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CYCLODEXTRINS, THEIR VALUE IN PHARMACEUTICAL TECHNOLOGY

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ABSTRACT

Cyclodextrins are cyclic oligosaccharides consisting of a variable number of glucose units (usually 6 to 8). The ring formed by cyclodextrins is externally very hydrophilic and relatively apolar internally. In liquid or solid medium, these molecules are capable of forming inclusion compounds with many other molecules. The inclusion compounds thus formed display interesting properties in comparison with the starting molecule.

In fact, inclusion may increase the stability of the guest molecules. Greater stability may be shown towards heat, resulting in lower volatility or higher thermal resistance. Greater stability may also be oxidation resistance. It may also concern the products in solution, whose hydrolysis may, in certain cases, be inhibited to varying degrees.

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For relatively insoluble active ingredients, inclusion may improve the solubility or dissolution rate. Depending on the stability constant of the inclusion compound formed, a better passage of the active ingredient through membranes may be observed. *In vivo*, this may be reflected by an increase in bioavailability, with a simultaneous increase in therapeutic effectiveness.

INTRODUCTION

Cyclodextrins have been known for nearly a century, having been isolated by Villiers <1> in 1981 from the degradation products of starch, and the description of their preparation, isolation and main characteristics was made by Schardinger in the years 1903 to 1911 <2,3,4>.

1 Cyclodextrins and inclusion compounds

Cyclodextrins are cyclic oligosaccharides produced by the enzymatic degradation of starch. The enzyme, cyclodextrin glycosyl transferase, is produced by different bacilli, especially *Bacillus macerans*. Depending on the reaction conditions, cyclodextrins contain six, seven or eight glucose units, connected by α-(1,4) bonds, known as α-, β- and γ-cyclodextrins. The particular form of the molecule requires a special arrangement of the different functional groups. On the whole, the interior of the cyclodextrin cavity is apolar in relation to water, and the exterior is hydrophilic.

Some of the properties of cyclodextrins are given in Table 1. Cyclodextrins are water-soluble, and β-cyclodextrin is the least soluble. Solubility increases sharply with temperature, allowing easy recrystallization on cooling.

One of the most interesting properties of cyclodextrins is their ability to form inclusion compounds with a wide variety of molecules, which apparently only have to satisfy a single condition: to be

Table 1

Properties of the main cyclodextrins

cyclodextrin	No. of glucoses	molecular weight	solubility in water (g/100 cm^3)	cavity dimensions (A)		
				depth	i.d.	o.d.
α cyclohexa-amylose	6	972	14.50	7.9 to 8.0	4.7 to 5.2	14.6 ±0.4
β cyclohepta-amylose	7	1135	1.85	7.9 to 8.0	6.0 to 6.4	15.4 ±0.4
γ cycloocta-amylose	8	1297	23.20	7.9 to 8.0	7.5 to 8.3	17.5 ±0.4

adaptable entirely, or at least partly, to the cavity of the cyclodextrins <5>. Inclusion compounds are usually prepared in a liquid medium.

In the case of water-soluble materials, a 'guest' product is added to an aqueous solution of cyclodextrin, usually in stoichiometric quantities. The mixture is heated with agitation for several hours, or even several days. The inclusion formed precipitates spontaneously or by cooling. The water solubility of the guest product can be increased by incorporating a suitable additive <6,7>. The mixture can also be freeze-dried or spray-dried <6,8,9,10>. The final product in this case is amorphous.

If the substance to be included is insoluble in water, it is dissolved in an organic solvent and added, with agitation, to a hot aqueous solution of cyclodextrin. Crystallization takes place within the following hours or days.

In some cases, the formation of the complex in the solid phase is thermodynamically spontaneous, although its stability is greater in

aqueous solution than in the solid phase <11>. Inclusion is normally achieved by microgrinding <11,12>.

The inclusion of a guest molecule in a cyclodextrin molecule constitutes a true molecular microencapsulation that is likely to alter the physicochemical and even the biological properties of the guest molecule considerably. This has encouraged research into application in the area of formulation. In Japan, these investigations culminated in the marketing of a prostaglandin E_2/ β-cyclodextrin complex, Prostarmon, marketed by Ono <13>.

At the pharmacotechnical level, the applications of inclusion are essentially in the improvement of molecule stability <14> and, above all, the improvement of their solubility and bioavailability <15>.

2 Improved stability

The improvement of stability may have three essential objectives: heat stability, oxidation resistance and hydrolysis resistance (or stability in aqueous solution).

2.1 Heat stability

Substances included in cyclodextrins to improve their stability may be liquid or solid.

2.1.1 Reduction of volatility

The reduction of volatility can be demonstrated by a rise in the boiling point or evaporation conditions of the liquids, or of sublimation for solids. Szejtli <16 to 20> prepared inclusion compounds with many volatile substances, including spices, plant flavours and essences, camphor, menthol and thymol. The inclusion compounds obtained facilitate the handling of the products, particularly due to the fact that they transform the liquid to solid.

The volatility of the substances is sharply reduced, and this was closely investigated with anethole <16>.

The value of these inclusions is to permit an improvement in the quality of the pharmaceutical forms in which they are incorporated, especially suppositories <18,19> and inhalations <17,20>. In suppositories, their melting point and hardness are often lowered by adding volatile substances, and the inclusion of these substances overcomes these drawbacks <19>. In the case of inhalations containing high proportions of volatile essences, the preparation is liquid, difficult to handle, and is sometimes volatilized too rapidly if mixed with boiling water. By solidifying the product, inclusion facilitates handling and slows down its vaporization whilst prolonging its effect <20>.

The reduction of volatility can be examined by differential thermal analysis or by thermogravimetry. These techniques were used by Uekama for inclusions of clofibrate in β-cyclodextrin <21>, cinnamic acid in β-cyclodextrin <22>, and benzaldehyde in α-, β- and γ-cyclodextrins <23>. Nakai <24> used thermogravimetry to analyze inclusions of parahydroxybenzoic acid in α- and β-cyclodextrins. The sublimation of parahydroxybenzoic acid at 180 °C and 210 °C is considerably reduced, particularly with α-cyclodextrin, and this is probably due to a closer adjustment of the molecule in the α-cyclodextrin cavity than in that of β-cyclodextrin.

An interesting stabilization achieved by inclusion in β-cyclodextrin is that of the 5-mononitrate of isosorbid <25>. This is a volatile substance, and, during the storage of tablets containing it, needles are formed at the surface, especially if the temperature and humidity are unfavourable. The inclusion eliminates this process and also reduces the degradation of the product with time.

2.1.2 Higher heat resistance

In the same way that inclusion raises the boiling point and evaporation and sublimation temperatures, it can also raise the melting point. This has been observed for metronidazole included in β-cyclodextrin <26> and for prostaglandin $F_{2\alpha}$ <27>. Another demonstration of higher heat resistance is the elevation of the decomposition temperature. Szejtli investigated a series of aromatic oils <16>. In the case of essence of marjoram, for example, the volatile compounds are liberated and can be identified by thin film chromatography above 100 °C in the case of the pure product, or in the form of a physical mixture with β-cyclodextrin, with their decomposition occurring at 240 °C. If inclusion is carried out, the volatile substances only appear above 160 °C, and decomposition only takes place above 300 °C.

2.2 Oxidation resistance

2.2.1 Oxygen

The protective action of complex formation with cyclodextrins can be investigated by placing the products to be tested in a Warburg apparatus, under oxygen, at 37 °C. The absorption of oxygen is measured at regular time intervals.

Using this method, Szejtli <28,29> showed an improvement in the stability of vitamin D_3, when it is complexed with β-cyclodextrin. From these results, it would appear that pure vitamin D_3 can fix 140 μℓ/mg of oxygen, and that the physical mixture gives worse results. On the other hand, the inclusion complex fixes only 11.2% of this amount over the same experimental time period (500 h).

Szejtli <16> used the same method to study the oxidation resistance of vegetable essences complexed with β-cyclodextrin.

2.2.2 Oxidation accelerators

Heat, light and metal salts (copper sulphate) all increase the degradation of vitamin D_3 by oxidation. This can be inhibited, and considerably reduced, by inclusion of the vitamin in β-cyclodextrin <28,29>. The product so treated can be presented in tablet form, having better stability against heat than tablets of the pure vitamin <28,29>. The complex vitamin D_3/ β-cyclodextrin preserves 94% of its therapeutic activity, even after being stored for seven days at 60 °C <30>.

Similarly, the inclusion of vitamin A in α-cyclodextrin increases its stability against heat <31>.

The sensitivity to light of clofibrate <21> and guaiazulene <32> is reduced by inclusion in β- and γ-cyclodextrins.

2.3 Resistance to hydrolysis and to degradation in solution

The foregoing results tend to imply that the inclusion of a guest molecule in a cyclodextrin generally imparts good stability to the molecule. In actual fact, this is not always the case, especially for stability in aqueous medium. Many molecules have been investigated, and the results vary considerably depending on the type of guest molecule, the type of cyclodextrin employed, and the pH of the medium. A number of results are reviewed below, to show their diversity.

The stability of vitamin K_3 inclusions in solution, investigated by Szejtli <33> is poor irrespective of the pH, and β-cyclodextrin actually accelerates decomposition.

Møllgaard Andersen and Bundgaard showed that the degradation of hydrocortisone included in β-cyclodextrin is accelerated in alkaline medium, whereas it is virtually unchanged in a neutral or

acidic medium <34>. This can be explained by the degradation mode of hydrocortisone, which is different in alkaline and acid media.

These authors <35> investigated the stability of betamethasone 17-valerate in aqueous alkaline solution, in which this substance undergoes a rearrangement into the less active 21-valerate. While α-cyclodextrin has no effect on this rearrangement, β-cyclodextrin accelerates it, and γ-cyclodextrin slows it down substantially. These results are explained by the differences of conformation of the inclusion compounds (1/1) formed.

Concerning nitrazepam, Møllgaard Andersen and Bundgaard <36> also showed that the presence of β-cyclodextrin has no effect on the hydrolysis of this substance in 0.1 M hydrochloric acid medium. This could be due to the ionization of the nitrazepam at this pH, since the ionized products do not easily form inclusions with cyclodextrins.

Various investigations have been conducted with aspirin. Nakai and Terada <12,37>, examining its stability in the solid state, associated with α-, β- and γ-cyclodextrins, in the form of inclusions, physical mixtures, or ground mixtures, showed that, if the acetoxyl groups are free, the molecule is relatively stable, and if they are connected by hydrogen bonds to the hydroxyls of the cyclodextrins, the aspirin molecule becomes unstable.

Nakai <23> investigated the hydrolysis of aspirin at pH 1.0 in the presence of α-, β- and γ-cyclodextrins. The degradation constant does not vary in the presence of α-cyclodextrin, but is reduced with β- and γ-cyclodextrins, with the effect of β-cyclodextrin being more pronounced. This is due to the impossibility of including aspirin in α-cyclodextrin, of its good inclusion in β-cyclodextrin, and its excessively loose inclusion in

γ-cyclodextrin, leaving a void into which a proton or molecule of water can penetrate.

The results of works concerning indomethacine are contradictory. For Szejtli <38>, inclusion in β-cyclodextrin does not protect this product from degradation at pH 8.0. In a patent, Sumimoto Chemical reports a stabilizing effect of the inclusion <39>, and Hamada <40> confirms this result, while the addition of α-cyclodextrin has no effect.

For barbiturates, Nagai <41> reported that the degradation of hexobarbital to the alkaline solution at pH 12 is increased by β-cyclodextrin and slightly decreased by α- and γ-cyclodextrins. Min <42> and Kyoko <43> reported an improvement in the stability of aqueous solutions of phenobarbital and various barbiturates by the addition of β-cyclodextrin.

Fujioka <44> investigating the degradation of bencyclane in acidic medium, showed that its inclusion caused a slowdown in this degradation, with the effect of the cyclodextrins rising in the order α, γ and β.

Proscillaridin is unstable in gastric medium. Uekama <45> showed that inclusions in α-, β- and γ-cyclodextrins reduce the instability at pH 1.46 and 37 °C. However, this result is only really significant with β- and γ-cyclodextrins, since the α cavity is too small and cannot protect the proscillaridin.

According to Møllgaard Andersen and Bundgaard <26>, the hydrolysis of metronidazole benzoate is slowed down by inclusion in β-cyclodextrin, and the inclusion also appears to slow down the growth of crystals in suspension.

Many patents, particularly Japanese, report the inclusion of prostaglandins in α- and β-cyclodextrins, as well as their

methylated derivatives <46 to 52>. Although their interpretation is often difficult, an improvement in stability generally appears in aqueous solutions, as well as in the storage of freeze-dried products.

Uekama <53> showed that the inclusion of prostaglandin E_1 in γ-cyclodextrin increased its heat stability and slowed down its conversion to prostaglandin A_1.

Many other substances have also been investigated, including ampicillin and methicillin, whose hydrolysis rates were significantly decreased by inclusion in β-cyclodextrin <54>. Similarly, the presence of β-cyclodextrin slows down the degradation of cinnarizine in acidic solution <55>.

3 Improved dissolution and bioavailability

3.1 *In vitro* investigations, Higher water solubility

3.1.1 Demonstration of the effect of cyclodextrins

Hamada <40> studied the influence of α- and β-cyclodextrins on the solubility of a series of non-steroid anti-inflammatory substances, by comparing it with that of glucose. For these products, glucose appears to have no effect, α-cyclodextrin is either ineffective or only slightly effective, and β-cyclodextrin causes an increase in solubility. This result is explained by the formation of inclusion compounds, in accordance with the size of the guest molecules in comparison with the dimensions of the cyclodextrin cavity.

It is unnecessary for the inclusion to be preformed for the higher solubility to occur. This was shown by Corrigan and Stanley, working on phenobarbitone <56>, and on benzothiazide derivatives <57>. In both cases, simple physical mixtures of the active

ingredients with β-cyclodextrin displayed better solubility than the active ingredients themselves. However, the products obtained after freeze-drying of a solution of these mixtures yielded better results. This can be explained either by the hydrophily of the freeze-dried products and their amorphous character, or by the existence in the freeze-dried mixture of a varying proportion of preformed inclusion compound.

3.1.2 Solubility diagram and stability constant

Higuchi's <58> solubility analysis method was applied by different authors to various active ingredients in the presence of cyclodextrins. Uekama, for example, studied digitoxin <59>, digoxin <60>, eighteen steroid hormones <61>, proscillaridin <45>, spironolactone <62>, clofibrate <21>, flurbiprofen <63>, propylparaben <64>, prostaglandins E_1 <53> and $F_{2\alpha}$ <27>. This method was also applied by Møllgaard Andersen to hydrocortisone <34> and to spironolactone <68>.

If the solubility increases linearly with cyclodextrin concentration, the curve is said to be of Higuchi's type A_L, and corresponds to the formation of an inclusion compound with the stoichiometry 1/1. The curves are of Higuchi's type B_S if, after a linear rise, a plateau is observed, followed by a decrease corresponding to the precipitation of a microcrystalline inclusion compound with a different stoichiometry.

The plotting of these diagrams serves to calculate an apparent stability constant from the straight part of the curves. This constant reflects the correct adjustment of the guest molecule inside the cavity of the host molecule. Hence, for example, the stability constants calculated by Seo and Uekama <62> for the inclusion compound of spironolactone with α-, β- and γ-cyclodextrins are 960, 27,500 and 7600 M^{-1} respectively. As a rule, steroids display better interaction with β- or

γ-cyclodextrins, as α-cyclodextrin is much too small to allow inclusion <61>.

3.1.3 Dissolution of inclusion compounds

Solubility diagrams remain too theoretical for practical application, because they are plotted when equilibrium is reached, in other words after four to ten days of agitation. Thus, the analysis of the dissolution kinetics of solid inclusion compounds is often preferable, because this can be used to reveal not only an improvement in solubility, but also the rate of passage into solution. These studies also help to point out the value of using a solid inclusion from the galenic standpoint, rather than the simple physical mixture <38,69>, or a freeze-dried or spray-dried product in other cases <9,10>.

A comparison of the inclusion compounds obtained with different cyclodextrins is interesting. Hence inclusion compounds with flurbiprofene in β- and γ-cyclodextrins <63> display stability constants of 5100 and 460 M^{-1} respectively, and the crystallinity of the inclusion in γ-cyclodextrin is less pronounced than that of the inclusion in β-cyclodextrin. The results of the dissolution of these substances reveal not only faster dissolution for the γ-cyclodextrin inclusion compound, but also a progressive dissociation of this compound in aqueous medium, rapidly causing precipitation of free flurbiprofene.

For the more convenient study of these dissociation mechanisms, rather than using the dissolution method consisting in dispersing a quantity of test product in the dissolution medium, it is often more interesting to use the rotary disc method. This method offers the advantage of linearizing the dissolution curves when dissolution is uniform, but, on the other hand, if the inclusion compound decomposes in aqueous medium, the released active ingredient reprecipitates, and the curve obtained by the rotary

disc method displays a negative curve versus time. Because it offers a particularly clear representation, this method has often been used <45,60,61,62,68,70,71>.

3.1.4 Diffusion through semi-permeable membranes

The foregoing studies help to establish a hypothesis according to which water-soluble inclusion compounds, by dissociation, increase the bioavailability of the active ingredients they contain, a hypothesis which needs to be substantiated.

This is why both Szejtli <72> and Uekama <21,62,71,73,74> investigated the possibilities of diffusion of active ingredients or their inclusion compounds through semi-permeable membranes. To do this, they employed systems comprising a cellophane membrane between a donor compartment and an acceptor compartment, each equipped with an agitation system. With the donor and acceptor compartments filled with water, and the test products (active ingredient alone and inclusion compound) added in the solid state in the donor compartment, then the diffusion of the inclusion compound is often not as significant as expected. In some cases, such as fendiline in β-cyclodextrin <72>, it is lower than that of the active ingredient alone, and, in other cases, such as that of flurbiprofene in β- and γ-cyclodextrins <71>, although it is better than that of the active ingredient alone, it does not agree with the comparative effect of these cyclodextrins on dissolution.

To explain this result, Uekama <71> compared it with that obtained by placing the solutions of active ingredient and inclusion compound directly in the donor compartment. In this case, the active ingredient (flurbiprofene) diffuses better than the inclusion compound. Diffusion is closely dependent on molecular size, and the inclusion compounds diffuse with greater difficulty than the

guest molecule. In addition, diffusion must be related to the stability constant: the higher the constant the less the diffusion (for inclusion compounds, 1/1, of flurbiprofene, $K\beta = 5100\ M^{-1}$ and $K\gamma = 460\ M^{-1}$).

These studies show that this investigative method is perhaps not a good indication of possible absorption *in vivo*.

3.1.5 Interface transfer

Hoping to develop an experimental model imitating the *in vivo* absorption of inclusion compounds, Uekama <64> used an *in vitro* dissolution model $S/L_W/L_O$ (solid phase/aqueous liquid phase/ organic liquid phase) <76,77>. The model consists of a rotary disc dissolver with an organic phase. With pure substances, good correlation was observed between the theoretical concentration of product passing from the solid phase to the organic liquid phase and the experimental values. With inclusion compounds, the mechanism is much more complex, and the theoretical calculation of diffusion becomes problematic. However, the observation of the concentration in the organic phase always remains a good simulation of *in vivo* absorption for active ingredients resorbed by passive diffusion.

3.1.6 *In situ* resorption

In addition to the *in vitro* experimental model, Uekama developed and used an *in situ* experimental model, S/L_W/*in situ* (solid phase/aqueous liquid phase/*in situ*). This model consists in perfusing *in situ* a predetermined length of the small intestine of an anaesthetized rat or rabbit, by the aqueous dissolution liquid of the test product, as its dissolution proceeds, and regularly determining the active ingredient in the blood of the animal. Uekama showed that good correlation exists between the results of the study of *in vitro* interface transfer and *in situ* absorption.

A study of the same type was carried out by Szejtli and Szente <38> who compared the absorption of indomethacine labelled with ^{14}C, alone or in included in β-cyclodextrin, in the small and large intestines of rats. In the case of indomethacine only, 56% were absorbed in the small intesting and 6% in the large intestine. In the case of included indomethacine, absorption was 68 and 66% respectively.

3.2 *In vivo* investigations, Bioavailability and pharmacokinetics

Whatever the value of the foregoing techniques, they can only offer firm hope of an improvement in bioavailability, and this must be checked in animals and in humans.

3.2.1 Oral administration

The inclusion of an active ingredient in a cyclodextrin may reduce its bitterness <44,78>, and, more interestingly, any harmful side effects, such as the attack of the stomach mucous membranes by certain non-steroid anti-inflammatory substances. This is what happens with phenylbutazone included in β-cyclodextrin, but is not observed with indomethacine or flufenamic acid <79>. The disappearance of the irritation of pirprofen on the mucous membrane of the throat is reduced by inclusion in β-cyclodextrin <80>.

Concerning bioavailability, an improvement is usually observed if the inclusion of an active ingredient has already improved its dissolution. Not only is the blood concentration higher, with its peak occurring sooner, but the area below the curve (plasma concentration/time) is also larger. These results can be obtained, for example, after the oral administration of inclusion compounds: digoxin/γ-cyclodextrin in the dog <59,60>, spironolactone/β- or γ-cyclodextrin in the dog <62>, phenytoin/β-cyclodextrin in the dog <65>, flurbiprofen / β- or γ-cyclodextrin in the rabbit <71>, acetohexamide/β-cyclodextrin in the rabbit <74>,

diazepam/γ-cyclodextrin in the rabbit <75>, ketoprofen/β-cyclodextrin in the dog <8>, ketoprofen, ibuprofen or flufenamic acid/β-cyclodextrin in the rabbit <8>, indomethacine/β-cyclodextrin in the rat <38>, but no favourable effect is observed in the rabbit <8>, and allobarbital, amobarbital, barbital, pentobarbital or phenobarbital/β-cyclodextrin in the rabbit <81>.

A similar result is obtained by the oral administration in humans of the inclusion compounds salicylic acid/β-cyclodextrin <82> or prednisolone/β-cyclodextrin <73>. These studies also reveal the value of the oral administration of freeze-dried drugs <65,83>. In some cases, the improvement in bioavailability caused by inclusion is such that a reduction in the dose administered can be considered. This applies in particular to the inclusion digoxin/γ-cyclodextrin (1/4) <59,60>.

It may sometimes be advantageous to administer an additive at the same time as the inclusion, to improve its *in vivo* effectiveness. This applies in particular to cinnarizine, whose inclusion in β-cyclodextrin increases its solubility at pH 3.0 to 6.8, but does not change its bioavailability. Accordingly, the stomach pH must be adapted to a better dissolution, and this is done by the simultaneous administration of $NaHCO_3$ <84>. For the same product, the administration of a competing agent, such as DL-phenylalanine, also proves to be interesting. After oral administration, the dissociation of the inclusion cinnarizine/β-cyclodextrin is facilitated by the presence of phenylalanine, which tends to supplant the cinnarizine in the cyclodextrin, causing the absorption of cinnarizine, now in the molecular state, to occur rapidly <85>.

Improved bioavailability should normally be reflected by an increase in therapeutic effect. This was observed by Koizumi, who investigated five barbiturates (phenobarbital, pentobarbital, amobarbital, allobarbital and barbital) <86>. Their effective

dose 50 was actually reduced to varying degrees by inclusion in β-cyclodextrin. In addition, with the exception of barbital, the latency time before the induction of sleep is generally shortened, while the duration of sleep is prolonged <86>.

Szejtli also observed therapeutic improvements by the administration of vitamin D_3 to rats <28,29,87>. Increases in urinary volume in the rat were observed by the administration of spironolactone included in γ-cyclodextrin, greater than those caused by spironolactone alone <88>.

3.2.2 Rectal administration

The rectal administration of suppositories containing active ingredients, alone or in cyclodextrin inclusions, is often reflected by greater bioavailability <71,74,89>. In actual fact, it appears that the type of excipient has a significant effect on the bioavailability of the active ingredient itself or of the inclusion compound <90>. This was observed with phenobarbital included in β-cyclodextrin, combined with Witepsol 55 or with Macrogol. In this case, it should be noted that the cyclodextrin tends to delay the absorption of phenobarbital in the rectum, so that the higher blood concentrations with the inclusion compound can essentially be attributed to a faster release of this compound (hydrophilic) than of the phenobarbital, based on the excipients employed.

3.2.3 Cutaneous administration

Otagiri and Uekama <91,92> investigated the release of betamethasone and the percutaneous absorption of beclomethasone dipropionate included in β- and/or γ-cyclodextrins, using hydrophilic bases. On the whole, the release of the active ingredients, measured through an artificial double-layer membrane or a cellophane membrane, was increased by inclusion.

Moreover, in the case of the beclomethasone dipropionate included in γ-cyclodextrin, an increase in the vasoconstrictor effect of the product was observed, which appears to reflect an improvement in percutaneous absorption <92>.

3.2.4 Ocular administration

Very few tests have yet been conducted on this method of administration. However, it is worthwhile noting the possibility of reducing local irritation caused by flurbiprofene, when the latter is included in β-cyclodextrin <93>. It also appears that the inclusion of sodium sulfacetamide in β-cyclodextrin improves its release from an ophthalmic ointment <94>.

3.2.5 Parenteral administration

While the non-toxicity of cyclodextrins by oral administration appears to be highly probable <95>, this cannot be said of parenteral administration. Tests have nevertheless been conducted by this method in animals.

Nagai <96> administered hexobarbital in the presence of α-, β- and γ-cyclodextrins in mice and rats by intervenous and intraperitoneal administration. A significant change in the pharmacokinetics of the product resulted from the presence of cyclodextrins. Ten and twenty minutes after intravenous administration, the following effects were observed in comparison with hexobarbital alone: higher blood and kidney concentrations, lower brain and liver concentrations, shorter sleeping time and prolonged latency period before induction of sleep.

CONCLUSIONS

Cyclodextrins display high inclusion capacity for non-hydrophilic molecules. The inclusion compounds thus formed should

normally be extremely valuable in pharmaceutical technology, because it has already been proved that they significantly enhance the storage of many products in the solid state and sometimes in liquid medium. Their greatest value is undoubtedly the possibility of substantially improving the bioavailability of products that are orally administered. Their use is likely to spread considerably after the long toxicity investigations have been completed.

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