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Evaluation of Hydrocortisone Sustained-Release Suppositories Prepared with Eudragit-Polyethylene Glycol Solid Matrix

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유드라짓 및 폴리에틸렌글리콜 고체 매트릭스로 제조한 히드로코르티손 좌제의 서방성 평가

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Hydrocortisone (HC) sustained-release suppositories were prepared by using a solid matrix of methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L_{100}^R: EL) as a poorly water soluble carrier and polyethylene glycole 1540 (PEG) as an water soluble carrier. HC release rate was controlled by complexation with β-cyclodextrin (β-CyD) which was confirmed by X-ray diffractometry, IR-spectroscopy and differential scanning calorimetry. Release rate of HC from the EL-PEG matrix suppositories decreased with increase of EL contents. The release rate from HC-β-CyD complex decreased in the following order: HC-β-CyD/PEG > HC/PEG > HC-β-CyD/$EL_{10\%}$-PEG > HC/$EL_{10\%}$-PEG > HC-β-CyD/$EL_{15\%}$-PEG > HC/$EL_{15\%}$-PEG > HC-β-CyD/$EL_{20\%}$-PEG > HC/$EL_{20\%}$-PEG. The crystallinity of HC in polymer matrix was identified using X-ray diffractometer and the surface of matrix suppositories after release test was examined by scanning electron microscopy. The sustained release of HC from these matrix suppositories was attributed to the network structure of EL.

Keywords—hydrocortisone, sustained-release suppositories, Eudragit L_{100}^R, polyethylene glycol 1540, solid matrix, β-cyclodextrin.

The possibility of using polymers as a vehicle for sustained-release suppositories has been examined[1-3]. These suppositories were prepared by using a solid matrix of methacrylic acid-methacrylic acid methyl ester copolymer, cellulose acetate phthalate, hydroxy propyl methyl cellulose phthalate or hydroxyproyl methyl cellulose acetate succinate as a poorly water-soluble carrier and polyethylene glycol as a easily water-soluble carrier[4,5].

EL is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalies, thus affording enteric film coatings which are soluble in intestinal fluids[6].

Hydrocortisone (HC) has been used as a corticosteroidal anti-inflammatory drug. Unfortunately HC carries the risk of side effects such as peptic

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ulceration, hypokalemic alkalosis and edema. And it has been found that HC has a high hepatic extraction ratio[7]. Recently, rectal administration has been studied as a delivery route to overcome the problem of mucosal irritation and to escape from the first-pass effect[8,9].

This study was performed to examine the sustained-release characteristics of HC from suppositories prepared by using a solid matrix of EL as a poorly water-soluble carrier and PEG 1540 as a water-soluble carrier. The release rate of HC which is very slightly soluble in water was also controlled by complexation with β-CyD to form a rapidly water-soluble drug.

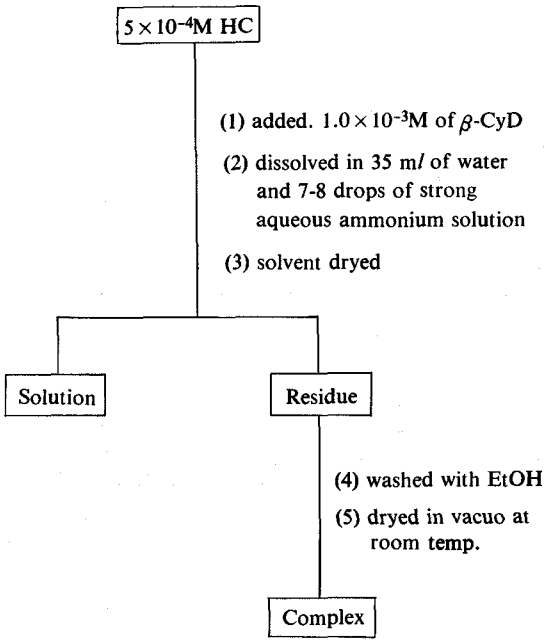
EXPERIMENTAL

Materials

Hydrocortisone was purchased from Han Seo Co., Ltd. Polyethylene glycol 1540 was obtained from Fluka-Granite, Switzerland. β-Cyclodextrin was purchased from Tokyo Kagaku, Japan. Eudragit L_{100}^{R} was obtained from Röhm Pharma. Gmbh, W. Germany. All other chemicals used were reagent grade.

Preparation of HC-β-CyD Inclusion Complex

HC and β-CyD with molecular ratio 2:1 were dissolved in aqueous ammonium solution, and then dried at 35 °C in vacuum. Non-included HC were washed with ethanol (Scheme 1).



Scheme 1. Method for preparation of inclusion complex: solvent drying method.

Examination of Inclusion Complex

• **UV Spectroscopy**—β-CyD equivalent to 1.0×10^{-3}M, 5.0×10^{-3}M, 7.5×10^{-3}M, 1.0×10^{-2}M was added into the experimental bottle containing 30 ml of HC solution (5.84×10^{-2}M) and then shaken for 3-4 days at 25 °C until equilibrium was achieved. After equilibrium, the effect of β-CyD on UV spectrum was measured.

• **IR Spectroscopy**—Infrared spectra for HC-β-CyD inclusion complex compared with physical mixture were observed by potassium bromide disk method, with a double beam, infrared spectrophotometer (Perkin Elmer Model 782, U.K.).

• **Differential Scanning Calorimetry (DSC)**—DSC was carried out with a differential scanning calorimeter (DSC-model 91, Du Pont Co., U.S.A.). The scanning temperature range was 30-250 °C and the scanning speed was 10 °C/min, using α-alumina as a standard material.

• **X-ray Diffraction**—Powder X-ray diffraction was carried out using a X-ray diffractometer (Rigaku Geigerflex 2025) with Ni-filtered Cu-K_α radiation.

Preparation of Suppository

Suppositories were prepared by the fusion method. HC or HC-β-CyD complex was added to the EL-PEG base which containing 10, 15 or 20% of EL in PEG. The well stirred mixture was poured into a stainless steel suppository mold to give a suppository weight of 2.5g and then allowed to stand for 30 min at 20 °C to solidify. The content of HC in one suppository was 100 mg. The weight variation test and content uniformity test were performed (Table I).

Crystallity Comparison of HC in Suppositories

In order to measure the crystallity of HC in the

Table I—*Weight deviation and content uniformity of HC suppositories and HC-β-CyD suppositories.*

Formulation		Weight deviation	Content of drug
Drug	Base	mean ± S.D. (g)	mean ± S.D.(%)
HC	PEG	2.47 ± 0.06	96.69 ± 0.01
	$EL_{10\%}$-PEG	2.46 ± 0.05	102.21 ± 0.01
	$EL_{15\%}$-PEG	2.48 ± 0.05	102.49 ± 0.01
	$EL_{20\%}$-PEG	2.49 ± 0.06	99.44 ± 0.01
HC-β-CyD	PEG	2.40 ± 0.05	96.55 ± 0.01
	$EL_{10\%}$-PEG	2.46 ± 0.05	96.39 ± 0.01
	$EL_{15\%}$-PEG	2.49 ± 0.05	104.91 ± 0.01
	$EL_{20\%}$-PEG	2.50 ± 0.06	104.91 ± 0.01

matrix, parts of the fusion prepared as described above was poured into aluminum holder, the solidified at room temperature. The X-ray diffraction spectra were determined with an X-ray diffractometer (Miniflex, Rigaku Denki, Ltd.; Cu-K_α radiation, 30 kV, 10 mA).

Release Test of Suppositories *in Vitro*

Each suppository was placed directly in a dissolution apparatus basket. The test solution was 900 m*l* of 0.2M phosphate buffer solution (pH 7.2) and regulated 37 ± 0.5 °C and rotated at 150 rpm. Dissolved drug was assayed spectrophotometrically at 247 nm with a spectrophotometer (Cecil, model 559).

Scanning Electron Microscopy

The surface of matrix suppository was observed with a scanning electron microscope (Hitachi S-570).

RESULTS AND DISCUSSION

Inclusion Complex of HC with β-CyD

Frank[10] has investigated that HC-β-CyD inclusion compound by proton magnetic resonance (^{1}H-NMR) and phase solubility analysis. In this study we prepared the HC-β-CyD complex by solvent drying method and examined the solid complex by IR spectrum, DSC and X-ray studies. First, the effect of β-CyD on UV spectrum of HC in aqueous solution is shown in Fig. 1. HC has the

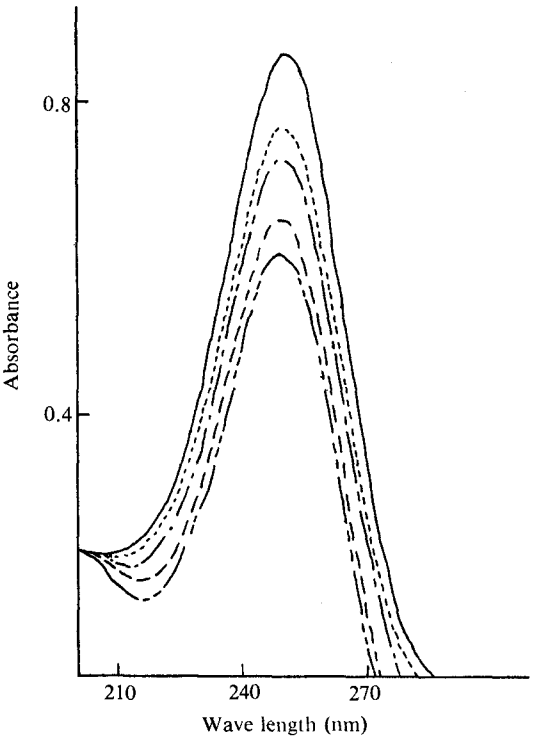


Figure 1—Effect of β-CyD on UV absorption Spectra of HC in aqueous solution
———: HC alone
------: 1.0×10^{-3}M β-CyD added
—·—·—: 7.5×10^{-3}M β-CyD added
— — —: 5.0×10^{-3}M β-CyD added
——·——: 1.0×10^{-3}M β-CyD added

absorption maximum at 247 nm. By adding β-CyD to HC solution, the maximum absorption wavelength shifts to shorter wavelength. This phenomenon may suggest that the HC molecules interacts with the asymmetric cavity of β-CyD. Fig. 2 shows the IR spectra of the physical mixture and the prepared complex of HC-β-CyD. The band at 1715 cm^{-1} due to the carbonyl stretching of HC shifts to the lower wave number. DSC curves of HC, HC-β-CyD physical mixture and HC-β-CyD prepared complex are shown in Fig. 3. An endothermic peak was observed around 210 °C for intact HC owing to melting. However this peak completely disappeared in HC-β-CyD complex. The x-ray diffraction patterns shown in Fig. 4 indicate that the crystallinity of HC was decreased in HC-β-CyD complex com-

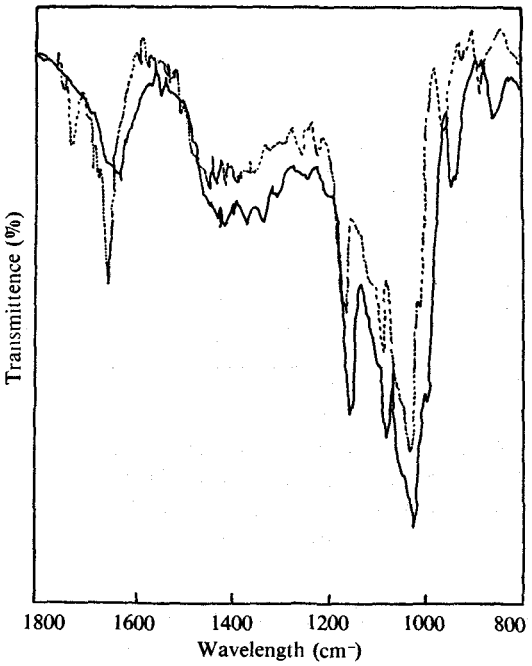


Figure 2—IR spectra of HC-β-CyD according to KBr disk method

——: HC-β-CyD complex

------: HC-β-CyD physical mixture

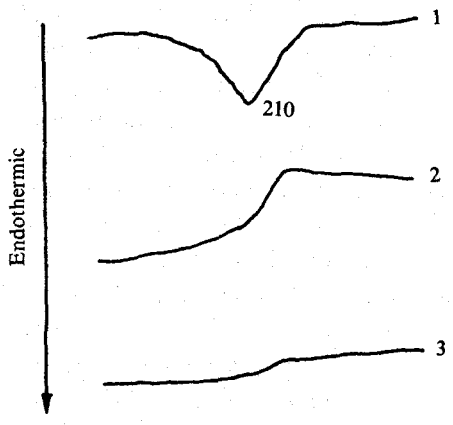


Figure 3—DSC thermograms of HC-β-CyD system

(1) HC alone

(2) HC-β-CyD physical mixture

(3) HC-β-CyD inclusion compound

pared to that of physical mixture. All these results of UV spectrum, DSC, IR spectrum and X-ray diffractometry are consistent with the data of Kurozumi *et al.*[11] who described the preparation of inclusion complexes of non-steroidal antiinflamma-

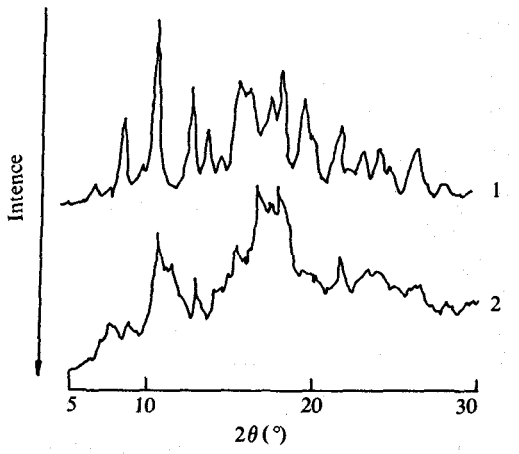


Figure 4—Powder X-Ray diffraction patterns of HC-β-CyD systems.

(1) HC-β-CyD physical mixture

(2) HC-β-CyD inclusion compound

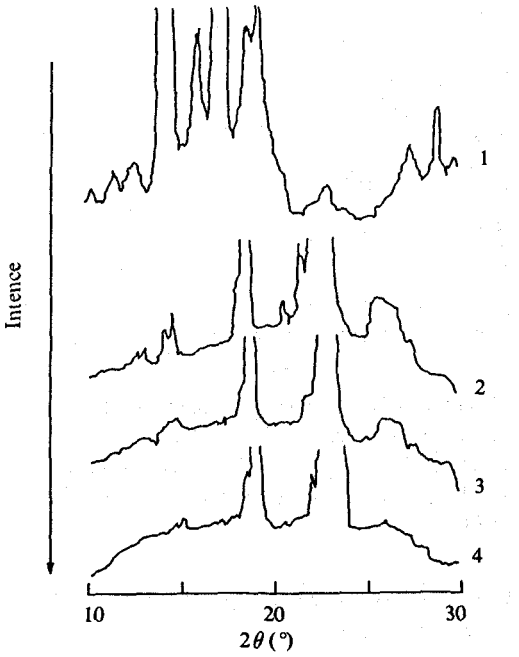


Figure 5—X-ray diffraction spectra of various suppository samples

(1) HC powder

(2) EL-PEG 1540 matrix material

(3) HC/EL-PEG 1540 suppositories, HC content 2.5%

(4) HC-β-CyD/EL-PEG 1540 suppositories, HC content 2.5%

tory agents and other slightly water-soluble drugs with α-and β-CyD, and thus it was suggested that

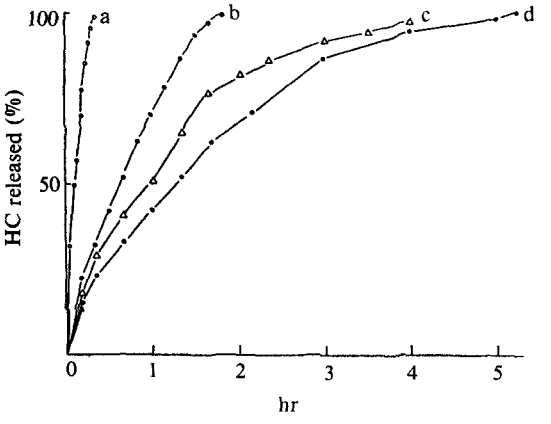


Figure 6—Effect of EL content on the released pattern of HC from suppositories *in vitro*
Key: a, HC in PEG; b, HC in $EL_{10\%}$-PEG; c, HC in $EL_{20\%}$-PEG; d, HC in $EL_{20\%}$-PEG.

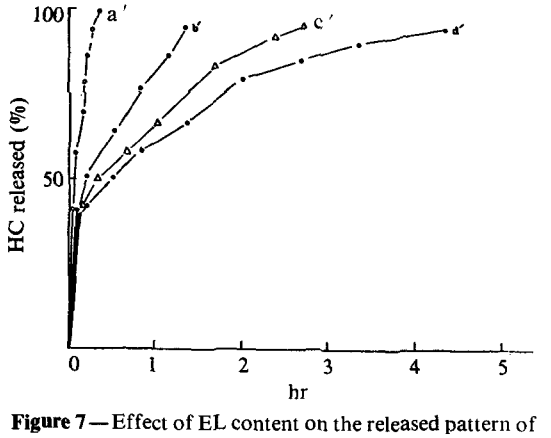


Figure 7—Effect of EL content on the released pattern of HC from HC-β-CyD suppositories *in vitro*
Key: a', HC-β-CyD in PEG; b', HC-β-CyD in $EL_{10\%}$-PEG; c', HC-β-CyD in $EL_{15\%}$-PEG; d', HC-β-CyD in $EL_{20\%}$-PEG.

the interaction between HC and β-CyD arose from inclusion complexation.

Crystallinity of HC in Matrices

Fig. 5 shows the X-ray diffraction spectra of HC powder, $EL_{20\%}$-PEG matrix material, HC/$EL_{20\%}$-PEG and HC-β-CyD/$EL_{20\%}$-PEG. There were no characteristic peaks of HC crystals (e.g., 14 and 17 °(2θ) in the spectra of HC/$EL_{20\%}$-PEG and HC-β-CyD/$EL_{20\%}$-PEG. Two major peaks at about 19° and 24 °(2θ) in these spectra were identified as being attributable to PEG1540. These results indicate that

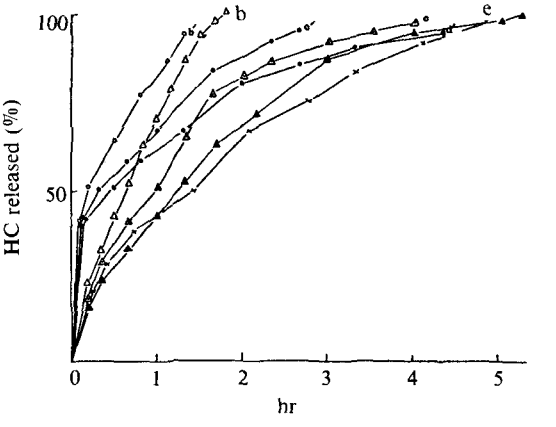


Figure 8—Dissolution pattern of HC & HC-β-CyD in PEG-EL solid matrix compared to commercial product
Key: a, b, c, d, the same as in Fig. 6; a', b'c', d', the same as in Fig. 7; e, commercial product

HC is present in an amorphous state in these matrices.

Release Patterns of HC from Suppositories *in Vitro*

The weght variation and content uniformity data of suppositories are in Table I with good consistency. Fig. 6 shows the effect of the content of EL on the release patter of HC from suppositories. The release rate of HC from PEG suppository was very high and the 50% of HC content was dissolved within 7 min. However, the release rate of HC from the EL-PEG matrix suppositories were decreased with increasing EL contnet. Fig. 7 and 8 shows the release rate of HC from HC-β-CyD/EL-PEG tend to be higher because of the improved solubility and decreased crystallinity of HC-β-CyD solid complex. These results indicate that the content of the poorly soluble carrier and drug solubility affect to the release rate of HC from the matrix suppository. Table II shows the 50% dissolved time ($t_{1/2}$) of HC from the prepared suppositories compare to commercial product which is prepared with lipophilic base.

Release Mechanism of HC from Matrix Suppositories

The release mechanism of HC from the EL-PEG marix suppositories was investigated by scanning electron microscopy. As shown in Fig. 9c and 9d, a

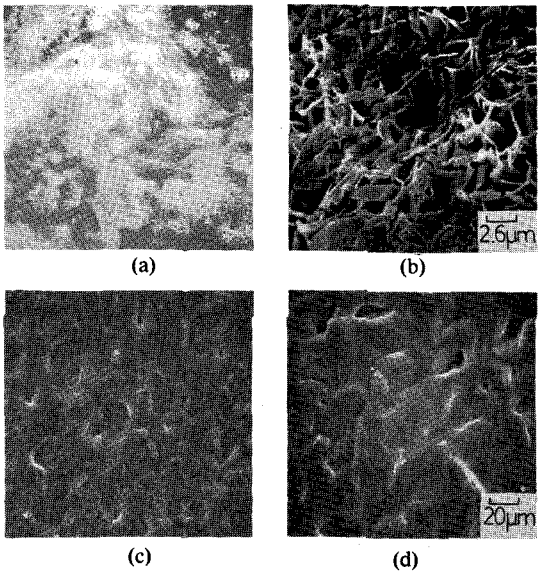


Figure 9—Scanning electron micrographs of the surface of EL-20
(a), (b); before the release test
(c): at 20 min after the start of the release test in 0.1M phosphate buffer solution (pH 7.2) at 37±0.2°C
(d): at 60 min after the start of the release test in 0.1M phosphate buffer solution (pH 7.2) at 37±0.2°C.

network structure of EL could be seen at the surface of $EL_{20\%}$ at 20 min after the start of the release test. This network structure made a different release pattern between the matrix suppositories which contain various amount of EL and which was prepared with only PEG as a base. The results illustrated by the photos (Fig. 9) suggest that the mechanism of sustained release of HC from the EL-PEG1540 matrix suppositories is very similar to that from the suppositories containing CAP-PEG200, HP55-PEG200 or As·MF-PEG 2000 matrix base discussed in previous paper[12].

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