TEXTILE SLOW-RELEASE SYSTEMS WITH MEDICAL APPLICATIONS

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Abstract

In the development of medical drug delivery systems, attention has been increasingly focused on slow- or controlled delivery systems in order to achieve an optimal therapeutic effect. Since the administration of drugs often requires a defined or minimum effective dosage in the human body, more conventional delivery systems such as tablets require relatively high doses, which can result in undesired toxic effects. Subsequent degradation of the drug in the human body will result in a drug concentration below the minimum effective level. Furthermore, there are situations where oral administration is less advisable, such as in cases of prolonged treatment or with people that are forgetful, which again results in ineffective treatment. Textile slow-release systems have the potential to overcome these negative aspects. Drugs containing transdermal patches for ex-vivo applications are already familiar; however, this paper will not deal with such applications, but with more advanced in-vivo textile slow-release systems. Due to enormous progress over the years in the fields of supramolecular chemistry, nanotechnology, and polymer science & technology, a number of promising drug delivery technologies have been developed. This review will focus on the opportunities of textiles bearing cyclodextrins, aza-crown ethers or fullerenes, as well as ion-exchange fibres, drug-loaded hollow fibres, textiles treated with nanoparticles and fibres with bioactive compounds in their embodiment. In this paper, the delivery systems will be discussed and compared in terms of biostability, biodegradability, controllability, toxicity, carcinogenicity, interface reactions, material costs and the fabrication process.

***Keywords**:* slow release systems, drug delivery, medical, cyclodextrins, aza-crown ethers, fullerenes, ion-exchange fibres, hollow fibres, nanoparticles, entrapment, encapsulation.

Introduction

Over the years, people have always tried to improve the quality and length of life, and with success. Positive developments in hygiene and nutrition have increased the average lifespan by several years. The growth in medical knowledge has also greatly contributed to this, and developments are still ongoing. Besides searching for solutions to medical problems, many attempts have been made to improve the comfort of application. Textile systems can be useful in this respect.
A specific aspect within the medical field is the delivery of drugs. Pills, ointments, injections and suchlike are already familiar; though these are useful in many cases, situations can be thought of in which other systems would be more applicable. In oral delivery systems (e.g. tablets, pills, capsules), the drug is absorbed in the stomach or intestinal tract [1, 2]. As some drugs become metabolised, either there or in the liver, they lose their efficacy before being able to fulfil their medical purpose. Consequently, relatively high doses are necessary to achieve an effect, which might give rise to liver toxic metabolites [1, 2]. Delivery through the skin circumvents the liver passage, allowing drug dosages to be reduced. Ointments are an alternative, but only for those therapeutic agents that will give no side effects in case of overdose [1]. Moreover, there are situations where oral administration is less applicable or impractical, e.g. with children, people with swallowing difficulties or people who are forgetful, for example because of dementia. Transdermal (through the skin) and *in-vivo* (inside the

body) drug delivery systems constitute a good alternative in these situations. Finally, with prolonged drug treatment, these systems are more preferable than daily injections or intake of pills.
One general benefit obtained from the use of textile materials is protection. Over the years, wearing comfort and the quality of textiles have improved, and textile materials now form an important aspect of our everyday lives. Besides the material itself, the structure is important. While dependent on the fabrication process, textile materials are often permeable, breathing structures, and usually treated to have an absorptive capacity. Therefore, textile materials have also found applications in the medical field. Their 'breathing' capability especially makes textile materials a useful basis for *ex-vivo* (outside the body) applications. Moreover, as people are used to wearing textile materials, it seems logical to examine these materials as a possible basis for drug delivery systems.
Over the years, a number of delivery methods have been developed. So-called *transdermal patches* are already familiar. Most such patches consist of multi-layer systems, in which in addition to an ointment (or other drug-containing substance), a regulatory system (e.g. a membrane) is used. This paper will not discuss these kinds of systems, but will essentially focus on the following promising systems:

- textiles bearing cyclodextrins;
- textiles bearing aza-crown ethers;
- textiles bearing fullerenes;
- ion-exchange fibres;
- drug-loaded hollow fibres;
- textiles treated with nanoparticles;
- fibres with bioactive compounds in their embodiment.

Because of their application in medicine, the delivery systems are mainly discussed in terms of features such as biocompatibility and controllability. Other aspects, which are usually important in textiles, e.g. colour fastness and washability, are not included in this study.
Practically the most important aspect of a drug delivery system is its biocompatibility, which nowadays is defined in the following terms: "the ability of a material to perform with an appropriate host response in a specific application". Important elements included in biocompatibility are toxicity, carcinogenicity and related issues as mutagenicity (inducing changes in genetic material that are transmitted during cell division) and teratogenicity (the ability or tendency to produce anomalies of formation). For biodegradable materials, not only should the parent material be harmless, but the degradation products as well. For most substances, the skin forms a natural barrier in entering the body, but with *in-vivo* applications extra care should be taken in order to avoid the introduction of harmful substances into the body. A second aspect of biocompatibility is the product's biostability and biodegradability. Depending on the application, a more or less biostable product is desirable. A general approach is that *in-vivo* applications have to be biodegradable, removing the need for an extra operation to remove the material. For many *ex-vivo* applications, biostability is desirable, although ultimately biodegradability would be beneficial, considering waste disposal. The interactions at the interfaces of the textile material and body tissue, e.g. the skin, form the third important biocompatibility aspect in developing a proper textile-based drug delivery system. Systems with excellent controllable delivery are of no interest if they lead to considerable irritation of the skin at the same time.
Another important aspect of a delivery system is its controllability. As mentioned before, in some of the conventional systems the risk of overdose is present. Using a slow-release delivery system, with which the drug can be delivered in a controlled way, might constitute a solution. Experiments will have to be performed to bring system release patterns into view. Preferably, a system should be controllable in such a way that release is possible within a certain range; that is, with any given system, different release patterns should be feasible responding to an individual patient's need.
Although difficult to quantify in the developmental stage, the material costs of a system are not irrelevant – there is no use in developing a system in which the benefits are cancelled out by the costs. In developing medical applications, costs are often 'allowed' to rise, so long as a unique product with a highly desired function is the result. However, in comparing different systems with virtually the same goal, the cost aspect cannot be neglected; for this reason, a short discussion on this topic is included here. Related to the cost aspect is the production process. Conventional production techniques will in most cases be beneficial in comparison to specially developed new techniques; generally speaking, the more complicated the technique, the higher the costs. Therefore, differences in system processing will be discussed and compared. Unfortunately , it will be difficult to make a quantitative analysis for many factors, and only qualitative considerations are given when comparing different textile slow-release systems.

Drug delivery systems

Cyclodextrins

Textiles bearing cyclodextrins consist of ordinary textile materials upon which cyclodextrin molecules have been fixed. Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides, built from a number of D-glucose units. The generally most common forms are the so-called α-, β- and γ-cyclodextrins (see figure 1 for an example). Because of the combination of a hydrophobic interior and a hydrophilic exterior, cyclodextrins can be useful components in the complexation of (hydrophobic) drugs. The ring size of cyclodextrins can be varied since different cyclodextrins have cavities of a different size, but still only selected groups of drug molecules that fit in the cavities can be used in complex formation. It is stated that complex formation is largely independent of the chemical properties of the drug molecule [3], making the group of drugs that are compatible with a particular cyclodextrin quite large. 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 [4]. Furthermore, several modifications of the parent cyclodextrins are possible. The derivatives can be reactive (e.g. cyclodextrin with a monochlorotriazinyl (MCT) group), more hydrophilic (by means of hydrophilic side groups, such as hydroxypropyl and hydroxyethyl), less hydrophilic (by means of lipophilic side groups, such as ethylhexyl glycidyl) or ionic (by means of ionic side groups, such as hydroxypropyl trimethyl ammonium chloride) [5].

Cyclodextrins have been successfully immobilised upon textile fabrics. There are a number of ways to attach the molecule to the textile material, which can be classified into two main categories, physical and chemical attachment. A specific example, which can be considered more as entrapment than attachment, is when cyclodextrin is spun into the fibre. This can only be achieved with materials whose fibres are made using melt or solution spinning, e.g. polyamide-6. Cooling the fibre leaving the spindle in a shock-wise manner causes the cyclodextrins to migrate to the surface [6], thus locating the cyclodextrins in the fibre's outer sphere. This will keep the cyclodextrin cavities accessible to the drug molecules. A second example concerns cyclodextrin derivatives bearing so-called 'anchor groups'. Anchor groups are able to penetrate textile fibres when the latter are in their amorphous state. These groups are mainly hydrophobic 'tails', such as alkyl or aryl groups [6], which fit excellently into the fibre's hydrophobic inner environment. 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 [7]. Upon lowering the temperature (below T_g), the fibre polymers are restricted in their motion and the anchor groups are captivated, thus fixating the cyclodextrins [4, 6].

When cyclodextrin derivatives are ionic in nature, the fixation with a textile fabric may be based on electronic interactions. A specific example is the interaction of HPTMAC[1]-β-cyclodextrin with polyacrylonitril fibres [4].

The chemical fixation of cyclodextrins can be achieved by reaction of textile fibre functional groups with the functional groups in the cyclodextrin. A straightforward example is the reaction of the accessible cyclodextrin hydroxyl groups with (among others) hydroxyl, carboxyl, amide or other acidic or basic groups [6]. Cyclodextrin derivatives can have other functional groups, such as MCT, which reacts through substitution of the chlorine atom by a negative polymer side group [4]. Another comparable fixation uses a third molecule as a kind of intermediate between fibre and cyclodextrin, for example a polymer. Upon polymerisation, these compounds react with both the hydroxyl groups of the cyclodextrins and a textile fibre functional group, e.g. the hydroxyl group of cellulose. Furthermore, some network formation takes place, which leads to a combined fixation and entrapment of the cyclodextrins [6].

The methods for treating the textile are thus quite simple. The method using anchor-bearing cyclodextrins is especially useful, since no fixation agent is needed, making it possible to use conventional textile treatment techniques and apparatus [4]. Furthermore, this method has virtually no limitations with respect to the textile materials that can be used.

Several tests [4, 8] have shown that the complexing power of cyclodextrins was maintained upon fixation. Hence, textiles treated with cyclodextrins can be used as drug carrying systems.

Fixating cyclodextrins upon a textile material does not only alter the complexation power of the system. With derivatives containing large hydrophobic/lipophilic side groups, the diffusion time for a water droplet is increased, whereas hydrophilic groups have the opposite effect. The surface resistance is changed by the fixation of cyclodextrin derivatives. The surface resistance decreases when increasing the amount of alkyl groups on the surface [4]. Another important change is the

[1] HPTMAC: hydroxypropyl trimethyl ammonium chloride

reactivity of treated fabrics, as the cyclodextrins introduce reactive hydroxyl groups to the textile surface.

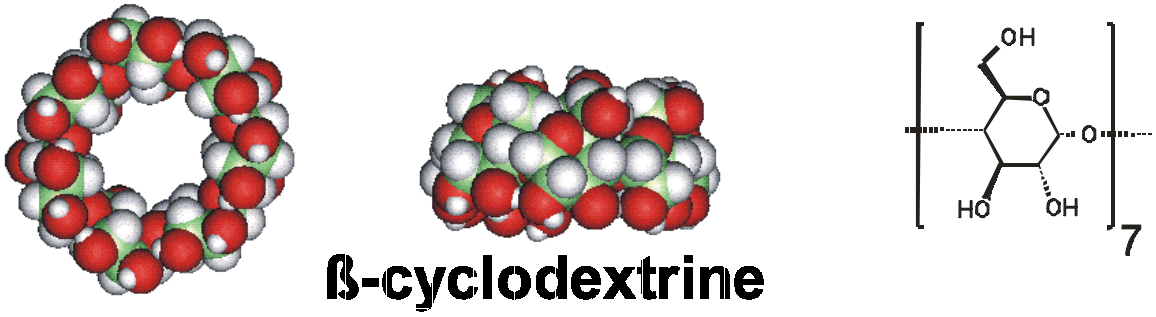

Figure 1. Structure of β-cyclodextrin

Aza-crown ethers

An alternative to the attachment of cyclodextrins to textile materials is the attachment of aza-crown ethers. The data on these kinds of systems are less detailed than for cyclodextrin systems, but still a few comments can be made. Aza-crown ethers are neutral, macrocyclic polyether molecules, in which the oxygen atoms are partially or completely replaced by nitrogen. In contrast with cyclodextrins, which have a 3D-structure, aza-crown ethers in their basic form are only 2D. The secondary amine groups are possible substitution spots. The molecules are capable of forming stable complexes with metal ions, in particular the so-called transition metals. Selectivity is governed by the (fixed) crown ring diameter, the number of heteroatoms in the ring, the ion diameter and the charge density of the cation [9]. Aza-crown ethers can be fixed upon textile materials without loss of the crown ether's complexing power. This was tested by treating cotton, PET and PA-6.6 with aza-crown ether 22DD (ACE 22DD)), ACE (22TT), ACE (22TTp$(NO_2)_2$) and ACE (22TrTr) [9]. See figure 2 for examples of the different structural formulas.

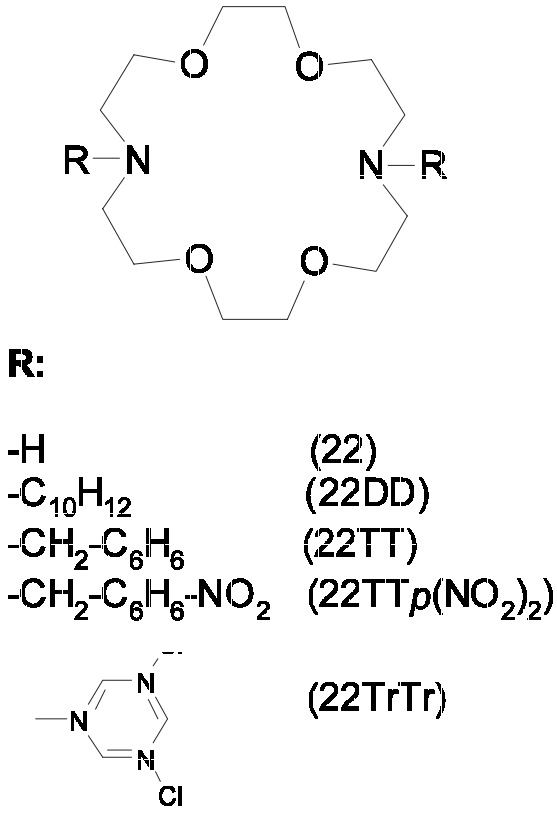

Figure 2. Several examples of the different structural formulas of some aza-crown ethers

Fixation is achieved by treating the materials with a flowing ACE-solution in trichloromethane (ACE (22TrTr) in combination with cotton) or water (the other systems) and heating [9]. Again, two main types of fixation can be distinguished, namely a chemical reaction of side groups of the aza-crown ether and the fibre, and the 'anchoring' of the aza-crown ethers through hydrophobic side groups. Increasing the temperature leads to an increased amount of fixed ligands, which is explained by the facilitated penetration of the hydrophobic tails at elevated temperatures.

Fullerenes

Another way to fix macromolecules is by the use of fullerenes. Fullerenes are a so-called allotropic form of carbon; the material consists of only carbon atoms. A well-known example is C_{60}, which is more or less shaped like a football. Inclusions of helium and other metal ions in the fullerene inner cavity have been reported. Furthermore, fullerenes themselves can act as a guest molecule in complexation with macrocyclic ligands, such as cyclodextrins [10]. The fullerene groups can be used as a starting point for self-assembling molecular layers, for example by combining them with cyclodextrins. Additionally, bound fullerenes are usually capable of reacting with other compounds. One possibility is a reaction with aza-crown ethers, which in their turn can bind other compounds and so on. In this way, layers with complexing capacity can be built [10]. Because of their olefinic, electrophilic character, fullerenes react in several addition reactions, e.g. in nucleophilic addition of amines. This can be used to achieve the permanent fixation of fullerenes to polymers such as PET, PA-6.6 and wool, which contain amine elements.

Ion-exchange fibres

As the name suggests, ion-exchange fibres are capable of exchanging ions. The principle has been known for quite some time and these fibres are already used in many applications, e.g. in wastewater treatment. Ion-exchangers bury either a positive or a negative electric charge, which is compensated by (mobile) counterions of opposite polarity. Mobile ions of the same sign (co-ions) can also be present. In cationic fibres, the bound ionic groups are formed by e.g. $–SO_3^-$, $-COO^-$, $-PO_3^-$ and $-AsO_3^-$. Anionic groups are those such as $–NH_3^+$, $-NH_2^+$, $-NH^+$ and $–S^+$. The principle of ion-exchange is based on the electroneutrality requirement. The exchange is generally a diffusional process, sensitive to concentration gradients, and the rate-determining step in ion exchange is the diffusion either within the exchanger itself or in the so-called diffusion boundary layer. Usually ion-exchangers take up some counterions in preference to others. This fact can be used in controlling the exchange [11]. Drug stability during storage improves upon bonding them in ion-exchange fibres.
The drugs act as the mobile counterion. They can be released by ions in bodily fluids, though this might disturb the homeostasis. Furthermore, in *ex-vivo* applications, the amount of such ions will probably be too low to achieve sufficient drug release. Hence, a co-solution of a salt, such as sodium chloride or sodium phosphate [12], is used. The sodium ions will replace the drug ions. and the latter will combine with (in this case) the chloride or phosphate ions. The salt can be encompassed in a gel (based for example on gelatin, agar or polyvinyl alcohol), which is then brought into contact with the textile fibre loaded with the drug. The salt will diffuse through the gel and the fibre, and thus release the drug [12]. An interesting application may be to use ion-exchange fibres for the regulated *in-vivo* delivery of insulin, in order to treat diabetes mellitus [13, 14]. In literature, chemically bonded drugs are mentioned as a variation on ionic drug-ionic fibre interaction [14].
Ion-exchange fibres suitable for drug delivery are already commercially available. Examples are the so-called *Smopex*® fibres, which consisting of a polyethylene backbone grafted with other polymers, e.g. poly(styrenesulphonic acid) (Smopex®-101) polyacrylic acid (Smopex®-102) or polyamide (Smopex®-108) [2, 11]. Besides using the commercially available ion-exchange fibres, it is also possible to graft ion-exchange groups to a (textile) fibre. Fibres suitable for this purpose include cellulosics and wool, but also synthetic fibres like polyethylene, polystyrene, polyacrylonitril, polyamide and carbon fibres [12]. The amount of functional groups grafted onto the fibres affects its loading capacity.

Hollow fibres

Hollow fibre systems can be seen as small tubes which can be filled with a drug. The fibre wall usually consists of a permeable membrane that can be used in controlling drug release. The fibres are advantageous in two ways, as they have a high surface area to volume ratio and a high loading

flexibility. The system can comprise hollow tubes filled with a liquid drug or a drug solution [15]. Another possible form is a hollow fibre in combination with (an) ion-exchange resin(s) [16]. Also, drug crystals dispersed in a polymer core [17] can be used. In yet another variety, drugs are dissolved in such a core [17]. The systems in which the drug is bound into a polymer are prepared by mixing the drugs with a polymer material, in order to give a drug-loaded core granulate. If desired, different drug/polymer granulates can be mixed. The mixture is heated in order to melt the polymer; the drug is dissolved in the polymer. After cooling, the mixture is granulated again. These granulates are used in co-extrusion together with granulates of the polymer which is to form the fibre membrane. Both granulates are molten (but not mixed), and by accurately controlling the two polymer flows through a spinneret, a coaxial fibre combining the polymer core and the fibre membrane is formed [17]. When drug crystals are desired, the melting of the polymer-drug combination before co-extrusion is skipped.

Nanoparticles

In the treatment of textile with nanoparticles that contain a functional agent (which can be a drug), the nanoparticles are permanently fixed on a textile fabric through chemical bonds, either by direct reaction of a particle side group and the textile, or by means of a linker molecule. The nanoparticle encapsulation is used to circumvent possible alterations and loss of functionality of the agent, which could be the case in a direct reaction between the agent and the textile. However, linkers for direct chemical attachment and also useful in controlled release are difficult to engineer, and must be developed for the various agents individually [18].
The nanoparticles consist of a drug, either surrounded by a synthetic, polymer shell or contained within a synthetic, 3D polymer matrix, both micrometric to nanometric in size. Encapsulation can be achieved by several methods, e.g. interfacial polymerisation, microemulsion polymerisation, precipitation polymerisation and diffusion. In general, the drug is brought into contact with a set of monomers, oligomers or polymers. These assemble around the payload; polymerisation will give the final particles. An alternative way is to prepare the nanoparticle in the absence of the drugs, which are absorbed by the nanoparticles following afterwards [18].
A wide range of applicable monomers, oligomers and polymers is available. Some very useful systems are those containing amine, hydroxyl or sulph-hydryl monomers or polymers combined with amine-, hydroxyl- or sulphhydryl-reactive monomers or polymers. Both hydrophobic and hydrophilic monomers can be used; the choice depends on the drugs to be encapsulated [18]. As an extra option, systems can be copolymerised with soft or rubbery monomers or polymers (e.g. acrylates or methacrylates), to improve wearing properties such as ‘skin softness’ and wrinkle and abrasion resistance [18]. The monomer or polymer systems used contain at least one component able to react with a textile material even after polymerisation. Wool and other animal fibres contain hydroxyls, amines, carboxylates and thiols. Synthetic fibres usually have a limited number of reactive groups. The same holds for cellulose and its derivatives as well as other plant materials, which have to react through their hydroxyl groups. In order to increase the possible particle-textile combinations, a bifunctional molecule can be used, for example to link an amine-reactive particle with cellulose (which contains no amine groups) [18]. For particle fixation, the textile material is exposed to a solution, dispersion or emulsion of the textile-reactive particles, by conventional methods such as soaking, dipping, spraying, fluid-flow or padding [18]. A catalyst may be present in the medium. The actual fixation takes place in the curing stage, which can take place while the textile is still in contact with the particle solution (dispersion, emulsion), but preferably after the drying stage. In the case of using a linker molecule, the textile material may first be treated with the linker and subsequently with the particle solution [18]. The contact time can vary widely, from seconds to days, as can temperatures and pressures [18].

Drugs incorporated in fibres

Another approach in creating textile drug-delivery systems is processing the drug in the fibre’s preparation stage. With the hollow fibres, there was still a distinct separation into fibre (the membrane wall) and drug (the core). Yet another way of incorporating drugs into fibres is to suspend or dissolve a bioactive compound (in particular a drug) into the polymer solution used to produce the fibres. If a bioactive compound is to be incorporated within or inside the polymer fibre, polymer selection is based upon the solubility of the drug in the polymer solution. If the drug is to be located between the fibres, this is of no concern. Instead, the drug can be suspended in the polymer solution before the actual spinning. The spinning will give nonwoven meshes of nano- and micron scale fibres. These fibres can be processed into matrices, linear assemblies and braided or woven structures, or be used in film

coating. Fibres can be spun from any polymer which can be dissolved in a solvent. This includes non-degradable polymers such as polyethylene, polyurethanes and polyethylene vinyl acetate copolymers, but also biodegradable polymers such as poly(lactic acid), poly(glycolic acid), poly(orthoesters) and poly(phosphazenes) [19]. An interesting development related to this kind of system is the synthesis of a biodegradable polymer with a drug incorporated into the polymer backbone. Upon degradation of the polymer, the drug is released again. It has been shown that polymers can be developed which are more easily degraded in the presence of certain enzymes, e.g. enzymes highly presence at infection spots. Hence, the drug release would be more or less 'triggered' by the infection (in this case) [20]. A serious drawback reported in the literature is the system's low efficiency. This can be explained by the fact that upon degradation of the polymer, the degrading 'scissions' are not always made perfectly at each junction of drug and polymer, and a number of non-functional rest products are formed [20]. These kinds of polymers have not yet been tested for processing into fibres and textile materials, but it might be an interesting option to experiment on this point. When doing so, it is not necessary to restrain oneself to drug-containing polymers only; for improvement of mechanical properties, for example, combinations with other (biodegradable) polymers can be made.

Toxicity and carcinogenicity

Cyclodextrin-bearing textiles can be considered as not harmful. Conventional textile materials can form the basis of the system, and the only harm could lie in the cyclodextrins. Detailed studies of the toxicity, mutagenicity, teratogenicity and carcinogenicity of some cyclodextrins and their derivatives have been made. These substances were potentially harmful only in extremely high concentrations, and no acute toxicity has been observed [7]. More detailed information on specific cyclodextrins can be found in the literature [21]. In general, they are considered to be non-toxic [22].
For aza-crown ethers, little specific data on toxicity and carcinogenicity has been found. It has been stated that aza-crown ethers are less toxic than their crown ether equivalents, due to the reduced influence on potassium leakage into and sodium leakage out of cells. Complexed ligands are much less toxic than uncomplexed ones. Besides, as aza-crown macrocycles have been investigated for medical purposes for a long time, e.g. for their use in antitumour treatment, in treatment of kidney stones and even as a drug element, it can be assumed that their toxicity and carcinogenicity is acceptable with respect to medical limits [23]. More specific data (although very limited) on the aza-crown ether used in the specific example described above (ACE (22DD)) can be found on the Internet[2]. Upon exposure, no harmful effects have been indicated in the information available. The material is not listed as being carcinogenic.
For fullerene-bearing textiles, it could be stated that these materials are not highly toxic, since free fullerenes are applied in other medical fields as well, implying a harmless effect of this group [24, 25].
In literature found on ion-exchange fibres, no comments are made on toxicity. As the polymer base materials are formed by common, non-toxic and non-carcinogenic materials, toxicity and carcinogenicity would have to stem from the ion groups attached to the polymer backbones. As the groups are bound to the polymer, no harm is to be expected from free ionic groups. Furthermore, the ion groups are neutralised by a suitable counterion 'at all times', be it either a drug or an electrolyte ion, hence the possible negative effect is cancelled. For *in-vivo* applications, the ion exchange fibre might present problems when it disturbs the homeostasis. Confining the use of ion-exchange fibres to *ex-vivo* applications, the subject of toxicity and such is practically irrelevant; if electroneutrality is maintained at all time, *in-vivo* applications will not give rise to problems either.
In drug-loaded hollow fibres, the material used for the hollow fibre matrix is generally a conventional material known to be non-toxic or non-carcinogenic, like polyurethane, nylon or polyethylene vinylacetate copolymers [15-17]. The possible toxic effect thus lies in the drug inside the hollow fibre. As drugs in high doses might have a toxic effect, it is crucial that the release patterns of the hollow fibres do not give rise to such doses. Furthermore, the way the drug is incorporated in the fibre is important. It is important to characterise their filling, because of possible biodegradability especially, but also with regard to fibre damage..
For textile materials treated with nanoparticles, the base materials are common and well-known textiles of both natural and synthetic origin. Hence, no toxicity is to be expected from them. By selecting the appropriate polymer materials for encapsulating drugs and such, no toxicity is to be expected thereof either. As nanoparticles are covalently bounded to the textile materials, they are thus

[2] source: http://www.emscience.com/catalogs

immobilised in possible *in-vivo* applications; no harm will be caused by particles wandering throughout the body.
For drug-loaded polymers, again the toxicity and carcinogenicity are determined by the choice of the polymeric material. In the case of non-degradable polymers, no problems are to be expected, but for biodegradable polymers, the degradation products should be non-toxic. Using materials such as poly(glycolic acid), which have been thoroughly investigated on aspects such as toxicity, no problems are to be expected for biodegradable polymers.

Biostability and biodegradability

For textile materials bearing cyclodextrins, the choice of the base material is decisive when concerning biostability and biodegradability. Materials like cotton or wool are fairly biostable, though not indefinitely [18]. In normal wear, body substances do not immediately damage them; mechanical forces and things like weather, UV radiation and attack by microorganisms are the principal cause of any damage. The materials' lifetime can be enhanced by treatment of the finished materials to require antibacterial, anti-insect or fungicidal effects, among others. Ultimately the materials will deteriorate, and in that sense they are biodegradable. Synthetic materials (e.g. nylons, poly(ethylene terephtalate) (PET)) are more biostable in that respect. The cyclodextrins themselves are readily biodegradable [22].
In literature on the fixing of aza-crown ethers on textile materials [9], no comments were made on changes in biodegradability. However, it is rather inappropriate to assume that introducing the aza-crown ethers did not lead to any drastic changes in the biostability and biodegradability. For aza-crown ethers in combination with silver ions, for example, the antimicrobial effects of the loaded groups might be considered as enhancing long-term biostability. (Ultimate) biodegradability depends, again, on the choice of the base material.
In literature concerning fullerene-treated textile material, no specific comments have been made on biodegradability or biostability. As common materials form the base, these will mainly govern the biodegradation pattern. As with aza-crown ethers, the fullerene groups can provide antimicrobial effects (e.g. by complexation of silver ions), implying increased biostability.
For ion exchange fibres, biostability and biodegradability is largely influenced by the choice of the base material. One such commercial available system is the Smopex® fibres. These materials, or at least their polyethylene backbones, are non-degradable. Also, traditional textile materials such as wool and cotton can be used – the biodegradability of these materials has been discussed before. The large amount of electrically charged groups in the fibre is bound to have an influence on biostability and biodegradability, although nothing is mentioned in the literature cited. It can easily be understood that a change in the fibre's equilibrium situation will lead to a reactive system, more susceptible to phenomena such as degradation. However, especially in *ex-vivo* applications such as textile coverings, there is unlikely to be any large disturbance of the equilibrium other than the desired one, which causes the release of the drug.
The biostability and biodegradability of a hollow fibre system depends on the material chosen for the fibre wall. Of course, with a non-degradable material such as polyurethane, the fibre remains intact. For some applications, especially *in-vivo*, biodegradability is desired, as it takes away the necessity to surgically remove the system. In such cases, biodegradable materials such as poly(lactic acid) or poly(glycolic acid) can be used. The choice of the material is very important, as biodegradation will interfere with the release rate.
With nanoparticles, the biostability and biodegradability of the system is primarily determined by the choice of the base material. As common textile materials form this, the same biostability and biodegradability considerations hold as for cyclodextrin treated materials (among others). For *in-vivo* applications, suitable materials have to be chosen, if they are desired to be biodegradable. The polymer material used for encapsulating the drug is not really important with respect to biostability or biodegradability of the systems as a whole. Practically all polymers are suitable for encapsulation, though the choice of polymer is of influence in the release pattern of the particle [18]. When desired, a biodegradable material can be chosen so that degradation will (partially) control the release of the particles' contents. A nanoparticle treatment is not limited to giving the textile material a drug releasing capacity. By encapsulation of appropriate agents, for example anti-fungal or anti-insect, biostability and non-degradability can be improved [18].
The biodegradability and biostability of the drug-loaded fibres is determined by use of the polymer. Again, biostability is guaranteed when using well-known polymer materials such as polyethylene or polyurethane. Though nothing has been mentioned in the literature, it is of course interesting to

investigate whether solubilising the drug into the polymer has an effect on polymer properties, one of which is biostability. For some polymer fibre systems, biostability is undesirable, as the release of the drugs depends upon degradation. Hence, the material is designed to have a fair biodegradation rate, e.g. by introduction of a large amount of ester linkages. Some control over the degradation rate can be achieved by choosing the appropriate monomers.

Interface reactions

For cyclodextrin textiles, some tests are performed which consider irritating or sensitising effects [7]. It should be borne in mind that there are several different cyclodextrins and derivatives, not all of which have yet been tested with regard to these effects. With aza-crown ethers, unfortunately no specific data was found on this aspect. For fullerenes, again, no comments were made in the literature. Based upon safety data, one could expect some problems, as C_{60} is marked as being 'irritating'[3], and contact with skin and eyes should be avoided. It is unclear how fixing and possible further complexation alters this behaviour.
For ion-exchange fibres, only *in-vitro* (in-the-lab) tests have been performed so far, using human cadaver skin [11], therefore no real statement can be made regarding possible interface reactions. It is questionable whether the large amount of charged groups in the system might give rise to phenomena such as skin irritation when the equilibrium is disturbed. As the latter is not likely to happen (in preparing ion-exchange fibres, the fibres are washed with water a few times without leading to any build-up of charge), no problems should be expected here.
With hollow fibres, irritation would stem from the choice of the fibre wall material. By choosing well-known fibres, which are known not to cause bodily responses and to be comfortable to wear, irritation is not an issue.
For textiles treated with nanoparticles, the textile materials themselves are unlikely to cause any undesired effects, as they are common materials which people are used to. For drug encapsulation, polymers with known, advantageous properties regarding interactions between the material and the human tissue will have to be chosen. As the list of useful polymers is almost infinite, a suitable solution for almost any situation is to be found [18].
As far as interface reactions are concerned, the drug-loaded fibres will present no problems as long as polymers are chosen that are considered to be 'safe', such as polyethylene. Again, it might be interesting to investigate the effect of drug solubilisation on polymer properties: one possibility would be the occurrence of surface modifications, which could be disadvantageous in respect of interface reactions. For biodegradable fibres, it is not only the fibre that might cause interface reactions, but also the degradation products.

Controllability

The mechanism of drug release from cyclodextrin complexes has been investigated in several experiments. An initial difficulty in making remarks on controllability is that practically every cyclodextrin derivative has its own release pattern, as do combinations of cyclodextrins with different drugs. This is due to the fact that the interactions governing the complexation strengths vary in every case (as expressed by k_1/k_{-1} in the formula below). The drug-cyclodextrin complexation and decomplexation (release) is an equilibrium process of the type:

$$D_1 + CD \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} D_1\text{-}CD$$

where D_1 is the drug, CD the cyclodextrin and D_1CD the drug-cyclodextrin complex. It is stated that for weakly complexed drugs, dilution is controlling decomplexation, as it shifts the equilibrium. For more strongly bound drugs in drug-cyclodextrin complexes, competitive displacement and protein drug binding are important as well; the former shifting the equilibrium by decreasing the available amount of free cyclodextrin, the latter by decreasing the available amount of the free drug [26]. The statements above are based upon experiments dealing with non-fixed cyclodextrins in oral delivery systems. As the fixation of cyclodextrins did not affect their complexing power, it can be reasoned that the release

[3] source: http://www.chemexper.com/

pattern is not influenced by the fixation either. However, a more detailed study on this topic is desirable. In literature, some experiments in changing the release pattern have been reported. Again, these concern non-fixed cyclodextrins. Two examples:

- Cyclodextrins can be used to overcome problems in drug solubilisation, e.g. water-insoluble drugs can be solubilised. Release is then based on changing the environment, for example from aqueous to lipophilic, and can be regarded as a 'triggered' release. Once triggered, the release is immediate and without delay [5].
- Drug release can be delayed by using pH-sensitive systems, e.g. systems that are less soluble in water at low pH, but soluble in neutral or alkaline regions due to the ionisation of an acidic group. In oral administration, this means that drug release can be delayed until the complexes have passed the stomach and reached the smaller intestine [5].

Unfortunately, no general rules concerning drug release can be derived from this kind of information. It can be stated that it is a question of 'trial and error' – that is, for a given situation, a particular complex has to be found which will give the desired pattern. For *ex-vivo* applications, it must therefore be concluded that once a combination of drug and cyclodextrin is chosen, the release pattern is fairly well set, unless a multi-layer system is created.
For aza-crown ether textiles, few comments can be made regarding the controllability of the system, as no real delivery takes place. It is however essential to investigate the possibility of the migration of the complexed ions (which was suggested in antimicrobial tests), and its effect on phenomena such as interface reactions. For fullerene systems, the same statement applies.
With ion-exchange fibres, the release pattern can be changed in several ways. An example: to activate Smopex® fibres, i.e. to create ionic groups, fibres were treated with NaCl. When a mixture of NaCl and NaOH was used, it appeared that drug binding increased, though the fraction of the drug content released was the same. Hence, increased drug release can be achieved by appropriate activation, though this leads to relatively greater drug wastage [11]. The drug release increased with a decrease in electrolyte concentration (the 'helper'), which can be explained by considering the drug equilibrium. It must be emphasised that the decreasing electrolyte concentration is a result of increased external volume: when the same amount of electrolyte is used, the external volume will be much higher in the case of lower concentrations. Hence, equilibrium is shifted towards release. However, the decreased electrolyte concentration increases the electrostatic affinity between the drug and the fibre. Apparently, the tendency to re-establish the drug equilibrium is the predominant effect. The opposite situation would be observed if the same external volume would be used for the different electrolyte concentrations, because in this case the shift in equilibrium would not be that great, and the affinity effect will be overriding [11]. Changes in the electrolyte can help to increase drug release. When $CaCl_2$ was used in combination with NaCl instead of NaCl alone, drug release is increased due to the stronger tendency of Ca^{2+} to bind to the ion exchange groups. This effect appears to be pH-dependent [11]. To summarise, drug release can be controlled to some extent by choosing the appropriate fibre-drug combination and by changes in the electrolyte solution, concentration, and composition as well as pH. In order to extend control over the release pattern of the drug from the fibre, so-called iontophoresis can be used. This method, in which the fibres are placed in an electric cell and subjected to an electric current, can be useful in releasing drugs that are not released in a passive way [2]. Furthermore, forced exchange can be used to overcome the large biological variations that can exist between patients. The strength of current can be used in controlling the release rate.
For hollow fibres, the fibre membrane usually controls the release. Several types of polymeric-controlled release systems have been developed for commercial applications. These can be categorised in three basic types, regarding the rate-controlling mechanism: diffusion-controlled, chemical reaction-controlled and solvent activation-controlled. Most control systems use one ore more of these mechanisms. Much attention has been paid to the mathematic modelling of controlled release from hollow fibres [27-29]. These mathematical treatments are beyond the scope of this review. With the drug present in the crystal state, the concentration of the dissolved drugs is determined by its saturation solubility. In this case, the release rate can be controlled by the thickness and permeability of the fibre membrane. As a consequence, this concept can only be used to control the release of a single drug [16]. When the release of more than one drug is to be controlled, it is necessary to dissolve the drugs completely. In this way, the release can be controlled independently by the concentration of each drug and by the membrane characteristics. The release is then influenced by the solubility and diffusion coefficient of a drug in the core polymer [17]. If a constant release is desired, the permeability of the bulk polymer (the core) for a specific drug should be much higher than the membrane permeability. Thus, by choosing the appropriate membrane material and thickness, a

specific release pattern can be established. However, once this is set, no further means of control remain. When release is not only diffusion-controlled, changes in the release environment (e.g. changes in solvent composition) can be used to control drug release.
With nanoparticles, the architecture of the particle shell or matrix can be formulated and fine-tuned to exhibit the controlled release of its contents, ranging from constant but prolonged release to zero release. The particle can be formulated with an almost infinite degree of designed characteristics via key structural features, such as cross-linking density, hydrophilic-hydrophobic balance of the copolymer units and the stiffness of the polymer network. Furthermore, erodible or biodegradable particles can be used to combine the release mechanisms of diffusion and erosion. In addition, the particles can be designed to respond to different stimuli to alter the rate of release. The polymers can be induced to undergo a distinct thermodynamic transition by the adjustment of any of a number of environmental parameters, e.g. pH, temperature, ionic strength, co-solvent composition, pressure or electric field. Examples are polymers that, based on the lower critical solution temperature transition, drastically cut off release when exposed to higher temperatures [18].
With fibres which incorporate the drug within, some control over drug release can be introduced by varying the choice of polymer used in the fibre (influencing drug diffusion), the diameter of the polymeric fibres (controlling diffusion distance), the concentration of polymer used in the fibre (influencing fibre structure) and the amount of drug loaded in the fibre (influencing concentration gradients) and biodegradability of the polymer (fast biodegradation enhancing drug release). Of course, these variables only apply to situations where the drug is located *within* the polymer fibre. The drug-loaded fibres can be combined with non-loaded fibres, either biodegradable or non-degradable, which can be used to change the distance over which a drug has to diffuse before it is set free into the body/onto the skin (among other factors), which hence constitutes another means of controlling drug release [19]. A release pattern is fixed once the fibre is prepared. As a final remark, it can be said that creating a proper release system is more or less a question of trial and error, as various drugs interfere differently with various polymers.

Material costs

For the textile materials treated with cyclodextrins, the base materials can be common textiles such as cotton, cellulosic or synthetic fibres such as PET. There is no need for pre-treatment of these materials, and hence, in comparing the system with other systems, the material costs are mainly determined by the cyclodextrins. Research in the cyclodextrin area has grown, leading to numerous publications and patents [7]. Biotechnological advancements have led to great improvements in cyclodextrin production, lowering production costs [3]. This phrasing can be used to assume that cyclodextrins, at least the parent ones (α-, β- and γ-dextrin) will have acceptable costs. Besides – and this should be emphasised – at least for *ex-vivo*, non-biodegradable materials, the cyclodextrins can be reloaded and hence the material can be recycled. In Table 1 a rough idea of the market prices of cyclodextrins is given:

Table 1. Market prices of different cyclodextrins (2002)

Natural Cyclodextrins		Prices[a]
α-cyclodextrin 99%	5g	€18.48
β-cyclodextrin 99%	5g	€9.24
γ-cyclodextrin 99%	5g	€130.90
Neutral Modified Cyclodextrins		
β-dimethyl cyclodextrin	5g	€150.92
β-trimethyl cyclodextrin	5g	€831.60
β-2-hydroxypropyl cyclodextrin	5g	€150.92
Ionic Modified Cyclodextrins		
β-cyclodextrin phosphate	2.5g	€485.10
β-carboxy methyl cyclodextrin	5g	€121.66
β-amino cyclodextrin	5g	€2710.40

(source: http://www.capital-hplc.co.uk/cdex.htm),
[a]Original prices in British pounds; exchange rate taken as £1 =€1.54

As can be seen in this table, when moving from unmodified to modified cyclodextrins, the prices rapidly increase. Unfortunately, for fixation upon textile materials using common textile-finishing

techniques, modification is a necessity. For medical applications, these costs might be acceptable. One should further bear in mind that the quantities mentioned in Table 1 are lab-scale quantities. For other applications, e.g. delivery of fragrances[4], the prices will have to drop. Thus, the desire to use cyclodextrins for other than medical applications might lead to even lower prices, due to further development and increased production, with large quantity sales.
Because of the relative cheapness of the base materials, the material costs of aza-crown ether treated textiles are mainly determined by the prices of the aza-crown ethers. As an indication, the market price of the aza-crown ethers, ACE (22) and ACE (22DD), used in literature can be taken: €53 and €212 for one gram, respectively[5]. This is considerably higher than the prices of cyclodextrin; besides, only anti-microbial activity without drug delivery capacity is achieved, making the material even more expensive in relative terms.
For fullerenes, again the main cost-determining factor is the fullerenes themselves. Some indications can be found on the Internet: market prices vary from €175[6] to €212[6] for 5g C_{60}, 99.5% pure and €304[7] to €901[7] for 5g C_{60}, ultra pure (>99.95%). Furthermore, in the fixation process γ-cyclodextrins turned out to be a useful solubilising agent, but as was shown, these materials are not very cheap.
In ion-exchange fibre systems, the textile material itself is the drug carrier. As mentioned, several ion-exchange fibres are available, e.g. the Smopex® range, based on grafted polyethylene. It is to be expected that these specialty fibres exceed the ordinary textiles in costs. However ordinary textiles such as cotton, can also be used to create exchange fibres. Besides, no extra carrier group is needed: once it is spun, the fibre is capable of carrying drugs, albeit that it has to be activated in order to create ionic groups. As the latter can be achieved by fairly simple salt solutions, this will not be of especial relevance when considering costs. The necessity for a release 'helper' might be disadvantageous, since this demands a different textile setup (e.g. the need for an extra electrolyte reservoir).
For drug-loaded hollow fibres, the costs can be divided. Of course, there are the costs of the fibre itself. It can be reasoned that producing hollow fibres demands more sophisticated techniques, which will show in the costs. Strictly speaking, this falls within the aspect of the manufacturing process and costs, and should not be taken into account here. As the fibre material can consist of common polymers, high costs are not to be expected thereof. As for the filling, it depends on how the drug is to be bound inside the fibre. Some alternatives, such as a polymer gel or crystallisation in combination with other substances, will give rise to additional material costs.
With nanoparticle-treated textiles, a great advantage concerning material costs is the ability to use common textiles as base materials, and thus, again, no great impact on material costs is to be expectedas a result. For nanoparticle synthesis, a broad range of materials is available, including the common ones. Not all of them are qualified as bulk polymers [18]. For specific polymer coatings, with specific release properties, costs can therefore rise.
The material costs in creating drug-loaded fibres are determined by the choice of the polymer. As common polymers such as polyethylene can be used, systems do not necessarily have to be expensive. When considering the material costs for the biodegradable polymers in which the drug is to be incorporated in the main chain, the drug itself should not be taken into account, as was not done in the other systems. Hence, only the other polymer ingredients, i.e. the monomers, basically form the material costs. Whether the system is costly or not thus depends on whether the monomers are bulk (and hence 'cheap') or not.

Manufacturing process

A major advantage immediately follows from the way the cyclodextrin-textile system is prepared. The attachment of the cyclodextrin groups is achieved by relatively simple and well-developed textile treatment techniques [8]. Furthermore, which may be even more important, it is possible to treat an already fabricated piece of cloth [4, 6]. Hence, the manufacture of the textile material can be separated from the actual system formation, offering the possibility of specialisation without having to deal with the problems concerned with textile production. A second advantage of the possibility of treating finished textiles is that it can be guaranteed that the cyclodextrin groups are mainly attached to the textile surface that will form the interface with (for example) the skin. Hence, the majority of the original drug-loading capacity is maintained, in contrast with preparing cloth from treated fibres. As a

[4] which can also be achieved with cyclodextrin treated textiles
[5] source: http://www.emscience.com/catalogs - original price in dollars; exchange rate taken $1 = €1.06
[6] source: http://www.mtr-ltd.com/pricelist.htm - - original price in dollars, exchange rate taken $1 = €1.06
[7] source: http://www.sesres.com/FullerenesPrices.asp - original price in dollars, exchange rate taken $1 = €1.06

final remark considering manufacture, it can be stated that only one textile treatment is necessary to create a feasible, drug-loadable system; this in comparison with the traditional multi-phase systems, in which separate layers have to be created [1]. For aza-crown ether textiles, the comments made above also apply.
For fullerene-treated textiles, the manufacturing process is, again, relatively simple, though techniques different from the conventional ones for textile treatment are used, which can be seen as a disadvantage. Besides, the fixation process takes more time in the case of fullerenes compared for example to cyclodextrins. In the examples, for cyclodextrins, preparation times were in the order of minutes to a few hours [4, 6], whereas in the case of fullerenes, fixation took a day or even more [10].
With ion-exchange fibres, the activation step can also be considered as being a disadvantage in the fabrication process, when the latter is considered as being the complete processleading to a system ready for drug loading. Nevertheless, as ion-exchange fibres are used in applications other than medical, e.g. wastewater treatment, removing metal out of liquors and such, it can be stated that the production of such fibres has passed the developmental stage and is now commercially attractive. This is stressed by the use of the ion exchange fibres found in the literature, which were commercially available.
The fabrication of many types of hollow fibres has developed in such a way that no great difficulties and hence no extreme costs are nowadays to be expected thereof. However, the hollow fibres have a great disadvantage in comparison with the other systems discussed so far, namely the coupling of loading the fibre to the manufacture in some cases, e.g. in the case of the drug crystals in the polymer core. This calls for specialisation, in the sense that those producing the fibres will also have to have a range of different drugs at their disposal.
With nanoparticle treatment, a great advantage is that it is applicable to both fibres and finished goods [18]. Thus, as with cyclodextrins, the specific treatment in order to get useful drug delivery systems can be decoupled from the fabric production. Furthermore, the application of the nanoparticles to the system can be achieved by known textile treatment techniques, which is also advantageous.
With fibres with drugs in their embodiment, the fabrication costs are of no real interest, as the techniques used are fairly simple. A far more interesting point is the fact that the drug is incorporated into the fibre while processing the fibre. As was mentioned with the hollow fibre systems, this is rather disadvantageous, as it calls for the availability of both polymers and various drugs on one production location.

System comparison

In the foregoing paragraphs, a number of textile delivery systems are discussed. As to be expected, some of them look more promising than others. Moreover, further development is desirable. In this paragraph, the systems' "weak spots" are discussed again, but now in comparison with other systems.
Concerning the aspect of toxicity, carcinogenicity and such, no real distinction is to be made between the systems, at least not based on the literature cited. The real toxicity stems from the drugs used themselves; this should not be taken into account, as it is virtually the same for all cases. It has been mentioned that especially in the case of the aza-crown ethers and fullerenes, additional research is desirable.
For biodegradability and biostability, the same statement holds. On the other hand, based on literature, the combination of cyclodextrins, aza-crown ethers and fullerenes with textile materials is to be applied more in the field of *ex-vivo* than *in-vivo* delivery systems. This is underlined by the textile base materials used, which are all representatives of those materials used in common clothing. In order to take advantage of the ability of system regeneration, *in-vivo* applications are even more 'out of the picture'. Biodegradable systems, which are more interesting for *in-vivo* applications, have not yet been explored. The same goes for nanoparticle treatment, which has been rather restricted to common textiles. As for the ion-exchange fibres, it is to be expected that these systems will consist mainly of non-degradable fibres, when considering the treatments these materials are subjected to.
However, it is interesting to explore the concept of combining biodegradable textile materials with cyclodextrins and nanoparticles, especially for *in-vivo* use. As an example: can the same fixating principles and treatment processes be used in combination with biodegradable polymers?
In-vivo biodegradable applications are more likely to come into view when using hollow fibre systems, drug-loaded polymers or polymers containing a drug in their backbone.
As for the interface reactions, it can be stated that the data in the literature cited is insufficient to make substantial comments, and no real comparison can be made here. It can be stated that at least the

cyclodextrin, nanoparticle, hollow-fibre system and some of the drug-loaded fibre systems can be freed of irritating effects. For the other systems, interface reaction experiments are desirable.
As for material costs, the most interesting systems will probably be those using the common textile materials as its base, such as the cyclodextrin system and the nanoparticle system. To some extent, the ion exchange system can be mentioned here too, as it was shown that it is possible to graft common textile materials with ion-exchange groups.
In fabrication, the cyclodextrin and nanoparticle systems will also be economically of most interest, as they can be prepared by using common textile-treatment techniques. As no further information was found on the grafting of textiles in order to get ion exchange fibres, no real comments can be made on this point. It is interesting, though, to have a further look at these systems, because ion exchange fibres are promising with respect to other aspects as well, especially controllability.
Since little distinction could be made between the systems by considering all aspects except controllability, the latter can be considered to be the most important aspect. As mentioned, for most systems release patterns can be controlled in their preparation, but once prepared, the release pattern is fixed. The only two real exceptions are the ion-exchange fibres and the nanoparticle systems. These systems could be controlled afterwards by means of such factors as electrolyte composition (in case of the exchange fibres) or pH. The most interesting systems at this point would therefore be the ion-exchange fibre system and the nanoparticle-treated textile systems.

Acknowledgements

The Textile Technology Group at the University of Twente acknowledges the financial support of the Foundation Technology of Structured Materials in the Netherlands and of the Dutch Ministry of Economic Affairs.

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