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RESEARCH PAPER

Development of a Directly Compressible Poly(Ethylene Oxide) Matrix for the Sustained-Release of Dihydrocodeine Bitartrate[#]

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ABSTRACT

The purpose of this study was to design and evaluate a directly compressible hydrophilic poly(ethylene oxide) (PEO) matrix for the oral sustained delivery of dihydrocodeine bitartrate (DHCT). A direct compression method was used to prepare PEO matrices, and the amount of PEO in the matrices was varied to optimize in vitro DHCT release profiles. In vitro release studies indicated that the matrices containing 20%–70% w/w of PEO with molecular weight of 5.0×10^6 showed a similar release profile, as estimated with DT50%, to that exhibited by a marketed product, DHC Continus®. In vivo bioavailability study revealed that the difference in the pharmacokinetic parameters such as AUC_{0-30} and T_{max} of the selected sustained-release formulation containing 60% w/w of PEO 5.0×10^6 and DHC Continus® was statistically insignificant ($p > 0.05$). Thus, it could be concluded that the extent of bioavailability of the sustained-release formulation developed here was similar to that of DHC Continus® although C_{max} values of these two preparations were significantly different ($p < 0.05$). From the data obtained in this research, hydrophilic PEO matrices were found to be a novel sustained-release carrier for the oral delivery of DHCT.

Key Words: Dihydrocodeine; Poly(ethylene oxide); Direct compression; Hydrophilic matrix; Sustained-release; Bioavailability.

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INTRODUCTION

To alleviate acute or malignant pain, morphine is mainly prescribed. However, for the management of a chronic pain, morphine has tended not to be used because of its dependency and tolerance.[1] Several opioid derivatives such as codeine and dihydrocodeine, have been chosen for the control of chronic pains. Dihydrocodeine (DHC) is a synthetic opiate that has been widely used for the treatment of chronic pain in terminal illness and severe breathlessness or as an antitussive.[2–4] In clinical practice, DHC therapy has side effects similar to those exhibited by morphine such as nausea, vomiting, drowsiness, and constipation. However, these side effects could be greatly reduced by using a sustained- or controlled-release dosage form.[5] The side effects are often associated with high blood concentrations of DHC. Thus, sustained- or controlled-release formulations can be used to maintain therapeutically optimal blood levels of DHC for an extended period of time without concurrent side effects. For instance, the controlled-release DHC tablets, at clinically relevant doses (60 and 120 mg), did not cause side effects such as nausea and emesis, dose-dependent impacts on constipation, and the constriction of the pupil as measured by orocecal transit time and pupillary light reflex in humans.[6]

Among the polymeric materials used for the design of oral sustained- or controlled-release dosage forms,[7,8] poly(ethylene oxide) (PEO) has been widely used because of their low toxicity and pH-independent swelling and drug release properties.[9–11] PEOs also are nonionic so that they are compatible with an ion-rich environment, limited only by the electrolyte concentration at which the polymers are salted out. Because PEOs are hydrophilic, the involvement of water or moist can make a wet granulation process problematic. Therefore, a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics would be desirable.[12] Furthermore, the dry process, such as direct compression technique, is known to be more economical (i.e., less time, space, materials, labor, and fewer steps) than wet granulation process and also avoids heat and moisture, which may decrease in a drug stability. Thus, the PEO matrices containing dihydrocodeine bitartrate (DHCT) were prepared by a direct compression method. In the present study, the objective was to prepare directly compressed PEO matrices for the sustained-release of DHCT and to evaluate the matrices for in vitro drug release properties. In vivo pharmacokinetic parameters for the selected sustained-release formulation of DHCT were also compared with those obtained from a commercially available product (DHC Continus®) in beagle dogs.

MATERIALS AND METHODS

Materials

Dihydrocodeine bitartrate was kindly supplied from Guju Pharmaceutical Company (Korea), and PEO resins were purchased from Union Carbide Corporation (Danbury, CT). Microcrystalline cellulose (Avicel® PH 102) was obtained from FMC Corporation (Newark, DE). Acetonitrile was an HPLC grade (Fisher Scientific, Pittsburgh, PA). All other chemicals were of analytical or reagent grade and were used as received. A marketed sustained-release DHC tablet (Lot. no. 82001; DHC Continus®) was obtained from Hyundai Pharmaceutical Company (Korea) for the comparative study of bioavailability with the formulation developed by the current study.

Preparation of Matrices

The formulations evaluated are shown in Table 1 together with their compositions. Poly(ethylene oxide) was used as a swellable hydrophilic polymer that controls drug release rates. The drug, polymer, and diluent were screened through #45 sieve and preblended manually. The lubricant was added and the blend was mixed again prior to compression. The tablet blends were directly compressed by using a single-punch press (Korsch, Germany). The tablets were round convexed type, 10-mm diameter, 3.5 ± 0.5-mm thick, and had hardness of 9–11 kg/cm^2.

In Vitro Drug Release Study

The release of DHCT from the matrix tablets was conducted according to the paddle method of USP XXIII using a Dissolution Tester (DST-600A, Fine Scientific Instruments, Korea). The dissolution medium was 900 mL of aqueous buffer (pH 1.2 or pH 6.8) maintained at 37.0 ± 0.5°C and the paddle speed was set at 100 rpm. At the predetermined time intervals, the dissolution samples (5 mL) were withdrawn up to 7 hr and replaced with the same volume of dissolution medium maintained

Table 1. Composition (mg) of matrices.

	Formulation code								
Ingredient	PL	PM	PH	PA1	PA2	PA3	PA4	PA5	PA6
DHCT	60	60	60	60	60	60	60	60	60
PEO 0.2×10^6	60								
PEO 0.9×10^6		60							
PEO 5.0×10^6			60	40	60	90	120	140	170
Avicel PH102	80	80	80	130	110	80	50	30	
Mg-stearate	2	2	2	2	2	2	2	2	2
Total weight	202	202	202	232	232	232	232	232	232

at $37.0 \pm 0.5^{\circ}$C. The amount of DHCT released was measured by using a UV-VIS spectrophotometer (Varian Carry 3, Australia) at 233 nm.

In Vivo Bioavailability Study in Beagle Dogs

The bioavailability of the selected sustained-release formulation of DHCT developed in the present study was comparatively evaluated with a commercially available sustained-release product (DHC Continus®). Six male beagle dogs (8–10 kg) were equally divided into two groups. After an overnight fast for at least 12 hr, test group (formulation PA5) and reference group (DHC Continus®) received a single oral dose of two tablets equivalent to 120 mg of DHCT. Serial blood samplings were made from the jugular vein with a 20-gauge, 1.5-inch needle attached to a heparinized 10-mL syringe. Systemic blood (5 mL) was collected at 0, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 30 hr for measurement of plasma DHC concentration by HPLC. The blood was placed in microcentrifuge tubes, centrifuged at 10,000 rpm for 10 min, and plasma was taken and stored at -70°C until analysis. This study used a crossover design with a washout period of 2 weeks.

HPLC Assay of DHC in Plasma

Plasma DHC was analyzed by using a column-switching HPLC system (Shiseido SI-1, Shiseido, Japan). The plasma samples were diluted 1:1 with 20 mM phosphate buffer (pH 6.9) and filtered with a 0.22-μm nylon membrane. Samples (100 μL) were injected into the HPLC system and assayed for DHC. The UV detector was set at 210 nm. Three columns were used for the column-switching HPLC: Capcell Pak MF Ph-1 SG 80, 4.6×50 mm, 5 μm for pretreatment; Capcell Pak C_{18} UG 120, 2.0×35 mm, 5 μm for concentration; Capcell Pak C_{18} UG 120, 1.5×250 mm, 5 μm for analysis, Shiseido, Japan. The mobile phase for the pretreatment of samples was 20 mM phosphate buffer (pH 6.9) with a flow rate of 0.5 mL/min. The mobile phase used for DHC assay consisted of 0.1% phosphoric acid and 50% acetonitrile (90:10, v/v) with a flow rate of 0.1 mL/min. The column temperature was 40°C and the limit of quantification was 1 ng/mL.

Statistical Analysis of Data

The results were statistically analyzed by using ANOVA and p values ≤ 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

In Vitro Release Study

Because of its noted potential as an excipient for controlled- or sustained-release formulations and very low toxicity, PEO was selected as a material for sustaining the rates of DHCT release. The control of the release rates of a drug from PEO matrices has been mainly achieved by changing molecular weight (i.e., viscosity grade) and amount of PEO. The aim of the in vitro release study was to determine suitable PEO type and the amount of PEO in the matrices.

We first prepared PEO matrices with different molecular weights containing DHCT (Table 1, formulations PL, PM, and PH). The amount of PEO in the matrices was set at 30% w/w, and the matrices had PEOs of three different molecular weights (i.e., 0.2×10^6, 0.9×10^6, and 5.0×10^6). The DHCT release

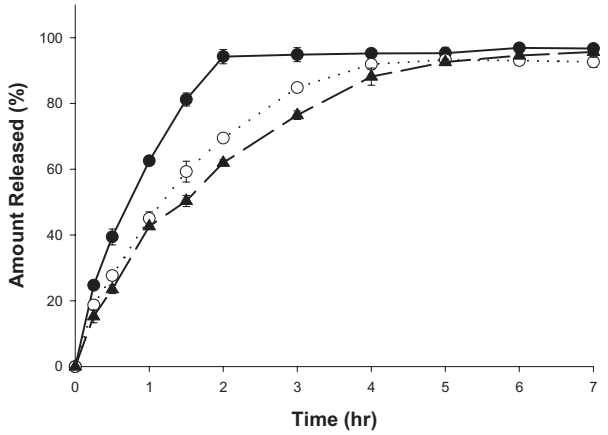

Figure 1. Effect of PEO molecular weight on DHCT release: ●, $Mw = 0.2 \times 10^6$; ○, $Mw = 0.9 \times 10^6$; ▲, $Mw = 5 \times 10^6$. Mean ± SE, $n = 3$.

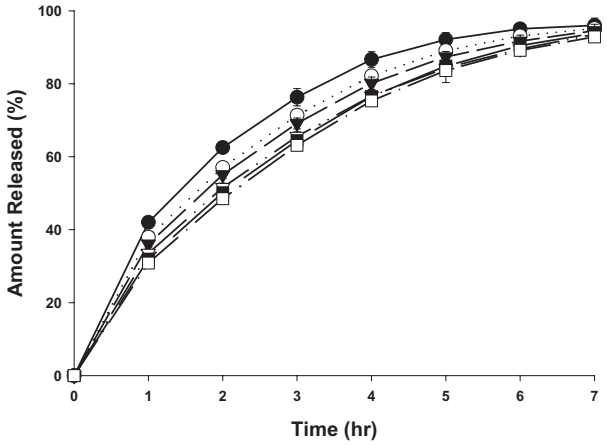

Figure 2. Effect of PEO ($Mw = 5 \times 10^6$) contents on DHCT release: ●, PEO 17%; ○, PEO 26%; ▼, PEO 39%; ▽, PEO 52% ■, PEO 60%; □, PEO 73%. Mean ± SE, $n = 3$.

profiles from matrices containing different molecular weights of PEO as a function of time were depicted in Fig. 1. The DHCT release was found to decrease as the molecular weight of PEO increased and the rank order of release rates was $0.2 \times 10^6 > 0.9 \times 10^6 > 5.0 \times 10^6$. When PEOs of 0.2×10^6 and 0.9×10^6 were used, over 60% and 40% of DHCT were initially released within 1 hr, respectively. This rapid initial release of DHCT from the PEO matrices of 0.2×10^6 and 0.9×10^6 can be attributed to a good water solubility of DHCT and the physicochemical nature of the polymer such as hydrophilicity of the polymer. The aqueous solubility of DHCT at 25°C, as determined by HPLC in our laboratory, is 222 mg/mL. Thus, free DHCT such as surface-associated DHCT was easily soluble in the aqueous release medium. Furthermore, in PEOs that possess a molecular weight of less than 2.0×10^6, the swelling and erosion of the polymers occur concurrently, resulting in an increase in the release of DHCT.[13] Thus, PEO with molecular weight of 5.0×10^6 was observed to be a suitable polymer for designing the sustained-release matrices for DHCT.

Figure 2 shows the release profiles of DHCT from matrices containing different quantities of PEO having a molecular weight of 5.0×10^6. The test formulations contained 17 (PA1), 26 (PA2), 39 (PA3), 52 (PA4), 60 (PA5), and 73 (PA6) % w/w of PEO, respectively. The DHCT release decreased with increasing PEO amount, as expected. From the observations reported by Kim,[13] transport of water into PEOs of molecular weight greater than 4.0×10^6 continues without erosion until the entire polymer is fully hydrated. Indeed, there was no noticeable erosion of the matrices during the swelling process, and the drug release was limited only by diffusion layers formed by water uptake. However, still around 30% of an initial dose of DHCT was released within 1 hr from all formulations investigated. This may be explained by the fact that the water penetration into the polymer matrix is much faster than the swelling process, so DHCT present in the unswollen domain of the polymer matrix as well as the surface-associated DHCT could be released initially.

The mechanism of DHCT release was analyzed by using a well-known empirical equation proposed by Ritger and Peppas.[14]

$$M_t/M_\infty = k \cdot t^n \tag{1}$$

where M_t is the drug released at time t, M_∞ is the quantity of drug in the matrices, k is the release rate constant, and n is the diffusional exponent. A linear regression analysis of the logarithmic form of Eq. (1) was performed by using the first 60% of a release curve to obtain the values of n and k. These release kinetic parameters are summarized in Table 2. According to the criteria for the diffusional exponent and mechanism of diffusional release from a swellable device with cylindrical shape, Fickian diffusion, and anomalous (non-Fickian) transport are characterized by $n = 0.45$ and $0.45 < n < 0.89$, respectively.[14] The values of diffusional exponent obtained ranged from 0.4 to 0.6, depending on the amount of PEO, but

Table 2. In vitro release and dissolution kinetic parameters.

Formulation code	PEO Content (w/w %)	Release kinetic parameters			Dissolution parameters	
		Diffusional exponent (n)	Release rate constant (k)	Correlation coefficient (R^2)	DT50% (hr)[a]	DE (%)[b]
PA1	17	0.434	0.448	0.964	1.29	71.79
PA2	26	0.483	0.400	0.979	1.59	68.32
PA3	39	0.504	0.379	0.982	1.73	66.66
PA4	52	0.535	0.350	0.988	1.95	63.98
PA5	60	0.566	0.333	0.988	2.05	63.60
PA6	73	0.579	0.321	0.989	2.15	62.42
DHC Continus®	—	0.435	0.466	0.945	1.18	70.07

[a]The time required for 50% of the drug to be released.
[b]Dissolution efficiency.

none of the formulations exhibited $n = 0.45$. Thus, DHCT release from PEO matrices of 5.0×10^6 is considered a non-Fickian diffusional process. Examples of non-Fickian or anomalous drug release from a swelling matrix are commonplace. Lee[15] stated that it is unlikely for drug diffusion to follow a Fickian mechanism when molecular relaxation of polymer chain occurs in addition to diffusion.

The time required for 50% of the drug to be released (DT50%, hr) and dissolution efficiency (DE, %) were response parameters of dissolution[16] (Table 2). The DE was obtained from the area under the dissolution curve up to 7 hr, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. The DT50% values of our sustained-release formulations gradually increased as the polymer contents increased. The DT50% of the commercially available controlled-release dosage form (DHC Continus®) ranged from 1.02 to 2.34 hr. The DT50% values of all formulations being investigated were also between 1.29 and 2.15 hr, indicating that our sustained-release formulations are expected to show a similar in vitro performance to that exhibited by the DHCT controlled-release product marketed. Khan[16] suggested that DE is a suitable parameter for evaluating in vitro dissolution data and can be used to compare an in vitro dissolution behavior with in vivo data. The DE values slightly decreased with increasing the polymer contents in the formulations. It was observed that the DE value of formulation PA1 (17% PEO) was only 1.15 times greater than that of PA6 (73% PEO), although there was a considerable increase in the amount of PEO incorporated. The release of DHCT from PEO matrices was independent of pH (Fig. 3), and the difference in the amount of DHCT released was less than 3% between two pHs. Although there was no significant difference between all the prepared formulations (PA1–PA6) and the commercial product with regard to in vitro release properties such as DT50% values, a matrix containing 60% of PEO 5×10^6 (PA5) was selected as a test formulation for in vivo comparative bioavailability study with the commercial product (DHC Continus® 60 mg). Figure 4 shows the release profiles of formulation PA5 and DHC Continus® in the pH 6.8 aqueous buffer. The release rate of DHCT from Continus® was greater than from formulation PA5. In the first 1 hr of the release study, the difference in the amount of the drug released was more than 10% between two preparations, but this difference was reduced with increasing time.

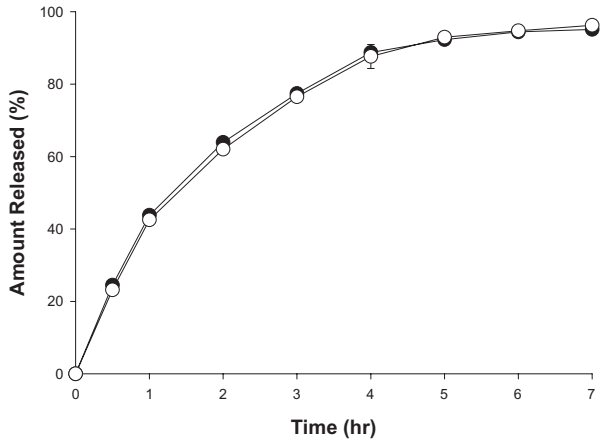

Figure 3. Effect of pH of dissolution medium on DHCT release: ●, pH 1.2; ○, pH 6.8. Mean ± SE, $n = 3$.

Table 3. Comparison of bioavailability parameters between test and reference formulations.

Drug	AUC_{0-30} (ngh/mL)	C_{max} (ng/mL)	T_{max} (hr)
Test (formulation PA5)	283.7 ± 109.5	34.4 ± 14.9[a]	2.2 ± 1.4
Reference (DHC Continus®)	293.2 ± 87.5	48.1 ± 20.3	1.8 ± 1.3

[a]Significantly different from reference at $p < 0.05$.

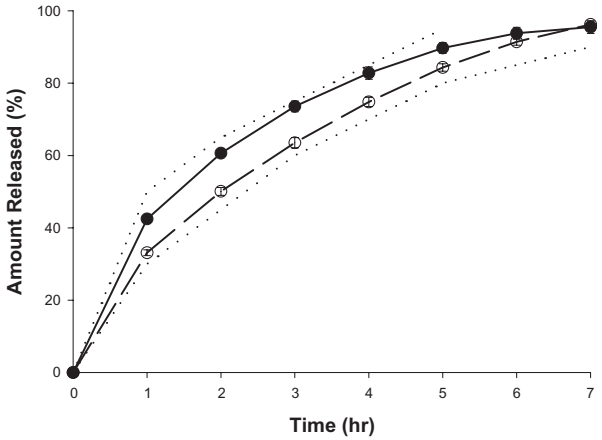

Figure 4. DHCT release profiles from formulation PA5 (○) and DHC Continus® (●). Mean ± SE, $n = 3$.

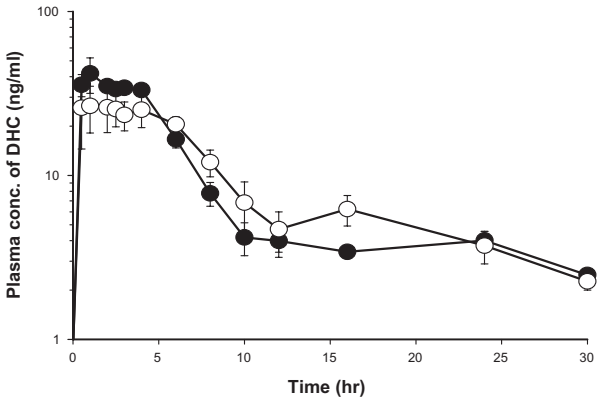

Figure 5. Mean plasma concentration-time profiles of DHC in beagle dogs (○, formulation PA5; ●, DHC Continus®). Mean ± SE, $n = 6$.

In Vivo Comparative Bioavailability Study

The in vivo bioavailabilities of test formulation (PA5) and reference formulation (DHC Continus®) were compared by using pharmacokinetic parameters such as the area under the plasma concentration time curve (AUC_{0-30}), peak plasma concentration (C_{max}), and time to peak plasma concentration (T_{max}). They are given in Table 3 together with statistical evaluation. The profiles of plasma concentration of DHC vs. time are also given in Fig. 5. From the pharmacokinetic parameters summarized in Table 3, the differences in AUC_{0-30} and T_{max} observed from formulations PA5 and DHC Continus® were not statistically significant ($p > 0.05$), whereas the difference in C_{max} of two formulations was found to be statistically significant ($p < 0.05$). In fact, AUC_{0-30} values were 283.69 and 293.16 ng h/mL for test and reference formulations, respectively, and the difference between AUC_{0-30} values of PA5 formulation and DHC Continus® was 3.2%. In DHC Continus®, C_{max} value was 1.4-fold greater than that of formulation PA5. The peak concentration of DHC is known to be proportional to the dose administered.[17] However, despite the significant difference in C_{max}, because the test and reference preparations have the same dose level and similar AUC_{0-30} values, it was expected that they might have a similar extent of bioavailability. The delayed T_{max} of formulation PA5 (2.2 hr) compared to that of DHC Continus® (1.8 hr) is probably due largely to a slower in vitro release profile of formulation PA5 (Fig. 4). It is interesting to note that T_{max} of a sustained-release dosage form, DHC Continus® (1.8 hr), was similar to those achieved by orally administered conventional tablets containing 30 or 60 mg of DHC (1.6 and 1.8 hr).[17] This similarity in T_{max} is probably attributed to the difference in the experimental models used (i.e., beagle dogs and human subjects). It can be also seen in Fig. 6 that, although a slightly slower absorption rate of DHCT was pronounced in formulation PA5 than in DHC Continus®, a similar absorption profile between formulation PA5 and DHC Continus® was observed. From the results obtained in the bioavailability study, even though there existed a little difference

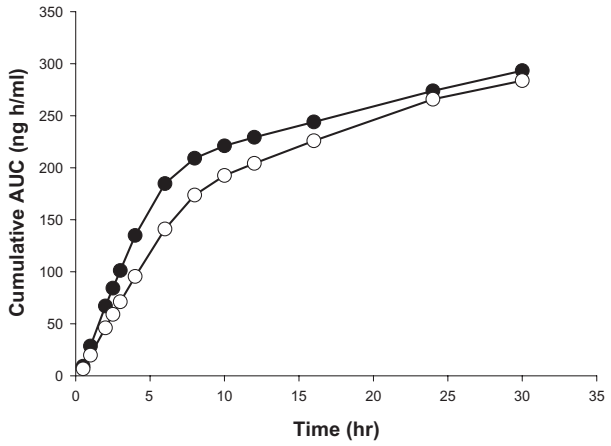

Figure 6. Cumulative AUCs of formulation PA5 (○) and DHC Continus® (●).

in the rate of bioavailability (BA), we may conclude that the extent of bioavailability of the sustained-release formulation PA5 is similar to that of DHC Continus®.

CONCLUSIONS

A directly compressible PEO matrix was prepared for the sustained oral delivery of DHCT. The current data from in vitro release studies demonstrated that the sustained release of DHCT can be achieved by incorporating in the matrices of PEO with molecular weight of 5.0×10^6. The optimum amount of PEO was found to be 20%–70% w/w in the matrices. The DHCT release from the PEO matrices did not follow Fick's law of diffusion. In vivo bioavailability study showed that the relative bioavailability of the selected PEO matrix preparation was similar to that of a marketed reference preparation (DHC Continus®). Therefore, it is concluded that PEO matrices can be used as a novel sustained-release carrier for the oral delivery of DHCT.

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