Stabilizing Effect of β-Cyclodextrin on Limaprost, a PGE<sub>1</sub> Derivative, in Limaprost Alfadex Tablets (Opalmon®) in Highly Humid Conditions

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Stabilization against humidity of Limaprost (a prostaglandin E<sub>1</sub> derivative), which is currently marketed as Opalmon®, was undertaken using β-cyclodextrin (β-CD). Aqueous solutions of Limaprost alfadex/dextran 40 were lyophilized with and without β-CD. Limaprost alfadex lyophilized with β-CD was more chemically stable in humid conditions than that without β-CD. Moreover, the addition of β-CD as an excipient to tablets of these lyophilized composites remarkably improved the stability of Limaprost, and Limaprost in this moisture-resistant formulation was chemically stable for 19 weeks at 30°C, 75% relative humidity (R.H.). Chemical analysis of Limaprost and its degradation products indicated that degradation proceeded in the inclusion form (i.e., within the CD cavity). Solid <sup>2</sup>H-NMR spectroscopic studies showed that β-CD constrained the molecular mobility of water in the solid state. These results suggested that the stabilization of Limaprost by β-CD was at least partly due to the restricted molecular mobility of water, which acted as a catalytic species for the degradation, and also to the protection of the five-membered ring of Limaprost from water catalytic dehydration through inclusion complex formation with β-CD.

Key words Limaprost alfadex; stability; β-cyclodextrin; Opalmon®; lyophilized composite; <sup>2</sup>H-NMR

To facilitate oral dosing and prevent overdosing,1–6) hospitals and pharmacies have recently adopted one-dose packaging, which involves placing tablets or capsules into small polyethylene or glassine paper bags. One-dose packaging is common when patients are prescribed an oral medication for short-term use (e.g., a few days to months), especially if the dosage varies during treatment. However, tablets or capsules must be removed from their original packaging material (e.g., a blister package) to prepare individual doses. Consequently, drugs with a poor chemical stability, especially those susceptible to environment conditions such as humidity, must be handled with care. A substantial challenge to pharmaceutical scientists is to improve the chemical stability of drugs.

Prostaglandin (PG) and its derivatives are well known for their poor stability against temperature and humidity.7–10) Limaprost alfadex is an inclusion complex of Limaprost, which is a prostaglandin E<sub>1</sub> derivative, and α-cyclodextrin (α-CD).11–13) Tablets containing Limaprost alfadex are stable for three or more years at room temperature in a blister with an aluminum bag package containing a desiccant (airtight conditions). However, tablets without a blister package in high humidity degrade, yielding mainly 17S,20-dimethyl-trans-Δ<sub>2</sub>-PGA<sub>1</sub> (11-deoxy-Δ<sub>10</sub>).14) We have investigated the effect of several saccharides, maltose, trehalose, mannitol and dextran, on the stability of Limaprost alfadex.15) However, maltose, trehalose and mannitol had no stabilizing effect under high humidity conditions, whereas dextran suppressed the degradation, i.e., the appearances of 11-deoxy-Δ<sub>10</sub> after stored at 25°C, 75% relative humidity (R.H.) for two weeks were 3.4, 3.7, 5.5, 17.7 and 1.2% for Limaprost alfadex alone and its composites with maltose, trehalose, mannitol and dextran, respectively. Trehalose did not improve the chemical stability of Limaprost, probably because trehalose is reported to stabilize mainly thermal degradations,16–21) but not water-catalyzed degradations, and its stabilizing ability decreases under higher humidity conditions, as demonstrated in the insulin/trehalose system.22) On the other hand, dextran improved the stability of Limaprost alfadex,23–27) which is utilized for the new formulation of Opalmon® tablets since 2006. The product specification for purity of this formulation is maintained for two months at 25°C, 75% R.H., but at a higher humidity (30°C, 75% R.H.), the specification is maintained for only one month.28) This has prompted us to further improve the formulation of Opalmon® tablets against high humidity.

In this study, we investigated the effect of β-CD on the stability of Limaprost alfadex in tablets stored in high humidity. Limaprost can be stabilized for three or more months in highly humid conditions such as 30°C, 75% R.H. by lyophilizing Limaprost alfadex with β-CD and formulating with β-CD as a tableting excipient. Water molecules are known to affect the stability of active pharmaceutical ingredients in drug products.29–30) The stabilizing mechanism of β-CD was qualitatively discussed from the viewpoints of the inclusion effect of β-CD and the molecular mobility of water in the excipients.

Experimental

Materials Limaprost alfadex is specified in the Japanese Pharmacopoeia (JP) XVI. All excipients used in this study were purchased in accordance with the specifications of JP XVI or Japanese Pharmaceutical Excipients. Deionized double-distilled water was used. All other chemicals and solvents were analytical reagent grade.

Preparation of Lyophilized Composites Containing β-CD Limaprost alfadex and dextran 40 or β-CD were dissolved in purified water, filled into glass vials, and lyophilized. Triomaster (Kyowa Vacuum Engineering Ltd., Japan) was used for lyophilization. Table 1 lists the formulations of the lyophilized composites. The composition amount of Limaprost alfadex
Table 1. Formulations of Lyophilized Composites with or without β-CD

| Additive          | Lyophilized composite without β-CD (mg) | Lyophilized composite with β-CD (mg) |
|-------------------|----------------------------------------|-------------------------------------|
| Limaprost alfadex | 50                                     | 50                                  |
| Dextran 40        | 350                                    | 50                                  |
| β-CD              |                                        | 50                                  |
| Purified water    | 1875                                   | 1875                                |
| Total             | 400                                    | 150                                 |

and dextran 40 in the lyophilized composite without β-CD is same as that of commercially available Opalmon® tablet.

Preparation of Limaprost Alfadex Tablets Containing β-CD Lyophilized composites were sieved, blended with β-CD and magnesium stearate as tableting excipients, and tableted by the direct compression method, and the resulting tablets were dried. The control formulation was blended with lactose hydrate instead of β-CD as the tablet diluents. Tablets were prepared using VELA (Kikusui Seisakusyo Ltd., Japan) with 6.5 mm punches and dies under about 1000 kg in the main compression pressure, and dried with a vacuum drier with 6.5 mm

Assays of Limaprost and 11-Deoxy-Δ10 in the Lyophilized Composites Lyophilized composites with different formulations were stored at 30°C, 75% R.H., and the contents of Limaprost and 11-deoxy-Δ10 were sampled weekly for eight weeks by HPLC. Additionally, the contents of Limaprost and 11-deoxy-Δ10 in the free and inclusion forms were separately analyzed using the following procedure. A lyophilized composite (80 mg) was vigorously suspended in an ethyl acetate solution (2.0 mL) to extract the free-forms of Limaprost and 11-deoxy-Δ10. After centrifuging, the supernatant was fractionated, desiccated, and redissolved in ethanol (1.0 mL). Then the contents of Limaprost and 11-deoxy-Δ10 were analyzed by HPLC. These values were treated as the free-form contents. The residue remaining after centrifuging was dried, dissolved in 40% ethanol (5.0 mL), and the Limaprost and 11-deoxy-Δ10 contents were analyzed by HPLC. These values were treated as the inclusion-form contents. The free-form contents (%) of Limaprost and 11-deoxy-Δ10 in the lyophilized composite were calculated according to Eqs. 1–4.

$$\text{free-form content (%) } = \frac{(a + b)}{(a + b + c + d)} \times 100 \quad (1)$$

$$\text{total 11-deoxy-Δ10 content (%) } = \frac{(b + d)}{(a + b + c + d)} \times 100 \quad (2)$$

$$\text{free-form content of 11-deoxy-Δ10 (%) } = \frac{b}{(a + b + c + d)} \times 100 \quad (3)$$

$$\text{inclusion-form content of 11-deoxy-Δ10 (%) } = \frac{d}{(a + b + c + d)} \times 100 \quad (4)$$

$a$, content of Limaprost in the free-form (Limaprost (μg) extracted by ethyl acetate); $b$, content of 11-deoxy-Δ10 in the free-form (11-deoxy-Δ10 (μg) extracted by ethyl acetate); $c$, content of Limaprost in the inclusion form (Limaprost (μg) obtained from the remaining residue after extraction); $d$, content of 11-deoxy-Δ10 in the inclusion form (11-deoxy-Δ10 (μg) obtained from the remaining residue after extraction).

HPLC conditions: Samples (100 μL) were assayed using a Prominence UFLC system (Shimadzu Corporation, Japan) with 4.6 mmφ, 15 cm length, octadecyl silica (ODS) Column at 215 nm in UV. The mobile phase was 0.02 M KH2PO4 (pH 4.2): MeCN: Propanol with a volume ratio of 9:5:2 and a flow rate of 1 mL/min. No remarkable degraded products, except 11-deoxy-Δ10, were detected in this study.

Measurements of Some Physicochemical Properties Lyophilized composites and tablets with different formulations were stored at 30°C, 75% R.H. Changes in the appearance, moisture content and crystallinity for each samples during storage were monitored for 8 weeks. To evaluate the appearance, scanning electron microscope (SEM) observations were carried out with a Hitachi TM-3000 (Tokyo, Japan). Moisture content was calculated by weight changes of the sample, according to Eq. 5.

$$\text{moisture content (weight change %) } = \frac{\text{(sample weight} - \text{initial weight)}}{\text{initial weight}} \times 100 \quad (5)$$

The crystallinity of samples were investigated by powder X-ray diffractometry (Rigaku-RINT Ultima®, Tokyo, Japan) under the following conditions: Ni-filtered Cu-Kα radiation (1.542 Å), 40 kV, 40 mA, divergent slit of 1.74 mm (1°), scanning slit of 0.94 mm (1°), receiving slit of 0.15 mm, and goniometer angular increment of 5°/min.

Assays of Limaprost and 11-Deoxy-Δ10 in Limaprost Alfadex Tablets Limaprost alfadex tablets containing β-CD as diluents were stored at 30°C, 75% R.H. and sampled weekly for 8 weeks. The contents of Limaprost and 11-deoxy-Δ10 in the tablets were analyzed via the method described above. To extract the free-forms of Limaprost and 11-deoxy-Δ10, 33 tablets were pulverized and vigorously suspended in an ethyl acetate solution (10 mL). After centrifuging, the supernatant was fractionated, desiccated, and redissolved in ethanol (2.0 mL). Then the contents of Limaprost and 11-deoxy-Δ10 were analyzed by HPLC. The residue remaining after the centrifugation was dried, dissolved in 40% ethanol (5.0 mL), and the contents of Limaprost and 11-deoxy-Δ10 were analyzed by HPLC. The free-form contents (%) of Limaprost and 11-deoxy-Δ10 in the tablets were calculated using Eqs. 1–5.

Solid 2H-NMR Spectroscopy Desiccators containing NaCl or LiBr saturated solution in deuterium oxide (D2O) were stored at 30°C or 25°C to create environments of 75% or 6% R.H., respectively. Samples of β-CD, lactose hydrate and dextran were placed in each desiccator for 9 d, and then subjected to NMR using a CMX-300 (Chemagnetics Co., Ltd.) spectrometer under the following conditions: temperature, room temperature; primary standard, D2O (external standard, 0 ppm); measurement nucleus, 2H nucleus; pulse width, 4.0 μs (90° Pulse); pulse repetition time, ACQTM = 81.92 ms, PD = 5 s; data points, 32768; SAMPO, 4096; spectrum width, 30.03 kHz; pulse mode, inversion recovery method with a quadrupole echo method; and sample rotation speed, 0 kHz.

Stability of Limaprost Alfadex Tablets Containing β-CD at High Humidity Limaprost alfadex tablets with the β-CD formulation were filled in high density polyethylene (HDPE) bottles, which were stored with their lids open at 30±2°C and 75±5% R.H. The 11-deoxy-Δ10 content was analyzed by HPLC after 0, 4, 5, 8, 12, 16, 18, 19, and 20 weeks. The stability of Opalmon® tablets (commercial product) was evaluated as a control group.
Fig. 1. Degradation Product (11-Deoxy-Δ10) in Lyophilized Composites with or without β-CD at 30°C, 75%R.H. over Time

Each point represents the mean±S.E. of three experiments. ◇: Lyophilized composite without β-CD, □: Lyophilized composite with β-CD.

Table 2. Free-Form Contents in Lyophilized Composites with or without β-CD at 30°C, 75%R.H. over Time

| Time, Weeks | Lyophilized composite without β-CD (%) | Lyophilized composite with β-CD (%) |
|-------------|----------------------------------------|-------------------------------------|
| 0 week      | 0.57 (0)                               | 1.67 (0)                            |
| 1 week      | 0.43 (0)                               | 1.61 (0)                            |
| 2 weeks     | 0.50 (0)                               | 1.43 (0)                            |
| 3 weeks     | 0.51 (0)                               | 1.30 (0.07)                         |
| 4 weeks     | 0.36 (0.25)                            | 1.13 (0.07)                         |
| 8 weeks     | 0.42 (0)                               | 0.78 (0.06)                         |

Free form content of 11-deoxy-Δ10 [see Eq. 3] is shown in parentheses.

Results and Discussion

Effect of β-CD on the Stability of Limaprost in Lyophilized Composites The lyophilized composites with and without β-CD [lyophilized composite (with β-CD) and lyophilized composite (without β-CD), respectively] were prepared according to the formulations in Table 1, and the stability of Limaprost in these composites was investigated. Figure 1 plots the appearance of 11-deoxy-Δ10, which is the main degradation product of Limaprost, over time upon storing at 30°C, 75%R.H. The total content of 11-deoxy-Δ10 in the free and inclusion forms was determined by Eq. 2. The appearance rate of 11-deoxy-Δ10 in the lyophilized composite (with β-CD) was slower than that of the lyophilized composite (without β-CD); the amount of 11-deoxy-Δ10 after eight weeks in the former composite was 7.1% compared to 14.7% in the latter, indicating that lyophilizing with β-CD significantly increases the chemical stability of Limaprost.

It has been reported[27] that the stability of Limaprost in the free-form is lower than that in the inclusion form. Therefore, the free-form contents (%) of Limaprost and 11-deoxy-Δ10 in the lyophilized composites (with and without β-CD) stored at 30°C, 75%R.H. were measured weekly for eight weeks (Table 2). The free-form content (%) [see Eq. 1] in both lyophilized composites was very low, less than 0.57% and 1.67% in the lyophilized composite (without β-CD) and the lyophilized composite (with β-CD), respectively. The content of 11-deoxy-Δ10 in the free-form was negligible (less than 0.25%) in both composites. Furthermore, the content of free 11-deoxy-Δ10 did not increase in either composite. These results suggest that drug degradation proceeds mainly in the inclusion form.

Figure 2 shows the appearance of 11-deoxy-Δ10 in the inclusion form over time [see Eq. 4]. The appearance rate of free 11-deoxy-Δ10 in Fig. 2 was almost the same as those in Fig. 1, which plots the total content of 11-deoxy-Δ10. These results indicate that the degradation of Limaprost proceeds in the inclusion form (i.e., within the CD cavity).

To gain insight into the stabilizing mechanism of β-CD, the effect of amount of β-CD in the lyophilized composite on the stability of Limaprost alfadex was investigated. As show in Table 3, the appearance of 11-deoxy-Δ10 after the storage of two weeks at 30°C, 75%R.H. decreased with increase in the amount of β-CD, i.e., 2.5, 2.0, 1.9 and 1.8% at the ratio of 1:0.4, 1:1, 1:2 and 1:3 (Limaprost alfadex: β-CD, w/w), respectively. It is reported that α-CD with the smaller cavity includes the ω-chain of prostaglandins, while β-CD with the larger cavity includes the five-membered ring.[32–34] These results suggested that the stabilizing effect of β-CD came from the preferable inclusion of the five-membered ring, a dehydration site, of Limaprost. It is of interest to note that in aqueous
solutions, PG degrades to 11-deoxy-\(\Delta^{10}\) and the 8-epimeric isomer of PG whose configuration at C8 is inversed. On the other hand, in the solid state, it degrades predominantly to 11-deoxy-\(\Delta^{10}\), but not to the 8-epimer. Because the formation of the 8-epimer accompanies the inversion of the C8 configuration of PG followed by the large conformational change of the C8 side chain, the epimerization is difficult to occur in the solid state where motions of the large molecule are highly restricted. On the other hand, the dehydration of PG to form 11-deoxy-\(\Delta^{10}\) is a local reaction around the five-membered ring, in which water molecules are importantly involved. Therefore, the stabilizing effect of \(\beta\)-CD may be ascribed at least partly to the inhibition of water access to the reaction site through the inclusion complexation, together with the restriction of molecular mobility of water in the solid state as described later.

**Physicochemical Properties of the Lyophilized Composites** To gain insight into the stabilization mechanism of \(\beta\)-CD, the changes in the physicochemical properties [e.g., crystallinity (powder X-ray diffractometry), appearance (visual observations and SEM), and weight change], were investigated for the lyophilized composites while storing at 30°C, 75%R.H. Both lyophilized composites (with and without \(\beta\)-CD) exhibited halo patterns in the powder X-ray diffractograms (Fig. 3), suggesting that both are in amorphous states. The fact that the diffractograms did not change upon storing for eight weeks indicates that the amorphous state is maintained.
Figure 4 shows the appearance of the lyophilized composite (with and without β-CD) after storing for eight weeks. The presence of β-CD influenced the appearance; the lyophilized composite (with β-CD) did not change after eight weeks, whereas the lyophilized composite (without β-CD) remarkably shrank after one week. Additionally, the surface of the lyophilized composite (with β-CD) did not change while storing, but that of the lyophilized composite (without β-CD) was rough with large cavities (Fig. 5). When stored at 30°C, 75%R.H., the weights of both composites increased due to moisture adsorption. The water content reached about 22% in the lyophilized composite (without β-CD) and about 17% in the lyophilized composite (with β-CD). These differences in moisture adsorption, surface morphology, and surface area may be partly ascribed to the physical stabilities of the drug in the composites; the lower stability of the lyophilized composite (without β-CD) may be due to the large water content and surface area compared to those of the lyophilized composite (with β-CD). In addition, the chemical stability of E-type prostaglandin increases upon complexation with β-CD because compared to α-CD, this host molecule predominantly includes the five-membered ring, which is the reactive site of

Fig. 6. Contents of Limaprost in the Free Form in Limaprost Alfadex Tablets (Formulations A, D) at 30°C, 75%R.H. over Time

○: Formulation A, □: Formulation D.

Fig. 7. Powder X-Ray Diffraction Patterns of Limaprost Alfadex Tablets (Formulations, A, D) at 30°C, 75%R.H. over Time

Formulation A

Formulation D

Lactose

β-CD

0 week

1 week

2 week

3 week

4 week

8 week

2θ (°)

2θ (°)
the guest. The inclusion of the five-membered ring in the β-CD cavity may stabilize Limaprost in the solid state, as described above. However, further studies are necessary to elucidate the inclusion mode in the presence of α- and β-CDs (i.e., the complex formation of α- and β-CDs separately, their fractions, or ternary complex formation with α- and β-CDs must be investigated).

Effect of Excipients on Stability of Limaprost in Tablets

To obtain Limaprost tablets with a much higher stability, the effects of tableting excipients on the stability of Limaprost in the lyophilized composites were studied. The lyophilized composite (with β-CD) or the lyophilized composite (without β-CD) was blended with β-CD or lactose as a tableting excipient, and the mixtures were compressed into tablets. The stability of the resulting four formulations were compared at 30°C, 75%R.H. Formulation A (−, −) contained the lyophilized composite (without β-CD) and lactose as the tableting excipient (i.e., β-CD was not in the tablet). Formulation B (−, +) contained the lyophilized composite (without β-CD) and β-CD as the tableting excipient (i.e., β-CD was only in the tablet formulation). Formulation C (+, −) contained the lyophilized composite (with β-CD) and lactose as the tableting excipient (i.e., β-CD was only in the lyophilized composite). Formulation D (+, +) contained the lyophilized composite (with β-CD) and β-CD as the tableting excipient (i.e., β-CD was in both the lyophilized composite and tablet formulation).

After storing for two weeks at 30°C, 75%R.H., the percentage of 11-deoxy-Δ10 was 4.4%, 3.4%, 4.5%, and 1.2% in the tablets with Formulations A, B, C, and D, respectively, indicating that Formulation D (+, +) has the largest stabilizing effect on Limaprost. Indeed, the appearance of 11-deoxy-Δ10 after one month under the same conditions was only 2.0% for Formulation D, whereas it exceeded 5% for the other formulations. The β-CD diffraction peaks of the added tableting excipient, whereas Formulation D gave diffraction peaks characteristic of lactose, which was the added tableting excipient, whereas Formulation D gave diffraction peaks of β-CD, which was the added tableting excipient. Storing did not alter the diffraction patterns in either tablet, suggesting that the phase of the solids does not change upon mixing the lyophilized composites and excipients or upon storing under these conditions.

Table 4. Stability of Opalmon® Tablets at 30°C, 75%R.H.

| Storage period (weeks) | Initial | 4 | 5 | 8 | 12 | 18 | 19 | 20 |
|------------------------|---------|---|---|---|----|----|----|----|
| Opalmon® tablet (Commercial product) | 0.5 | 4.5 | 5.7 |
| Formulation D (Moisture resistant formulation) | 0.3 | 1.7 | 2.5 | 3.5 | 4.2 | 4.7 | 5.0 | 5.4 |

Molecular Mobility of Water in Excipients

Excipients in the dosage form affect the degradation rates of active pharmaceutical ingredients due to humidity. Near-infrared or solid NMR spectroscopic studies have suggested that the mobility of water molecules adsorbed in the excipients depends on humidity, and molecules with a high mobility contribute to the degradation of the active pharmaceutical ingredients. To gain insight into the stabilization mechanism of the excipients, we evaluated the molecular mobility of D2O adsorbed in β-CD and dextran, both of which suppressed the degradation of Limaprost, and lactose as a control, using solid 2H-NMR spectroscopy by measuring the spin–lattice relaxation times (T1) of deuterium atom. Figure 8 shows the 2H-NMR spectra of β-CD, dextran and lactose hydrate stored at 30°C, 75%R.H. for 9 d. Lactose hydrate exhibited a relatively sharp peak and a broad peak at 2.95 ppm, which were attributed to free water and crystalline water molecules, respectively. Dextran exhibited one sharp peak at 1.75 ppm, indicating that D2O molecules in dextran exhibited isotropic mobility. On the other hand, β-CD exhibited two relatively sharp peaks, indicating that D2O molecules in β-CD exhibited axisymmetric mobility. The T1 values were 14.5, 6.2, 5.2 ms in lactose hydrate, dextran, and β-CD, respectively. The T1 value of β-CD did not change after storing at 25°C, 6%R.H. for 9d (i.e., 5.5 ms). These results suggested that the molecular mobility of D2O increased in the order of β-CD<dextran<lactose hydrate and this order was in accordance with their stabilization effect on Limaprost. These results suggest that the water molecules in β-CD are constrained more tightly than those in lactose hydrate. This constrained mobility of water molecules may suppress the degradation rate of Limaprost and contribute to the improved stability of the Limaprost tablets.

![Fig. 8. 2H-NMR Spectra (Hz) of D2O Adsorbed in Lactose, Dextran and β-CD Stored at 30°C, 75%R.H. for Nine Days](attachment:image.png)
Stability Study of Limaprost Tablets with Formulation D under High Humidity

Formulation D (moisture resistant formulation) containing β-CD in both the lyophilized composite and excipient was remarkably more stable in high humidity. We compared the long-term stability of this moisture resistant tablet to Opalmon® tablet (commercial product) in highly humid conditions (Table 4). The commercial product deviated from its product specification (5% of 11-deoxy-Δ^10 in purity) when stored at 30°C, 75% R.H. (i.e., 5.7%) after five weeks. In contrast, the present moisture resistant tablet exhibited the specified stability at least for 19 weeks.

Conclusion

Lyophilized composites with β-CD stabilized Limaprost in the solid state in highly humid conditions, and adding of β-CD as a tableting excipient further improved the stability of Limaprost in tablets of the lyophilized composites (with β-CD). This moisture resistant tablet maintained the specified stability at least for 19 weeks at 30°C, 75% R.H. (i.e., the appearance of 11-deoxy-Δ<sup>10</sup>≤5% for 19 weeks). The stabilization of β-CD may be due to the lower water content and surface area, the constrained mobility of water molecules adsorbed in β-CD, together with the inclusion effect of CDs, although further studies are necessary to elucidate the detailed stabilization mechanism.

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