PROSTAGLANDINS AND THEIR CYCLODEXTRIN COMPLEXES

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ABSTRACT. Generally, prostaglandins (PG) are unstable and insoluble in water, though they exhibit strong biological activities in minute amount. The most difficult problem in developing PG preparations is how to stabilize and solubilize PG without loss of their activities. We have successfully developed the pharmaceutical preparations contaning PG complexes with cyclodextrins (CD). These preparations are already on the market, namely $PGE_2 \cdot \beta$-CD Tablet and $PGE_1 \cdot \alpha$-CD Injection. Moreover, PG and PGI_2 derivatives are now under development as a form of CD complex.

1. INTRODUCTION

In 1960, prostaglandin (PG) was purified and the structure was also identified by Bergström and his co-workers [1]. After this discovery, many biochemists have clarified its biological mechanism in human body. In the field of organic chemistry, PG was totally synthesized by Corey et al. in 1969 [2]. Thereafter, a variety of PG derivatives have been synthesized by many chemists. Recently, as the PG biosynthesis map became clear, the target of study has changed to thromboxane (TX), prostacycline (PGI_2), leukotriene, and also to the antagonist and enzyme inhibitor (Fig. 1). As shown in Fig. 1, the biochemical study has advanced rapidly. In the pharmaceutical field, however, the main study is focused on the formulation of PG derivatives and it has just been started to develop the formulation of PGI_2 derivatives, TX synthetase inhibitor and TX antagonist. This paper is mainly concerned with the usefulness of cyclodextrin (CD) in pharmaceutical preparations of some PG derivatives (Fig. 2).

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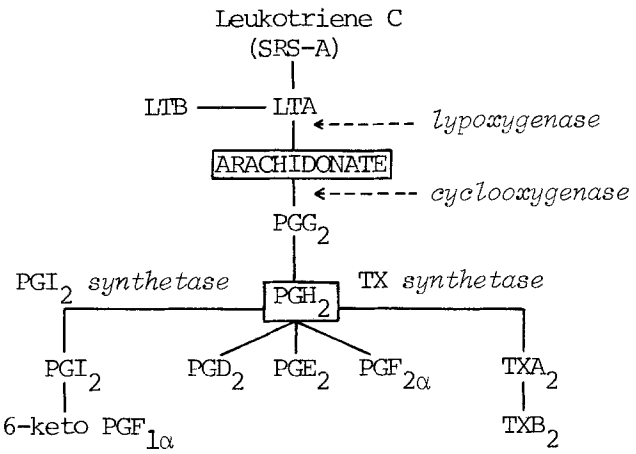

Figure 1. Arachidonate Cascade

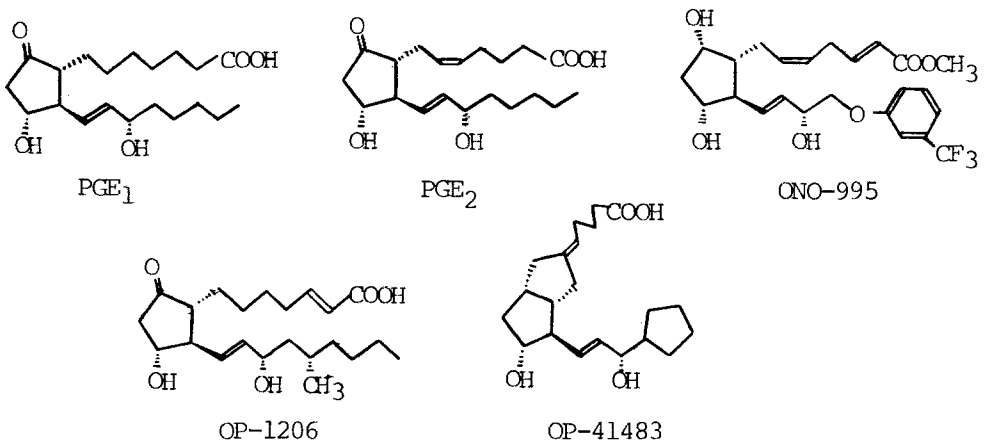

Figure 2. Chemical Structures of Prostaglandins and Their Derivatives

2. PROSTAGLANDIN-CYCLODEXTRIN COMPLEXES

The PG-CD preparations developed so far are $PGE_2 \cdot \beta$-CD Tablet and $PGE_1 \cdot \alpha$-CD Injection, and PG and PGI_2 derivatives are now under development in the form of CD complex, as shown in Table I.

The most difficult problem in developing PG preparations is how to stabilize and solubilize the PG without loss of biological activity. The PG chemicals are changed in their physicochemical properties by CD complexation. The improved properties are as follows.

1. Stability and solubility
2. Content-uniformity in formulation and ease of handling by powderlization

2.1. Stabilization and Solubilization

Stability and solubility of PG were greatly improved by using CD (Table II). As is apparent in Table II, the PG-CD complexes are remarkably stabilized and can be manufactured as pharmaceutical products [3, 4, 5].

2.2. Content-Uniformity and Powderlization

Since the PG activity is very high and most patients receive a single unit dose, PG preparations should be carefully designed from the viewpoints of the content-uniformity. The usual method to distribute the active ingredient in excipients is as follows.

1. Dissolve in water or organic solvents
2. Mix or disperse well in excipients

However, when the amount of active ingredient is very small and chemically unstable, the usual method cannot be employed, and the only method to improve the content-uniformity in dosage form is the increase in drug amount. As the result of PG-CD complexation, the amount of active ingredient increases enabling easy to adjust the content-uniformity, and also improve the low melting point problem by powderlization of PG. Thus, the development of the PG dosage forms as a CD complex in a manufacturing scale can be achieved.

2.3. The Other Problems

Since one of the rate controlling factors of PG absorption is known to be the dissolution rate, the PG-CD complex is equilibrated in water as PG + CD $\rightleftharpoons$ PG-CD complex. When PG is administrated and absorbed in the human, the equilibrium will be shifted to the increase in free PG. Thus, immediately after administration of PG-CD complex, the PG concentration in blood reaches a peak and then decreases rapidly. PG in the CD complex usually exists as a monomolecular form at the absorption site, which may also consequently provide a great bioavailability. In such a situation, however, it is necessary to consider the side effect occurring due to the rapid absorption of PG.

Taking account of these factors, we have throughly selected the final dosage form, in particular for the objective disease.

TABLE I PG-CD Preparations

PG-CD	Content/Dosage Form	Objectives
PGE_2·β-CD	500μg/Tab.	Induction of labor
PGE_1·α-CD	20μg/Amp.	Buerger's disease Raynaud's disease
*ONO-995·β-CD	100μg/Tab.	Neurogenic bladder
*OP-41483·α-CD	100, 200μg/Tab. 20, 100μg/Amp.	Anti-thrombosis
*OP-1206·α-CD	5μg/Tab. 2.5μg/Tab.	Peripheral vascular disease

*under development

TABLE II Stability and Solubility of PGE and PGE -CD Complexes

Drugs	Stability for 30 days at 40°C	Solubility in water at 25°C
PGE_2	10 %	0.7 mg/ml
PGE_2·β-CD	90 %	3 mg/ml
PGE_1	15 %	0.1 mg/ml
PGE_1·α-CD	95 %	5 mg/ml

3. SOME EVIDENCE OF INCLUSION COMPLEXATION

The inclusion complex formation of various PG with CD in aqueous solution and in solid state have been reported [6-10]. This contribution is intended to describe briefly the ONO-802-CD complexation, as an example.

Figure 3 shows the equilibrium phase solubility diagrams obtained for ONO-802 with β- and γ-CD in water. The plots show the typical Bs-type solubility curves [11]. The initial rising portion is followed by plateau region and then decrease in total concentration of ONO-802 with precipitation of the complexes was observed. These powders corresponded to 1:2 ONO-802-CD complexes [12]. Figure 4 shows the powder X-ray diffraction patterns of β-CD , γ-CD and their ONO-802 complexes. The diffraction patterns of complexes were apparently different from those of CD, indicating the constitution of a new solid phase. When the diffraction patterns of the complexes were indexed on the basis of a two-dimensional hexagonal unit cell [13], the calculated d-spacings were in excellent agreement with those observed (Table III). This suggests that ONO-802 is included within the CD cavities to give a channel type structure.

The dissolution rate and chemical stability of these CD complexes were found to be significantly superior to ONO-802 itself [14]. Furthermore, the crystallinity of the complex facilitates the pharmaceutical formulation, which is difficult with uncomplexed ONO-802 because it occurs as a viscus oil. These results indicate that the CD complex have great utility to improve the pharmaceutical properties of PG.

4. FUTURE ASPECTS

Although PG-CD complex has very interesting properties, PG is biosynthesized where it is needed, and is used in the same organ or tissue. This means that dosage form and administration route should be designed as specific as possible to particular disease. In other words, a different dosage form should be designed depending upon the therapeutic purpose. We are now dedicating ourselves for the development of new dosage forms which may be able to be targetted such as chemically modified CD and liposome. Furthermore, to minimize the side effect, the development of pro-drug and transdermal systems are now under way. The above concept is also applicable to future novel compounds such as PGI_2 derivatives, TX-antagonist, TX-inhibitor, lipoxygenase inhibitor, and SRS-antagonist etc.

We believe that the formulation design will be the key issue for the future development of clinically acceptable dosage forms, and we are trying to contribute to the materialization of the monument in our Research Institute reading "Dedicated to man's fight against desease and pain".

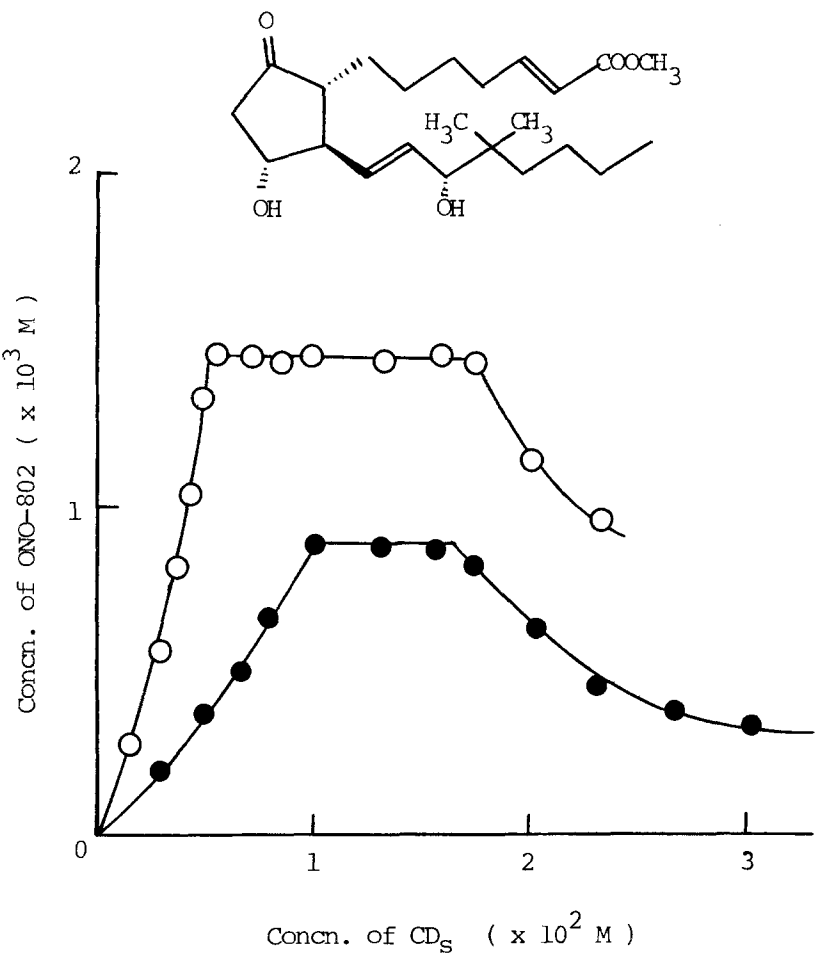

Figure 3. Phase Solubility Diagrams of ONO-802-CD Systems in water at 25°

Key ; ○, β-CD ; ●, γ-CD

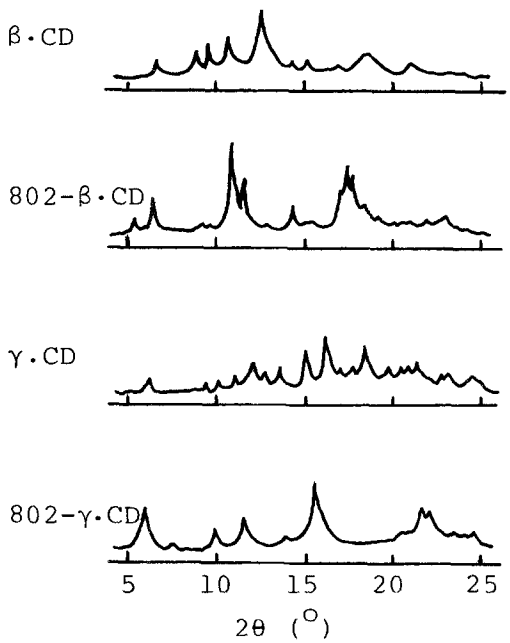

Figure 4. Powder X-Ray Diffraction Patterns of 802-β·CD and 802-γ·CD Systems

TABLE III X-Ray Diffraction Data for 802-β·CD and 802-γ·CD Complexes

Complex	hkl[a]	d(Å) Obs.	d(Å) Calcd.[b]
802-β·CD	200	13.39	13.39
	220	7.76	7.73
	420	5.05	5.05
802-γ·CD	200	14.98	14.98
	220	8.65	8.63
	400	7.49	7.53
	420	5.66	5.65
	620	4.15	4.13

a) Hexagonal indicies.

b) Calculated on the basis of the hexagonal unit cells with a=b=30.92 Å for 802-β·CD complex and a=b=34.59 Å for 802-γ·CD complex.

REFERENCES

1. S. Bergström and J. Sjövall, Acta Chem. Scand. 14, 1693 (1960).
2. E.J. Corey, I. Vlattas and K. Harding, J. Am.Chem. Soc. 91, 535 (1969).
3. Ono Pharmaceutical Co. Jap. Pat. 790979 (1975).
4. Ono Pharmaceutical Co. Jap. Pat. 1007787 (1980).
5. Ono Pharmaceutical Co. Jap. Kokai 54-103844 (1979).
6. K. Uekama, F. Hirayama, K. Ikeda, and K. Inaba, J. Pharm. Sci. 66, 706-711 (1977).
7. K. Uekama and F. Hirayama, Chem. Pharm. Bull. 26, 1195-1200 (1978).
8. K. Uekama, F. Hirayama, T. Wakuda, and M. Otagiri, Chem. Pharm. Bull. 29, 213-219 (1981).
9. K. Uekama, F. Hirayama, A. Fujise, M. Otagiri, K. Inaba, and H. Saito, J. Pharm. Sci. 73, 382-384 (1984).
10. K. Uekama, A. Fujise, F. Hirayama, M. Otagiri, and K. Inaba, Chem. Pharm. Bull. 32, 275-279 (1984).
11. T. Higuchi and K.A. Connors, Adv. Anal. Chem. Instr. 4, 117-212 (1965).
12. F. Hirayama, M. Otagiri, K. Uekama, and K. Inaba, Kobunshi Ronbunshu 39, 643-648 (1982).
13. K. Takeo and T. Kuge, Agr. Biol. Chem. 34, 1787-1795 (1970).
14. K. Uekama, F. Hirayama, Y. Yamada, K. Inaba, and K. Ikeda, J. Pharm. Sci. 68, 1059-1060 (1979).