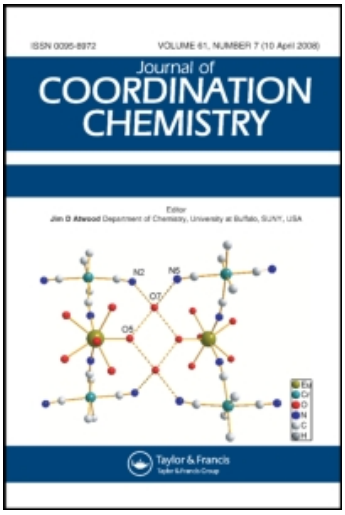

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INDUSTRIAL USES OF CYCLODEXTRINS AND THEIR DERIVATIVES

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Cyclodextrins as well as their derivatives have the ability of encapsulating in their cavity a wide variety of molecules, conferring on them new physicochemical characteristics. For this reason, they are proposed for many uses in various industries. When they are empty, they can be used for their ability to trap certain molecules, or because they can transform gases or liquids into solids, improve stability, decrease undesirable side effects, enhance solubility, increase absorption through biological membranes, and prolong the release of the encapsulated molecule.

Keywords: Cyclodextrins, cyclodextrin derivatives, industrial uses, stability, solubility, bioavailability

INTRODUCTION

Discovered more than one century ago, cyclodextrins are actually fascinating molecules both for scientists and for technologists. This is the consequence not only of their ring shape, but more specifically of their ability to encapsulate a large variety of molecules, the most important requirement being their steric hindrance. This molecular encapsulation confers on the guest molecule new physicochemical properties of great value for many industries.

The recent appearance on the market of various derivatives, differing by their solubilities, increases the interest aroused by this kind of molecule.

MAIN CHARACTERISTICS OF CYCLODEXTRINS AND DERIVATIVES

Natural Cyclodextrins[1]

The natural cyclodextrins available on the market are α-, β- and γ-cyclodextrins, constituted respectively of 6, 7 and 8 glucose units. There is no cyclodextrin with fewer than 6 glucose units, because of the high internal tensions which would then appear at the level of the ring. Cyclodextrins with more than 8 glucose units (9) have been described, but they are of very low stability.

The conformation of the molecule is such that the hydrophilic hydroxyl groups are situated on both sides of the ring: primary hydroxyls on the narrower side (because of the tensions) and secondary hydroxyls on the wider side. The glucosidic groups of the inside of the cavity confer somewhat hydrophobic properties (it behaves like a Lewis base).

The most important characteristics from the standpoint of the ability of cyclodextrins to encapsulate molecules, and hence to change their physicochemical

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properties, are the internal diameter of cavity and the water solubility. The diameter increases from α- to β- to γ-cyclodextrin: almost 5, 6 and 8 Å respectively. The small cavity of α-cyclodextrin allows the encapsulation of only very small molecules and, for example, it is very often too small to encapsulate most of the pharmaceutical molecules. For large molecules, γ-cyclodextrin is the most convenient, but until now it has been a very expensive product because it consists of a by-product of α- and β-cyclodextrin preparation. However, it seems that the industrial production of γ-cyclodextrin is now well under control, because the price is decreasing rapidly and significantly.

The water solubility varies in a rather surprising manner from α- to β- to γ-cyclodextrin. In fact, the solubility at 25°C is respectively 14.50, 1.85 and 23.20 g/100 ml. Thus, β-cyclodextrin, which, during the last few years, was the most commonly-employed cyclodextrin, is the least water-soluble one. This seems to be explained by the odd number of glucoses in the ring, allowing dimerization in solution with a concomitant decrease in solubility.

Cyclodextrin Derivatives[2]

The greater part of cyclodextrin derivatives are highly water-soluble products, and others have varying solubilities.

- Water-soluble derivatives.

Methyl cyclodextrins are among the first water-soluble derivatives described. Methylation of cyclodextrins concerns either all C2 secondary and C6 primary hydroxyl groups (dimethyl cyclodextrins), or all the hydroxyls: C2, C3 and C6 (trimethyl cyclodextrins).

The water solubility of the β-cyclodextrin derivatives is 57 and 31 g/100 ml for dimethyl and trimethyl respectively (compared with 1.85 for the mother product). However, a disadvantage of methylated cyclodextrins is their decrease in solubility with an increase in temperature.

Hydroxypropyl cyclodextrins are rather different products because hydroxypropylation does not result in a selective substitution as in the case of methylation. As the hydroxyl reactivity changes as the reaction proceeds, a mixture of products is obtained with various degrees of substitution. The consequence is that the existence of so many types of hydroxypropyl cyclodextrin in the same reaction product leads to an impossibility of crystallization and, consequently, to the obtention of amorphous compounds.

Hydroxypropyl cyclodextrins are highly water-soluble, not only as a result of their chemical structure, but also because of their amorphous structure. Their dissolution is endothermic, so there is no decrease in solubility with increasing temperature. Their exact water solubility is difficult to determine, because of the viscosity of the solution obtained. It is, however, more than 50 g/100 ml at 25°C.

Hydroxyethyl cyclodextrins more or less resemble hydroxypropyl cyclodextrins. In fact, hydroxyethylation of cyclodextrins results in a mixture of hydroxyethyl cyclodextrins with various degrees of substitution. They are highly water-soluble: more than 50 g/100 ml at 25°C.

Various branched cyclodextrins have been described, such as mono- or di-glucosyl, maltosyl and glucopyranosyl α- and β-cyclodextrins. They are highly soluble in water (di-glucosylβ-cyclodextrin: 140 g/100 ml).

The most investigated cyclodextrin derivatives and the easiest to find on the market are the hydroxypropyl cyclodextrins.

- Other derivatives.

Ethylation of cyclodextrins, like methylation, leads to well-defined products: di- and triethyl cyclodextrins with very low water solubility: $5.0.10^{-3}$ and $1.8.10^{-3}$ g/100 ml respectively at 25°C.

Carboxymethyl ethyl cyclodextrin has a pH-dependent solubility: below pH 2.5, solubility is almost constant (1 to 1.5 g/100 ml), it then increases sharply above pH 4 (10 g/100 ml), and at pH > 6 the product is freely soluble.

Cyclodextrin polymers with low molecular weight (3000 to 6000) are readily soluble in water, whilst those with a molecular weight above 10,000 can only swell in water and form insoluble gels.

Metabolism and Toxicity[3]

Due to their possible utilization in the pharmaceutical and food industries, it is necessary to know something about the metabolism and toxicity of cyclodextrins.

- Natural cyclodextrins.

After oral administration, cyclodextrins are hydrolyzed, not in the small intestine but only in the colon. This hydrolysis more or less resembles that of starch, but with a lower initial rate due to the fact that cyclodextrins are totally resistant to β-amylases active on the end groups, and sensitive only to α-amylases active in the middle of the chains. Degradation increases from α- to β- to γ-cyclodextrin, in such a manner that there does not appear to be enough time for α-cyclodextrin degradation in the gastrointestinal tract. Furthermore, α- and β-cyclodextrins can be absorbed, but only poorly by the small intestine[4,5]

Oral administration of cyclodextrins does not result in an acute toxicity, and long-term administration leads to no significant change in the organs or biological values.

Parenteral administration of cyclodextrins has completely different consequences. The intramuscular administration of β-cyclodextrin results in ulcerations, and its intravenous administration has nephrotoxic and hæmolytic effects. Probably due to its better water solubility, γ-cyclodextrin is not so nephrotoxic as α- and β-cyclodextrins, and it is less hæmolytic.[6]

This means that cyclodextrins, especially β- and γ-cyclodextrins, can be used for oral administration, but that their use for parenteral administration is not recommended without taking due care of the dose administered.

- Cyclodextrin derivatives.

Cyclodextrin derivatives, due to their various substitutions, behave like xenobiotics: they are not recognized as natural sugars and are not metabolized in the gastro-intestinal tract. In long-term administration, they can affect weight gain and lipid metabolism, because they are able to form complexes with normal molecules of the gastro-intestinal tract.[7]

By parenteral administration, hydroxypropyl, and more especially hydroxyethyl cyclodextrins are less hæmolytic than the mother cyclodextrins,[7] when methyl cyclodextrins are more hæmolytic.[6]

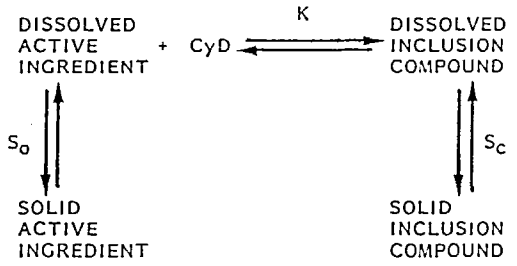

FIGURE 1 Mechanism of inclusion formation in aqueous medium.

Ability to Form Inclusion Compounds

As mentioned previously, cyclodextrins by their hydrophobic cavity are capable of including guest molecules of various types and especially, but not solely, hydrophobic molecules. The inclusion reaction can occur in various ways.[8] It generally takes place in aqueous or organo-aqueous solution (coprecipitation), or in a slurry (kneading method), or by simple heating in a sealed container, and also by simple grinding. However, it seems that a certain amount of water is necessary, or at least some humidity.

The reaction mechanism can be explained by what occurs in aqueous medium (Figure 1). The reaction is a succession of equilibria leading to the super molecule of the inclusion compound, more or less soluble in water. The rate of formation of the super molecule is governed by a constant K, the stability constant, characteristic of the tendency of the inclusion compound to dissociate itself in the presence of water.

This stability constant is a function of the good fit of the guest molecule inside the host molecule, and it depends, *inter alia*, on the nature of the cyclodextrin and on the spatial configuration of the guest molecule (and obviously also on its electrical charges, hydrophily and hydrophobicity). Its knowledge is especially important for the predction of the chemical stability of the inclusion compound or the possible release of the included molecule.

In the case of cyclodextrin derivatives, inclusions can be obtained in the same way as with natural cyclodextrins, the only factor to be taken into account being the steric hindrance of the substituents, which can sometimes reduce the cavity entrance. Such inclusion compounds can modify the physicochemical properties of the guest molecule, as in the case of natural cyclodextrins. However, their great value lies in the higher, or lower, water solubility of the guest molecule with its repercussions on the solubility of the inclusion compound itself, compared with the solubility conferred by natural cyclodextrins.

INDUSTRIAL APPLICATIONS[9–12]

The industrial applications proposed are numerous, and concern many industries, as demonstrated by the numerous patents dealing with such subjects. It is impossible

to report in a simple paper all the examples in the literature and to explain them. It seems better to classify the various uses of cyclodextrins by their mode of action, and to give examples in the various industries.

Use of "Empty" Cyclodextrins, and Their Ability to Create Inclusion Compounds

It is interesting to incorporate free cyclodextrins ("empty" cyclodextrins) in various products in order to benefit from their encapsulating power with respect to free molecules: gaseous or dissolved.

In cosmetology, empty cyclodextrins are capable of including volatile substances, such as malodorous products, so that they can be used as a deodorant in liquid body deodorants[13] or breath fresheners[14–17] in order to trap clinging and unpleasant odours (fish, garlic, cigarettes, alcohol). They can be used in the form of liquids, powders, tablets, chewing gums, toothpastes, sprays and mouthwashes.

In Japanese cooking, fish is widely used, but some fish have strange odours that can destroy the taste. The nitrogen-containing compounds responsible for these odours can be included in cyclodextrins. The odour of fish paste products is improved by the masking effect caused by adding cyclodextrins.[18] When raw fish is dipped into a cyclodextrin solution, the resulting product has less odour, and this has been proposed for raw sardines and mackerel. The addition of cyclodextrin can also decrease the characteristic odour of mutton.[19] The unpleasant odour developed by rice during its storage can be eliminated by cooking the rice in the presence of β-cyclodextrin.[20]

Another use in the food industry of the trapping power of cyclodextrins concerns the removal of caffeine from tea. In this matter, cross-linked polymers of cyclodextrins seem to be more effective than β-cyclodextrin.[21]

In the tobacco industry, cyclodextrins are used to decrease the nicotine and tar rates of cigarette smoke. They can form the greater part of the filter[22] or serve as an additive in the cellulose.[23,24]

In laundering, cyclodextrins can include detergent molecules, and thus act as defoaming agents. Their addition to the rinsing water in laundries, fixes the last traces of detergents and can result in a reduction in water consumption.[25]

A pharmaceutical and cosmetological use of cyclodextrins lies in the treatment of acne: it seems that cyclodextrins can complex the excreted fatty acids.[26,27]

Still in pharmacy, it seems that intravenously administered hydroxypropyl β-cyclodextrin is capable of solubilizing lipophilic products such as triglycerides or cholesterol. However, it does not appear that solubilization results directly from the action of hydroxypropyl cyclodextrin, but that it is a catalytic effect, because it is never used in concentrations competing seriously with the natural carriers of lipids already present in the circulation. In fact, natural carriers are highly targeted, and thus cannot take care of unusual calamities in the organism, which then uses the cyclodextrin carrier to alleviate excessive accumulations of lipophilic products.[28]

Transformation of Gases into Solids

It is possible to include small molecules, such as gases, in α-cyclodextrin to turn them into solids. This was demonstrated 30 years ago by Cramer and Henglein[29,30] with chlorine, krypton, xenon, oxygen, ethylene, methane, propane and butane.

The crystalline complexes are stable at ambient temperature, even after storage for 18 months.

The inclusion of ethylene in cyclodextrin is very interesting for agriculture, because ethylene is an extremely effective hormone-like agent for plants. The ripening process of fruits and the abscission of leaves are more or less connected with the intracellular production of ethylene. The inclusion compound can be prepared in aqueous medium.[31,32] Tomatoes sprayed with a solution of the complex ripened 4 days before the controls.

The inclusion of krypton 85 is used in electric batteries.[33]

Transformation of Liquids into Solids

This transformation is generally investigated for highly volatile liquids such as essential oils used in the flavouring of industrial foods. Szejtli has trapped the following oils in β-cyclodextrin: dill, coriander, marjoram, sage, raspberry, lemon, cinnamon, carrot, aniseed, orange, thyme, peppermint, sweet cumin, celery, garlic, onion, tarragon, caraway, basil, bay leaf and mustard.[34] The microcrystalline complexes produced are non-hygroscopic and almost odourless powders. The aroma content is 6 to 15%, and more often 8 to 10%. They are stable in the dry form and protected from oxidation. Stability tests show that aroma inclusion complexes stored in sealed containers at ambient temperature lose less than 5% of their active ingredient content after two years. Despite the fact that aroma substances normally contain many components, it seems that they are all included in the cyclodextrin in the same proportions as in the initial oil.[35,36] However, this last result may be discussed and is probably not valid for every kind of essential oil, as demonstrated for the fruits of *Oenanthe aquatica* tincture.[37]

As explained previously, in liquid medium an inclusion compound is always in equilibrium between the undissociated super molecule and the dissociated form. This explains that when the solid flavour is in the mouth, the saliva rapidly displaces the equilibrium from the undissociated form to the dissociated form (according to the stability constant K), and the aroma is then free. Furthermore, it seems that the general taste of the aroma is not affected by the taste of the cyclodextrin itself.[38] This is demonstrated by tests carried out on foods (including sausages).[39,40]

Perfumes can also be encapsulated in order to be used in the preparation of detergents, to reduce the considerable part which is lost during production and storage.[41] When the detergent is used normally, the perfumes are displaced by the surfactant molecules. The extent of this displacement varies according to the chemical nature and steric factors of the competing molecule.

Hydroxypropyl β-cyclodextrin can also be used as well as natural β-cyclodextrin to encapsulate fragrance materials.[42]

Liquids of a completely different nature than essential oils, perfumes and various aromas can be encapsulated in cyclodextrins. This is the case for a light alcohol such as vinegar.[43] This powder form maintains an excellent flavour, and has a high reputation among people who use vinegar, not only as a simple seasoning, but as a health food, because it is convenient to carry.

DDVP (O,O-dimethyl-2,2-dichlorovinyl-phosphate) is a volatile, flammable, explosive, liquid insecticide, which acts mainly as a contact poison. It can be included advantageously in β-cyclodextrin. Its complex is crystalline and contains 16.2% of the active ingredient in a 1:1 molecular ratio.[31,44] The complex has no gas effect,

but is nonetheless active as a contact insecticide and acaricide. Normal DDVP is so volatile that, after two days, 0.1% DDVP does not kill a single beetle, even after a contact time of 300 minutes, whereas the complex kills 70%. However, the instantaneous effect of the complex is much less than that of the free DDVP, but the complex is much better when the duration of the effect is to be considered.[44]

Improvement in Stability

The encapsulation of a guest molecule in a cyclodextrin cavity can normally lead to a protective effect from environmental factors such as heat, light and oxygen.

In the food industry, spices included and transformed into powder by cyclodextrins exhibit good stability when they are heated during industrial food processing.[45–48] The same result is obtained for the inclusion of fruit flavours, so it is possible to use smaller amounts of included flavours than natural ones. Furthermore, such flavours last for a longer period than the liquid products.[49–51]

A very interesting increase in stability can be obtained for unstable liposoluble vitamins: A, D, E and K.[52] The vitamin inclusion most investigated is the vitamin D_3/β-cyclodextrin complex,[53,54] for which the resistance to oxidation is considerably improved.

The inclusion of vitamins greatly improves preparations for animal husbandry. The products are normally blended in a great mass of fodder and distributed over a large surface area. In such circumstances, the decomposition of normal vitamins is very fast, but is slowed down by inclusion.[54]

Another kind of product included in cyclodextrin with the main objective of increasing stability is represented by pyrethroids. These are excellent insecticides in the human environment. They are harmless for mammals because of a strong knock-down activity to insects. Their disadvantage is their sensitivity to ultraviolet light and oxygen. They can be stabilized by inclusion in β-cyclodextrin.[55–57] such inclusions are used successfully in Japan for the treatment of tea plantations, rice paddies and ornamental plants.

Methylparathion is another insecticide. It is a contact poison, not volatile but which decomposes rapidly. Its inclusion in β-cyclodextrin not only improves its stability but, as a consequence, enables the reduction of the dose in plant treatment.[58,59]

Decrease in Undesirable Side Effects

In the same way that the inclusion of a guest molecule inside the cavity of a cyclodextrin can decrease its attack by the surrounding factors, it can also protect the surrounding medium from undesirable side effects of the host molecule.

This could be especially interesting for pharmaceutical applications. For instance, non-steroidal anti-inflammatory substances are often aggressive for the stomach mucosa. It has been demonstrated that the inclusion of phenylbutazone in β-cyclodextrin reduces its irritating power. However, such a result is not obtained for every kind of anti-inflammatory drug, and there is no decrease in the irritancy provoked by indomethacin or flufenamic acid.[60] This inconsistent result can be explained in two ways. First, if the stability constant of the inclusion compound is low, then it decomposes rapidly in the liquid medium of the stomach and the free active ingredient behaves normally. Secondly, very often the included molecule is not

completely masked by the cyclodextrin, because of its steric hindrance: the part outside can be the aggressive part, and this is what happens with indomethacin.[61]

Cosmetic products are also capable of provoking some irratation, especially by the perfumes they contain, and because the irritating power of the perfumes is enhanced by the emulsifying agents often present in the formula. Their inclusion in a cyclodextrin can considerably decrease this type of side effect.[62,63] It can be used, for example, in shampoos which contain a large amount of surfactants.

Another kind of pharmaceutical side effect is the irritating taste which some products have, such as pirprofen. Its inclusion in β-cyclodextrin reduces the irritation caused to the mucous membrane of the throat.[64] The same result can be obtained for ibuprofen[65] and flurbiprofen,[66] or on simply bitter tastes such as those of tiaramide and its salts,[67] suloctidil[68] and alclofenca.[69]

Sometimes it is merely the masking of an unpleasant odour which is sought. In cosmetics, cyclodextrins are used to diminish the odour of mercaptan used in permanent hair preparations.[70,71] Similarly, by including iodine in cyclodextrins, it is possible to mask the odour of this antiseptic, and consequently to use it in preparations for the prevention of tooth decay.[72]

Enhancement of Solubility

Because they are rather hydrophobic inside their cavity and hydrophilic outside, cyclodextrins are capable of easily including hydrophobic molecules and conferring on them hydrophilic characteristics. Thus, cyclodextrins and their hydrosoluble derivatives can be used as dissolving agents. This effect is investigated with two different objectives: either to benefit from the natural advantages of a liquid product, or as the first step to an increase in the ability of insoluble substances to be absorbed through various membranes.

The increase in solubility is governed partly by the solubility of the cyclodextrin employed, and it is necessary to recall that β-cyclodextrin, the most common one, is the least soluble natural cyclodextrin. Among the hydrosoluble derivatives, the hydroxypropyl cyclodextrins appear to occupy an important place on the market of the future.

The increase in solubility depends not only on the guest cyclodextrin, but also on the stability constant of the inclusion compound obtained. A good example is a pharmaceutical one, which concerns flurbiprofen included in β- and γ-cyclodextrins.[73] The free flurbiprofen has a very low solubility which increased notably by inclusion in β-cyclodextrin and considerably by inclusion in γ-cyclodextrin. However, the stability constants of the two inclusions were significantly different: $5100\,mol^{-1}$ for β and only $460\,mol^{-1}$ for γ. Thus, after dissolution of the inclusion compounds, decomposition of the flurbiprofen/γ-cyclodextrin complex is much more important than that of the flurbiprofen/β-cyclodextrin complex, and consequently the poorly water-soluble flurbiprofen precipitates.

In pharmacy, however, an increase in solubility is very frequently desired, especially for parenteral administration. From this standpoint, the hydroxypropyl derivatives, less nephrotoxic and less hæmolytic than the mother cyclodextrins, could be of great value if the doses administered are large. An example of increase in water solubility is that of melphalan (L-phenylalanine mustard), an anticancer drug used in breast and ovary carcinoma and in multiple myeloma.[74] It presents rather low water

solubility and, furthermore, very low stability in solution. Its inclusion, either in β-cyclodextrin or in hydroxypropyl β-cyclodextrin, improves these two parameters.

With respect to pesticides, most of them are poorly water-soluble, and the advantage of formulating them in solutions is to increase the degree of dispersivity in order to ensure a homogeneous distribution of a small amount of the substance on to a large surface. However the contact toxicity of some products, such as pyrethroids, is considerably decreased, because the hydrophilic complex is not absorbed directly through the lipophilic regions of the body of the insect. But if such complexes are not toxic to non-phytophag insects, they can enter the organism of herbivorous insects through their intestinal tract. Their toxicity will then depend on the rate of the detoxification processes.[75]

The use of insoluble fungicides can similarly be facilitated by inclusion in cyclodextrins.[75]

In cosmetology, face and eye lotions are compositions with simple formulae. Clear and slightly tinted, they consists essentially of water, usually containing small amounts of water-soluble astringent substances. Some lotions nevertheless contain liposoluble substances. To preserve a clear preparation, the most widely-used technique is that of micellar solubilization, but the presence of the surfactant may increase the irritant effect of the lotion. The use of an inclusion helps to overcome this drawback. Vitamin E, which is employed to clean and whiten sunburned complexions, can be included in cyclodextrin, as well as some of its derivatives.[76] Similarly, isopropyl myristate can be incorporated in face lotion after inclusion.[77]

In the food industry, the addition of β-cyclodextrin to canned citrus products[78–80] or bamboo shoots[81] prevents precipitations. Sweetening agents (chalcone and dihydrochalcone), which precipitate easily by cooling, no longer precipitate after addition of β-cyclodextrin.[82]

Increased Absorption Through Biological Membranes

Very often the main objective of the pharmaceutical use of cyclodextrins is an increase in the bioavailability of an active ingredient. Cyclodextrins and their derivatives are not direct absorption enhancers. If at times they can increase the bioavailability of a drug, it is only in the case of products presenting very low water solubility, or rather very slow dissolution, without presenting problems of absorption rate. Furthermore, the hydrophilic external part of the inclusion compound does not confer on it good conditions for absorption through the lipophilic membranes of the gastro-intestinal tract or the skin, or through any kind of mucosa. Consequently, the active ingredient molecule, in order to be absorbed easily, must be free of the cyclodextrin protection. In other words, it is only the free active ingredient resulting from the inclusion compound dissociation which is absorbed, especially because the poorly water-soluble active ingredient is more or less lipophilic, a condition which, after dissociation into the molecular state, facilitates absorption through lipophilic biological membranes. Only a small part of the whole inclusion compound, or of the free cyclodextrin itself, can be absorbed through the biological membranes (Figure 2), and this is the case for α-cyclodextrin inclusion compound only, but possibly also in lower proportions for β-cyclodextrin. Thus, to have a significant increase in bioavailability, it is necessary to have good water solubility of the inclusion compound, but with a rather low stability constant.

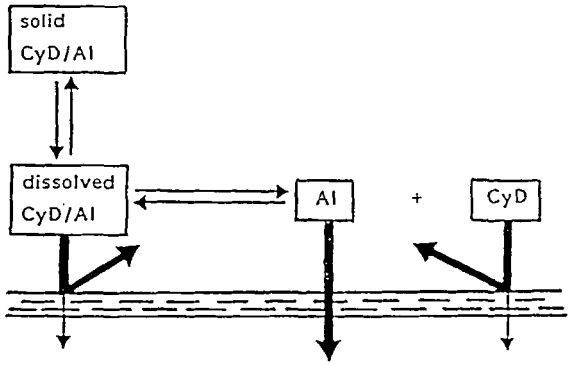

FIGURE 2 Absorption mechanism through a biological membrane of an active ingredient included in a cyclodextrin.

In pharmacy, the examples of an increase in bioavailability by inclusion in a cyclodextrin are numerous, even if they are mainly concerned only with investigations on animals. For oral administration, we can mention the following active ingredients: digoxin,[83,84] spironolactone,[85,86] phenytoin,[87] acetohexamide,[88] diazepam,[89] flurbiprofen,[90] ketoprofen,[91] ibuprofen,[91] flufenamic acid,[91] indomethacin,[92] prednisolone,[93] and many barbiturates: allobarbital, amobarbital, barbital, pentobarbital and phenobarbital.[94]

Similar results are obtained with water-soluble derivatives such as methyl cyclodextrins. For example, trimethyl β-cyclodextrin doubles the bioavailability of flurbiprofen,[95,96] and more than triples that of ketoprofen.[97] It also increases the bioavailability of ubidecarenone[98] and vitamin K_3,[99] and is more efficient than trimethyl β-cyclodextrin for carmofur (HCFU).[100,101]

Sometimes the increase in bioavailability is such that it is possible to propose a decrease in the dose administered.[84]

An increase in bioavailability can also be obtained for other administration routes such as rectal,[102,103] dermal,[104] ocular[105] and sublingual.[106]

If the stability constant of the inclusion compound is too high to allow a rapid release in the molecular state of the hydrophobic active ingredient, it is possible to displace it by a competing agent. Thus the concomitant oral administration of DL-phenylalanine is proposed in order to displace cinnarizine from the β-cyclodextrin cavity.[84]

An identical absorption mechanism can be observed for pesticides[75] through vegetal membranes or insect digestive tract. The consequence is particularly interesting with respect to phytophag insects, because they can eat leaves containing the insecticide inside and not outside, where it may be blown away by rain and wind. Furthermore, the intestinal absorption of the product by the insect may be increased.

Prolonged Release of Active Ingredient

Cyclodextrins are often used to improve the water solubility of poorly-soluble ingredients, and to accelerate their release from a given form. However, β-cyclodextrin, the most commonly employed cyclodextrin, has only low water solubility (1.85 g/

100 ml), and furthermore it is capable of including water-soluble molecules (if they are less hydrophilic than water itself). In such conditions, hydrophilic products may have a slow release rate after inclusion in β-cyclodextrin or in its insoluble derivatives, such as ethyl cyclodextrins.

In the pharmaceutical field, ethyl cyclodextrins can be used to decrease the water solubility of active ingredients, such as diltiazem or isosorbide dinitrate, and to obtain and *in vivo* prolonged release capable of counterbalancing the short half-life of the products.[107,108] However, the examples are rare, because, from the administrative standpoint (marketing approval), the use of a cyclodextrin in a specialty is not easy, and there are many well-known processes which can be used for the same purpose without any problems.

An interesting example of prolonged release obtained with cyclodextrins concerns a sex pheromone component (1,7-dioxaspirol[5,5] undecane) of the olive fruit fly, *Dacus oleae*. Flies are necessary for flower fecondation, and it is interesting to be able to attract them with their corresponding sex pheromone. The pheromone of *Dacus oleae* can be included in α-, β- and γ-cyclodextrins, and the inclusions can be used as pheromone dispensers in an integrated programme aimed to control the olive fruit fly.[109]

CONCLUSION

The possible uses of cyclodextrins in industry are numerous, and we have given just a glimpse of some of these possibilities resulting from their ability to include a wide variety of host molecules.

There are many other examples in which the cyclodextrins are used as classic raw materials, without taking any account of this inclusion ability. This is the case, for example, of their use as tablet excipients in pharmacy,[110–112] or as stabilizers in emulsion technology.[113–115] However, in the latter case, there is no explanation concerning the stabilization mechanism. We have to be very careful with respect to patents in which cyclodextrins are used without a logical rôle.

However, due to their remarkable property of including molecules, and also to the fact that the variety of derivatives available on the market is regularly increasing, and their price decreasing, we have to be ready to encounter them continually during our daily life.

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