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DEVELOPMENTS IN CYCLODEXTRIN APPLICATIONS IN DRUG FORMULATIONS

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ABSTRACT. With regard to recent developments in cyclodextrin (CD) applications in drug formulations, here will be described on the basis mainly of (a) novel preparative methods of CD inclusion complexes, (b) effects of CDs on bioavailability and disposion of drugs and (c) absorption enhancement by CD derivatives in transdermal application. (a) When inclusion complex of cinnarizine (CN) with β-CD was prepared by a spray-drying method, it was very stable under heating and highly humid conditions. (b-1) CDs gave influence on hypnotic potency and disposition of barbiturates in intravenous and intraperitoneal administrations. (b-2) The bioavailability of CN on oral administration of the complex, which was comparable with that of CN alone, was enhanced by simultaneous administration of competing agents, such as DL-phenylalanine. (c) When tolnaftate (TOL), antifungal drug, was administered percutaneously in the form of the complex with dimethyl-β-CD and water-soluble β-CD polymer, it was absorbed in the skin, and the concentration was kept high compared with the case of TOL alone.

1. INTRODUCTION

It may be said that recent developments in cyclodextrin (CD) applications in drug formulations are concerned with: stabilization; enhancement of solubility; novel preparative methods of inclusion complexes; enhancement of bioavailability; reduction of topical or hemolytic side effects on administration; absorption enhancement in transdermal application.

As it is well known, the advantage of using CDs mainly comes from the inclusion complex formation.

When it is considered to use some excipients in pharmaceutical preparations, the safety of the materials upon the administration should be guaranteed. Regarding this point, CDs are confirmed to have no problem (1-3). At the present, α- and β-CD are included in Japanese Standards for Ingredients of Drugs, a kind of Japanese national formulary.

β-CD is the most practical to use, but its complexes are usually slightly soluble. Therefore, various derivatives of CDs are under development (4-6). Alkylation of hydroxyl function of CDs has resulted in an enhanced water-solubility and these derivative have been found to be effective in binding guest molecules. An application of water-soluble CD polymers to pharmaceutical preparations is under investigation (7). Anyway, it may take a time to guarantee the safety upon the administration of the derivatives which are not yet officially registered, and thus it takes time to get some products of these derivative on the market.

Already in Japan, there are commercial products of prostaglandins with α- and β-CD on market which have been developed by Ono Pharmaceutical Company (8). Therefore, CDs often play a very important role in materializing new drugs.

From the methodological point of view to a development of CD application in pharmaceutical formulation, the way of approach seems to have been almost established. For example, in stablization or solubilization, usually the effect of the addition of CDs is examined first, and then a further investigation and evaluation of the preparation is done in comparison with the preparations without CDs or with the existing formulations.

Here will be described some new approaches to CD applications in pharmaceutical formulations on the basis of our recent trials. They are concerned with (a) preparative methods of CD inclusion complexes (9); (b) effects of CDs on bioavailability and drug disposition (10); and (c) absorption enhancement by CD derivatives in transdermal application (11).

2. SPRAY-DRYING METHOD TO PREPARE CD INCLUSION COMPLEXES

2.1. Preparative Methods of CD Inclusion Complexs in Solid State

Most common preparative methods of includion complexes in solid state are a coprecipitation method based on phase solubility, and kneading. However, these methods may be suitable in preparation of the complexes in laboratory scale, but not in manufacturing scale. The present situation that the materialized products of CD complexes are not so many may be partly due to a difficulty in preparation of them in manufacturing scale.

More than ten years ago, when it was at the early stage of CD applications in pharmaceutical formulations in Japan, the authors developed a preparative method of inclusion complexes by freeze-drying (12). Recently, the authors tried to develop a spray-drying method to prepare the inclusion complex, because spray-drying method generally can be extended to production on a large scale (9).

2.2. Inclusion Complex of Cinnarizine (CN) with β-CD by Spray-drying Method

CN is widely used orally for a treatment of cerebral diseases. It is physico-chemically a weak base and its solubility in water is very poor, and its bioavailability is variable depending on the products and the condition of administration. Clinically, preparations of CN are usually administered to old patients. Many of these patients are in achlorhydria or anacidity. Therefore, it is necessary to develop a preparation of CN which dissolves well. In a series, the authors confirmed the inclusion complex formation of CN with β-CD (11).

The process of the spray-drying method was: the solution, in which CN was dissolved at pH 11.00 with 1 N NaoH, was made pH 7.0 with 1 N HCl, and then spray-dried.

In comparison with this method, usual coprecipitation methods take 7 days to obtain the product. Moreover, the filtration process is necessary. There is, therefore, a difficulty in preparing the preparation on a large scale. The spray-drying method gives a good yield in a short time and may be suitable for an extension to a manufacturing scale. Between the preparations by coprecipitation and spray-drying, there was no remarkable difference in powder X-ray patterns and dissolution behavior.

Concerning the stability of CN, it was confirmed that no degradation took place in the process in the spray-drying method. CN is rather stabilized with β-CD. When the preparations were examined under heating and high humid conditions, they were found to be quite stable. The dissolution rate of the samples stored under high humid conditions was rapid compared with the initial value. This result may be due to the increase of the water content in the sample, as it gives no serious problem in final formulation design, but rather favorable.

As a result, it may be possible that a spray-drying method affords a promising means for preparations of solid inclusion complexes on a manufacturing scale, if the drug is fitting to this method.

3. INFLUENCE OF CD ON HYPNOTIC POTENCY AND DISPOSITION OF BARBITURATES IN INTRAVENOUS AND INTRAPERITONEAL ADMINISTRATIONS

3.1. Complex Formation of Barbiturates with CDs

Barbiturates are known to form stable inclusion complexes with CDs in aqueous solution. When the stability constants of inclusion complexes of hexobarbital (HBA), thiopental (TPA) and pentobarbital (PBA) with CDs were determined, those with β-CD were the largest, then with γ-CD next, and with α-CD the smallest for these three drugs (10a).

3.2. Effect on Sleeping Time in Intravenous Administration in Mice

In the dose of equimolar/kg, the sleeping time was significantly shorter in administration of drugs with β-CD, γ-CD and α-CD in the order of the stability constant than the respective drugs alone, while there was no difference between the cases with Pullulan and dextran

and that of HBA (10a), as shown in Table I.

Table I. Effect of Additives on Sleeping Time of HBA, TPA and PBA in Mice after Intravenous Administration

Additives	Sleeping time (min)		
	HBA	TPA	PBA
None	13.88 ± 1.43	24.67 ± 2.16	44.05 ± 4.40
α-CD	5.05 ± 0.82	19.57 ± 2.33	39.29 ± 3.01
β-CD	2.60 ± 0.33	14.97 ± 1.08	26.00 ± 3.70
γ-CD	4.68 ± 0.63	25.25 ± 2.57	28.22 ± 3.60
PUL	14.15 ± 1.62	14.81 ± 2.55	45.15 ± 4.85
DEX	12.00 ± 1.25	17.08 ± 2.12	40.02 ± 2.03

Each value represents the mean ± S.E. of more than 7 determinations.

Regarding the effect of concentration of the additives on sleeping time of HBA after intravenous administration in mice, a linear relationship was found between the sleeping time in logarithmic scale and the molar ratio of additives to HBA. The sleeping time decreased with an increase in concentration of CDs, and was almost constant for the cases of Pulluran and dextran.

3.3. Effect on Sleeping Lag in Intraperitoneal Administration in Mice

In the case of intraperitoneal administration, it was possible to determine the sleeping lag of barbiturates, though it was impossible in intravenous one because the onset of the effect was so rapid.

As shown in Figure 1 (10b), the sleeping lag was significantly larger in the presence of β-CD than that of corresponding drugs alone. On the other hand, the sleeping time was significantly shorter in the presence of β-CD than that of corresponding drugs alone, as it was similar to the case of intravenous administration.

The difference in hypnotic potency between the two routes of administration might come from the reason that barbiturates and CDs, which were administered intraperitoneally, were not rapidly diluted by systemic circulation and also had to take a process of the penetration into the vein.

Therefore, in general it is possible that CDs give influence on the permeation of drugs. This situation gets predominant in the case of injections.

In case of oral administration, the enhancement of dissolution

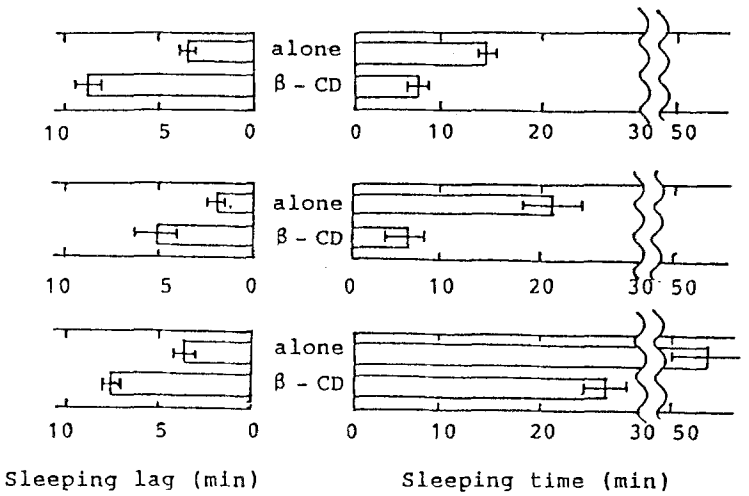

Figure 1. Effect of β-CD on Sleeping Lag (left) and Sleeping Time (right) of HBA (top), TPA (middle) and PBA (bottom) in Mice after Intraperitoneal Administration.
Drug (215.3/kg) with and without β-CD (215.3μmol/kg) was simaultaneously administered to mice.
Each bar represents the mean ± s.e. of more than 5 determinations.

rate of drugs by complex formation with CDs overcomes the inhibitory effect of the complex formation on the permeation of drug molecules, if the stability constant is not so high. However, in such a case as CN with β-CD which will be described next, the inhibitory effect of the complex formation on the permeation through intestinal membrane may not be negligible.

4. ENHANCEMENT OF BIOAVAILABILITY OF β-CD COMPLEX ON ORAL ADMINISTRATION WITH A COMPETING AGENT.

4.1. Complex Formation of CN with β-CD and Its Effect on the Bioavailability

As mentioned already, the inclusion complex formation of CN with β-CD was confirmed by the solubility method, X-ray diffractometry and IR spectrophotometry. Then, it was found that the dissolution rate of CN was enhanced 30 time or more by the complex formation with β-CD compared with that of intact CN at pH 5.0, while the bioavailability of CN in beagle dogs was not enhanced in oral administration of the inclusion complex.

Usually, an inclusion complex formation of a drug with β-CD brings about an enhancement of solubility, dissolution rate of the drug, and as the result, the bioavailability is enhanced. However,

the bioavailability is not always enhanced. The absorption rate through membrane itself may generally be lowered by the complex formation, because only free drug molecules can be absorbed. Therefore, if the stability constant is large, the complex formation is not so effective in an enhancement of the bioavailability. The inclusion complex of CN with β-CD may be an example of this case.

The stability constant of the inclusion complex of CN with β-CD which was determined by the solubility method was 6,200/Mol (13). This is a very large one, as in many cases it is of the order of 100/Mol. Therefore, the fact that there was no enhancement of bioavailability of CN by the complex formation with β-CD was due to this large stability constant of the complex.

4.2. Process of Drug Absorption from the Complex and Role of the Competing Agent

Th authors attempted to enhance the bioavailability of CN by administering its β-CD complex together with another compound which competes with the β-CD in complex formation in aqueous solution, as this additive is called competing agent (10d).

As shown in Figure 2, in the case of the complex alone, the

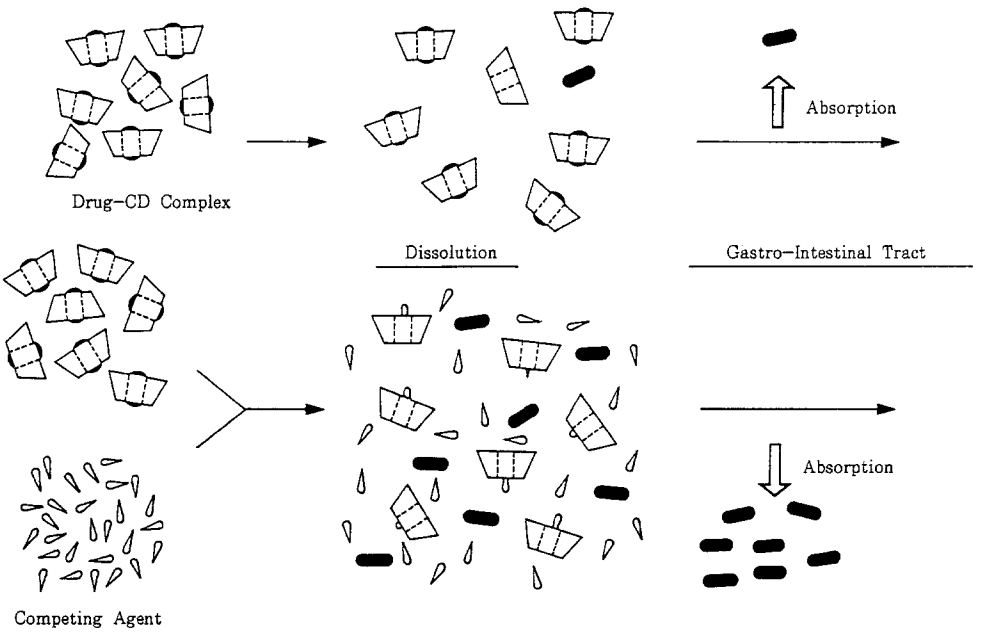

Figure 2. Process of Drug Absorption from Cyclodextrin Complex and Role of a Competing Agent

concentration of free drug is not high. On the other hand, when the complex is administered together with the competing agent, both the complex and the competing agent dissolve, and the concentration of

free drug that is available for absorption may increase.

As the competing agent, DL-phenylalanine was chosen, because it has been reported that L-phenylalanine forms an inclusion complex with β-CD with a stability constant of 1000/Mol. Moreover, DL-phenylalanine seems to be a pharmaceutically acceptable excipient.

The plasma level-time curves in comparison between CN alone and its combination with DL-phenylalanine showed that DL-phenylalanine does not act as an absorption promoter to CN directly, while those in comparison between the complex alone and its combination with DL-phenylalanine showed that the administration of the complex with DL-phenylalanine brings about a clear increase in plasma level and AUC. Therefore, it can be said that DL-phenylalanine acts as the competing agent.

4.2. Enhancement of Bioavailability of CN with an Increase of the Amount of DL-Phenylalanine as the Competing Agent

The bioavailability parameters in the combination of the complex with DL-Phenylalanine, C_{max} and AUC, increased with the dose of DL-phenylalanine. There was observed no change in T_{max} in the simultaneous administration with DL-phenylalanine, though the reason is not clear because a bioavailability phenomenon is a quite complicated one.

When C_{max} and AUC were plotted against the dose of DL-phenylalanine, there was a linear relationship between C_{max} and the dose. On the other hand, AUC increased hyperbolically with the dose of DL-phenylalanine. It may be difficult to explain the difference in profile between C_{max} and AUC. Anyway, it can be said that the increase in the concentration of free CN by the competing agent enhanced C_{max} and AUC.

4.3. Evaluation of Competing Effect by In Vitro Method

In order to investigate the effect of the competing agent on the in vitro membrane permeability of CN, the apparent penetration rate constant was determined using a Sartorious Absorption Simulator (10d). The experiment was done also in comparison with L-isoleucine and L-leucine.

As shown in Figure 3, the penetration rate of CN decreased with the addition of β-CD (No. 3). This may be due to a decrease in the concentration of free drug by the inclusion complex formation with β-CD. When DL-phenylalanine was added, the penetration rate constant was restored (No. 5). This means an increase in free drug concentration by the competing action of DL-phenylalanine. DL-phenylalanine did not affect the penetration rate of CN in the case without β-CD (No. 2).

When L-leucine and L-isoleucine were added, the penetration rate constant was restored (No. 6 and 7, respectively). Therefore, L-leucine and L-isoleucine also have some competing action, and L-isoleucine is stronger than L-leucine with respect to this activity.

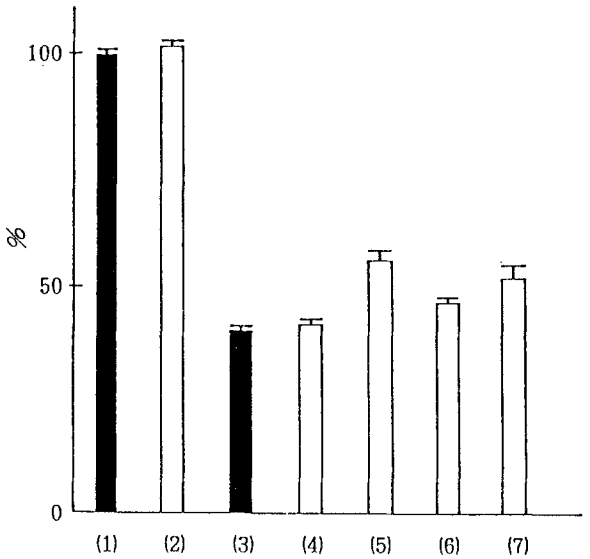

Figure 3. Apparent Penetration Rate Constant of CN from the Solutions containing the Additives in Comaparison with that of CN alone (%)

(1) CN alone (200mg); (2) CN (200mg) + DL-Phe;
(3) CN (200mg) + βCD (1232mg);
(4) CN (200mg) + βCD (1232mg) + DL-Phe (897mg)
(5) CN (200mg) + βCD (1232mg) + DL-Phe (1424mg)
(6) CN (200mg) + βCD (1232mg) + L-Leu (1424mg)
(7) CN (200mg) + βCD (1232mg) + L-Ile (1424mg)

4.4. Competing Effect of L-Isoleucine

As L-isoleucine showed a competing effect with β-CD in in vitro penetration study in Figure 3, it was examined in absorption study in beagle dogs (10e). C_{max} increased linearly with the dose of L-isoleucine in the combination of the complex L-isoleucine. AUC also increased in a similar way.

5. ABSORPTION ENHANCEMENT IN PERCUTANEOUS ADMINISTRATION OF DRUGS

5.1. Effects of CDs on Skin Barrier

In the pharmaceutical field, development of transdermal therapeutic systems (TTS) is booming, and thus skin has become a matter of interest because of its potency as the route of systemic administration. However, skin is essentially a barrier against

penetration and permeation of external substances including drugs. One of the available method to improve the transdermal absorption of drugs is to reduce this barrier function of skin by the aid of enhancers.

Sezaki and his group (14) investigated the effects of β-CD and di-O-methyl-β-CD on percutaneous penetration of butylparaben, indomethacin and sulfanilic acid through the skin obtained from a guinea pig, and gave a proposal as: the complex of drug with CD does slightly penetrate the skin; the drug penetration is decreased as a consequence of the decrease of the free drug fraction by the complex formation with CD; CD enhances the percutaneous penetration of hydrophilic molecule, such as salicylic acid, by varying the skin barrier function; the effect of cyclodextrin on the percutaneous drug absorption can be regulated to some extent by means of its chemical modification such as methylation. Here, the effect of CDs on the skin barrier may be most important in absorption enhancement and it seems to be related to extraction of its components, such as cholesterol and triglyceride, by the complex formation.

5.2. Effects of Dimethyl-β-CD and Water-Soluble β-CD Polymer on Percutaneous Absorption of Tolnaftate

Tolnaftate (TOL) is an antifungal drug and is one of the practically insoluble drugs. Actually, this substance results in a poor percutaneous absorption, and so it is worth trying to enhance the topical bioavailability.

As an *in vitro* result, the solubility of TOL increased with an increase of dimethyl-β-CD (11). There was a difference in x-ray diffraction pattern between the coprecipitate and the physical mixture of TOL with dimethyl-β-CD. The thermogram by differential scanning calorimetry also gave a similar result. Dissolution profile of the coprecipitate was also different from the physical mixture.

The powder preparations for external use of TOL alone, the physical mixture and the coprecipitate mentioned above were applied to the shaved back of mice in the form of slurry, and the plasma and skin concentrations were determined by HPLC method.

As the result, the skin concentration of TOL was the highest in the case of coprecipitate with dimethyl-β-CD. The physical mixture also gave a high skin concentration compared with TOL alone.

When water-soluble β-CD polymer for the percutaneous absorption of TOL, in the same way as the above case of dimethyl-β-CD. The complex formation of drugs with this CD polymer will be published (7). The skin concentration of TOL was the highest in the case of coprecipitate. The physical mixture also gave a high skin concentration compared with TOL alone. Additionally, when the plasma concentration of TOL was determine, the tendency was similar to the skin concentration.

These results suggested that the powder dosage form composed of the coprecipitate of TOL with dimethyl-β-CD or water-soluble cyclodextrin polymer may afford a useful means for percutaneous absorption of drugs.

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