Utilization of cyclodextrins in industrial products and processes

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During the last ten years the production of cyclodextrins has increased from several hundred to several thousand tons, and besides α-, β- and γ-cyclodextrins, methylated and hydroxypropylated cyclodextrins are also produced on an industrial scale. For other purposes (chromatography, catalysis, reagents, diagnostics, specific drug formulations, *etc.*), about a hundred different cyclodextrin derivatives and complexes are commercially available. A dozen cyclodextrin-containing drugs have already been approved and marketed. Around 130–140 new cyclodextrin-related papers, patents (applications) and conference abstracts are published each month. The largest number of publications deals with actual or mainly potential pharmaceutical applications of cyclodextrins, but the largest amount of them is used in foods, cosmetics and toiletry products. A similar intense development is expected for the next decade.

Supramolecular chemistry produces an astonishing variety of new and very spectacular 'host' molecules, which form inclusion-type associations with appropriate 'guest' species (ions, radicals, molecules) called inclusion complexes, adducts, cryptands, *etc.* To most of these host–guest associations some potential practical utilization(s) is (are) attributed.[1]

Some of these new synthetic hosts are highly specific, *i.e.* their molecular (or ionic) recognition capacity prefers a given ion or molecule. This type of host will deliver highly specific and sensitive sensors, or entrapping agents, sequestrators, for specific ions. This means that these hosts will be used only in rather restricted fields and amounts. Produced for a very limited market, generally by complicated synthetic procedures, from expensive starting substances, the majority of these hosts will remain expensive speciality chemicals, further burdened with toxicological and environmental pollution problems.

Of all inclusion complex forming hosts known, the cyclodextrins (CDs), being of natural origin, organic, biocompatible substances, seem to have unique status: the availability of the raw material (starch) is not only unlimited but also cheap; the technology of their production is a relatively simple enzymic conversion; the production is free from any environmental pollution problems: practically, there is no unusable byproduct, and no polluting substance escapes the apparatus; they are non-toxic, biologically degradable substances (the main primary degradation product is glucose); their utility, of course within well defined limits, seems to be inexhaustible: it is difficult to find any group of chemical products (drugs, cosmetics, food, plastics, paper, textiles, pesticides, photographic materials, *etc.*) or processes (formulation, catalysis, separation, stabilization, *etc.*) with no convincing examples for the use of CDs.

No wonder that, while at beginning of the 1970s CDs were considered as rare, expensive, toxic, but very challenging curiosities, ten years later, around 1980, several companies began simultaneously to offer industrially produced CDs and adequate toxicological studies documented the harmlessness of CDs when used as recommended. However, rapid development of the CD market had to face: lack of approval from the authorities (for use in food, drugs, cosmetics, *etc.*); the potential consumers did not know for what purposes and how they should use CDs (to be a pioneer is risky, and costs a lot of money); the marketed amount was small, and consequently the prices were high.

Now, around the mid-1990s, CDs are produced in thousands of tons, their price is rapidly reaching the level which is acceptable for most potential users, in most countries one or more CDs are approved in one specific product, or generally, for any purposes, and the number of products and processes which consumes the produced CDs is increasing continually.

All this is supported by the remarkable increase of the CD literature.

CD literature

While 25 years ago *ca.* 8–10 papers and patents were published on CDs per month, 5 years ago this number had increased to 20–25, and presently (1996) about 130 new papers, patents, conference abstracts are dedicated to cyclodextrins (*i.e.* on average, 4 new publications per day). The number of CD publications currently available (in July 1996) is *ca.* 13000.

The classification of CD papers (abstracted by CD-News[2] in January–November 1994) according to their profile is illustrated in Fig. 1. Classification of the 197 lectures and posters presented at the 8th International Cyclodextrin Symposium in April 1996 (Budapest) resulted in a practically identical distribution pattern.[3]

Around 17% of all CD papers are dedicated to the fundamentals of cyclodextrin chemistry and technology, where the really original important results are represented by papers on the synthesis of new, chemically modified CDs and on the biological effect of CDs (toxicology). The many papers on new sources of CTG-ase enzyme, its enzyme kinetics and methods of production of cyclodextrins are mainly reproductions of earlier works.

The next group (*ca.* 20% of all CD papers) consists of all fundamental inclusion phenomena studies which are not directly practice-oriented: energetics and kinetics of inclusion, X-ray, NMR, EPR, circular dichroism and Raman spectroscopy, thermal analysis, interaction of CDs with specific guest types, enzyme modelling with CDs, preparation and analysis of cyclodextrin complexes, *etc.*

The largest group of CD papers is dedicated to the pharmaceutical application of CDs. The majority of drug molecules are poorly soluble in water, and consequently their biological absorption is slow and frequently far from complete, many drug molecules are rather sensitive to oxidation, thermal decomposition, light, ions, *etc.* Many drug molecules are ideal complex-forming partners for cyclodextrins. This is a very productive field, and considering the lengthy development and

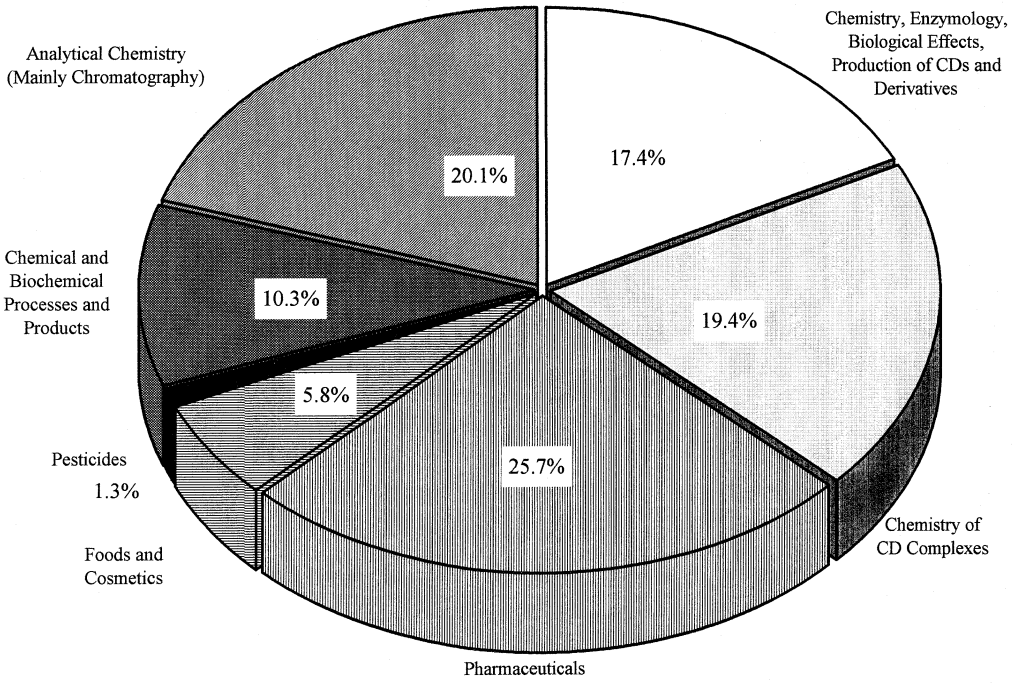

Fig. 1 Distribution of 1072 CD-related publications, abstracted by CD-News for January to November 1994

the strict requirements for approval of a new chemical entity (a cyclodextrin complex of a well known drug molecule is always considered to be a new chemical entity) it must be considered as a significant achievement that about a dozen drugs have already been approved and marketed in cyclodextrin-complexed form. This number, in the next few years, is expected to display an explosion-like increase. Nevertheless, the large number (>4000) of drug–CD-related papers and patents is a little misleading, because many authors publish the same results in different journals under different titles, but with virtually identical content, re-discoveries are published frequently, simply because the authors did not read the earlier literature and have discovered something that was published ten or fifteen years earlier, but even if only about 30% of the published papers disclose really new and significant results, it is almost hopeless for a single scientist to read all the relevant literature in this field.

The number of CD publications in the field of food and cosmetics (fourth group) is rather modest (*ca.* 6%) but in fact more than 70% of all produced cyclodextrins are used in food and cosmetics (Fig. 2). If a drug substance is complexed with cyclodextrins and marketed in several countries it may need 20–40 tons of cyclodextrin per year (except for the successful prostaglandin E_1–α-CD complex, the yearly production of which needs only several kilograms of α-CD because one vial contains only 20 μg PGE_1 and 646 μg α-CD). However, only a single toiletry product, *e.g.* fragrance tissue, which needs no authority approval, needs hundreds of tons of β-cyclodextrin every year!

The application of cyclodextrins in pesticide formulation (fifth group) represents a very modest fragment (*ca.* 1%) of the CD literature, because the pesticide industry needs very cheap auxiliary materials. The price of cyclodextrins is not low enough for the pesticide industry, but when one considers that practi-

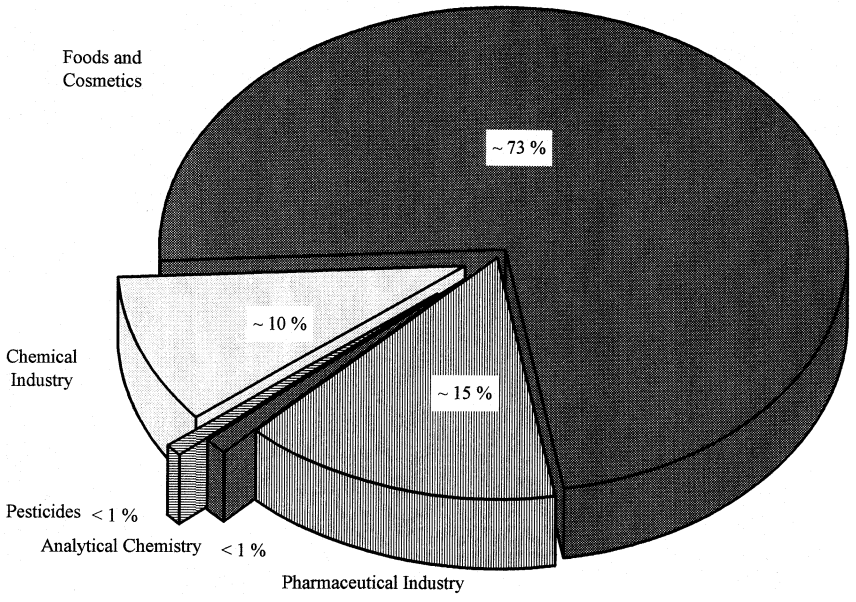

Fig. 2 Estimated segments of the CD market (1996)

cally the same effects can be attained by formulating a pesticide molecule with CDs, as is the case for drug molecules, when the price of technical quality cyclodextrins drops below $3 per kg, the pesticide industry will use up many thousand of tons.

At present, about 10% of the CD literature is dedicated to the application of cyclodextrins in chemical and biotechnological industries (sixth group); however, this number is expected to grow rapidly. This article attempts to survey mainly this section of the CD literature.

The last group involves the application of cyclodextrins in analytical chemistry, and diagnostic preparations. The analytical application of CDs means mainly the application of cyclodextrins in chromatography. While ten years ago most papers in this field were on the subject of the application of CDs in gas chromatography, and five years ago in HPLC, nowadays the application of CDs in capillary zone electrophoresis dominates. Cyclodextrins display unprecedented potential for use in chiral separation on the chromatographic scale. For these purposes only small amounts of CDs or, more frequently, of specific chemically modified cyclodextrins, *e.g.* methylated, carboxymethylated or ionic derivatives (sulfated, carboxylated, aminated, *etc.*) are needed, and it is difficult to find a separation problem on the analytical scale which could not be solved by using CDs.

In view of the overwhelmingly large number of CD publications, it is no wonder that about 400 reviews have been published on CDs; the vast majority of them summarize only a specific section of the very broad field, and only a few dozen of them cite more than 100 references. Only a few monographs[4–6] attempted to give a well documented survey of all the CD literature or, without claiming completeness, to summarize the essence of some or of a single specific subject area.[7–10]

The development of all CD chemistry and technology is reflected most spectacularly by the proceedings (or minutes) of the international CD symposia. The first such symposium was held in Budapest in 1981, the second in 1984 in Tokyo, and since then they have been held every second year. The volumes containing the papers submitted for publication are 400–650 pages long, and as well as comprising the actual results and trends of CD research, they illustrate how the main research focus is shifting from fundamental research towards the colourful variety of industrial applications.[11–17]

Since 1985 a monthly abstracting service, CD-News[2], has been publishing the abstracts of CD-related papers and patents, as well as any available information on CDs *e.g.* new CD-containing products, conferences, approvals, actual trends.

The Cyclodextrins

Upon the addition of cyclodextrin glycosyl transferase enzyme (CGT-ase) to an aqueous solution of starch, every sixth or seventh of the eight α-1,4-glycosylic linkages is split, but the majority of the maltodextrinyl radicals formed, instead of reacting with a water molecule (hydrolysis), react with their own non-reducing end, resulting in a six-, seven- or eight-membered macro-ring. These cyclic maltodextrins are called α-, β- and γ-cyclodextrins (Schardinger dextrins, cyclomaltooligoses, cycloamyloses, *etc.*). Their IUPAC name is about five printed lines long, and consequently is never used.

As well as these three 'parent' CDs, some minor CDs also exist: nine-, ten-, eleven- or twelve-membered rings are also formed in very small amounts. From the α-1,6-branched fragments of amylopectine 'branched' CDs are formed; moreover, recently the chemical synthesis of a five-membered (pre-α-) CD has been published.

In reality these 'rings' are empty 'cylinders' (Fig. 3). On one edge all the primary C(5)—CH_2OH groups of the constituent glycopyranose units are arranged, with all secondary C(2)— and C(3)—OH groups on the other edge. The internal cavity

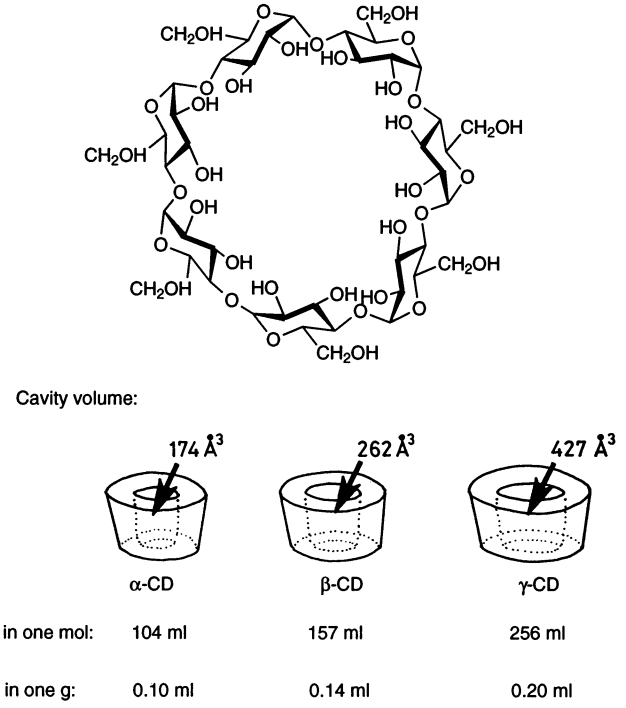

Fig. 3 Structure of β-cyclodextrin and the approximate cavity volumes of α-, β- and γ-cyclodextrins

of these cylinders are 'lined' with H atoms and glycosidic O bridges, therefore they are relatively hydrophobic, while the outer surface, particularly the secondary side, is hydrophilic.

The CDs ('hosts') are soluble in water, and when hydrophobic molecules ('guests') which are compatible with the CD-cavity dimensions (their geometrical dimensions, shape and charge make a more or less tight fit possible) are added to an aqueous CD solution, a so-called inclusion complex is formed. Many well studied factors play roles in the formation and stabilization of these association-type host–guest complexes.

CD derivatives

For several reasons (price, availability, approval status, cavity dimensions, *etc.*) β-CD is the most widely used and represents at least 95% of all produced and consumed CDs. It is used for many purposes; however, its anomalous low aqueous solubility (and the low solubility of most of its complexes) is a serious barrier to its wider utilization. Fortunately, by chemical or enzymatic modifications the solubilities of all CDs can be improved markedly, and instead of the 18 g dm^{-3} aqueous β-CD solutions 500+g dm^{-3} aqueous β-CD derivative solutions can be prepared easily.

In cyclodextrins every glucopyranose unit has three free hydroxy groups which differ in both function and reactivity. The relative reactivities of C(2) and C(3) secondary, and the C(6) primary hydroxy groups depend on the reaction conditions (pH, temperature, reagents). In β-CD, 21 hydroxy groups can be modified by substituting the hydrogen atom or the hydroxy group with a wide variety of groups, *e.g.* alkyl, hydroxyalkyl, carboxyalkyl, amino, thio, tosyl, glucosyl, maltosyl, and thousands of ethers, esters, anhydro-, deoxy-, acidic, basic, *etc.*, derivatives can be prepared by chemical or enzymatic reactions. The aim of such derivatization may be: to improve the solubility of the CD derivative (and its complexes); to improve the fitting and/or the association between the CD and its guest, with concomitant stabilization of the guest, reducing its reactivity and mobility; to attach specific (catalytic) groups to the binding site (*e.g.* in enzyme modelling); or to form insoluble, immobilized CD-containing structures and polymers, *e.g.* for chromatographic purposes.

From the thousands of CD derivatives described in hundreds of scientific papers and patents, only a few can be used for medicinal purposes. The first selecting factor is the availability of such derivatives. Complicated multistep reactions, using expensive, toxic, environment-polluting reagents and purification of the products by chromatography are feasible for the preparation of derivatives only on the laboratory scale. To produce tons of CDs at an acceptable price, only about a dozen of the known CD derivatives can be considered.

The industrially produced, standardized and available (even in ton amounts) β-CD derivatives are the heterogeneous, amorphous, highly water soluble methylated β-CD and 2-hydroxypropylated β-CDs (Fig. 4). Owing to their heterogeneity, these products cannot be crystallized, which is important, *e.g.*, for the production of liquid drug formulations. Much more important however, is, that these derivatives cannot form crystalline cholesterol complexes. β-CD has a particularly high affinity for cholesterol: the parenterally administered β-CD is not metabolized in the organism, but forms insoluble cholesterol complex crystals in the kidneys, resulting in nephrotoxicity.

The first hydroxypropyl-β-CD containing drug formulations are already approved and marketed in several countries.

A methylated β-CD is more hydrophobic than β-CD itself, therefore it forms a more stable (but soluble) complex with cholesterol. Its affinity to cholesterol is so strong that it is capable of extracting cholesterol from blood cell membranes, resulting in haemolysis at around 1 mg cm^{-3} concentration. Hydroxypropyl-β-CD (HPBCD) is more hydrophilic than β-CD, therefore it forms a less stable complex with cholesterol. Nevertheless, upon parenteral administration it collects cholesterol in the circulating blood and transfers it to the kidneys. The HPBCD will be excreted, mainly in unchanged form, but, in a chronic treatment with large doses, leaves the cholesterol in the kidneys depleted.

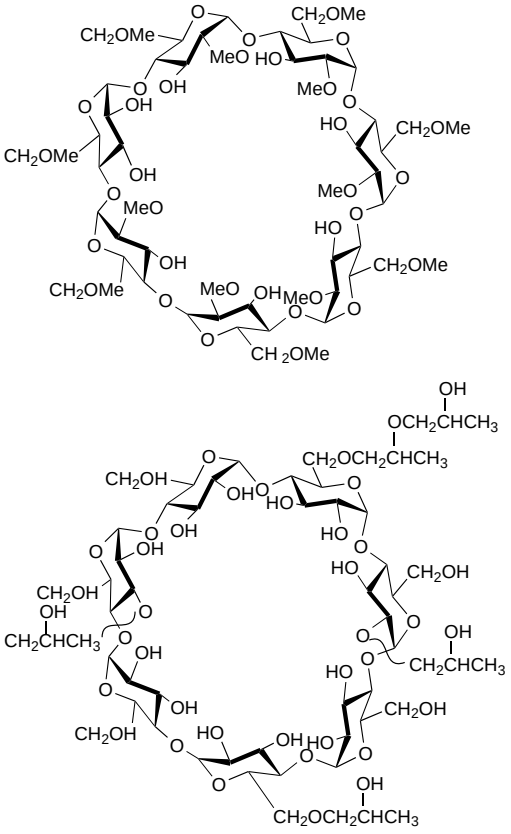

Fig. 4 Structure of crystalline heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) and of randomly hydroxypropylated β-cyclodextrin. The industrially produced non-crystallizable randomly methylated β-CD (RAMEB) also contains about 14 methoxy groups, but in a random distribution.

A particular methylated β-CD, heptakis(2,6-di-*O*-methyl)-β-CD, (DIMEB) is a crystalline product. It is extremely soluble in cold water but insoluble in hot water, therefore its purification and the isolation of its complexes are technically very simple. For more than a decade it has been the subject of many studies, particularly as a solubilizing agent for poorly soluble drugs. Up to now no better solubilizer has been found among the CDs, but, apart from highest haemolysing capacity, its production cannot be realized at an acceptable price level. Large amounts of highly toxic wastes are the byproducts of its synthesis, therefore nowadays the somewhat weaker solubilizer, but much cheaper, randomly methylated β-CD (RAMEB) is produced and marketed. DIMEB will remain, at least until an economic synthesis route is discovered, a relatively expensive fine chemical, used in chromatography, diagnostics, *etc*., *i.e.* where only small amounts are needed. In almost all cases RAMEB can be used instead of DIMEB.

Reacting β-CD with starch in the presence of pullulanase enzyme, one or two maltosyl or glycosyl groups will be attached to the primary side of the CD ring with α-1,6-glycosidic linkages. The product is the so-called 'branched' CD (mono- or di-maltosyl, or mono- or di-glucosyl CD) which is very soluble in water, being a heterogeneous, non-crystallizable substance. It is produced, and used in the food industry, mainly in Japan, for example for the production of stable flavour powders.

The interest in peracyl CDs is increasing. All acetylated CDs from peracetyl to peroctanoyl esters have been studied, partly as retard drug carriers, partly as bioadhesives, film-forming substances to be used in transdermal drug delivery systems.

Very intensive work has been carried out on the development of heptakis(sulfobutyl)-β-CD, which is very soluble in water, non-crystallizable, and even at extremely high doses seems to be free from any toxic side-effects. At present it can be used as a chiral separating agent in capillary zone electrophoresis, but the aim of the intensive research is to develop it as a parenteral drug carrier for the preparation of aqueous injectable solutions of poorly soluble drugs.

CD sulfates possess many similar properties as heparin without its anti-coagulating effect. The present study is focused on the anti-angiogenetic effect of the derivatives because they can apparently reduce the blood supply of tumour tissues through inhibiting the formation of new arteries.

Monochloro-triazinyl β-CD is produced on an industrial scale from CDs and cyanuric chloride. It is reactive with cellulose fibres in alkaline media (see later).

To elongate the actual CD cavity, substituents are attached to the primary or secondary side. This elongation may be hydrophilic, in which case hydroxyalkyl groups are attached to the ring, or hydrophobic, for example, by substituting the primary hydroxy groups with long fatty acid chains, 'medusa'-like molecules can be prepared. These molecules behave as detergents, while retaining their complex-forming ability. The coming years will decide how these derivatives might be utilized.

The chair conformation of the CD ring can be modified by inverting the positions of some hydroxy groups. For example, by removing the tosyl group in alkaline medium from a CD-tosyl derivative, 2,3-anhydro derivatives can be prepared. Upon opening the anhydro ring one hydroxy group will take up an inverted position, and in this way cycloaltrins are formed. By eliminating an appropriate leaving group from the primary side, 3,6-anhydro-CDs are formed. Because of the twisted conformation of the anhydro glucopyranose unit the properties of CDs (*e.g.* solubility) are increased strongly.

It is possible to close one side of the CD cavity, for example by over-bridging the primary or secondary side with an appropriate bifunctional substituent. It is expected that these

over-bridged CDs will form more stable complexes with certain guests.

The essence of photodynamic tumour therapy is that such compounds must be delivered to the tumour tissues, which upon exposure to strong light become toxic through isomerization, splitting, *etc*. In this case, upon strong light irradiation the photosensitive molecules will become toxic just to the tumour cells. For such targeting of the drug very stable (10^5–10^7 dm^3 mol^{-1}) complexes are needed. The duplex homo- or hetero-dimers of CDs (constructed only from one or two different CDs) form complexes which are more stable (by several orders of magnitude) than the singular CDs. By interconnecting two CDs with appropriate bridges such duplex CD derivatives have been prepared (Fig. 5) which can form stable complexes with photosensitive porphyrinoid structures and to transport them to the target organs.

Recently, 'antennae'-bearing CDs have been reported. Such oligosaccharide units are attached to the CDs, which are receptor-specific, *i.e*. they will be bonded in the living organism only on certain specific receptors. The aim of this work is to synthesize a receptor-targetting carrier, *i.e*. the drug complexed with an antenna-bearing duplex CD would transport the specific drug just to the target organ.

The most complicated CD derivatives are synthesized for enzyme-modelling experiments. By dimerizing amino acid CD derivatives, hydrolase enzyme models have been prepared, which approximate the activity of natural enzymes.

A dozen different CD derivatives are used in gas chromatography, liquid chromatography and capillary zone electrophoresis.

For other industrial purposes where toxicological demands do not play a decisive role, epichlorohydrin cross-linked, hydroxyethylated, or sometimes apparently rather fancy, but by their uses justified, mixed ether–esters like heptakis(2,6-di-*O*-methyl)-3-*O*-trifluoracetyl-β-CD and similar derivatives, are produced and utilized.

It is very probable that for drug-carrier purposes four or five different CDs will be developed and produced in the future, because no one of them alone is able to fulfil all the very strict requirements which are usual in the case of a parenteral drug carrier.

CD complex types

In an aqueous solution the slightly apolar cyclodextrin cavity is occupied by water molecules which are energetically unfavoured (polar–apolar interaction) and therefore can be substituted readily by appropriate 'guest molecules' which are less polar than water (Fig. 6). The dissolved cyclodextrin is the 'host' molecule, and the 'driving force' for complex formation is the substitution of the high-enthalpy water molecules by an appropriate guest molecule. One, two or three cyclodextrin molecules contain one or more entrapped guest molecules (most frequently the host : guest ratio is 1 : 1); this is the essence of 'molecular encapsulation'.

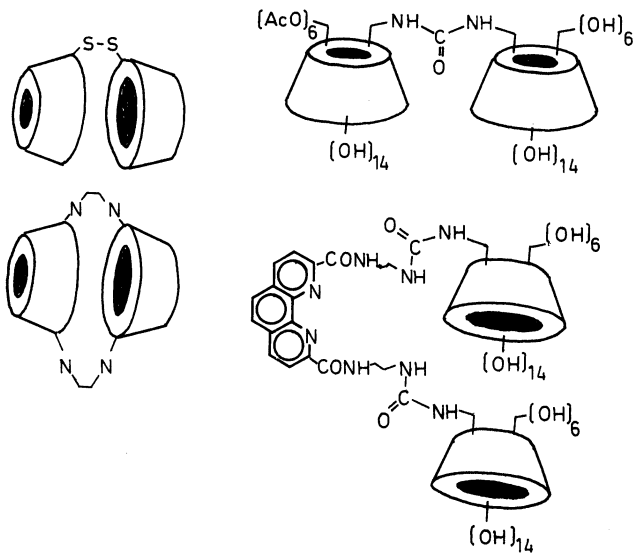

Fig. 5 'Duplex' CD structures with appropriate guest molecules can form inclusion complexes of up to $K_{ass} \approx 10^6$–10^9 dm^3 mol^{-1}

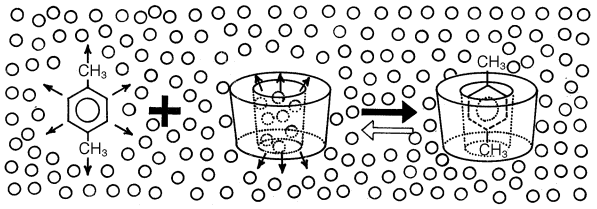

Fig. 6 Schematic representation of inclusion complex formation. Small circles represent water molecules, which are repulsed both by the hydrophobic (potential guest) *p*-xylene, and the hydrophobic cavity of the truncated CD cylinder. The driving force for inclusion is mainly the substitution of the polar–apolar interactions [*e.g*. between the apolar CD cavity and polar water, or the apolar potential guest (*p*-xylene) and water] for apolar–apolar interactions (between the guest and the CD cavity).

The formed inclusion complexes can be isolated as stable crystalline substances. Upon dissolving these complexes an equilibrium is established between dissociated and associated species, and this is expressed by the complex stability constant, K_a.

The association of the CD and drug (D) molecules and the dissociation of the formed CD–drug complex is governed by a thermodynamic equilibrium:

$$CD + D \rightleftharpoons CD{\cdot}D$$

$$K_{1:1} = \frac{[CD{\cdot}D]}{[CD][D]}$$

This is the simplest, and most common, case; however, 2 : 1, 1 : 2, 2 : 2, or even more complicated associations, and higher-order equilibria exist, almost always simultaneously.

Recently, surprisingly high solubilization effects have been reported upon the formation of so-called multicomponent complexes, which consist of a CD, a basic type guest and an appropriate hydroxy acid. The hydroxy acid certainly forms a salt with the basic guest molecule, and moreover forms hydrogen bonds with the hydroxy groups of the CDs. Up to 20 000-fold solubility enhancement effects could be attained (Table 1). For example, the dose of the poorly water soluble Terfenadine (an anti-allergic drug) is 60 mg, which can be dissolved only in 6 dm^3 water. In the form of a multicomponent CD complex, the 60 mg drug can be dissolved in <1 cm^3 water, so it can be injected or applied as a nasal spray.

Cyclodextrins belong to the most appropriate rotaxane-forming molecules. A long slim guest molecule can be threaded through the CD cavity, then both ends can be terminated by bulky groups or the terminal groups can be ionised and therefore the threaded molecule can not slip out from the cavity (Fig. 7). Various environmental effects (pH, irradiation, electric field, *etc*.) may cause this threaded molecule to rotate around its axis, otherwise its mobility is restricted. Similarly the CD ring's mobility is also restricted, it can only move along the axis.

By threading a long slim guest through a number of CD rings, a 'molecular necklace' can be prepared (Fig. 8). Recently a nylon–CD complex has been reported by reacting the β-CD complex of hexamethylenediamine with CD-complexed diacyl chloride. In this way new materials with quite interesting properties can be produced.

Table 1 Amount of hydroxypropyl-β-cyclodextrin necessary to dissolve a single dose of Astemizol, Domperidon and Terfenadine in water

drug	single dose/mg	amount of 10% HP-β-CD solution/ml	ternary system drug–HP-β-CD–hydroxy acid			HP-β-CD/g	
			ternary component	molar ratio	water/ml	in binary system	in ternary system
Astemizol	10	29	malic acid	1:1:2	0.1	2.9	0.03
Domperidon	10	105	tartaric acid	1:1:1	0.3	10.5	0.03
			citric acid	1:1:3	0.4	10.5	0.03
Terfenadine	60	49	citric acid	1:2:2	0.8	4.9	0.35
			tartaric acid	1:2:2	1.2	4.9	0.35
			lactic acid	1:2:2	6.0	4.9	0.35

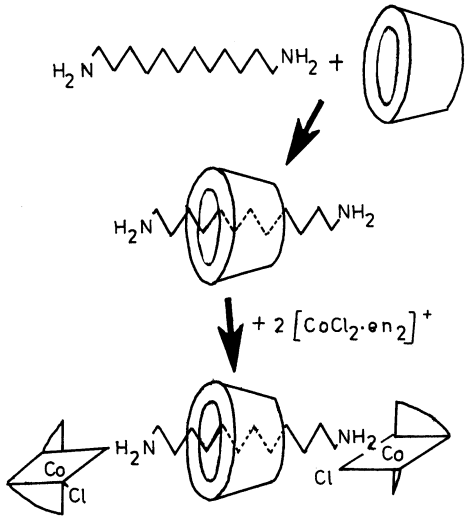

Fig. 7 Rotaxane: one α,ω-diaminoalkane is threaded through a CD ring, then both terminal amino groups are converted to bulky groups (*e.g.* reacting with cobalt chloride–ethylenediamine). The 'axis' molecule cannot slip out from the CD ring, but can rotate freely within it.

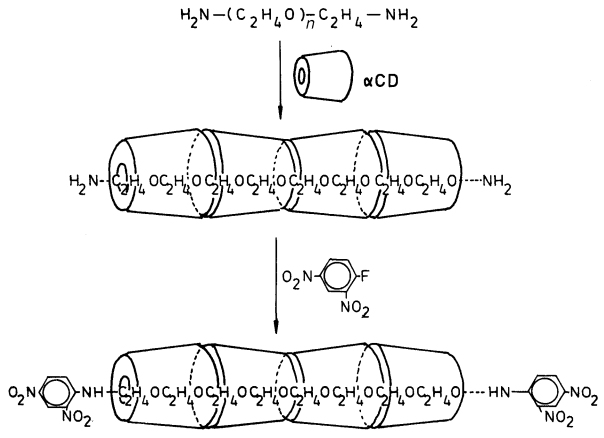

Fig. 8 'Molecular necklace' (polyrotaxane): a long slim poly(ethylene oxide) chain can be threaded through a series of CD rings; by terminating both ends of the chain with bulky substituents (*e.g.* reacting with 1-fluoro-2,4-dinitrobenzene) the structure is stabilized, with no covalent link

'Molecular tubes' can be prepared by complexing polyethylene glycol–bisamine with α-CD, then the formed polyrotaxane is reacted with 2,4-dinitrofluorobenzene. This way both ends of the long-chain guest are terminated by bulky groups. Upon reacting this polyrotaxane with epichlorohydrin the vicinal CD rings will be interconnected through glyceryl bridges between the primary and secondary sides of the CDs. Finally, upon exposure to strong alkali, the dinitrofluorobenzene groups will split off and the long polymer chain will slip out from the polymeric tube (Fig. 9).

Metal ions can be complexed with CDs in three ways: (i) the metal ion reacts with the hydroxy groups of the CD molecule; (ii) the metal ion forms a coordination complex with usual organic ligands and this coordination complex will be included in the CD cavity; (iii) the metal atom is bound covalently in an organometallic compound which will form a regular inclusion complex with a CD molecule.

For case (i): a hydroxy complex is not an inclusion complex, it is more likely to be an outer-sphere complex, *e.g.* Cu^{2+} or Mn^{2+} ions in alkaline solutions form such CD-hydroxy–metal complexes.

Case (ii) means the formation of ternary complexes: CD + organic ligand + metal ion. This is a real second-sphere coordination metal complex, *e.g.* a ferrocene is a coordination complex which consists of an iron ion sandwiched between two cyclopentadienyl molecules, forming a stable iron coordination complex. This coordination complex can form a true inclusion complex with CDs and this inclusion strongly modifies the physical and chemical properties of the included coordination complex.

Case (iii), the complexation of organometallic compounds (this is a binary complex) also results in the modification of important properties of the included compound, *e.g.* in pharmaceutical preparations.

Ferrocene complexes can be prepared easily, in crystalline form, in good yields. The excess of sublimable ferrocene can be removed easily by vacuum sublimation, while the CD-bound ferrocene is stable up to the temperature of decomposition of the CDs (Fig. 10).

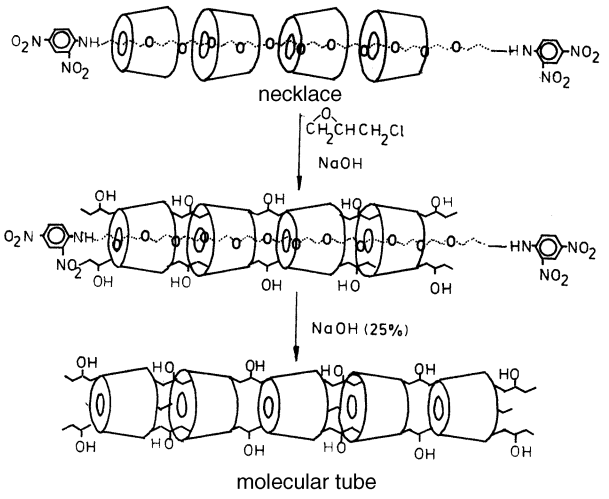

Fig. 9 'Molecular tube': the CD rings in the molecular necklace can be interconnected, *e.g.* by epichlorohydrine in alkaline solution. After removing the terminating bulky groups (by strong alkali) the axis molecule will slip out from the tube.

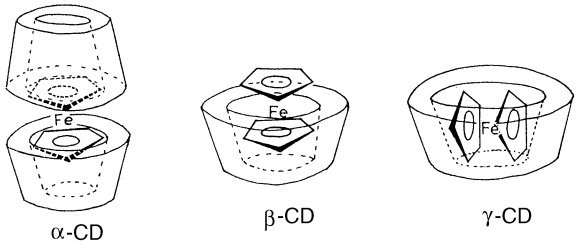

Fig. 10 A ferrocene molecule can be accommodated only sandwich-like between two α-CDs, horizontally and partially penetrates into one β-CD, while in γ-CD it is fully incorporated, and its equatorial axis coincides with the symmetry axis of the γ-CD.

The orientation of an ionizable ferrocene within the CD cavity depends on the pH of the solution (Fig. 11). On the basis of circular dichroism spectra the ferrocenecarboxylic acid was assumed to orient itself inside the CD cavity parallel to its axis, while the ionized carboxylate ions were perpendicular to it (at pH 9 in water).

In aqueous solution the antitumour carboplatin forms an 1:1 complex with α-CD, but not with β- or γ-CD (Fig. 12). The cyclobutane ring penetrates the CD cavity, with additional stability arising from hydrogen bonds between the ammine ligands and the hydroxy groups. Dimethyl-α-CD forms a similar complex with carboplatin. In contrast, the platinum phosphine complex *trans*-[$Pt(PMe_3)Cl_2(NH_3)$] forms a 1:1 complex with β-CD but not with α-CD, and the hydrophobic trimethylphosphine ligand resides in the CD cavity.

Primary effects of inclusion on guest properties

The most important primary consequences of the interaction between a poorly soluble guest and a CD in aqueous solution are as follows. (i) The concentration of the guest in the dissolved phase increases significantly, while the concentration of the dissolved CD decreases. This latter is not always true, however: ionized guests or hydrogen-bonding (*e.g.* phenolic) compounds may enhance the solubility of the CD. (ii) The spectral properties of the guest are modified. The chemical shifts of the anisotropically shielded atoms are modified in the NMR spectra, when achiral guests are inserted into the chiral CD cavity they become optically active, and show strong induced Cotton effects on the circular dichroism spectra; sometimes the maxima of the UV spectra are shifted by several nm, fluorescence is greatly improved because the fluorescing molecule is transferred from the aqueous environment into an apolar surrounding, *etc.* (iii) The reactivity of the included molecule is modified. In most cases the reactivity decreases, *i.e.* the guest is stabilized, but in many cases the CD behaves as an artificial enzyme, accelerating various reactions and modifying the reaction pathway. (iv) The diffusion and volatility (in the case of volatile substances) of the included guest decrease strongly. (v) The formerly hydrophobic guest, upon complexation, becomes hydrophilic, therefore its chromatographic mobility is also modified.

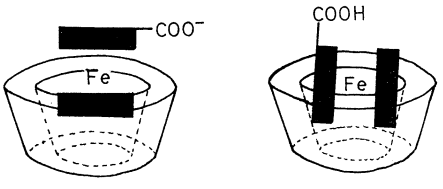

Fig. 11 Orientation of ferrocenecarboxylic acid in the CD cavity depends on the electrical charge of the guest

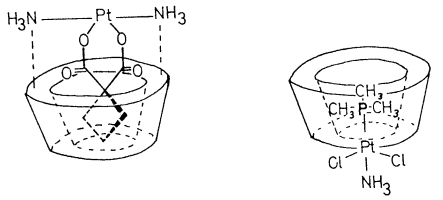

Fig. 12 Structure of the antitumour carboplatin–α-CD complex and of the trimethylphosphineplatinum–β-CD complex. In the former the cyclobutane is included in the α-CD cavity (forms no complex with β-CD); in the latter the trimethylphosphine ligand is included in the β-CD-cavity (no complex is formed with α-CD).

In the solid state, the important consequences are as follows. (i) The complexed substance is molecularly dispersed in a carbohydrate matrix forming a microcrystalline or amorphous powder, even with gaseous guest molecules. (ii) The complexed substance is effectively protected against any type of reaction, except those with the CD hydroxy groups, or reactions catalysed by them. (iii) Sublimation and volatility are reduced to a very low level. (iv) The complex is hydrophilic, easily wettable and rapidly soluble.

When in an aqueous system the formation of the CD inclusion complex can be detected, *e.g.* by NMR or circular dichroism, or through a catalytic effect, it does not mean that a well defined crystalline inclusion complex can be isolated. The two main components of the driving force of the inclusion process are the repulsive forces between the included water molecules and the apolar CD cavity on the one hand, and between the bulk water and the apolar guest on the other hand. This second factor does not exist in the crystalline (dry) state. Therefore it is not uncommon for complex formation to be convincingly proven in solution, but nevertheless the isolated product is nothing other than a very fine dispersion of the CD and the guest.

In the following section the versatile industrial utilization of cyclodextrins will be illustrated. Considering the vast volume of pertinent literature, even a highly incomplete list of references would have to involve hundreds of them. The readers are referred to the most detailed monographs[5,6] and the most recent CD symposium volumes.[3,14–17]

Cyclodextrins in drugs

The complexation of a drug molecule with a CD should be taken into consideration in the following cases:[18] the drug is poorly soluble, therefore its bioavailability (upon oral, dermal, pulmonar, mucosal, *etc.*) application is incomplete or irregular; because of the low dissolution rate, even in the case of complete absorption the time for the orally administered drug to reach the effective blood level is too long, so that reduction of the lag time of the pharmacological effects is required; because of the low solubility no aqueous injectable solution (or other liquid formulation) can be prepared; the drug is chemically unstable: because of its autodecomposition, polymerization or degradation by atmospheric oxygen, absorbed humidity, light, *etc.*, no marketable formulation with a satisfactory shelf-life can be produced; the drug is physically unstable: volatilization or sublimation result in losses, by migration the originally homogeneous product becomes heterogeneous, by its hygroscopicity it liquifies in open air; the acceptability of the drug is bad, because of a bad smell, bitter or irritating taste; the drug is a liquid, but its preferred pharmaceutical form would be a stable tablet, powder, aqueous spray, *etc.*; the dose of the lipid(-like), barely homogenizable drug is extremely low, therefore content uniformity of the product is problematic; the drug is incompatible with the other components of the formulation; relief of serious side effects (throat, eye, skin or stomach irritation) is required; because of the extremely high biological activity (in the case of drugs of extremely low doses), working with such powder is rather dangerous.

The advantageous results of CD complexation of (CD-complexable) drugs are as follows: improved bioavailability

from solid or semi-solid formulations (Fig. 13); enhanced stability, increased shelf-life; reduced side-effects; uniform, easy to handle powders, even from liquids; aqueous, injectable solutions from poorly soluble drugs can be prepared.

Speaking only of the numerous advantages of drug–CD complexation can be very misleading, because there are just as many limiting factors which restrict the applicability of CDs to certain types of drugs, because not all drugs are suitable for CD complexation. Many compounds cannot be complexed, or complexation results in no essential advantages. Inorganic compounds are generally not suitable for CD complexation. Exceptions are non-dissociated acids (HCl, HI, H_3PO_4, *etc.*) halogens, gases (CO_2, C_2H_4, Kr, Xe, *etc.*). Inorganic salts, *e.g.* KCl, Fe salts, cannot be complexed.

General preconditions (not without exceptions!) for the formation of a medicinally useful CD complex of a drug molecule are as follows: more than five atoms (C, P, S, N) should form the skeleton of the drug molecule; the solubility of the drug molecule in water should be less than 10 mg cm^{-3}; the drug melting point temperature should be below 250 °C (otherwise the cohesive forces between the molecules are too strong); the molecule should consist of less than five condensed rings; its molecular mass should be between 100 and 400 (with smaller molecules the drug content of the complex is too low, large molecules do not fit the CD cavity).

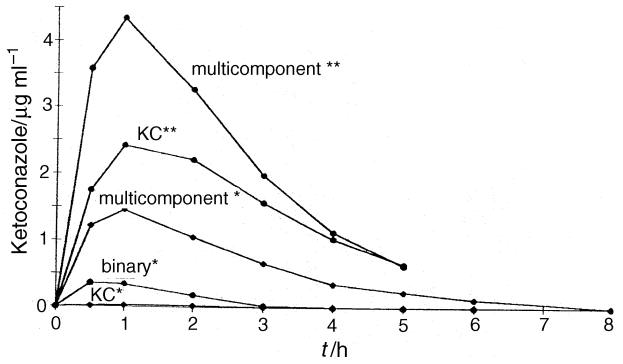

Fig. 13 Enhancement of bioavailability of Ketoconazole. When this drug is administered orally to rats in multicomponent complex form the bioavailability is improved significantly. In the absence of gastric acid (the achlorohydric state was provoked by Omeprazole treatment) no Ketoconazole can be detected in the blood. When the classic binary complex is administered, only modest absorption is attainable, but administration of the multicomponent complex causes the blood level to reach the required level. (AIDS patients require this drug to treat their mycotic infections, but usually they have low gastric acidity, therefore the drug cannot be absorbed from the usual formulations.) *: gastric pH 6.5–8; **: gastric pH 1.7.

Strongly hydrophilic, very small or very large molecules, *e.g.* peptides, proteins, enzymes, sugars, polysaccharides, generally cannot be complexed. Nevertheless, when large, water-soluble molecules contain appropriate complex-forming side-chains, *e.g.* an aromatic amino acid in a polypeptide, they will react with CDs in aqueous solutions, resulting in modified solubility and stability (*e.g.* the stability of an aqueous solution of insulin, and of many other peptides, proteins, hormones and enzymes, is improved significantly in the presence of an appropriate CD).

An insurmountable limiting factor in selecting the drug for complexation is the dose of the complex that has to be administered. A fundamental requirement is that the mass of a tablet should not exceed 500 mg. Since the drugs to be complexed have molecular masses between 100 and 400, and CDs have rather large molecular masses (972, 1132 and 1297 for α-, β- and γ-CD, respectively), 100 mg of complex contains only about 5–25 mg active ingredient. If a single dose of a drug is not more than 25 mg then even a complex with an active substance content of 5% can carry the necessary dose in a single tablet of mass 500 mg, otherwise the possibility of a powder sachet or sparkling-tablet formulation has to be taken into consideration. Thus, in the case of complex-forming drugs, the relationship of the required dose and the molecular mass determines the feasibility of oral administration in CD-complexed form.

Similarly, the volume of an injection should be less than 5 cm^3, or even better not more than 2–3 cm^3, *i.e.* to dissolve the necessary amount of the drug in 2–3 cm^3 of 40% HPBCD solution, 800–1200 mg HPBCD can be used. In liquid formulations the use of CD derivatives in large excess is possible,

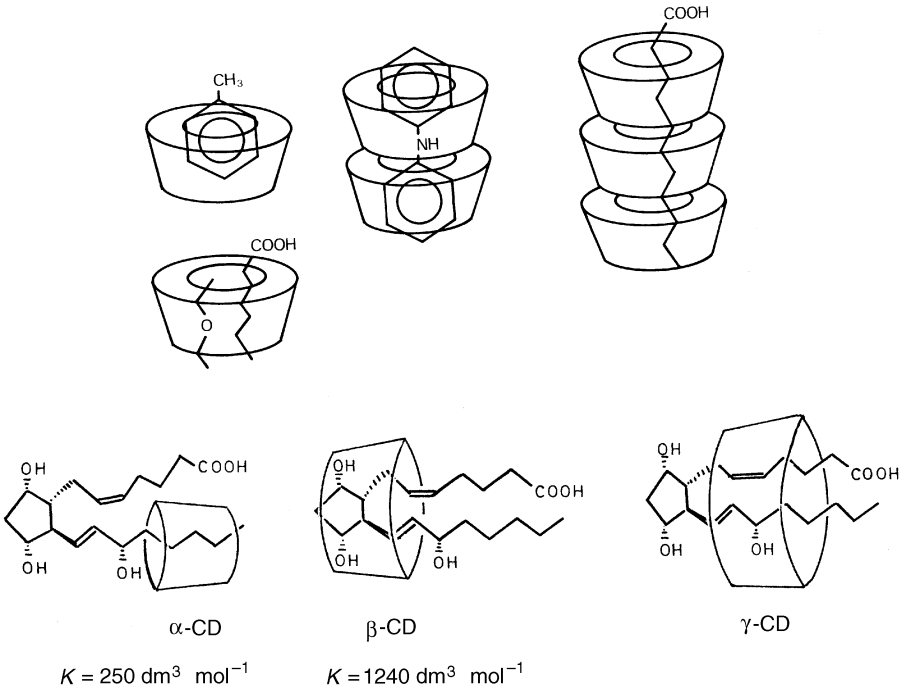

Fig. 14 Structures of various CD complexes. Toluene fits well into a β-CD cavity, for diphenylamine two β-CDs form a 'capsule'. A long-chain fatty acid can be accommodated by three or more α-CDs. In case of prostaglandin E_1 the α-CD accommodates only the aliphatic chain of the unsaturated cyclic hydroxy fatty acid, but this is enough to convert it into a water-soluble complex. β-CD can accommodate the cyclopentane moiety, but γ-CD is too wide for this guest.

Table 2 Some approved and marketed CD-containing pharmaceutical products

drug	trade name	formulation	indication	company/country
PGE_1–α-CD 20 μg/amp.	Prostavasin	intraarterial	chronic arterial occlusive disease, *etc.*	Ono, J. Schwarz, D.
PGE_1–α-CD 500 μg/amp.	Prostandin 500	infusion	controlled hypotension during surgery	Ono, J.
PGE_1–β-CD	Prostarmon E	sublingual tablet	induction of labour	Ono, J.
OP-1206–γ-CD	Opalmon	tablet	Buerger's disease	Ono, J.
piroxicam–β-CD	Brexin, Cicladol	tablet, sachet and suppository	Analgesic, anti-inflammatory	Chiesi, I, Masterpharma, I. D., B., NL., stb.
garlic oil–β-CD	Xund, Tegra, Allidex, Garlessence	dragées	anti-atherosclerotic	Bipharm, Hermes, D., Pharmafontana, H., D., USA
benexate–β-CD	Ulgut, Lonmiel	capsules	anti-ulcerant	Teikoku, J., Shionogi, J.
iodine–β-CD	Mena-Gargle	gargling	throat disinfectant	Kyushin, J.
Dexamethasone, Glyteer–β-CD	Glymesason	ointment	analgesic, anti-inflammatory	Fujinaga, J.
nitroglycerin–β-CD	Nitropen	sublingual tablet	coronary dilator	Nippon Kayaku, J.
Cefotiam-hexetil–α-CD	Pansporin T	tablet	antibiotic	Takeda, J.
new oral cephalosporin (ME 1207)–β-CD	Meiact	tablet	antibiotic	Meiji Seika, J.
thyaprofenic acid–β-CD	Surgamyl	tablet	analgesic	Roussel-Maestrelli, I.
chlordiazepoxide–β-CD	Transillium	tablet	tranquilizer	Gador, Ar.
hydrocortisone–HPβCD	Dexacort	liquid	mouthwash against aphta, gingivitis, *etc.*	Icelandic Pharm., Isl.
itraconazol–HPβCD	Sporanox	liquid	AIDS, oesophagal candidiosis	Janssen, B.

e.g. in the case of a Prostavasin injection the molar ratio of prostaglandin E_1 to α-CD is 1:11 (20 μg PGE_1 + 646 μg α-CD per dose) (Fig. 14).

A 3000 I.U. vitamin D_3 tablet contains only 0.075 mg cholecalciferol, a Prostarmon-E tablet contains only 0.5 mg PGE_2, the active ingredient content of a nitroglycerin tablet is 0.5–4 mg; these and similar drugs are ideal for CD complexation, but even the 20 mg piroxicam-containing Brexin tablet is a widely marketed successful product (Table 2).

If the K_a stability constant of a complex is low ($< 10^2$ mol^{-1}) the existence of the complex can be evidenced in solution, but upon removing the water the obtained product is often only a intimate mixture (*e.g.* a coprecipitate) which contains the host and guest in a fine dispersion. Removing the water also results in the elimination of an important component of the driving force for complexation: the repulsive forces between water and the hydrophobic drug. Upon contact with water complex formation is an instantaneous process, *i.e.* in solution the guest is really included in the CD cavity, and dissociation–association equilibrium is reached within seconds.

In such cases the guest is not protected against external destructive factors, like oxygen or humidity, but if the guest is stable enough, only its low solubility causes problems; such intimate mixtures can be utilized for preparations *e.g.* of solid formulations of improved bioavailability. If, however, the guest is unstable then only full complexation (also prevailing in the anhydrous state) can help.

In cases of extremely high complex stability constants ($> ca.\ 10^4$ dm^3 mol^{-1}) the bioavailability can even be reduced. The complex is practically not absorbed; only the released, molecularly dispersed (dissolved) drug molecules are absorbed. In such cases the co-administration of an even better complex-forming competitor molecule (*e.g.* phenylalanine) can help.

Hundreds of published examples illustrate the stabilizing, solubility- and bioavailability-enhancing, side-effect-reducing and advantageous technological effects of CD complexation of instable, poorly soluble, locally irritating drugs.

CDs in foods and cosmetics

Flavour substances are generally volatile substances which deteriorate readily. Most of them (*e.g.* terpenoids, phenylpropane derivatives) form stable complexes with CDs, and in dry complexed form remain stable for long periods, without any further protection, at room temperature. Such powder flavours are approved, produced and used in several countries, *e.g.* France, Japan, Hungary; for example, a lemon-peel oil–β-CD complex mixed with powdered sugar is used in pastries, spice-flavour mixtures complexed with CDs are used in the preparation of canned meat, sausages, *etc.* In Germany the garlic oil–β-CD complex is marketed as odourless dragées (to substitute the garlic, and a number of various unstable garlic preparations, consumed to reduce the blood cholesterol level). In USA the FDA have not yet generally approved the consumption of any CDs in drugs or foods, but the garlic oil–β-CD complex is already approved, and is available on the US market.

Similarly, the number of cosmetic products which contain CDs is on the increase. Suntan lotions, long-lasting perfumes and dermocosmetic products of leading cosmetic companies often contain CDs, to eliminate the unpleasant odour of some vital component, or just to decelerate the perfume release rate, leading to long-lasting effects, *etc.*

In the USA, at present the largest amount of β-CD is used in dryer-added perfumed fabric softener sheets. The non-woven tissue impregnated with a mixture of a waxy fabric softener and a perfume–β-CD complex is added to the laundered textiles after washing but prior to drying, providing a long-lasting fabric freshness and an agreeable scent.

In Belgium low-cholesterol butter is produced. The molten butter is mixed with β-CD, which does not react with triglycerides but forms complexes with cholesterol, and the β-CD complex is easily removable from the butter. More than 90% of the cholesterol can be removed in one step. The butter does not retain any CD. Other low-cholesterol milk products, like cheese and even low-cholesterol egg, are produced by this technology.

CDs in textiles, fibres and papers

Binding CD to fibres chemically or by adsorption opens new ways for the preparation of perfumed textiles, with slow release of the perfume. Even the opposite, *i.e.* binding distasteful smells (*e.g.* of sweat), can be performed. β-CD bound by dimethylol-

carbamide to viscose or polyamide rayon can absorb butyric acid from aqueous solution.

Monochlorotriazinyl-β-CD (MCT) is the first reactive cyclodextrin derivative manufactured on an industrial scale. The monochlorotriazinyl group is used widely in reactive textile dyes as a reactive anchor. This derivative is able to form stable covalent bonds with nucleophilic groups and can be prepared easily in water in an effective one-pot synthesis from cyanuric chloride and β-CD in a yield of *ca.* 90% based on the triazinyl group. The optimized degree of substitution, DS = 0.4 per anhydroglucose unit, assures a good complexing capacity even when the derivative is fixed to surfaces like textiles. This cyclodextrin derivative containing 2–3 reactive groups in the ring can be used as a building block for new CD derivatives, as a cross-linking agent or as an excellent material for surface modification. The immobilized (wash-fast) cyclodextrin can be loaded with perfumes, or insect repellents, which are released only slowly by the effect of body-heat and released humidity (perspiration), and simultaneously can bind the distasteful-smelling components of perspiration (deodorizing effect) (Table 3).

Wash-fast insect-resistant fibres were prepared by treating fibres with a composition containing an organic insect-proofing agent, a cyclodextrin or a low molecular mass cyclodextrin polymer, and a siloxane. For example, treating acrylic fibres with a solution containing 0.34% β-CD and 0.14% isobornyl-thiocyanoacetate (based on the fibre mass), produced a woven fabric which even after 20 washings showed an insecticide property.

By fixing CD or CD polymer fragrance complexes to the melt mixture of synthetic fibre polymers (*e.g.* polyester) and weaving fabric from such fibres, wash-fast fragrant fabrics can be produced.

β-CD modifies the mechanism of interaction between cotton fibres and direct dyes used for trichromatic dyeing of cotton. 4-Aminoazobenzene is incorporated into the cavity of β-CD with its monosubstituted phenyl group. This is why CD acts as a retarder in dyeing processes in the 'finishing' bath, diminishing the rate of dyeing. This retarding effect increases the affinity of the dyestuff for the textile, but decreases the rate of diffusion into the fabric.

For colouration of polyester fibres, so-called dispersions-dyes are used, which are very poorly soluble in water (0.1–10 mg dm^{-3}). Without using solubility-enhancing agents (tensides), uniform dyeing is not possible. CDs, however, can substitute the tensides, *e.g.* a 0.3 g dm^{-3} conversion mixture (which contains all three cyclic and non-cyclic dextrins) has been shown to be approximately equivalent to 1 g dm^{-3} Levegal HTN (a non-ionic tenside). Both these solubility-enhancing agents resulted in acceptable dyeing homogeneity, while without them the colouration was very heterogeneous, both with Resolin Orange RL and Resolin Rot FB.

By treating textile materials with CD-containing finishers, the physically fixed CDs allow easy removal of sweat or sweat degradation products from the textile by prevention of their penetration to the fibre interior.

CDs represent a new class of auxiliary substances for the textile industry. It is very important that their chemical oxygen demand (in waste water) is lower than that of the usual textile auxiliary substances. While the chemical oxygen demands (in mg g^{-1}) for the widely used tensides NP10, Uniperol O and Gisapon 1555 are 2020, 1930 and 2290, respectively, for β-CD this value is only 1060.

The β-CD complex of *o*-methoxycinnamaldehyde has been incorporated into shoe insoles to inhibit microbial growth and foul odours. Cotton fabric was immersed into the *o*-methoxy-cinnamaldehyde and a β-CD-containing ethanol–water mixture to attain a loading of 10 g active ingredient per m^2. This fabric was placed between two chlorovinylidene sheets. Symptoms such as athlete's foot, rashes, blisters and dry skin were effectively controlled.

An adsorbent composed from carboxymethylcellulose, CD and hexamethylolmelamine adsorbed non-ionic surfactants but did not adsorb anionic dyes. By treating dyeing waste waters with this adsorbent, the waste water could be recycled for dyeing with a further addition of dyes.

The anti-foaming capacity of β-CD can be utilised in laundries and also in the flotation of ores, *e.g.* limonite.

Fragrant paper or paper containing protective substances can be prepared using CD complexes of perfumes, insecticides, rust inhibitors, mould- and mildew-proofing agents, fungicides and bactericides. These complexes have to be mixed with the pulp and water before drying. The retention time of these active ingredients is extended greatly. For example, a fenitrothion β-CD complex sprayed on a wet paper web, passed between drying rollers heated to 100 °C, and wound to give insecticide containing paper, has been shown to be effective for more than six months.

CDs in adhesives and coatings

Epoxy resin adhesives are produced and stored as separated components mixed just before utilisation. By complexing the curing agent (polymerization catalyst) with β-CD a one-package composition can be prepared. Layering such a composition between metal plates and heating to 130 °C for 5 min will cause binding to take place.

The properties of cyanacrylate adhesives can be improved significantly by heptakis(2,6-di-*O*-butyl-3-*O*-acetyl)-β-CD. The ethyl-2-cyanacrylate monomer is stabilized with 20 ppm phosphoric acid, 20 ppm SO_2 and 100 ppm hydrochinon. Various amounts of dibutylacetyl-β-CD are added to this mixture, and using as an adhesive, *e.g.* to bind hard cartoon papers by quick heating to 200 °C, the polymerisation (binding) of cyanacrylate has been accelerated, and the tear strength of the binding increased significantly (Table 4).

Emulsion-type coatings (paints) contain emulsion polymer binders, to give after drying a resistant, continuous protecting film on the coated surface. To ensure the formation of a good film, the applied layer must contain various compatible components, like solvent, pigment, thickener and binder. The rheological properties of the paint are determined by the thickener, which is usually a hydrophobically modified polymer, like polyurethane, polyacrylamides, cellulose ethers, *etc.* To avoid a concomitant too high viscosity (which makes the formation of a uniform surface coating difficult), viscosity suppressors must be added to the emulsion.

Table 3 Possible applications of MCT-finished textiles[19]

application	examples
fragrance release	laundry perfuming
odour absorption	sweat absorption
controlled release	antimicrobial (hospital) textiles
	insect-repellent textiles
stabilisation	active ingredients

Table 4 Effect of heptakis(2,6-di-*O*-butyl-3-*O*-acetyl)-β-CD on the binding time and tear strength at sticking hard cartoon paper (150 g m^2) with ethyl-2-cyanacrylate adhesive[20]

dibutylacetyl-β-CD added (% v/w)	binding time/s	tear strength after 30 s/N cm^{-1}
0	>180	5
0.05	80	7
0.10	30	10
0.20	20	15

The viscosity can be reduced by adding organic solvents to such emulsions, but the use of organic solvents must be avoided because of safety, health-damaging and environmental polluting effects. Surfactants can strongly reduce the viscosity of such emulsions, but their use results in the formation of a less resistant coating.

The viscosity-enhancing effect of hydrophobically modified macromolecules in aqueous emulsions is based on the hydrophobic–hydrophobic interactions between these molecules. Upon adding CDs to this emulsion the CD molecules will associate with the hydrophobic sites and, being strongly hydrated, inhibit the association of the macromolecules, resulting in a strong reduction of the viscosity.

As can be seen from Table 5, RAMEB was the most effective viscosity suppressor.

CDs in plastics and rubber

CD complexes of NCO-containing compounds can be utilised as cross-linking agents, *e.g.* for foamed polyurethane sheet production. The cross-linking agent–β-CD complex is stable at ambient temperature, it only becomes reactive on heating.

CD complexes are compatible with thermoplastic resins. Mixing a dry pulverised CD complex of a perfume, for example a geraniol–α-CD complex, with a thermoplastic resin (polyethylene) and moulding it yielded plastic products with long lasting (at least six months) fragrance. Rapid loss of the perfume by volatility and thermal decomposition can be avoided in this way.

Upon mixing CD complexes of thymol, eugeneol, isobutylquinoline, *etc.*, with molten PVC a natural leather odour emitting (leather-like) material was prepared, *e.g.* for automobile door internal coverings.

By complexing dyes with CDs, which are used for colouring plastics, a more homogeneous colouration can be obtained.

CDs can be used, for different purposes, in plastic laminates, films and membranes. Biodegradable plastics have been prepared by blending not more than 10% β-CD complex with the plastic substance. The role of the CD is to protect the plastic from the action of deteriorating agents during the useful life of the article. However, when the plastic article is discarded and microbial action begins, the β-CD is degraded and the deteriorating agent is released. This agent is chosen from the group of substances well known to cause embrittlement, cracking or other physical degradation of the plastic, *e.g.* surfactants. The entire piece of plastic erodes, leaving behind small fragments of the former article.

The Fe_2SO_4–γ-CD combination has been shown to be effective for the inhibition of the permeation of oxygen through polypropylene laminates. Membranes for ultrafiltration have been prepared from mixtures of aromatic poly(ether sulfones) and 1–34% CD or CD derivatives. The filtering effectiveness and permeability of the CD-containing membranes were higher than those of equivalent conventional products. Homogeneous transparent amorphous membranes with good physicomechanical properties and more than 15 vol% pores of equal dimensions were prepared by dispersion of dimethyl-β-CD or triacetyl-β-CD in cellulose acetate. CD-containing water-resistant membranes can separate enantiomers of racemic mixtures, *e.g.* DL-tryptophan. Coating a thermoplastic resin sheet with a thin layer of CD or a CD derivative, and vacuum forming for 25 s at 150 °C gave container lids with good mosaic patterns. UV-curable ink-printed cards (*e.g.* telephone cards) can be produced with a perfume–β-CD complex mixed into the printing inks. A calendar page printed with fruit design was coated with an orange fragrance containing β-CD complex and it emitted the fragrance for about three months.

Rubber compositions with improved resistance to ozone, ageing and discolouration contain CD complexes of various antioxidants.

The cord strength of polyester fibres used for reinforcement of rubbers can be improved by CDs. Their resistance to heat and degradation is better after treatment with a CD solution. For example, the tear strengths of γ-CD-treated cord before and after vulcanization were 15.6 and 14.7 kg, respectively, *vs.* 15.6 and 12.4 kg. respectively, without γ-CD treatment.

Upon complexing the vulcanizing agents with CD, no vulcanization occurs during working or kneading the rubber but only after vulcanizing agent is released by heating at the moulding temperature.

Table 5 17.5 g ACRYSOL RM-8 (a hydrophobically modified polyurethane thickener) was emulsified in 77.6 g water then 4.9 g of each CD was added to the emulsion.[21] The viscosity was determined by a Brookfield viscometer

CD	viscosity/mPa s
HP-γ-CD	> 100 000
HP-α-CD	19 200
HP-β-CD	5 200
random methylated-β-CD (RAMEB)	802

CDs in photographic and recording materials

Important properties such as the relative sensitivity and fog of silver halide-containing photographic materials can be improved by adding CDs to light-sensitive photographic gelatin layers.

Additives, dyes, stabilizers and fog inhibitors used in the photographic industry should be fixed to a certain layer of the film or photopaper. This can be achieved by using derivatives with 'heavy' side chains. It seems to be more convenient to prepare the water-soluble polymer complexes of these substances. In complexed form their mobility is reduced markedly, and they become fixed to the layer required. Diminished diffusion can be observed on preparing, processing or storing the film. Another advantage of the soluble polymer complex is that poorly soluble, or even water-insoluble, stabilizers can be applied to the film in aqueous solutions. A CD–gelatin composition as the photographic layer shows lower water absorption and accelerated diffusion of the developing agents.

A thermal recording sheet which contains a colourless benzylleucomethylene blue–β-CD complex and an acidic developer [$Ni(NO_3)_2$] exhibits high sensitivity and good light resistance. Photochromic materials can be produced by complexing a spiropyran, a dithizone metal complex, a triphenylmethane dye or a fulgide with γ-CD. Complexation increases the stability of the light-produced colour and decreases the colour density of the unirradiated materials. Complexing sodium-1,4-dihydroxyanthraquinone-2-sulfonate with α-CD, dissolving it in water and poly(vinyl alcohol) then coating onto a support gave a laser-recording medium. The included guest is photoisomerisable. By dissolving CD in a photosensitive solution of a diazonium salt, more stable photosensitive diazo-type copying materials can be produced.

CDs in catalysis

Heating an aqueous solution of $RhCl_3$ and α- or β-CD at reflux, followed by further refluxing in the presence of EtOH, gives a black colloidal dispersion of Rh particles of diameter 28 Å. The colloidal dispersion is an effective catalyst in the hydrogenation of alkenes at 30 °C under atmospheric pressure. Platinum dispersions can be stabilised similarly by CD. Aggregation is probably retarded by the CDs. As the catalyst activity, *e.g.* in systems used for solar-energy conversion, is related to the size of Pt particles, this colloid stabilising effect of CDs may eventually be utilised.

The benzoin-isopropyl ether–β-CD complex is an effective catalyst for photopolymerization of vinyl polymers.

The following examples have been selected to illustrate the potentials of CDs in detoxification of dangerous substances by catalysing their decomposition.

Trichlorfon is a crystalline, contact stomach poison insecticide. At its production after isolating the crystalline Trichlorfon, the remaining mother liquor contains a considerable amount of very toxic non-crystallizable Trichlorfon. In alkaline solution its decomposition proceeds *via* the elimination of one molecule of HCl, whereby the unsaturated reaction product rearranges to the stable Dichlorovos (DDVP), which is a very toxic volatile liquid. β-CD accelerates this process and, if enough β-CD is present in the system, the crystalline DDVP–β-CD complex is immediately formed, and can be isolated as a poorly soluble, stable microcrystalline product. After CD treatment the disposition of the much less toxic waste is easier and the DDVP–β-CD complex itself is a useful insecticide. A similar detoxification of chlorobiphenyls, by eliminating a molecule of hydrochloric acid through direct photolysis in aqueous maltosyl-CD, has also been reported.

The very dangerous acetylcholin esterase-inhibitor neurotoxic agents, soman and sarin, can be deactivated by β-CD. The isopropyl methyl phosphonofluoridate is hydrolysed by alkali, but by using β-CD even at pH 7.4 and 25 °C a considerable detoxification is achieved. This process appears to be as fast in human plasma, *in vitro*, as in tris buffer. This may eventually be used to improve emergency medicinal therapy, and can certainly be used for detoxification of the environment when soman is spilled accidentally.

CDs in biotechnology

The application of cyclodextrins in biotechnology began only in the 1980s, but rapid development is expected in this field.

The majority of biotechnology processes mean an enzyme-catalysed transformation of a substrate in an aqueous medium. The main difficulties which used to arise are as follows: the substrate is hydrophobic, sparingly (or hardly at all) soluble in water; the enzyme or the enzyme-producing microbial cells are sensitive to the toxic effects of the substrate or to inhibitors which can even be the product of the transformation; the substrate or the product is unstable under the conditions of the enzymatic transformation; isolation of the product from the very heterogeneous system is difficult.

Cyclodextrins and their derivatives enhance the solubility of complexed substrates in aqueous media, and reduce their toxicity, but they do not damage the microbial cells or the enzymes. As a result, the enzymatic conversion of lipophilic substrates can be intensified (accelerated, or performed at higher substrate concentrations) both in industrial processes and in diagnostic reagents, the yield of product-inhibited fermentation can be improved, organic toxic compounds are tolerated and metabolized by microbial cells at higher concentrations, and compounds in small amounts can be isolated simply and economically from complicated mixtures (Fig. 15).

Some examples illustrating the rapidly growing and promising uses of cyclodextrins in various operations are: the intensification of the conversion of hydrocortisone to prednisolone, the improvement in the yield of fermentation of lankacidine and podophyllotoxin, the stereoselective reduction of benzaldehyde to L-phenylacetyl carbinol, and the reduction in toxicity of vanillin to yeast, or organic toxic substances to detoxificating microorganisms. In the presence of an appropriate cyclodextrin derivative (*e.g.* 2,6-dimethyl-β-cyclodextrin), lipid-like inhibitor substances are complexed. The propagation of *Bordatella pertussis* and the production of pertussis toxin therefore increases up to 100-fold. Cyclodextrins and their fatty acid complexes can substitute for mammalian serum in tissue cultures.

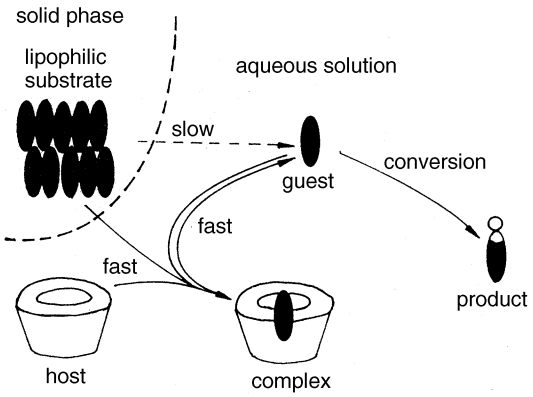

Fig. 15 Principle of intensification of the enzymatic (microbial) transformation of poorly soluble lipophilic substrates. The CD complexation of the substrates improves their wettability and solubility, *i.e.* enhances their concentration in the aqueous phase where the reaction takes place. In many cases the reaction is accelerated through continuous removal of the inhibiting products by CD complexation.

Until recently, the Leprae bacillus (*Mycobacterium leprae*) was considered to be uncultivatable under *in vitro* conditions. The most important energy source for the bacillus is palmitic (or stearic) acid which, however, cannot penetrate the thick, strongly hydrophilic shell of the mycobacterium. By solubilizing the fatty-acids (or fatty alcohols), however, with dimethyl-β-cyclodextrin, the mycobacterium can be cultivated *in vitro*, on a synthetic medium. This discovery will facilitate the screening of drugs against similarly difficult microorganisms.

CDs in environmental protection

Biological waste water treatment means that dissolved organic and frequently toxic substances are oxidised, hydrolysed, degraded by a large number and variety of yeast and bacteria which are present in the biological sludge. The waste waters of the food industries are generally liable to biological degradation, but those of the organic chemical industry, containing *e.g.* pesticides, drugs, their intermediaries, which are really 'hard' environment polluting agents, are usually more or less resistant to biological degradation, and are often devastating for the detoxifying microorganisms. These chemicals can be tolerated and metabolized by the microbial flora of the activated sludge system only up to a certain level. When the toxic concentration level is exceeded the microbial flora are proportionally paralysed, and the biological activity of the sludge decreases more or less irreversibly. To avoid this unwanted effect, an alternative is the partial and temporary masking of the toxic substances by converting them to non-toxic CD inclusion complexes. Swollen insoluble CD polymers (*e.g.* cross-linked with epichlorohydrin) can be used to remove polychlorinated biphenyls or detergents like lithium dodecylsulfate[20] and naphthalene-2-carboxylate from water. Tributylphosphate can be removed from water by converting it into an insoluble β-CD complex. The method is recommended for treatment of waste water from nuclear fuel reprocessing plants. Cross-linked β-CD polymers containing polymer membranes can be used to remove volatile halogenated organic compounds from tap water.

It is estimated that industry emits about 2% of the 200 million tons of solvents produced annually by the organic chemical industry. Recovery of a small fraction of such substances is performed by solid or liquid absorbers. An alternative method to those used normally, *i.e.* cooled condensers or absorbers filled with actived carbon or silica gel, is the application of CD solutions. CDs can also react with appropriate guest molecules in the gas or vapour phase.

Upon bubbling a large volume of air containing solvent

through a CD solution, below the temperature at which the complex crystallizes, an immediate precipitation of the crystalline complex is observed. The molar ratio of guest molecule: CD is generally 0.4–1 : 1. With increasing temperature the solubility of CDs increases, but the complex stability decreases strongly. Using epichlorohydrin-modified highly soluble β-CD, 80–95% of 1,2-dichloroethane could be removed from 35–80 mg solvent per dm^3 air in pilot experiments. Recovery of chlorinated organic compounds like $CHCl_3$, CCl_4, C_2HCl_3, C_2Cl_4 and of hydrocarbons has been reported using various CDs. β-CD solution can be used to remove bromine and iodine, not only from air, but even from gaseous chlorine, during electrolysis of NaCl.

Odorous gases (*e.g.* at treatment of industrial wastes, fecal sewage, or slaughterhouse effluents) can be deodorized by CD solutions, by bubbling the gases through a CD solution, or by atomizing the CD solution with compressed air to form a mist curtain and passing the waste gases through this mist curtain.

Ozone can be removed from waste gases by using the CD complexes of terpenoids (*e.g.* limonene) in the corona discharge part of the electrical appliance.

It is not reasonable to wash toxic organic substances out of soil using organic solvents (costs, additional pollution, danger of explosion, *etc.*); only aqueous systems can be taken into account. Detergents, however, also have strong effects on the environment. CDs could probably be used successfully to wash poorly soluble toxic substances out from the upper layers of soil. CDs will be metabolized without causing any problem, and the solubilized toxic substances are certainly more available for the soil microorganisms. Promising experiments for mobilization and microbial degradation of polyaromatic hydrocarbons in polluted soils are in progress.

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