Application of Polyvinyl Acetate as Release Controlling Agent in 17β-Estradiol Implant Matrices

นิพนธ์ต้นฉบับ

Original Article

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2554;6(3):214-221

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Thai Pharmaceutical and Health Science Journal 2011;6(3): 214-221

บทคัดย่อ

วัตถุประสงค์: เพื่อทดสอบว่า polyvinyl acetate (PVAc) ทั้งชนิดน้ำหนักโมเลกุลต่ำ (113k) และสูง (500k) ในการเป็น release controlling agent ในระบบ implant matrix system ของ 2% 17β-estradiol (E_2) **วิธีการศึกษา:** ใช้สาร plasticizer สองชนิดคือ triethyl citrate (TEC) ซึ่งเป็นละลายน้ำ และ diethyl phthalate (DEP) ซึ่งไม่ละลายน้ำ เพื่อเปลี่ยนค่าความยืดหยุ่นของเมทริกซ์ ใช้สาร polyvinylpyrrolidine เป็น releasing modifier ใช้วิธี solvent evaporation เพื่อเตรียม solid dispersion ของ E_2 ในโพลิเมอร์ แล้วอัดในแม่พิมพ์ให้ได้ implant matrix ขนาดเส้นผ่านศูนย์กลาง 2 มม. และยาว 10 มม. **ผลการศึกษา:** พบว่า PVAc ทั้งชนิดที่มีน้ำหนักโมเลกุลสูงหรือต่ำ เมื่อไม่ผสม plasticizer ให้อัตราการปลดปล่อย E2 ไม่ต่างกัน ใน phosphate buffer pH 7.4 โดยปลดปล่อย 14% ในช่วง 28 วัน ส่วน PVAc ที่ผสม plasticizer ให้อัตราการปลดปล่อย E2 ที่ต่างกัน โดยการปลดปล่อย E_2 เพิ่มขึ้นเมื่อสัดส่วน plasticizer เพิ่มขึ้น และเมื่อเติม PVP K30 พบว่าอัตราการปลดปล่อยเพิ่มขึ้น ลักษณะจลนศาสตร์การปลดปล่อย E_2 จาก implant matrix ที่มี PVAc เป็น release controlling agent สามารถอธิบายได้ด้วย Higuchi model ซึ่งอธิบายการปลดปล่อยด้วยกระบวนการแพร่ **สรุป:** สามารถใช้ PVAc ในระบบนำส่งยาแบบเนิ่นสำหรับ matrix implant ของยา 17β-estradiol

คำสำคัญ: 17β-estradiol, implant, polyvinylacetate, triethyl citrate, diethyl phthalate, polyvinylpyrrolidone

Abstract

Objective: To apply two different, low (113K) and high (500K), molecular weights polyvinyl acetate (PVAc) as the release controlling agent in 2% 17β-estradiol (E_2) implant matrix system. **Method:** Two plasticizers, triethyl citrate (TEC, a water-soluble plasticizer or diethyl phthalate (DEP, a water-insoluble plasticizer) were incorporated to alter the flexibility of the matrix. Polyvinylpyrrolidone (PVP K30) was used as the releasing modifier. Solid dispersion of E_2 in polymer was prepared by solvent evaporation method and compressed in a mold to have an implant matrix of 2 mm in diameter and 10 mm in length. **Results:** The unplasticized PVAc of different molecular weights did not provide difference in E_2 release rate in phosphate buffer pH 7.4, about 14% of E2 was gradually released from the matrices during 28 days. Implants using plasticized PVAc of different molecular weights gave different drug release rates. E_2 released from implants increased with increasing weight percent of plasticizers and adding PVP K30 promoted more drug release. Release kinetic of the PVAc implant matrix was best described by Higuchi model which indicated drug release by diffusion process. **Conclusion:** PVAc could be applied in 17β-estradiol matrix implant for long term drug delivery.

Keywords: 17β-estradiol, implant, polyvinylacetate, triethyl citrate, diethyl phthalate, polyvinylpyrrolidone

Introduction

17β-estradiol (E_2) is the most potent natural estrogen and mainly prescribed in case of postmenopausal symptoms as a part of hormone replacement therapy (HRT), either alone or in combination with another female hormone.[1] Furthermore, long-term therapy can prevent cardiovascular disease and osteoporosis.[2] Estradiol has a good oral absorption but poor bioavailability because of first-pass metabolism. As a result, oral route administration leads to undesirable side effects due to increased levels of active metabolites including estrone and estriol in the blood circulation.[3] Although a transdermal patch of estradiol offers a number of advantages over oral route, once detached the patient will not receive optimum treatment. Subcutaneous implant delivery system may be favorable choice for HRT. E_2-implant is protected from the first-pass metabolism of traditional oral route and thus offers the patient compliance.

Several contraceptive implants containing different progestogens were developed and commercially available. It has been reported that the polymers used as carriers in controlling drug release from matrix implant such as silicone elastomer and ethylene vinyl acetate (EVA) copolymer.[4] It has been continuously reported for an application of different polymer carriers in controlling drug release form matrix implant. Several studies attempted to use acrylate polymers, i.e. Eudragit RS and Eudragit RL, as a release controlling agent in 17β-estradiol and norethindrone implant.[5-7]

Vinyl polymer such as polyvinyl acetate (PVAc) has been widely used as a release controlling agent in orally controlled release system. PVAc is water insoluble polymer which is

slightly hydrophilic and able to absorb water to a slight extent. PVAc has been reported to be effective in controlling the release of various chemical entities, including theophylline and chlorpromazine hydrochloride.[8-10] But the application of this polymer in implant matrix system has not been reported. PVAc might be regarded as non-bio-degradable polymer. As far as literature search has been done, there has been no report on an investigation of biodegradability of PVAc. PVAc emulsion was developed and tested as liquid embolisation materials in rats and in a patient, it was observed that PVAc did not induce a deleterious reaction in living tissue.[11]

Polyvinylpyrrolidone (PVP) is a water soluble polymer often used as releasing modifier in matrix system. It has a significant effect on the release rate, because it is rapidly leached from the system to form the pore structure, which then allows the active agent to diffuse out faster than it would have done otherwise. Diffusion of the dissolution medium into the matrix is also facilitated. The mechanisms and the extent by which this polymer might affect drug release have been subjects of some studies.[12,13] Moreover, the release rate can also be modified by varying the physicochemical and mechanical properties of the matrix. A plasticizer is an additive that is added to polymer making it softer, more flexible (by decreasing the glass-rubber transition temperature, Tg, of polymer), and easier to process. The plasticizers may increase the amount of drug release with increasing chain mobility of the polymer by altering polymer structure.[14]

The aim of the present study was to investigate an application of TVAc with two different molecular weights as release controlling agent in matrix implant containing 17β-estradiol as an active agent. In addition, drug release from PVAc matrices containing various weight percents of plasticizer and PVP as release modifier were studied.

Method

Materials

17β-estradiol (E_2) and benzalkonium chloride (BAC) were purchased from Fluka Chemica, Germany. Polyvinyl acetate (PVAc) with molecular weight of 500,000 (500K) and 113,000 (113K) were purchased from Sigma-Aldrich Chemical Co., Inc. (USA). Polyvinylpyrrolidone (PVP) K30 were purchased from Seinghai Chemical Industrial (China). Triethyl citrate (TEC) and diethyl phthalate (DEP) were purchased from Fluka Chemica, Germany. Acetonitrile was of a HPLC grade purchased from Fisher Scientific, UK.

Preparation of E2 in Polymer Solid Dispersions

Various compositions of drug-polymer solid dispersion as presented in Table 1 were prepared. Weighed amounts of PVAc, PVP and plasticizer and the drug were dissolved in 10 mL ethanol. This mixture was poured onto a glass plate and the solvent was allowed to evaporate off overnight at 30 ^{o}C. Dried samples were kept in a desiccator over silica gel beads for the further experiments.

Preparation of Implants

The viscous solid dispersion mass prepared according to the procedure described above was packed into plastic syringe then injected into the mold of rod shape with 2 mm in diameter, then compressed to a solid dispersion with the punch at a constant pressure of 1500 psi for 60 seconds using hydraulic press (Caver®, USA). The mold was kept at a temperature of 50 ^{o}C for 1 hour. The implant samples were kept in a desiccator over silica gel beads for further experiments. Weight of an implant was about 25 mg.

Table 1 Formulations of implant containing 2% E_2 using different MWs of PVAc* with and without different percent weights of PVP and plasticizers**.

Formulation code	Plasticizer (%)	Mixing ratio of PVAc:PVP
E_2-implant	-	100:0
E_2-10% plasticizer implant:	10	100:0
-PVP 10%	10	90:10
-PVP 20%	10	80:20
-PVP 30%	10	70:30
E_2-15% plasticizer implant:	15	100:0
-PVP 10%	15	90:10
-PVP 20%	15	80:20
-PVP 30%	15	70:30
E_2-20% plasticizer implant:	20	100:0
-PVP 10%	20	90:10
-PVP 20%	20	80:20
-PVP 30%	20	70:30

* Two molecular weights were used: 500K or 113K.

** Two plasticizers were used: TEC or DEP.

Thermal Analysis

Thermal analysis was carried out using differential scanning calorimetry apparatus with a refrigerated cooling system (Model 822^{e}, Mettler Toledo, Schwerzenbach,

Switzerland) to determine Tg of polymer and solid dispersions. The calorimeter was calibrated using indium. Approximate sample of 3 - 5 mg was added to standard aluminium pan with cover and scanned using heating 0 °C to 200 °C at 5 °C/min; cooling down to 0 °C at 20 °C/min; heating up to 200 °C at a rate of 5 °C/min.

Content of E_2 and DEP in Implant Matrix

The content of E_2 and DEP in the matrix was quantitatively determined by validated reversed phase HPLC method (Shimadzu Class VP, Japan) modified from the report by Ye and Chien (1996).[15] A Synergi Fusion-RP ODS column (5 µm; 250 x 4.6 mm in diameter, Inersil®) was used as an analytical column. Prednisolone was used as an internal standard. The solution for E_2 content analysis was prepared by dissolving the matrix implant with 10 ml methanol, and 50 µl of internal standard solution was added. The solution was adjusted to volume with mobile phase. Samples of 50 µl were injected and a water:acetonitrile combination of 50:50 (v:v) was used as the mobile phase at a flow rate of 1.0 ml/min. The UV detector was operated at 280 nm. Under these conditions, the E_2 and DEP peaks appeared at retention times of 7.9 and 9.9 min., respectively.

Drug release study

Release studies of E_2 implants were conducted in phosphate buffer (PB) pH 7.4 with 3.5% w/v benzalkonium chloride under sink conditions. The E_2 implants were individually placed in a screw-capped test tube containing 3.0 ml of release medium. The sample test tubes were constantly shaken at 120 rpm in a shaking incubator at 37 °C. Release medium was taken out periodically and replaced by fresh release medium. The samples were filtered through 0.45 µm membrane filter and analyzed for E_2 using HPLC method as described above.

Results and Discussion

An E_2 implant produced by compressing a solid dispersion prepared by solvent evaporation in a mold is shown in Figure 1(a). E_2 implant was in rod shape and translucent matrix with diameter of 2 mm and length of 10 mm. Furthermore, the E_2 implant after in vitro release study became opaque as shown in Figure 1(b).

(a)

(b)

Figure 1 Photographs of E_2-implant using PVAc as a release controlling agent (a) before in vitro release study (b) after in vitro release study.

DSC with heating program as described was applied to determine the glass-rubber transition temperature (Tg) of E_2 implants prepared using low and high molecular weight PVAC with and without a plasticizer and PVP are presented in Tables 2 and 3. It was observed that the Tg values of pure low and high MW PVAc were apparently not different, 45.23 and 45.72 °C, respectively. The Tg of E_2 implant prepared using low and high molecular weight of PVAc were determined to be 46.26 °C and 46.93 °C, respectively, which slightly increased comparing with pure polymer without drug. When 10%, 15%, and 20% of TEC or DEP was incorporated to high MW PVAc implant, the Tg values were determined in the following order: 29.80, 24.64 and 18.48 °C for TEC and 32.97, 26.72 and 21.64 °C for DEP, respectively. For low MW PVAc implant, the Tg values were determined in the following order: 29.56, 23.81 and 18.98 °C for TEC and 30.64, 25.89 and 20.89 °C for DEP. The addition of plasticizer from 10% to 20% caused a pronounced decrease in Tg values. These effects on significant Tg decrease could be related to a flexibility of the structure of polymer molecules and the compatibility of the plasticizers with the polymers. Both TEC and DEP apparently exhibited the same degree of Tg value reduction. This indicates that both TEC and DEP would be also the efficient plasticizer for thermal processing of PVAc, ie. hot melt extrusion process, to

prepare controlled release products. It was observed that adding PVP into the implant formulations slightly changed Tg values at all levels of plasticizer. It seemed that when varying PVP amounts from 10 to 30% did not much alter Tg values of the implants.

Table 2 Tg of E_2-implant using low molecular weight PVAc (113K) when incorporated with different amounts of PVP and plasticizers.

Formulation code	Tg (°C)	Formulation code	Tg (°C)	Formulation code	Tg (°C)
Pure E_2	84.64	Pure PVAc	45.23	E_2-implant	46.26
E_2-10%T implant:	29.56	E_2-20% T implant:	18.98	E_2-15% D implant:	25.89
PVP 10%	28.31	PVP 10%	16.73	PVP 10%	25.31
PVP 20%	28.23	PVP 20%	18.81	PVP 20%	23.97
PVP 30%	26.97	PVP 30%	18.48	PVP 30%	23.39
E_2-15%T implant:	23.81	E_2-10% D implant:	30.64	E_2-20% D implant:	20.89
PVP 10%	22.81	PVP 10%	30.81	PVP 10%	19.31
PVP 20%	22.72	PVP 20%	30.22	PVP 20%	19.23
PVP 30%	21.39	PVP 30%	30.90	PVP 30%	17.22

* T = TEC, D = DEP

Table 3 Tg of E_2-implant using high molecular weight PVAc (500K) when incorporated with different amounts of PVP and plasticizers.

Formulation code	Tg (°C)	Formulation code	Tg (°C)	Formulation code	Tg (°C)
Pure PVAc	45.72	E_2-implant	46.93		
E_2-10% T implant:	29.80	E_2-20%T implant:	18.48	E_2-15%D implant:	26.72
-PVP 10%	31.40	-PVP 10%	19.06	-PVP 10%	27.49
-PVP 20%	29.23	-PVP 20%	16.56	-PVP 20%	27.40
-PVP 30%	29.69	-PVP 30%	17.81	-PVP 30%	25.48
E_2-15% T implant:	24.64	E_2-10% D implant:	32.97	E_2-20%D implant:	21.64
-PVP 10%	23.64	-PVP 10%	32.90	-PVP 10%	22.48
-PVP 20%	22.56	-PVP 20%	33.07	-PVP 20%	15.57
-PVP 30%	21.90	-PVP 30%	31.98	-PVP 30%	20.32

* T = TEC, D = DEP

In all cases, E_2 content in matrix implants was found to be well within 97 - 103%. Moreover, the standard deviation of each formulation was very low, confirming homogeneous dispersion of the drug in the matrices. The E_2 release of all formulations was studied in phosphate buffer pH 7.4 with 3.5% w/v BAC. The E_2 release from the matrices using two polymer carriers of high and low MW PVAc are presented in Figure 2. The PVAc of different molecular weights did not provide difference in E_2 release rate. About 14% of E_2 was gradually released from the matrices during 28 days. The porosity and tortuosity of polymeric network seemed not to be the important factors in controlling E_2 release from this system. From the previous study by Wiranidchapong (2006), it was indicated that poor solubility of E_2 in the release medium would predominate in controlling the release rate of E_2 from implant matrix using acrylate polymer (solubility in 3.5 % w/v BAC in PB 7.4 at 37 °C was 891.29 µg/ml)[7]. So the difference of the MW of PVAc used as the carrier might not significantly change E_2 release profiles.

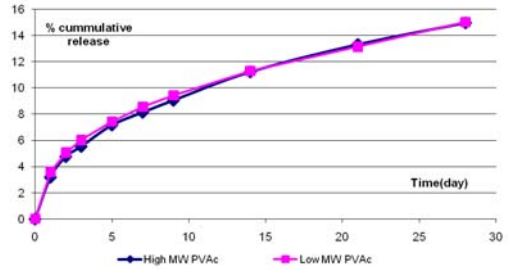
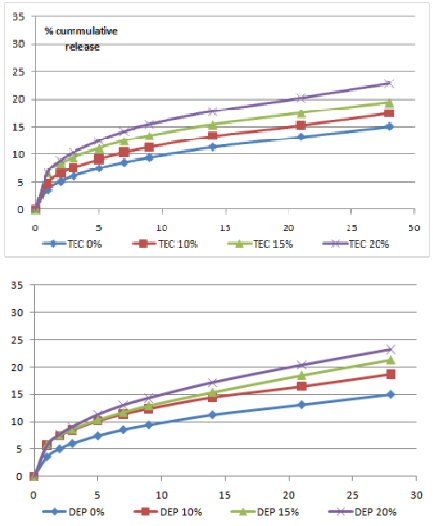


Figure 2 The release of E_2 from matrix implants using different low (113K) and high (500K) molecular weight PVAc.

The dissolution profiles of E_2 from matrices of low and high MW PVAc with 0, 10, 15 and 20 % TEC or DEP are shown in Figure 3 and 4. Increasing the plasticizer amount resulted in an increase in drug release for all formulations when compared with the matrices without plasticizer. The obtained results indicated that the E_2 release from PVAc of various weight percents of plasticizer increased in the following order: 20%, >15%, >10%, and >0%. Comparing with implants without plasticizer, adding plasticizers from 10 to 30% caused an increase of drug release between 2-8 % for low MW PVAc implants but drug release increasing were higher between 8-13 % for high MW PVAc implants.



(a)

(b)

Figure 3 The release of E_2 from matrices using low molecular weight PVAc with 0%, 10%, 15% and 20 % of TEC (a) and DEP (b) at various time intervals for 28 days.

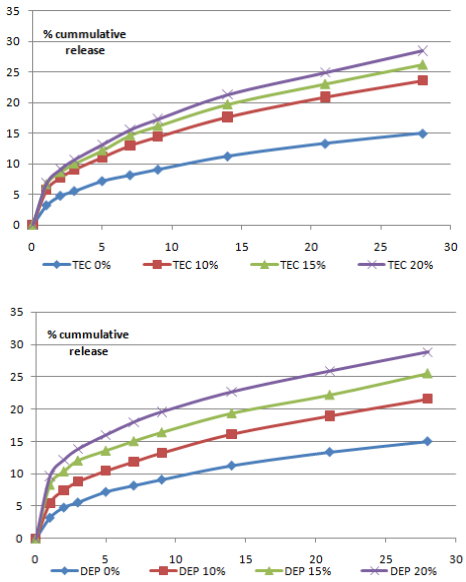


Figure 4 The release of E_2 from matrices using high molecular weight PVAc with 0%, 10%, 15% and 20% of TEC (a) and DEP (b) at various time intervals for 28 days.

Drug release from each implant was fitted to three different release models: the zero order, the first order, and the Higuchi model. The zero order model can be expressed as the following equation:

$$Q_t = Q_0 + k_0 t,$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in release medium, and k_0 is the zero-order release constant. The first-order model can be expressed according to the equation:

$$Q_t = Q_0 e^{-k1t},$$

where Q_t is the amount of drug remaining in the matrix at time t, Q_0 is the initial amount of drug in the matrix, and k1 is the first order release constant. The Higuchi model equation is expressed below:

$$Q_t = k_H t^{1/2},$$

where Q_t is the amount of drug released in time t, k_H is the Higuchi release constant.

The coefficient of determination (R^2) obtained from each fit was used as a criterion to choose the best model for drug release. It was found that Higuchi model was best described for drug release characteristic. The Higuchi release rate (% $hr^{-1/2}$) were calculated and plotted against the percentage of plasticizers as presented in Figure 5. The effect of 10%, 15% and 20% of TEC on drug release was different from 10%, 15% and 20% of DEP. In case of the implants using low MW PVAc, the Higuchi constant of 10% of DEP (2.938% $hr^{-1/2}$) was slightly faster than that of 10% TEC (2.860% $hr^{-1/2}$). The Higuchi release rate of the matrices with 15% and 20% of DEP (3.527% $hr^{-1/2}$ and 4.032% $hr^{-1/2}$, respectively) was also clearly faster than those with 15% and 20% of TEC (2.914% $hr^{-1/2}$ and 3.656% $hr^{-1/2}$, respectively). In case of the matrices using high MW PVAc, the Higuchi release rate of matrices with all levels of TEC (4.169% $hr^{-1/2}$, 4.953% $hr^{-1/2}$ and 5.049% $hr^{-1/2}$) was faster than those with DEP (3.695% $hr^{-1/2}$, 3.950% $hr^{-1/2}$ and 4.498% $hr^{-1/2}$). Adding plasticizer in matrices increased drug release when compared with the release rate of unplasticized implants using low MW PVAc (2.723 % $hr^{-1/2}$) and high MW PVAc 2.604 % $hr^{-1/2}$). It was seen that an increase of plasticizer amount in matrices caused an increase in release rate. The effect of TEC on drug release was different from the system containing DEP depending on the MW of PVAc. These results indicated the influence of different types and various weight percents of plasticizer to drug release rates. As it has been shown that both TEC and DEP are good plasticizers for PVAc by effectively reducing the Tg of implants. Therefore, both plasticizers increased chain mobility of polymer resulting in an increase of drug release.[16] However, an increase of plasticizer causing a decrease of polymer composition in the formulation might also have an increasing influence on the drug release rate in particular at 20% level of plasticizer.

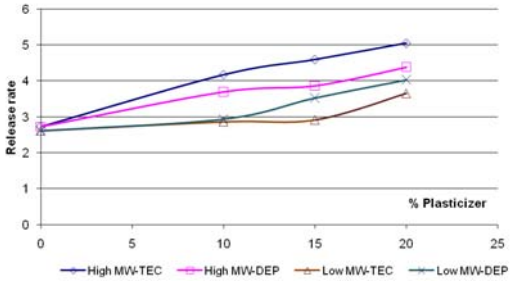


Figure 5 The Higuchi release rate (% $hr^{-1/2}$) of the matrix implants using low and high molecular weight PVAc containing various percentages of TEC or DEP.

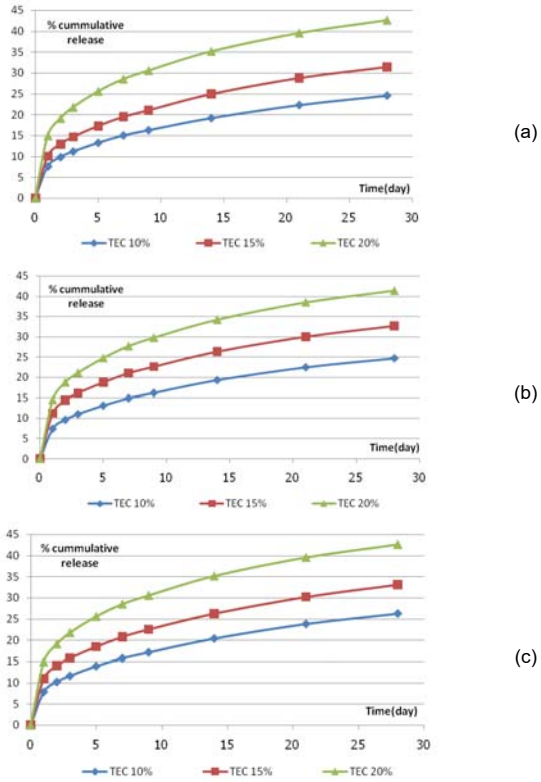
Surprisingly, plasticized PVAc implants showed the effect of MW on drug release when compared with the implants using the polymer without plasticizer. As it was seen implant using PVAc of low MW exhibited slower drug release rate than of high MW at the same level and type of plasticizer. This effect could be the different leaching of plasticizer from the implant matrices. Bodmeier and Paeratakul (1992)

indicated leaching of plasticizer from acrylic or ethylcellulose film depending on type, concentration, water solubility and affinity for polymer of plasticizer as well as other ingredients that adding in polymeric film.[17] Leaching of plasticizer in dissolution medium could alter it mechanical property and permeability of polymer. To demonstrate this effect, the DEP content remaining in the matrix after immersion in dissolution medium for 28 days was, therefore, determined as presented in Table 4. The low MW PVAc implant containing DEP exhibited a loss of plasticizer approximately up to 35 - 39 % when compared with that of high MW of PVAc implants showed about 25 - 26% loss. Leaching of plasticizer from the matrix might compete with E_2 release from the implant system. Therefore higher leaching of plasticizer from low MW PVAc implant resulted in slower drug release rate than that of high MW PVAc implant.

Table 4 Amount of DEP content remaining in low and high MW PVAc before and after immersion in dissolution medium for 28 days.

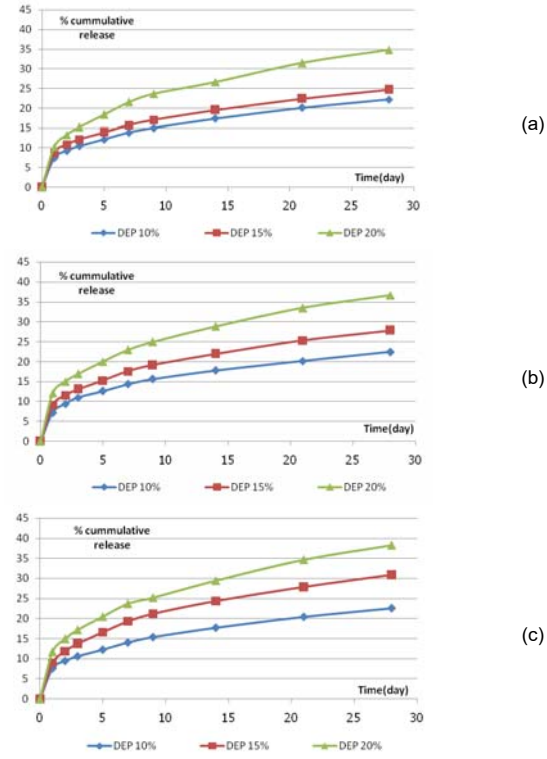
	Diethyl Phthalate (DEP)(%)					
	Low MW PVAc			High MW PVAc		
	10	15	20	10	15	20
Before immersion	98.87	92.72	91.47	89.91	92.22	90.21
After immersion	58.94	57.08	54.94	64.48	67.20	63.51
Plasticizer loss	39.63	35.64	36.53	25.43	25.02	26.70

The cumulative releases of E_2 from matrix composed of PVP 10, 20, and 30% with 10, 15, and 20 % TEC or DEP are shown in Figure 6-9. PVP was added as a water-soluble polymer additive to modify the release profile of E_2 from the matrix implants. During dissolution process, the PVP leached and created more porous matrix through which the drug diffused[13]. It was seen that PVP exhibited an increasing effect on drug release when adding in plasticized PVAc implants. When increased the amount of PVP levels between 10-30% in PVAc matrices with all TEC or DEP levels from 10, 15 and 20%, the E_2 release from low MW PVAc implants at day 28th increased from 24.61-26.26% to 31.44-33.13% and 41.43-42.60%, respectively, for TEC and 22.17-22.62% to 24.68-30.88% and 34.84-38.28%, respectively, for DEP; but in case of high MW PVAc implants the E_2 release at day 28th increased from 31.64-36.50%, 36.24-41.18% to 44.80-4.57%, respectively, for TEC and 35.96-37.37%, 41.22-42.36% to 45.43-48.13%, respectively, for DEP.



(a) (b) (c)

Figure 6 The release of E_2 from low MW PVAc matrices containing 10% (a), 20% (b) and 30% (c) PVP, with 10%, 15% and 20% of TEC at various time intervals for 28 days.



(a) (b) (c)

Figure 7 The release of E_2 from low MW PVAc matrices containing 10% (a), 20% (b) and 30% (c) PVP, with 10%, 15% and 20% of DEP at various time intervals for 28 days.

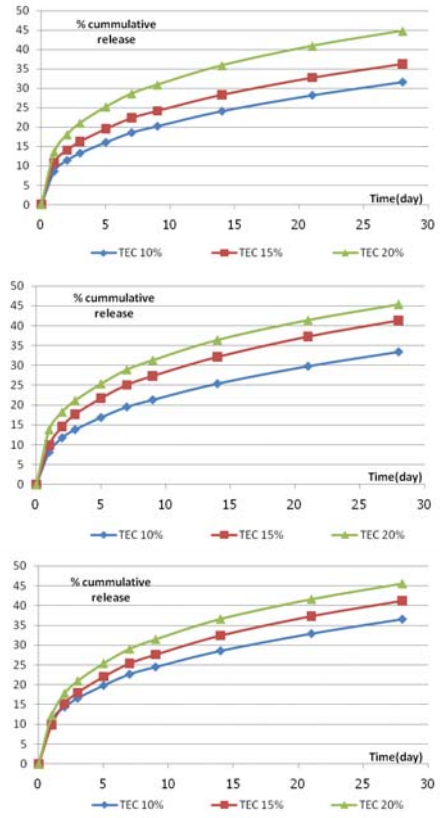


Figure 8 The release of E_2 from high molecular weight PVAc matrices containing 10% (a), 20% (b) and 30% (c) PVP, with 10%, 15% and 20 % of TEC at various time intervals for 28 days.

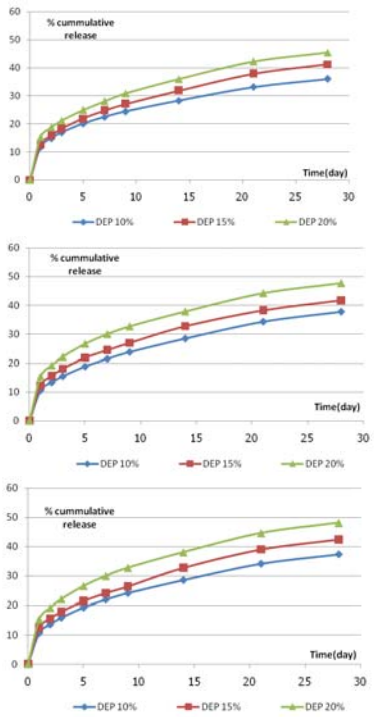


Figure 9 The release of E_2 from high molecular weight PVAc matrices containing 10% (a), 20% (b), 30% (c) PVP, with 10%, 15% and 20% of DEP at various time intervals for 28 days.

It was found that all profiles were best fitted to Higuchi release model. The plots of the Higuchi release rate of all formulations in relationship with percentage of added PVP at various TEC or DEP levels were presented in Figure 10. It was likely that the change of PVP quantity from 10 to 30 % did not exert much more effect on drug release from the matrices. It was observed that addition of plasticizers gave more effect on drug release of the matrices.

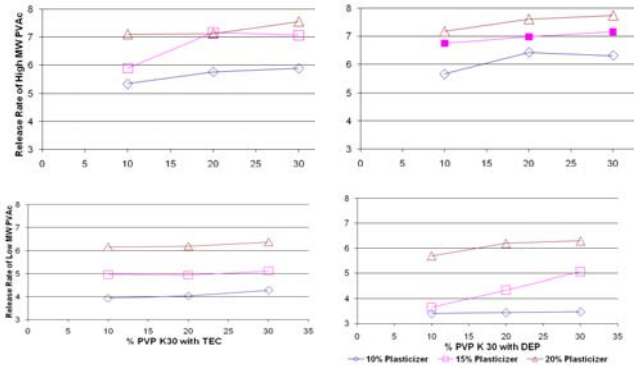


Figure 10 Effect of % PVP in the implant matrices on the Higuchi release rate (% $hr^{-1/2}$) of E_2 from low (113K) and high (500K) MW PVAc implants containing different % TEC and DEP.

Conclusion

PVAc could be used as a release controlling agent in an implantable controlled release drug delivery system of E_2. The E_2 implants using PVAc alone released approximately 14 % of E_2 within 28 days. Incorporation of plasticizers and water soluble polymers could modify E_2 release rate. Leaching of plasticizer from the PVAc matrices should take into account that may affect on theirs drug release behaviors. The information obtained from this study would be useful in future work when apply the hot melt extrustion (HME) technique to prepare a solid dispersion implant device using PVAc as the polymeric base.

Acknowledgements

This work was financially supported in part by the Graduate School, Chulalongkorn University.

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Editorial note
Manuscript received in original form on March 15, 2011;
accepted in final form on December 30, 2011