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PHARMACEUTICAL USES OF CYCLODEXTRINS AND DERIVATIVES

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ABSTRACT

Due to their particular conformation, cyclodextrins have the remarkable characteristic of being able to include various kinds of molecule inside their hydrophobic cavity, conferring on them an environmental hydrophily. These inclusion compounds have completely new pharmacotechnical properties, but the most important ones concern increases in water solubility and bioavailability. When administered orally, the inclusion compounds decompose, allowing the free active ingredient to be absorbed by the gastro-intestinal mucosa. However, a certain proportion of inclusion compound is absorbed without any dissociation.

Some cyclodextrin derivatives are very interesting because of their very high water solubility, and also because of their low parenteral toxicity compared with the original ß-cyclodextrin. However, in parenteral administration, it is absolutely necessary to study the pharmacokinetic and pharmacological characteristics of the inclusion compound, which must be considered as the true active ingredient.

INTRODUCTION

Many molecules synthesized by the pharmaceutical industry, despite their very promising pharmacological properties, never appear on the market as pharmaceutical specialties. The reason most often given for this failure is the low water solubility of these products, and at times their quasi-insolubility, resulting in poor bioavailability.

Cyclodextrins and some of their derivatives, through their ability to include various kinds of molecule in their hydrophobic cavity, can appreciably change not only the water solubility of the guest molecule, but also many of its other unsatisfactory pharmacotechnical characteristics.

MAIN CHARACTERISTICS OF CYCLODEXTRINS

Physicochemical characteristics of cyclodextrins [1,2,3]

Three natural cyclodextrins are available on the market: α-cyclodextrin (cyclohexaamylose), ß-cyclodextrin (cycloheptaamylose) and γ-cyclodextrin (cyclooctaamylose), consisting of 6, 7 and 8 glucose units respectively. These glucose molecules are linked by α-(1,4) bonds, causing the formation of torus molecules, on which the primary hydroxylic groups are situated on the narrowest side of the ring, and the secondary hydroxylic groups on the larger side. The interior of the cavity is rather hydrophobic whereas the exterior is highly hydrophilic. These characteristics enable the cyclodextrins to entrap various kinds of guest molecule, which apparently have to satisfy a single requirement: a steric hindrance compatible with the size of the cyclodextrin cavity.

From the pharmaceutical standpoint, the internal diameter of α-cyclodextrin (≅ 5 Å) is generally too small to include the majority of active ingredients. ß- (≅ 6 Å) and γ- (≅ 8 Å) cyclodextrins are more suitable. Until now, γ-cyclodextrin was only a by-product of α- and ß-cyclodextrin preparation, with, accordingly, a prohibitive price for its use in pharmaceutical manufacturing. However, it seems that things may change in the forthcoming years or even months.

The consequence is that most of the work carried out on the pharmaceutical uses of cyclodextrins has been undertaken with ß-cyclodextrin. Unfortunately, if cyclodextrins are water-soluble, ß-cyclodextrin is the least soluble: only 1·85 g/100 ml compared with 14·50 g/100 ml for α-cyclodextrin and 23·20 g/100 ml for γ-cyclodextrin. Nevertheless this poor solubility of ß-cyclodextrin can be considered as high solubility compared with many insoluble active ingredients, and is sufficient to improve appreciably both their solubility and bioavailability.

Metabolism and toxicity of cyclodextrins

After oral administration, cyclodextrins are not hydrolysed during their transit through the small intestine, hydrolysis occurring only in the colon. Their metabolism is more or less comparable with that of starch, but with a slower initial rate, due to the fact that cyclodextrins are totally resistant to ß-amylases, which degrade only free end groups, but they can be attacked by α-amylases active inside the molecules. However, their degradation rates are quite different, α-cyclodextrin having the slowest and γ-cyclodextrin the fastest [4]. It seems that α-cyclodextrin is not (or is only partially) degraded in the gastro-intestinal tract. Furthermore, α- and ß-cyclodextrins are poorly absorbed by the small intestine [5,6].

The oral administration of cyclodextrins does not result in an acute toxicity. Long-term administration leads to no significant change in organs or biological values [4].

The consequence of the parenteral administration of cyclodextrins is completely different: the intramuscular administration of ß-cyclodextrin results in ulcerations, and its intravenous administration in nephrotoxicity and hæmolytic effects [4]. Probably due to its high water solubility, γ-cyclodextrin is not so nephrotoxic and is less hæmolytic than both α- and ß-cyclodextrins [7].

This therefore means that cyclodextrins, especially ß and γ, can be used as host molecules for the administration of guest molecules presenting unsatisfactory pharmacotechnical characteristics. On the other hand, their use by the parenteral route is not recommended.

CYCLODEXTRIN INCLUSION COMPOUNDS

Preparation of inclusion compounds

Cyclodextrins are capable of forming inclusion compounds with a wide variety of molecules, the main requirement being that the guest molecule fits, at least partly, into the cyclodextrin cavity.

Various methods have been described for preparing inclusion compounds [8]. One of the best methods consists in dissolving the cyclodextrin and the active ingredient in water or in an organo-aqueous solvent, the inclusion compound precipitating spontaneously or after cooling the medium. In some cases, drying is necessary to separate the inclusion. Another method, very interesting from the industrial standpoint, is the kneading method: this consists in adding the active ingredient to a slurry of cyclodextrin and then kneading thoroughly to obtain a paste which is then dried. In liquid medium, the formation of an inclusion is governed by an equilibrium reaction between the host and guest molecules.

Pharmacotechnical characteristics of inclusion compounds

The interest of including an active ingredient in a cyclodextrin has been the subject of many review papers [2,9,10,11]. A short outline is given here.

- Transformation of liquids into powders

Essential oils can be included in ß-cyclodextrin [12]. The solid compounds obtained enable better handling of the products. They are said to contain all the constituents of the original substances but, due to the high complexity of the composition of essential oil or tincture, it seems difficult for the inclusion process to be of the same magnitude for each type of component [13].

- Enhancement of stability in the solid state

Inclusion in cyclodextrins can improve the heat stability of the included molecule, not only by reducing the volatility of liquid products [12], but also by reducing the tendency to sublimation of some solid products [14].

One of the major interests of inclusion is its possibility to enhance oxidation resistance. This has been demonstrated especially by Szejtli on vitamin D_3 [15,16].

- Resistance to hydrolysis

If the result of the inclusion is generally favourable concerning the stability in the solid state, this is not the case concerning stability in aqueous solution. In fact, the result varies considerably depending on the type of guest molecule, the type of cyclodextrin employed and the pH of the medium [2,10].

For example, the degradation of hydrocortisone included in ß-cyclodextrin is accelerated in alkaline medium, whereas it is virtually unchanged in neutral or acidic medium [17].

Doxorubicin associated with α-, ß- or γ-cyclodextrin complexes only with γ-cyclodextrin to a substantial extent, resulting in an increase in its stability in acidic medium [18]. ß-cyclodextrin is efficient in improving the aqueous stability of melphalan [19].

- Improvement in stability in the pharmaceutical form

Due to the general improvement in stability in the solid state, the concomitant improvement in stability in solid dosage forms, such as tablets or capsules, is obvious. More interesting are the results concerning an improvement in stability in semi-solid dosage forms, such as suppositories and ointments.

Various interesting results have been reported for these two kinds of dosage form. For suppositories containing AD-1590 (an acid non-steroidal anti-inflammatory agent), a stabilizing effect is obtained by inclusion in ß-cyclodextrin [20]. For ointments, the stabilizing effect of ß-cyclodextrin has been demonstrated for TBP (tixocortol 17-butyrate 21-propionate) included in ß-cyclodextrin and incorporated either in vaseline or in an o/w emulsion [21].

- Enhancement of water solubility

Whatever the interest of the previous utilization possibilities of cyclodextrins, their main value lies in their ability to enhance the water solubility of poorly soluble products [3,11]. Examples are too numerous to be reported, but they concern (among others) steroids [22], benzodiazepines [23,24], benzothiazides [25], barbiturates [15], naproxen [26] flurbiprofen [27], indomethacin [28], retinoic acid [29], melphalan [19], etc.

When inclusion is possible with various cyclodextrins, the best solubility or dissolution rate is obtained with the most soluble cyclodextrin (γ-cyclodextrin). However, if the stability constant of the inclusion (reflecting the good adjustment of the guest molecule to the host molecule cavity) is low, decomposition of the inclusion can occur in water solution leading to a reprecipitation of the guest product solubilized in excess [27].

- Improvement in bioavailability

When poor bioavailability is the consequence of low solubility and not of a low absorption rate, an increase in solubility can then solve this problem. In such a case, cyclodextrins are extremely valuable.

For solubility and dissolution rates, there are numerous examples of an increase in bioavailability after oral administration of an inclusion compound instead of the pure product [3,11]. One of the most representative is that concerned with digoxin and γ-cyclodextrin [30]: after oral administration of the inclusion (1:4) of digoxin in γ-cyclodextrin, the area under the plasma concentration curve obtained with the inclusion compound containing 50 μg of digoxin is higher than that obtained with 100 μg of pure digoxin. A decrease in the dose administered must be investigated.

Behaviour of inclusion compounds in the gastro-intestinal tract

In the same way that the formation of an inclusion compound in liquid medium is governed by an equilibrium reaction between host and gest molecules, when a preformed inclusion compound is placed in contact with water (gastro-intestinal

juices), it dissolves and decomposes following the equilibrium reaction: solid inclusion ⇔ dissolved inclusion ⇔ free cyclodextrin + free active ingredient.

This free active ingredient, which is generally hydrophobic, is presented in the molecular state to the lipoid mucosa of the gastro-intestinal tract, and is easily resorbed, resulting in a displacement of the previous equilibrium, and with the appearance of new free molecules of active ingredient.

If the stability constant of the inclusion compound that governs this equilibrium is high, then the dissociation is weak, and even if the solubility of the inclusion compound is high, the bioavailability of the active ingredient may remain very low, because there are very few free molecules of active ingredient available for resorption through the mucosa.

It is possible to increase the inclusion dissociation by administering concomitantly a competitive agent. This is the case for cinnarizine included in ß-cyclodextrin. Its plasma concentration is significantly improved by the concomitant administration of DL-phenylalanine [31]. However, it appears difficult to generalize this phenomenon to classic drug administration, because of the possible pharmacological and toxicological properties of the competitive agent used. In fact, in the intestinal tract, bile salts have the same competitive activity [5,6].

Despite this decomposition mechanism, and the ability for the free active ingredient to be resorbed alone, small amounts of inclusion compound can also be resorbed without any decomposition [6]. This means that it is necessary to know not only the pharmacokinetics and pharmacology of the pure active ingredient, but also those of the inclusion compound.

After emptying, the ß-cyclodextrin follows its intestinal transit, and is hydrolysed by α-amylases, and any possible bile salts present are released. It is not exactly the same for α-cyclodextrin, which is more resistant to hydrolysis, and which can be eliminated without degradation. Hence α-cyclodextrin keeps its inclusion potency throughout the gastro-intestinal tract, and is probably capable of including other components as well as bile salts.

CYCLODEXTRIN DERIVATIVES [32]

Water-soluble cyclodextrin derivatives

- Methyl cyclodextrins

Among the first water-soluble cyclodextrin derivatives are methyl cyclodextrins: dimethyl cyclodextrins, resulting from the selective methylation of all C2 secondary hydroxyls and all C6 primary hydroxyls, and trimethyl cyclodextrins, resulting from the methylation of all the hydroxyls (C2, C3 and C6). Their water solubility is much higher than that of the parent cyclodextrin, especially in the case of ß-cyclodextrin: 1·85, 57 and 31 g/100 ml at 25 °C for ß-cyclodextrin, dimethyl and trimethyl ß-cyclodextrin respectively. However, their solubility decreases with an increase in temperature [7,33].

Administered by the oral route, they behave like xenobiotics: they are resistant to bacterial hydrolases, and are eliminated by the fæces. In long-term administration, they can affect weight gain and lipid metabolism [7].

In parenteral administration, despite their potential pharmacotechnical interest [34], they unfortunately exhibit a higher hæmolytic effect than ß-cyclodextrin itself [7].

Their pharmaceutical utility thus appears to be more or less interesting, especially when compared with other water-soluble cyclodextrin derivatives.

- Hydroxypropyl cyclodextrins

The hydroxypropylation of cyclodextrins does not result in a selective substitution, as in the case of methylation: although the number of hydroxyls in a cyclodextrin molecule is constant, the hydroxyl reactivity type changes as the reaction proceeds, leading to a mixture of products with various degrees of substitution [35,36]. The concomitant existence of many types of hydroxypropyl cyclodextrin in the same reaction product explains the impossibility of crystallization and, consequently, the obtainment of amorphous compounds.

Hydroxypropyl cyclodextrins are highly water-soluble, not only as a result of their chemical nature, but also because of their amorphous structure. Their dissolution is endothermic, so there is no decrease in solubility with increasing temperature. Their water solubility at 25 °C is higher than 50 g/100 ml.

As with methyl cyclodextrins, hydroxypropyl cyclodextrins are not hydrolysed by the gastro-intestinal amylases. They are able to form complexes with bile salts, and long-term toxicity studies have shown an increase in their synthesis, responsible for liver enlargement [37].

The main interest of hydroxypropyl cyclodextrins lies in their parenteral administration, because they present a lower hæmolytic activity than the original cyclodextrin, dihydroxypropyl ß-cyclodextrins being less hæmolytic than the hydroxypropyl form, the hæmolytic activity decreasing with increasing degree of substitution [38]. They cause no irritation to the muscle, even at relatively high concentrations [38].

Hydroxypropyl ß-cyclodextrin is now readily available on the market.

- Hydroxyethyl cyclodextrins

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 [39]. They are highly water-soluble (more than 50 g/100 ml at 25 °C) [40].

They have a particularly low hæmolytic activity (lower than that of hydroxypropyl cyclodextrins) [37], and they seem to be even less irritating for the muscle than the latter [40].

- Branched cyclodextrins

Various branched cyclodextrins have been described, such as glucosyl, maltosyl and glucopyranosyl α- and ß-cyclodextrins, and diglucosyl, dimaltosyl and dipyranosyl ß-cyclodextrins [41,42,43,44,45]. All are more water-soluble than γ-

cyclodextrin, the most soluble being diglucosyl ß-cyclodextrin: 140 g/100 ml at 25 °C.

They are less hæmolytic than the parent cyclodextrin, the least hæmolytic branched ß-cyclodextrin being dimaltosyl ß-cyclodextrin [44].

Other cyclodextrin derivatives

- Ethyl cyclodextrins

Ethylation of cyclodextrins reduces their water solubility in proportion to the degree of substitution: $5{\cdot}0 \times 10^{-3}$ and $1{\cdot}8 \times 10^{-3}$ g/100 ml at 25 °C for diethyl and triethyl ß-cyclodextrins respectively [46].

Although this cyclodextrin derivative can be used to sustain the release of an active ingredient [46,47], many other well-known methods are commonly used in the pharmaceutical industry, with the same objective.

- Carboxymethyl ethyl cyclodextrins

Carboxymethyl ethyl ß-cyclodextrin is characterized by 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 [48].

The product is proposed for preferential drug release in the intestinal fluid with a very slight release in the gastric fluid [48].

- Cyclodextrin polymers

Cyclodextrin polymers are substances containing at least two cyclodextrin units. ß-cyclodextrin polymers with a 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 [49].

Polymers with high molecular weights can be used as tablet excipients: they have good disintegrating properties [50].

INCLUSION IN CYCLODEXTRIN DERIVATIVES

Inclusion compounds can be obtained with cyclodextrin derivatives in the same way as with natural cyclodextrins, and the only factor to be taken into account is the steric hindrance of the substituents which can sometimes reduce the cavity entrance.

Such inclusion compounds can modify the water solubility and bioavailability of the guest molecule, can improve its stability, and decrease side effects [32], as in the case of natural cyclodextrins. However, their great value compared with natural cyclodextrins lies in solubility modifications, either with respect to a decrease (ethyl cyclodextrins) or a very high increase. In the latter case, hydroxypropyl and hydroxyethyl cyclodextrins are particularly interesting, not only due to their amorphous character leading to highly water-soluble amorphous inclusions, but also because of their low parenteral toxicity [38,40]. In fact, a hydroxypropyl ß-cyclodextrin inclusion compound of an antimicotic drug is already announced by Janssen for next year [51].

CONCLUSION

Natural cyclodextrins, by their ability to include various kinds of active molecule, have already proved their value in pharmaceutical technology. Many derivatives have recently appeared. The most interesting seem to be the highly water-soluble forms: hydroxyethyl and hydroxypropyl, which also exhibit lower parenteral toxicity. The now reasonable price of hydroxypropyl ß-cyclodextrin will allow very fast development of this product on the pharmaceutical market.

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