Voncina and Le Marechal, 2005), ion-exchange fibres (e.g. Jaskari *et al.*, 2000, 2001; Skundric *et al.*, 2002; Vuorio *et al.*, 2003, 2004), fibres containing (microencapsulated) drugs (e.g. Nelson, 2002; Liao *et al.*, 2005), microparticles (e.g. Gupta *et al.*, 2001; Berkland *et al.*, 2002) and (biodegradable) nano-fibres containing drugs



3.2 Different length scales.



3.3 Functionality in textile materials.

produced by electrospinning (e.g. Kenawy *et al*., 2002; Zeng *et al*., 2003, 2005).

In the development and design of advanced textile drug deliverable systems various factors will affect performance of the release system apart from delivering the required amount of drug efficiently, precisely and for a defined period of time (controllability: dosage control, rate control and time control), like biocompatibility, biostability and biodegradability.

3.2 Mechanisms of drug release

For optimal performance textile drug release systems should be controlled in accordance with pharmaceutical requirements. As has been stated in the previous section, the objective of drug delivery systems is to deliver a defined amount of drug efficiently, precisely and for a defined period of time. By the selection of suitable carriers or host-molecules in textile drug release systems the rate and/or time of controlled release can be adjusted and regulated. Among other reasons this explains today's interest in advanced (textile) drug delivery systems.

3.2.1 Some typical release mechanisms

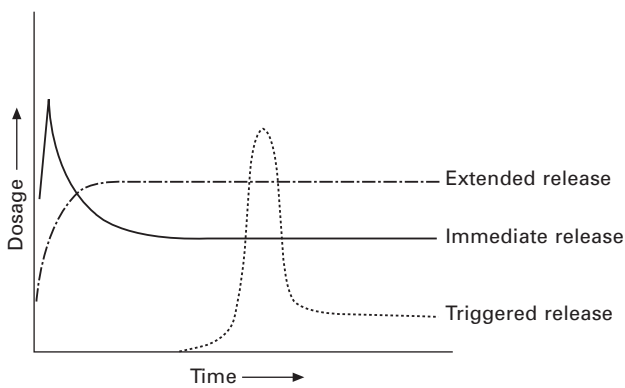
In general a few typical different types of release can be recognised relevant in textile drug delivery systems; immediate release, extended release and triggered or delayed release (e.g. Uekama *et al*., 1998; Sansom, 1999). The different mechanisms are illustrated schematically in Fig. 3.4. Various, sometimes interchangeable, terms are used as well, and other delivery types do exist, like e.g. targeted drug delivery, site specific delivery, pulsed delivery, controlled delivery of multiple drug combinations (see Fig. 3.4), or modified delivery. Modified delivery is often a combination of other mechanisms in order to obtain more complicated dosage patterns (Uekama *et al*., 1998). The release mechanisms mentioned will be illustrated using several examples.

Immediate release

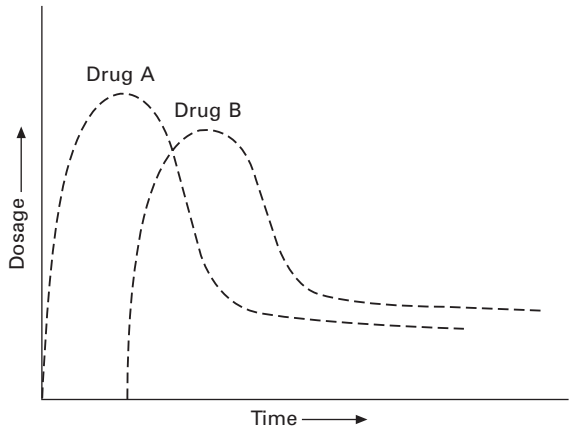
In immediate release formulations, the drugs are available within a relatively short time. The rate is controlled by factors such as, for example, digestion in the stomach or intestinal tract, dissolution of the drugs and uptake of the drugs by the body. Initially the concentration increases rapidly, followed by a sharp decline as illustrated schematically in Fig. 3.5. Often a relatively high concentration is necessary to achieve the desired effect, dosing is quite often frequently. This type of release is required in situations where immediate action is essential. Other, often more conventional, formulations than textile drug delivery systems seem more appropriate and effective in immediate release of drugs.

Extended release

In extended release, sometimes called prolonged or sustained release, the availability of drugs is maintained at a lower concentration and for a prolonged



3.4 Different release mechanisms.

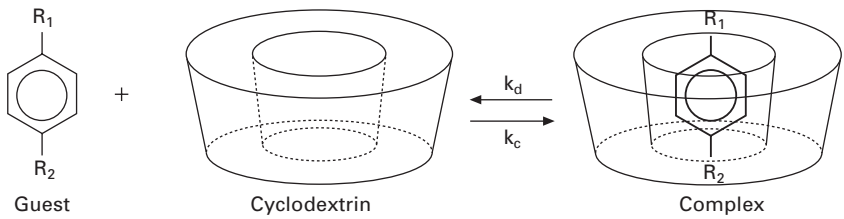


3.5 Controlled delivery of multiple drug combinations.

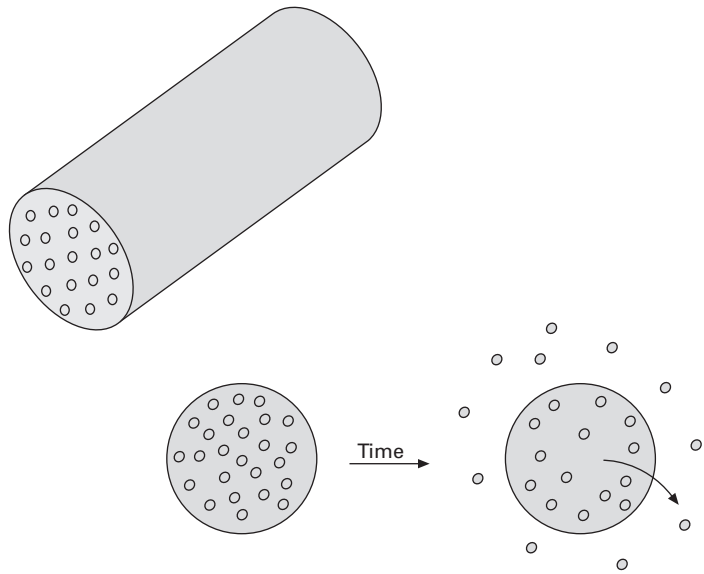
time compared to immediate release systems. In extended release systems the drug is delivered at a (very) slow rate and for a prolonged period of hours, days or even years, thereby usually reducing dosing frequency. The system can simply release the medication at a variable but slow rate, or release the medication at a constant rate over an extended period of time. Extended release systems are often slow release systems. Different principles are used to control the rate in extended release systems, such as diffusion, decomplexation, dissolution, ion exchange, erosion and degradation.

In diffusion controlled release systems the drugs are simply incorporated in the polymer matrix of the textile fibres, in hollow fibres or in fibres containing (micro-)encapsulated drugs. The concentration gradient and the diffusion coefficient of the drug in the polymer material determines the release rate. A typical example of a decomplexation controlled release system is textile materials bearing cyclodextrins (see Fig. 3.6). In decomplexation controlled systems, drugs can be incorporated in a host molecule bound to textile fibres. The complexation and decomplexation constants, k_c and k_d respectively, depend on the interactions between the drug, the guest molecule, and the cyclodextrin, the host molecule.

Fibres bearing encapsulated drugs are an example of a dissolution controlled release system (see Fig. 3.7). In dissolution controlled drug release systems, drugs are released by dissolution of the polymer. The release rate is thus determined by the dissolution rate of the polymer used to encapsulate the drug. This type of system can be relevant when designing triggered or delayed release systems as well (see below). Some drugs can be bound to ion-exchange materials. In ion-exchange textile drug release systems, the release rate of drugs bound to ion-exchange fibres is determined by ionic properties or the pH of the surrounding liquid and the choice of the ion-exchange material.



3.6 Schematic representation of cyclodextrin-guest complex formation.



3.7 Release of drugs encapsulated in fibre.

This type of system can also be relevant when developing triggered or delayed release systems (see below).

Erosion and degradation controlled systems use a polymer matrix that is slowly eroded or degraded. As the polymer matrix is degraded or eroded the drugs are released. The erosion or degradation speed of the matrix carrying the drugs determines the release rate of the drugs. Like the previous two systems, this type of system can also be relevant when developing triggered or delayed release systems (see below). Biodegradable polymers and block copolymers (Kumar *et al*., 2001), for example, find their application in this type of release system.

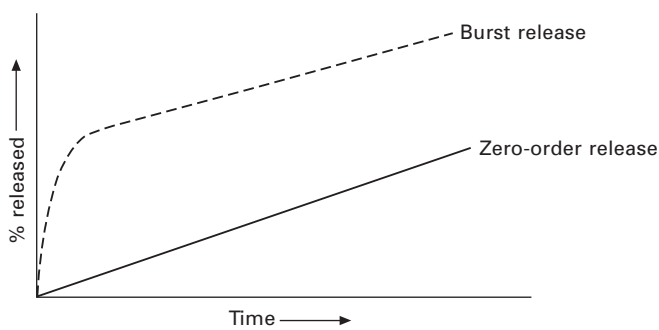
Triggered or delayed release

The release of drugs from triggered or delayed release systems is determined by an (external) trigger/stimulus or time. The resulting release can be of the

immediate type or slow-release type, depending on the design and the materials chosen. The degree and rate of erosion, degradation or dissolution are, apart from the matrix, a function of, e.g., pH, temperature, ionic strength, or even light and this determines time delay in delayed release systems. The release of the drug from the delivery system might also be triggered by a specific event, situation, or change in the environment such as a change in pH, temperature, ionic strength or even by an externally controllable trigger-like ultrasound for example (Bruinewoud *et al.*, 2004). Triggered release systems control drug dosage autonomously over an extended period of time, thus enabling precise dosage levels or more complicated dosage patterns.

3.2.2 Kinetics aspects of drug release

Textile drug delivery systems have the potential to meet the need for versatile delivery systems that are able to adapt to different pharmacological demands and to deliver drugs at a sufficiently well defined rate over a certain amount of time. A remarkably interesting feature of polymer-based drug-release systems is the potential of complex and novel release profiles, thereby increasing effectiveness and minimising toxic effects (Wise *et al.*, 1987; Berkland *et al.*, 2002), yet most developments in textile drug delivery systems emphasise slow release. Some pharmaceuticals require a constant but slow release rate for several hours, days or weeks. This seems relatively simple to achieve, nevertheless, such zero-order drug release kinetics is not that easily achieved. In zero-order release kinetics, the drug release rate is constant and independent of the drug concentration itself. Some textile drug release systems show pre-steady-state burst kinetics (see Fig. 3.8). In the initial phases a significant amount of the drug is already released (the 'burst'-phase) from the delivery system, followed by the desired period of zero-order kinetics. Burst release is undesirable because of potential toxic (side-)effects and drugs released in the initial phases are not available for slow release, thereby decreasing the efficiency of the delivery system. Release kinetics is strongly influenced by



3.8 Burst- and zero-order release.

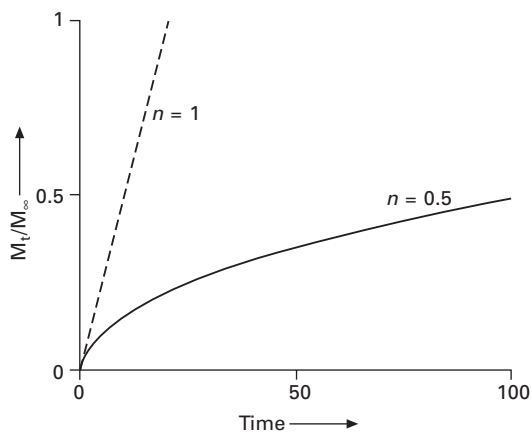
the surrounding environment and the choice of drug and carrier. There are numerous factors affecting kinetics and the amount of drug released from a carrier material, for example, molecular weight of the drug, concentration, diffusion coefficient, adsorption and desorption constants, charge (ion-exchange), degree of polymerisation, (bio)degradability, erosion of the carrier, ionic strength, temperature and pH.

Data of drug release from polymers or transdermal patches are generally analysed using a relatively simple model; the Korsmeyer equation (Korsmeyer *et al.*, 1983).

$$\frac{M_t}{M_\infty} = k_k t^n \qquad 3.1$$

where, M_t/M_∞ is the fractional release of the drug, M_t is the amount released at time t, M_∞ is the total amount of drug in the drug delivery system, k_k is a the Korsmeyer constant, a kinetic constant characteristic of the drug/polymer system, t is the release time and n is a diffusional exponent which characterises the mechanism of release. Zero-order drug release is characterised by $n = 1$, Fickian dominated diffusion is characterised by $n = 0.5$, and for non-Fickian diffusion $0.5 < n < 1$ (see Fig. 3.9). Models like the Korsmeyer equation are a very useful tool in analysing data of release systems, and can as such be used to improve delivery systems. Theoretical or predictive modelling of drug release kinetics of different delivery systems can of course act as a tool in the design and optimisation of such systems though that requires more advanced specific models. For example Vuorio *et al.* (2003) describes modelling of ion-exchange drug delivery systems, but such system-specific models are outside the scope of this chapter.

Transdermal textile drug delivery systems are often characterised and evaluated by determination of drug release into a certain liquid. In the design



3.9 Zero-order and Fickian diffusion (Korsmeyer equation).

and development of transdermal textile drug delivery systems it is essential to quantify to which extent a system controls the overall drug delivery rate and pattern across the skin. Guy and Handgraft (1992) defined that in steady-state conditions the total resistance to transdermal drug delivery is:

$$R_{total} = R_{skin} + R_{delivery\ system} \quad 3.2$$

where R_{total} is the total resistance to transdermal drug transport, R_{skin} is the resistance to drug transport across the skin and $R_{delivery\ system}$ is the resistance to drug release from the delivery system. Because the skin, and thus the resistance to drug transport across the skin, changes from person to person, age and anatomical site, drug delivery is preferably controlled by the delivery system.

3.3 Characteristics and application of drug release systems

In this section the potentials, constraints and characteristics of some specific textile slow release systems will be reviewed; cyclodextrins, ion-exchange fibres and drug-containing fibres (microencapsulated), microparticles and drug-containing nano-fibres produced by electrospinning.

3.3.1 Cyclodextrins

Cyclodextrins are considered as a relatively new class of molecules that have been widely investigated in the last three decades. They are the topic of an increasing amount of scientific papers on textile slow release systems as well. Despite their 'modern' image, cyclodextrins have been known for over 100 years and have already been described by Villiers in 1891 (Szejtli, 1998). The first patent on cylodextrin-inclusion complexes goes back to 1953 including the application of cyclodextrins in drug formulations (Freudenberg *et al*., 1953), and the first application in textiles was already patented in 1982 (Szejtli *et al*., 1980, 1982). In addition cyclodextrins have been used in complexation of dyes (Buschmann and Schollmeyer, 1997a). Cyclodextrins are able to form complexes with a variety of long-chain aliphatic or aromatic molecules like drugs, pesticides, hormones, detergents, fragrances and vitamin B. Other host-guest type systems exist, based on, for example dibenzo-crown ethers, aza-crown ethers or fullerenes (Buschmann, *et al*., 1997b; Denter *et al*., 1998a,b), but among all potential hosts, cyclodextrins seem to be the most attractive ones. The main reasons are:

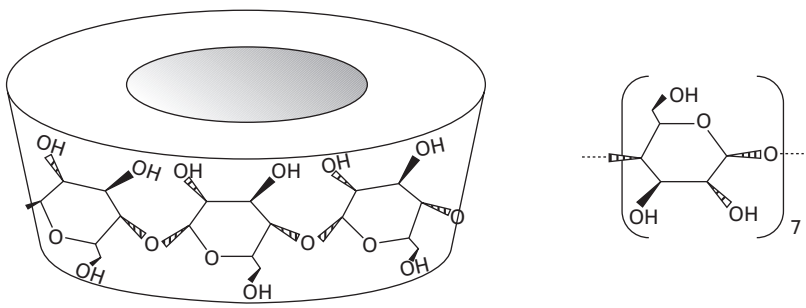
- Cyclodextrins are semi-natural; they are enzymatically (amylase) produced from strarch, a renewable substrate.
- Since the end of the last century cyclodextrins are available in large quantities (over ten thousand tons/year). With the increase in production,

the price has been reduced considerably. Derivatives are industrially produced as well (e.g. methyl-, butyl-, 2-hydroxypropyl-, glucosyl-, maltosyl-, carboxymethyl-cyclodextrins) (Loftsson, T. and Brewster 1996; Szejtli, 1998).

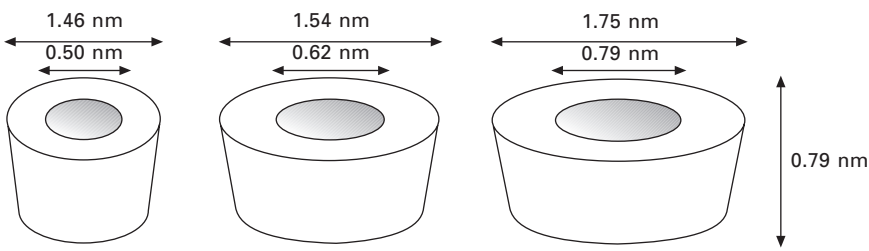
- Cyclodextrins are from a toxicological point of view fairly safe, β-cyclodextrins are licensed as food additive.

Cyclodextrins are cyclic (α-1,4) linked D-glucopyranose residues. The most common cyclodextrins are α-, β-, and γ-cyclodextrin, which consist of six, seven or eight glucopyranose units respectively (see Fig. 3.10). Owing to the lack of free rotation of the units, cyclodextrins are not perfectly cylindrical but conical. Smaller cyclodextrins do not exist, as a result of sterical factors. Cyclodextrins of more units exist, but their cavity is not cylindrically shaped. The cavity is collapsed, therefore the actual space is smaller. For example, the cavity of δ-cyclodextrin (nine glucopyranose units) is smaller than that of γ-cyclodextrin. The approximate geometric of dimensions of α-, β-, and γ-cyclodextrins are schematically shown in Fig. 3.11 and some chemical and physical properties are listed in Table 3.1.

Most studies of the application of cyclodextrin-textile drug delivery systems focus on β-cyclodextrins. The cavity or the interior of the cyclodextrin molecule is rather hydrophobic, whereas the outer surface is hydrophilic. The hydrophobic interior is mainly responsible for complex formation. Despite the hydrophilic



3.10 Schematic representation of β-cyclodextrin.



3.11 Dimensions of α-, β-, and γ-cyclodextrin.

Table 3.1 Some characteristics of cyclodextrins (Loftsson *et al.*, 1996; Szejtli, 1998)

	α	β	γ
Number of glucopyranose units	6	7	8
Molecular weight	972	1135	1297
Cavity diameter (nm)	0.47–0.53	0.60–0.65	0.75–0.83
Diameter (nm)	1.46±0.4	1.54±0.4	1.75±0.4
Height (nm)	0.79±0.1	0.79±0.1	0.79±0.1
Approximate cavity volume (Å^3)	174	262	427
Solubility in water at 25 °C (g/l)	145	185	232
Diffusion coefficient (m^2/s)	$3.4 \cdot 10^{-10}$	$3.2 \cdot 10^{-10}$	$3 \cdot 10^{-10}$
pK at 25 °C (potentiometry)	12.332	12.202	12.081

character of the outer surface the solubility of β-cyclodextrin is limited. Modification of the hydroxyl groups of the outer surface of the cyclodextrin can increase solubility, for example, by substitution of a hydroxypropyl or a carboxymethyl group, or decreasing solubility, for example, by substitution of an ethylhexyl glycidyl or an acetyl-group (Denter *et al.*, 1997; Hedges, 1998).

Complex formation is largely independent of chemical properties of the drug molecule as such, apart from the fact that the drug should fit in the cavity of the specific cyclodextrin, and thus the group of drugs compatible with a certain cyclodextrin is rather large (Loftsson and Brewster, 1996). This is underlined by the different types of drugs that have been investigated in drug-cyclodextrin complexes; varying from neutral to ionic, and from basic to acidic (Hirayama and Uekama 1999).Van der Waals forces are important in drug-cyclodextrin complex formation, complex formation is demonstrated to be enthalpy driven (Loftsson *et al.*, 1996). Drug-cyclodextrin complexation and decomplexation, i.e., the release of the guest from the host, is an equilibrium process. Assuming a host-guest ratio of 1:1, which is most frequently the case, we can write:

$$\mathrm{CD} + \mathrm{Drug} \underset{k_d}{\overset{k_c}{\rightleftarrows}} \mathrm{CD\text{-}Drug}$$

$$K = \frac{k_c}{k_d} = \frac{[\mathrm{CD} - \mathrm{Drug}]}{[\mathrm{CD}][\mathrm{Drug}]} \qquad 3.3$$

where k_c and k_d are the complexation and decomplexation constants respectively and depend on the interactions between the drug, and the cyclodextrin. The enthalpy of complexation and decomplexation varies for different drug-cyclodextrin combinations, thus k_c and k_d differ as well for different drug-cyclodextrin combinations. Most scientific papers on cyclodextrin-drug complex formation deal with free cyclodextrins, like oral formulations, and not with cyclodextrins fixed to a substrate like textile materials. As fixation

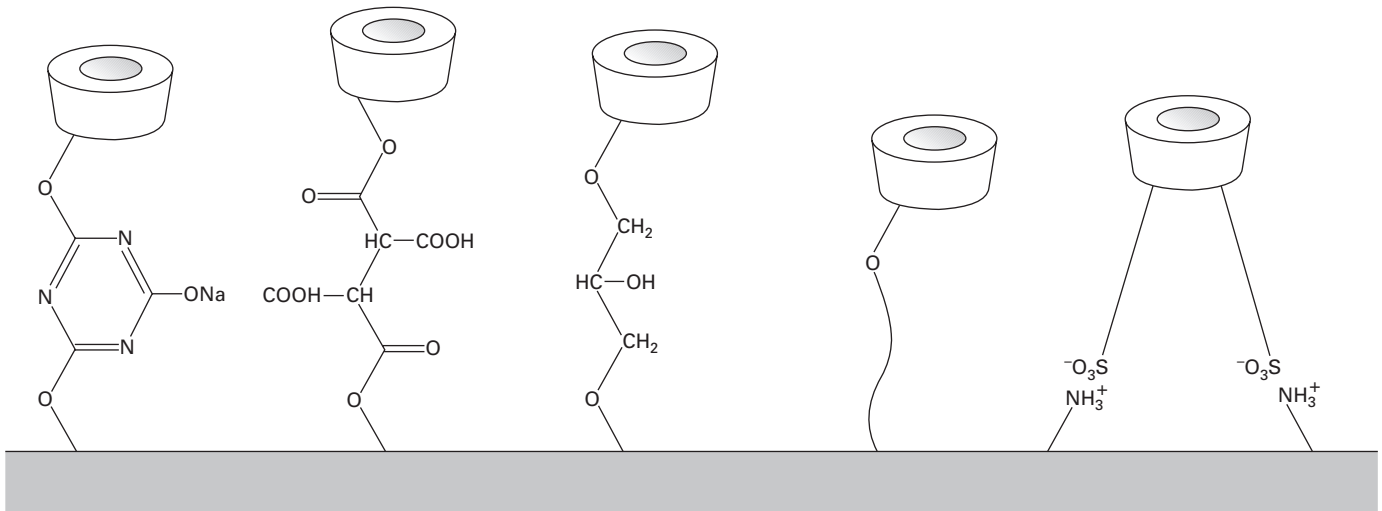
of cyclodextrins does not affect complexation power, it can be reasoned that the release pattern is not influenced by fixation either. For drugs with a weak interaction with the host, the drug release rate is controlled by dilution and degradation of the drugs as it shifts the equilibrium. For drugs with a stronger interaction with the host, competitive displacement affects the release rate too by decreasing the available amount of un-complexed cyclodextrin. Cyclodextrins can even be used to develop triggered or delayed release systems, for example, by a pH change or for water-insoluble drugs, changing the environment from aqueous to lipophilic will trigger drug release. Once the release has been triggered, the release is instantaneous and without delay. Currently, textile drug delivery systems based on cyclodextrins are mainly designed on the basis of experience and trial and error and not on the basis of specific design rules; the release pattern is to a large extent determined by the specific combination of drug and cyclodextrin.

Production of textile fibres bearing cyclodextrins

A variety of chemical and physical techniques exist for the production of textile fibres bearing cyclodextrins at their surfaces. An important feature is that attachment of cyclodextrin molecules is already achieved by conventional and well-developed as well as less conventional technologies (Denter and Schollmeyer 1996; Breteler *et al*., 2002). Therefore textile drug delivery systems based on cyclodextrins have the potential to be produced by existing textile mills. Cyclodextrins can be fixed to the surface of textile fibres permanently or non-permanently; permanent fixation can be via covalent bonding (reaction of functional groups) as well as non-covalent bonding (cross-linking). Non-permanent techniques also exist, like anionically or cationically modified derivatives on, e.g., polyamide-6. In Fig. 3.12 various possibilities are schematically illustrated. The method preferred depends on application and on the fibre material itself (Denter and Schollmeyer, 1996).

Fixation of cyclodextrins by an anchor group is feasible when the anchor group or chain is capable of penetrating the textile fibres when the latter are in their amorphous state. Anchor groups are mainly hydrophobic ‘tails’, such as long alkyl chains that fit into the fibre’s hydrophobic inner environment, like PET. The hydrophilic outer surface of the cyclodextrin will prevent complete penetration into the fibre; hence, the functional cavity remains accessible on the fibre’s surface (Buschmann *et al*., 2001). Upon lowering the temperature below the glass temperature, the mobility of the polymers is restricted thereby captivating anchor groups and fixating the cyclodextrins.

Grafting of cyclodextrins on textile materials seems most promising. α-, β- and γ-cyclodextrins have already been grafted on textile fibres like cotton, Tencell, wool, polyester, and polypropylene (for example, Denter and Schollmeyer 1996; Lee *et al*., 2000; Le Thuaut *et al*., 2000; Martel *et al*.,



3.12 Schematic representation of cyclodextrin fixation: triazinyl, 1,2,3,4,-butanetetra-carboxylic acid, glyceryl ester, 'anchoring' of cyclodextrin with a long hydrophobic alkyl chain on, e.g., PET, anionically modified cyclodextrin (e.g. by sulfoalkylether on polyamide).

2000; Lu *et al*., 2001; Breteler *et al*., 2002; Lo Nostro *et al*., 2002; Martel *et al*., 2002a,b,c,d; Szejtli 2003; Voncina and Le Marechal 2005). Grafting of cyclodextrins on polypropylene to produce non-woven reactive filters was via activation of the polypropylene substrate by electrobeam, followed by grafting using glycidyl methacrylate (GMA). Three different approaches are often described in scientific literature: one approach is based on acryl-amido-methylated-β-cyclodextrin (CD-NMA), one on poly(carboxylic acids) and one on monochlorotriazynyl-β-cyclodextrin (MCT-CD).

Acryl-amido-methylated-β-cyclodextrin (CD-NMA)

In this grafting procedure cellulose is oxidised by cerium (IV), producing a free radical on the cellulose backbone. Due to consumption of cerium (IV) by CD-NMA as well it is beneficial to add the initiator, cerium (IV), before addition of the acryl-amido-methylated-β-cyclodextrin (Lee *et al*., 2000). Grafting of CD-NMA was for one hour at 40 °C, and grafted β-cyclodextrins were mainly at the cellulose surface. The system studied was not evaluated for drug release properties, but for release of an antimicrobial component, benzoic acid, and a fragrance.

Polycarboxylic acids

Polycarboxylic acids have been used in production of cotton, wool and polyester fabrics carrying α-, β- and γ-cyclodextrins (e.g. Martel *et al*., 2002a,b,c,d). 1,2,3,4,-butane-tetra-carboxylic acid (BTCA), polyacrylic acid and citric acid have been used as grafting agents. A cyclic anhydride is formed that reacts with hydroxyl groups of cellusose, forming an ester bond under the influence of heat and/or the presence of a catalyst, such as sodium dihydrogen hypophosphite. The remaining two carboxylic groups can again form a cyclic anhydride that can react with the cyclodextrin or with another cellulose chain. Process conditions vary with different textile substrates.

Monochlorotriazynyl-β-cyclodextrin (MCT-CD)

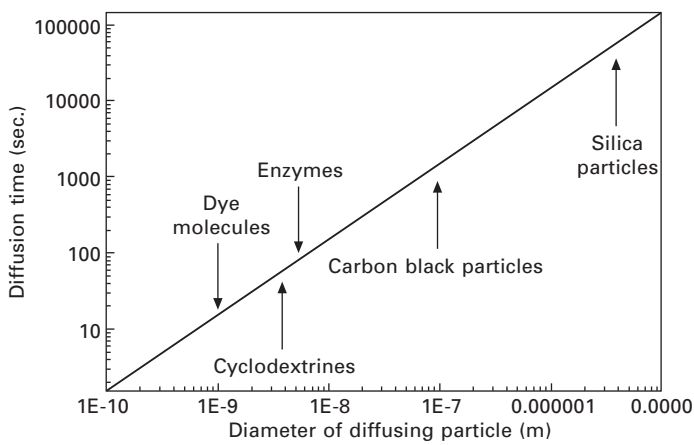
Monochlorotriazynyl-β-cyclodextrin (see Fig. 3.12) is a reactive cyclodextrin derivative that can be covalently linked to nucleophilic substrates, like cellulose, by a condensation reaction (Moldenhauer and Reuscher 1999, Lo Nostro *et al*., 2002). Fixation of MCT-CD can be carried out in conventional textile finishing equipment. The fabric is simply dipped into the liquid containing the dissolved MCT-CD, followed by squeezing of the fabric. Fixation takes place at elevated temperature. Alkaline or acidic fixation are both possible. For alkaline fixation a fixation temperature of 150 °C results in a fixation yield of 80–85%. Fastness of the MCT-CD finish is reported to be very good

(Moldenhauer *et al*., 1999). Apart from these methods, cyclodextrins can also be spun into the fibre. This can be achieved only with materials in which fibres are made using melt or solution spinning like polyamide-6. Cooling of the fibre leaving the spindle in a 'shock-wise' (or rapid) manner causes the cyclodextrins to migrate to the surface. Thereby the cyclodextrin molecules remain accessible as a host for drug molecules (Poukalis *et al*., 1992).

Mass transport of cyclodextrins in textile materials

The time-determining step in a cyclodextrin impregnation process is often the transport of the molecules to the surfaces of the textile fibres in the yarn, especially in wet-to-wet applications. The porous textile structure will hinder free liquid flow, consequently diffusion of molecules through the pores to the fibre surfaces will be the main transport mechanism. This is a relatively slow process. The diffusion coefficient of un-complexed cyclodextrins is $3.2 \cdot 10^{-10}$ m^2/s, the diffusion coefficient of a cyclodextrin-guest complex will be lower (Szejtli 1998; De Azevedo *et al*., 2000; Cameron and Fielding 2001). As an illustration, the time needed to remove 90% of various particles and cyclodextrin molecules from a yarn by diffusion as a function of the particle diameter has been calculated (see Fig. 3.13). For details on the calculation see Nierstrasz and Warmoeskerken 2003. The time needed before for cyclodextrins to adsorb at the fibre surfaces is consequently also much more than for regular textile chemicals.

Cyclodextrins are from a toxicological point of view considered to be safe; cyclodextrins are used as food additives and are considered harmful only in extremely high concentrations (Buschmann *et al*., 2001). Toxicological properties of the groups used in fixation of cyclodextrins should, however,



3.13 Time needed to remove 90% of particles from a yarn by diffusion as a function of the particle diameter.

not be neglected. Biodegradability and biocompatibility of textiles bearing cyclodextrins is mainly determined by the choice of the textile material itself. Therefore this is not considered to be a factor affecting application of cyclodextrins as a textile drug delivery system.

3.3.2 Ion-exchange fibres

Ion-exchange is a technique that has been known for quite some time and ion-exchange materials are widely used in various separation applications. Ion-exchange fibres have some advantages over other ion-exchange materials like a fast ion-exchange rate and a high separation capacity (Chen *et al.*, 1996). Ion-exchange fibres find their application in, for example, waste-water purification (Soldatov *et al.*, 1999), uranium enrichment from seawater (Chen *et al.*, 1996) and in textile drug delivery systems as well (Jaskari *et al.*, 2000, 2001; Skundric *et al.*, 2002; Vuorio *et al.*, 2003, 2004). Ion-exchange fibres have either a positive or a negative electric charge, which is compensated by mobile counter-ions of opposite charge. The overall charge depends on the pK-value of the functional groups, and is thus a function of the pH. In cationic fibres, ionic groups of ion-exchange fibres are formed by, for example, SO_3^-, COO^- or PO_3^-; anionic groups are, for example, $-NH_3^+$, $-NH_2^+$ or $-NH^+$. The principle of ion-exchange is based on the electroneutrality condition. Ion-exchange generally is a diffusional process, sensible to concentration gradients; the rate-determining step in ion exchange is diffusion either within the exchanger itself or in the so-called diffusion boundary layer. The amount of functional groups affects the loading capacity. Generally, the feature that ion-exchangers take up certain counter-ions in preference to others, influences specificity of the exchange process.

Many drugs are charged at physiological pH, therefore they can act as mobile counter-ions, and this allows them to be used in ion-exchange delivery systems. In addition drug stability during storage improves upon bonding them in ion-exchange fibres. Ion-exchange fibres suitable for drug delivery are already commercially available, examples are *Smopex*® fibres from SmopTech Co., consisting of a polyethylene backbone which is grafted with other polymers, e.g., poly(styrenesulphonic acid) (Smopex®-101) polyacrylic acid (Smopex®-102) or polyamide (Smopex®-108). Besides commercially available ion-exchange fibres, it is also possible to graft ion-exchange groups to textile fibres. Suitable fibres are cotton, flax, cellulose (derivatives) and wool, but also synthetic fibres like polyethylene, polystyrene, polyacrylonitril, polyamide and carbon fibres are possibilities (Järnström and Hirvonen 2001).

Both *in-* and *ex-vivo* ion-exchange drug delivery applications are developed. *In-vivo* the drugs can be released by ions present in bodily fluids, however, this might disturb homeostasis whereas in *ex-vivo* or transdermal applications the concentration of ions, like Na^+ and Cl^-, needed for the exchange process

is determined by excretion through the skin. Consequently the release process might be difficult to control and will probably be relatively slow. To increase control, to reduce fluctuations and to increase drug permeation, ion-exchange is combined with iontophoresis (Jaskari *et al*., 2000, 2001; Vuorio *et al*., 2003, 2004). At physiological pH the human skin is negatively charged. As a result cationic drugs permeate the skin more easily than anionic drugs. Cationic drugs can associate with negative domains present in the skin, thereby neutralising the charge of the skin and hindering the iontophoretic process (Raiman *et al*., 2003). Different ion-exchange fibres and drugs for transdermal iontophoretic drug delivery have been characterised, such as tacrin, propranolol, metoprol and nadolol with Smopex®-101 with strong ion-exchange groups and Smopex®-102 with weak ion-exchange groups (Jaskari *et al*., 2000, 2001; Vuorio *et al*., 2003, 2004). The ion-exchange material serves as a reservoir and a means to control delivery rate. In combination with iontophoresis drug release permeation across the skin may be controlled. Release kinetics are affected by the choice of the ion-exchange material and solution. Often, burst-release type is observed, however, when properly designed and controlled zero-order kinetics seems to be possible.

Skundric *et al*. (2002), studied ion-exchange fibres for *in-* and *ex-vivo* applications. Cation-exchange fibres based on polyacrylonitrile (PAN) were developed with –COOH as functional group. The potential of PAN fibres was evaluated because of good chemical stability and durability within living organisms, thereby avoiding problems that might result from biodegradation. Ion-exchange fibres with antibacterial properties (gentamicin sulphate, an antibiotic), or anaesthetic properties for, e.g., postoperative treatments (procaine hydrochloride) were successfully produced using PAN fibres with a functional carboxyl group. A very interesting development is the application of PAN ion-exchange fibres for the controlled delivery of insulin, to treat diabetes mellitus. The three different ion-exchange delivery systems, based on PAN fibres with functional carboxyl groups, exhibit burst-release type kinetics, however, satisfactory results were obtained with *in-vivo* experiments in rats with artificially provoked diabetes over a period of one month (Skundric *et al*., 2002).

Toxicity, biocompatibility and biodegradability of ion-exchange materials are to a large extent determined by the choice of polymer. Toxicity could stem from ionic groups attached to the polymer backbones or degradation products of the polymers. In literature no specific comments were made on toxicity, biocompatibility and biodegradability as such, apart from the fact that PAN is chemically stable and durable within living organisms. In general it can be stated that in *ex-vivo* applications toxicity of ion-exchange materials is less critical, especially when compared to *in-vivo* applications.

3.3.3 Drug-containing fibres, microencapsulated drugs, microparticles and nano-fibres produced by electrospinning

Other often studied approaches in constructing textile drug delivery systems are based on polymeric systems in which the drugs are incorporated, e.g., hollow fibres, incorporating the drug during fibre preparation, polymer microcapsules containing the drug, and electrospinning. As in ion-exchange materials, toxicity, biocompatibility and biodegradability of ion-exchange materials are to a large extent determined by the choice of polymer. Hollow fibres drug delivery systems are small tubes filled with a drug (Ostad *et al*., 1998). The fibre wall consists of a permeable membrane. The permeability of the membrane, chemical properties of the membrane and the radius controls drug release rate. Advantages of the hollow fibres are that they have a high surface area to volume ratio, and a high loading flexibility. Hollow fibre drug delivery systems comprise a hollow membrane filled with a liquid drug or a drug solution.

In hollow fibres, there still is a distinct separation in fibres and drug. Another method to incorporate drugs into fibres or particles is to suspend or dissolve a drug into a polymer solution used to produce the fibres. Selection of the polymer is based upon the solubility of the drug in the polymer solution. Drug loading efficiency is limited, and most often burst kinetics is observed. The resulting fibres can be further processed using regular techniques, like weaving.

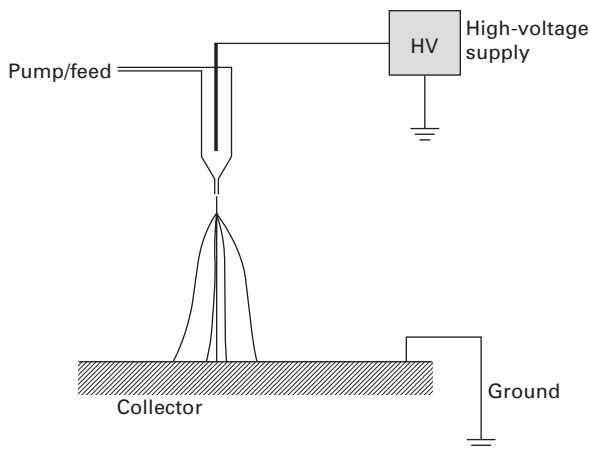
Particles containing drugs can be fixed to other textile fibres by reaction or cross-links. The drug release rate is determined by the radius of the fibre or particle, the concentration gradient, the diffusion coefficient of the drug in the polymer material, erosion of the material, or electrostatic interactions in case of polyelectrolytes (Liao *et al*., 2005). Burst kinetics is most often observed (Gupta *et al*., 2001), however, when properly designed, zero-order kinetics seems possible in case of uniform micro-particles with controlled diameter (Berkland *et al*., 2002). An interesting application is the application of biodegradable polymers such as poly(lactic acid). Upon degradation of the polymer, the drug is released. Drug release can thus be ‘triggered’, even by specific local conditions such as an infection for example (Woo *et al*., 2000).

Another technology is to produce particles containing drugs is encapsulation (Nelson, 2002). Encapsulation can be achieved by a variety of methods, such as interfacial polymerisation, microemulsion polymerisation, precipitation polymerisation and diffusion. The drugs are brought into contact with monomers, oligomers or polymers. These assemble around the drugs and subsequent polymerisation produces the final particles. High drug loads are possible. Applications of encapsulated materials in textiles are not only in

drug delivery systems, but in, for example, durable fragrances, skin softeners and insect repellents as well. Microencapsulated phase change materials are already applied in textile materials to reduce extreme temperature fluctuations.

A fairly new promising technology in the application of polymer based textile drug delivery systems is electrospinning (Kenawy *et al*., 2002; Zeng *et al*., 2003, 2005), even though the idea of electrospinning dates back to 1938 (Formhals, 1938). In electrospinning fibres are produced of nanoscopic dimensions. Depending on the experimental conditions, set-up and polymers fibre diameters are in the range of 16 nm up to 2 μm, which is orders of magnitude smaller than the diameter of fibres produced in conventional spinning processes (Jeager *et al*., 1998; Bergshoef and Vancso 1999). Owing to their nanoscopic diameter, it is even possible to produce transparent composite materials (Bergshoef and Vancso, 1999). The technology for electrospinning is fairly straightforward (see Fig. 3.14). In electrospinning a strong electric field (5–45 kV) is applied to a polymer solution held in a capillary. At the critical field strength, depending on the polymer solution but typically around 10 kV, electrical forces overcome surface tension forces that keep the liquid in the capillary and a charged jet of the solution is ejected. The jet moves towards the collector. The solvent evaporates during spinning, and a non-woven mat is formed on the collector (Jeager *et al*., 1998; Bergshoef and Vancso, 1999).

Kenawy *et al*. (2002) produced electrospun poly(L-lactic acid) (PLA) and poly(ethylene-covinyl acetate) (PEVA) fibres and blends thereof containing tetracycline, an antibiotic. The fibres were spun at 15 kV from chloroform solutions, containing a small amount of methanol to solubilise the tetracycline hydrochloride. Blends of electrospun PEVA and PLA fibres typically had a diameter of 1–3 μm, while electrospun PLA fibres had diameters of 3–6 μm.



3.14 Schematic representation of set-up for electrospinning.

In initial drug release experiments burst release was observed, but smooth drug release has been described for a period of five days.

Zeng *et al*. (2003, 2005) tried to improve size distribution of the diameter of biodegradable electrospun PLA fibres to improve drug release characteristics. Fibres were spun at 30–45 kV from a chloroform-acetone solution. The influence of different surfactants (triethyl benzyl ammonium chloride, sodium dodecyl benzene sulphate and PPO-PEO ether) on fibre diameter and fibre uniformity was evaluated. The release kinetics of rifampin (an antibiotic), paclitaxel (an anti-tumour agent), doxorubicin and doxorubicin hydrochloride (a broad spectrum anti-tumour agent) was evaluated. Fibres spun at 23 kV in the absence of surfactant had diameters in the range of 0.3–4.2 μm, while fibres spun at 42 kV in the presence of triethyl benzyl ammonium chloride had diameters in the range of 0.3–0.5 μm. Fibres spun at 41 kV in the presence of sodium dodecyl benzene sulphate had diameters in the range of 0.68–1.35 μm, and fibres spun at 32 kV in the presence of PPO-PEO ether had diameters in the range of 0.34–1.35 μm. The release characteristics were determined in the presence of proteinase K, an enzyme capable of degrading the PLA fibres. In the absence of proteinase K no drug release was reported, release is triggered by degradation of the polymers. For the fibres produced in the presence of surfactants nearly zero-order kinetics was observed. This clearly demonstrates the potential of electrospun drug delivery systems compared to other polymeric drug delivery systems.

3.4 Future trends

As has been mentioned in paragraph 3.3, more often than not textile drug delivery systems based on, e.g., cyclodextrins are mainly designed on the basis of experience and trial and error, and not on the basis of specific design rules. Drug release rates and patterns are to a great extent determined by the combination of guest and the host or the carrier material. For *ex-vivo* applications this is not necessarily a problem hindering actual developments yet, but for *in-vivo* applications, where control of drug release rates is much more delicate and development costs are of another order of magnitude, this might block developments. This is a point of concern, that can possibly be addressed by, e.g., advanced computational techniques and more complicated release systems. Some polymer drug delivery systems suffer from burst-release kinetics. Novel techniques such as electrospinning clearly have the potential to combine triggered release with zero-order release kinetics. Today, most electrospinning processes are typically at lab-scale and not at industrial level though electrospinning is a technique strongly developing and up-scaling of the process is a matter of time.

A topic not being dealt with in this chapter is the potential of biotechnology in the development of textile drug delivery systems. However, it seems

reasonable to expect that biotechnology will play a major role in textile drug delivery systems in the near future. Presently, strong efforts are being made to functionalise (bio-)polymer materials using enzymes, and enzymes have in principle the possibility to bind host- or drug-molecules to fibres. The development of innovative biodegradable materials can have a strong influence on the design of triggered drug release systems.

To meet pharmaceutical demands, industrial production of textile drug delivery systems require special production facilities apart from sufficient environmental and safety measures. The developments of suitable minimal application techniques, such as nozzles or digital finishing technology, have the potential to meet these demands and to increase efficiency, and competitiveness. This will allow actual implementation into the textile industry. Apart from applying these technologies in advanced drug textile delivery systems, new developments and applications of textiles or textile fibres bearing cyclodextrins are expected in the field of environmental protection, separation technology, and functional textile materials like sensoric, antibacterial and antifungal textiles (hygienic textile) or textiles releasing fragrances and adsorbing unwanted odours (Szejtli, 2003; Buschmann *et al*., 2001).

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