Study on Volume Ratio and Plasticizer Screening of Free Coating Membranes Composed of Ethyl Cellulose and Chitosan

Wen He,[1,2] Yumin Du,[2] Lihong Fan[2]

[1]*Department of Pharmacy, Renmin Hospital of Wuhan University, Wuhan 430060, People's Republic of China*
[2]*Department of Environmental Science, Wuhan University, Wuhan 430072, People's Republic of China*

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ABSTRACT: The aim of this study was to optimize the formula of free blended coating membrane of ethyl cellulose (EC) and chitosan (CS), including their suitable ratio range and the best plasticizer used. The dry films were produced by a casting/solvent evaporation method, with different volume ratio of EC and CS solution plasticized by various plasticizers, respectively. The wet films were prepared by immersing dry films in pH 6.8 phosphate buffer saline (PBS) for 24 h. The promising ratio range of EC/CS was below 20/5 or 20/6 with various plasticizer, which was determined by comparing the viscosity of the blended solutions and the morphology of the blended films. The efficiency of plasticization was evaluated by measuring glass transition temperature (T_g). All the testing plasticizers have good compatibility with EC or CS and dibutyl phthalate (DBP) have the strongest efficiency inducing the lowest T_g (39.9°C) of the film. Mechanical properties were evaluated by the ratio of tensile strength (T) to elastic modulus (E). In the wet state, the films with DBP had the highest T/E value (1.2). The results of leaching of plasticizers also verified that DBP was the most stable plasticizer in the films. The release rates of tetramethylpyrazine phosphate (TMPP) through the pellets coated with the blended films of EC/CS (20 : 6 v/v) plasticized by various plasticizers showed that the more water-soluble the plasticizer was, the more quickly TMPP dissolved from the coated pellets, which further indicated that the water-insoluble plasticizers (such as DBP) could be more applicable to keep the sustained or controlled release property of the blended films in wet state. J Appl Polym Sci 100: 1932–1939, 2006

Key words: free coating membranes; ethyl cellulose; chitosan; plasticizer; extended drug release

INTRODUCTION

Because of high biocompatibility, biodegradation, and low toxicity, chitosan (CS), a natural polysaccharide from chitin, is an interesting material in pharmaceutical applications. Nowadays, it has been employed as a multifunctional adjuvant widely used in many dosage forms, such as films,[1–3] tablets,[4,5] microparticles,[6,7] hydrogels,[8,9] and so on. Recently, much attention has been focused on sustained or controlled drug release properties of CS. Especially in tablets and pellets, it could be utilized not only as an extended-release matrix, but also as a promising extended-release coating membrane material.[10] CS also could be blended with a hydrophobic coating material, such as ethyl cellulose (EC), in appropriate ratios to adjust desirable drug release rate from core tablets or pellets. Blends of EC and CS as delayed or sustained drug release coating film material have not previously been investigated. In this study, EC is chosen as the major coating component and CS as the minor component to form blended coating films with different proportions of EC and CS to determine the most promising proportion range for practical application.

Besides the two major components, the type and concentration of plasticizer used in the coating film also play an important role in good quality and stability of the blended film. Film tests in dry state are usually performed to optimize the formula of coating films, but in wet state, water-soluble plasticizer could dissolve quickly, leading to significant changes in the film mechanical properties. The film could become more fragile. Meanwhile, the water-soluble components in core tablets or pellets could also dissolve to form higher osmotic pressure than that of outside solution, resulting in smashing of the coating film. Those unfavorable changes in wet state could ultimately give rise to losing extended release ability of the coating membrane.[11] So, it is very important for the plasticizer to keep stable in the coating film even in wet state. In this study, the effect of different plasticizers, including water-soluble and water-insoluble

Correspondence to: Y. Du (duyumin@whu.edu.cn).
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ones, on the morphology and mechanical properties of the blended coating films composed of EC and CS and the model drug release rate from pellets coated with the blended films were investigated. Additionally, the concentration changes of those plasticizers were detected in wet films to screen the best plasticizer used in the blended films.

EXPERIMENTAL

Materials

Chitosan (CS) with molecular weight of 210 kDa and degree of deacetylation of 95% was supplied by Haipu Biothechnology (China) and ethyl cellulose (EC, ethocel, 10 cps, ethyl substitution degree of 48.0–49.5%) was from Shanghai Colorcon Coating Technology, China. Six types of plasticizer including propylene glycol (PG), triacetin (TR), dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), and diethyl sebacate (DES) were analytical pure and supplied by Huiyou Fine Chemical Plant, China. Glycerol was pharmaceutical grade and purchased from Nanchang Baiyun Pharmaceutical Chemical Plant. Tetramethylpyrazine phosphate (TMPP) was conformed to the standard in the China Pharmacopoeia 2000 edition (Chp2000) and purchased from Beijing Yanjing Pharmaceutical Factory, China.

Preparation of dry and wet films of EC and CS in different ratios

The polymeric films were produced by a casting/solvent evaporation technique. EC solution (2.5% W/V) was prepared by dissolving EC in anhydrate ethanol at 25°C, while CS solution (2.5% W/V) was attained by dissolving CS in 2% (v/v) acetic acid, with magnetic stirring in water bath at 30°C. Referring to the ratio of EC and HPMC,[12] we decided the volume ratio of EC and CS solution was 20 : 2, 20 : 3, 20 : 4, 20 : 5, 20 : 6, 20 : 7, and 20 : 8, respectively. After the addition of the seven types of plasticizer (3% w/w), respectively, the viscosity measurements were carried out using a conventional Ubbelohde viscometer that was placed in a thermostatically controlled bath with a precision of 0.01°C and the viscosity was calculated according to the reference.[13] Then, the blends were left to stand until removal of trapped air bubbles, poured quantitatively on glass petri dishes, and dried in an oven at 40°C till constant weight. The thickness of each dry film was determined in 10 different places of the films with a micrometer (The Guiling Measuring Tool Factory, China). The morphology of each dry blend membrane was detected with naked eyes and an optical microscope (CK 40, Olympus, Japan). The interaction between EC and CS was examined by FTIR (SX-170, Nicolet, USA). The wet films were prepared by immersing dry films in pH 6.8 phosphate buffer saline (PBS) at 37°C, with stirring rate of 100 rpm for 24 h, and then were being taken out to remove surface water with filter paper.

Determination of T_g of different blended films

Dynamic mechanical thermal analysis (DMTA) was performed on an MK Ivdynamic viscoelastic spectrometer (Rheometric Scientific, USA) under the following conditions: frequency of 10 Hz, heating rate of 10°C/min, and scanning of temperature range of 30–200°C. The curves of EC, CS, and blended films containing various plasticizers were recorded.

Mechanical properties of dry and wet blended films

Before mechanical testing, the dry films were stored at the condition of 25°C ± 2°C and RH 30% ± 5%. The wet films underwent the mechanical testing as soon as they were taken out from PBS and removed the surface water. During the testing, the room conditions were 25°C ± 2°C, RH 80% ± 5%. All dry and wet films were cut into rectangles of 10 mm × 70 mm. The films were fixed between the two grips of a universal testing machine (CMT6503, Shenzhen SANA Test Machine, China), with the test area of 10 mm × 50 mm and the stretch rate of 5.0 mm/min. Each experiment was repeated at least five times.

Determination of dissolution rate of each plasticizer in the blended films and water uptake of each film

Rotating basket method in Chp2000 was used to detect the dissolution of each plasticizer in blended films in 200 mL PBS of pH 6.8 at 100 rpm and 37°C ± 0.5°C, using ZRS-8 Intelligent Dissolution Apparatus (Radio Factory of Tianjin University, China). At various time intervals (0, 4, 8, 12, and 24 h), about 300 mg wet films were cut and removed from the medium. After removing the surface water with filter paper, the films were weighted (m_1). Films were put into a desiccator till it reached constant weight (m_2). The remains of the plasticizers in the films were detected. The analytical method used was high pressure liquid chromatograph (LC-9A HPLC, Shimadzu, Japan) with column of ODS-C_{18}, mobile phase of methanol for TR and DES (determination wavelength of 217 nm), while methanol and purified water of 4.5 : 5.5, 7 : 3, and 8.5 : 1.5 v/v for DMP, DEP, and DBP (determination wavelength of 260 nm), respectively, with flow rate of 1.0 mL/min. As for PG, gas chromatograph (GC) was employed with CP-sil-8CB large caliber capillary column by Programmed Temperature Ascending method. Concentration of glycerol was determined by

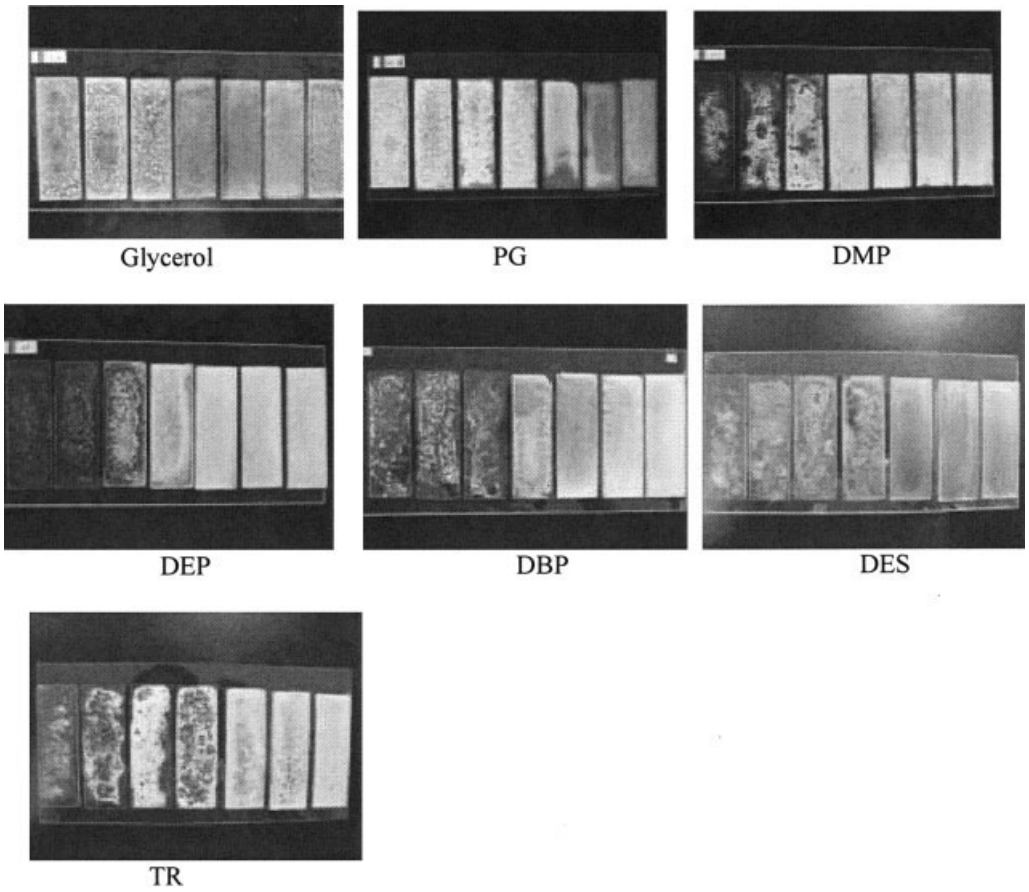

Figure 1 Optical graphs of the blending films in different ratios of EC solution and CS solution (from the left to the right: 20 : 2, 20 : 3, 20 : 4, 20 : 5, 20 : 6, 20 : 7, and 20 : 8 v/v) plasticized by 3% w/w various plasticizers.

sodium hydroxide titration, according to Chp2000. The water uptake fraction% (f) was calculated by the following equation: $f = (m_1 - m_2)/m_2 \times 100\%$ ($n = 5$).

Determination of permeability of blended films with different plasticizer

The oral dosage form chosen for the study was a spherical pellet, ~1 mm in diameter, containing a water-soluble model drug substance (TMPP) mixed with microcrystalline cellulose in the proportion of 65:35% by weight. The pellets were coated with a film formulation consisting of EC and CS with various plasticizer (3% w/w) in a fluidized bed (WSLD 5, Glatt, Haltingen, Germany) till a 3% increase in weight. The diameter of the spray nozzle was 0.5 mm and the speed of spray was 1.0 mL/min. The temperature of the bed and the spray nozzle was 38 and 36°C, respectively. The coated pellets were hand filled into No. 0 hard gelatin capsules (fill weight 260 mg). The dissolution of TMPP from the capsules in 900 mL PBS of pH 6.5 was monitored using rotating basket method (37°C ± 0.5°C, 50 rpm) and ultraviolet spectrophotometry (UV-2201 Shimadzu spectrophotometer) at 295 nm was used for TMPP determination.

RESULTS AND DISCUSSION

Morphology of different blended films

Optical graphs of the blending films in different proportions of EC and CS plasticized by various plasticizers are shown in Figure 1. All systems exhibited morphology typical to nucleation and growth mechanism of phase separation, with CS-rich domains dispersed in an EC-rich matrix exhibiting incompatibility between EC and CS. These properties were much similar to those of EC- and HPMC-blended coating films.[14] However, some interaction via the unsubstituted hydroxyl groups in molecules of EC and CS and hydroxyl groups of EC with ammonium groups of CS did occur, which was proved by FTIR spectra (Fig. 2). A band at 3489 cm^{-1} has been attributed to —OH group stretching vibration in EC matrix, while a band at 3427 cm^{-1} to —NH_2 and —OH group stretching vibration in CS matrix. In the blending film, a shift to 3406 cm^{-1} is shown, and the peak becomes wider, which indicates hydrogen bonding is enhanced. With the increase of CS volume (20/2–20/8 v/v of EC/CS), the intensity of hydrogen bonding was increased. The compatibility between EC and CS was improved, re-

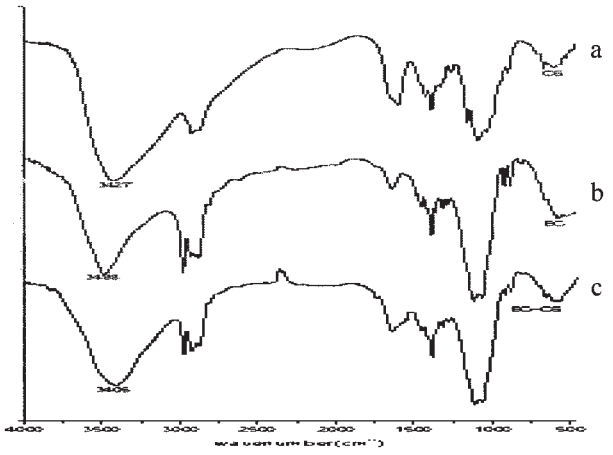

Figure 2 FITR spectra of (a) CS, (b) BC, and (c) EC with CS of 20 : 6 v/v.

sulting in the more homogeneous surface state. The ratio of 20 : 5 v/v seemed to be the turning point with glycerol, PG, DMP, DEP, and DBP as the plasticizer, while with TR and DES, the turning point changed to the ratio of 20 : 6 v/v (Figs. 1 and 3). When the concentration of CS was increased in blends, the viscosity of the blended solutions was increasingly dropped. The solutions of the first three testing proportions of EC and CS, i.e. 20 : 2, 20 : 3, and 20 : 4 v/v, were so sticky (with viscosity of above 40 cpa. s) that they all exhibited gel properties, which were probably hard to be applied as coating materials. So, the best ratio range of EC/CS was below 20/5 with glycerol, PG, DMP, DEP, and DBP as plasticizer and below 20/6 with DES and TR as plasticizer. Meanwhile, the polymer incompatibility was not only due to the solvent system, thermodynamic incompatibility of the two polymers, and their different volume proportions but also had certain relationship with the chosen plasticizer. When the concentration of different plasticizers was unchanged (3% w/w), and the preparation method was also paralleled, then the changeable parameters were the type of plasticizers and the ratio of EC and CS. As shown in Figure 3, the morphologies of the films plas-

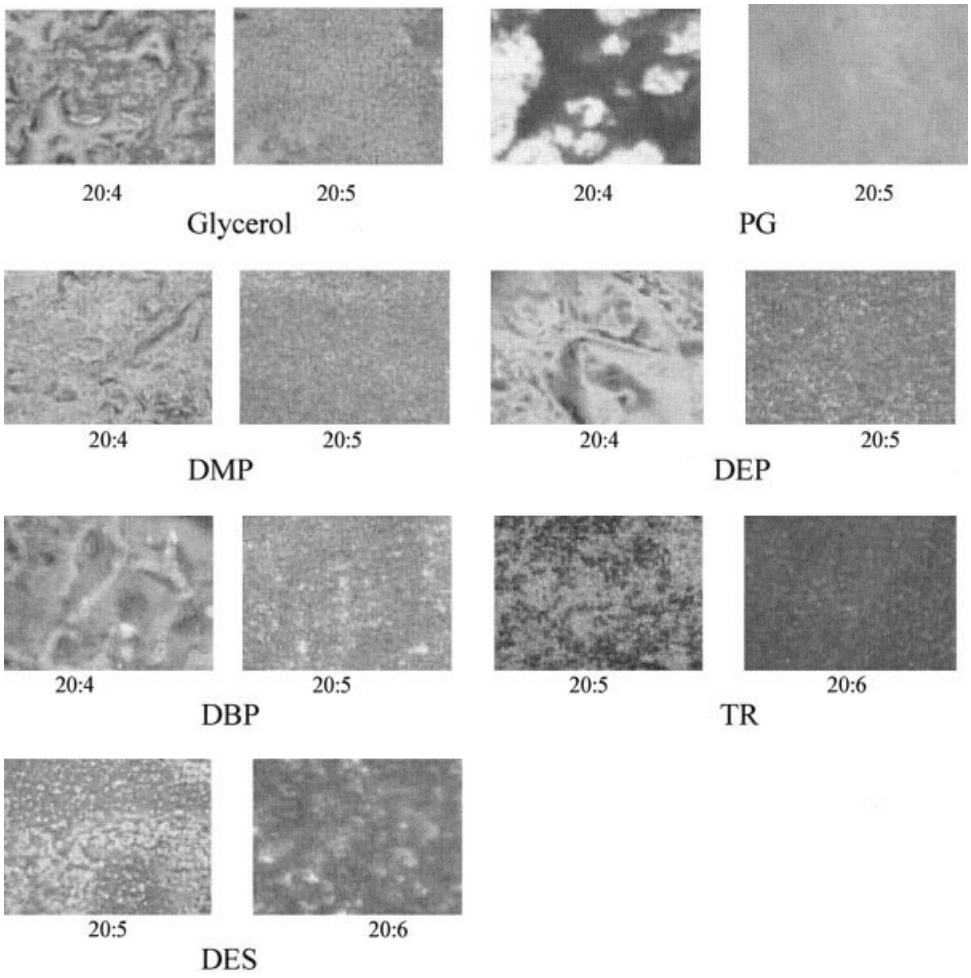

Figure 3 Contrast of optical micrographs of EC and CS blending films at the turning point and before the point with 3% (w/w) various plasticizers (magnification ×200).

ticized by various plasticizers had significant difference from each other in the size of the dispersion phase. We also observed that the effect of thickness of coating films on the film morphologies was very noticeable. In general, the thicker the films, the larger size of disperse phase was. In our study, the thickness of each dry film was then controlled inside the limits of 80 ± 5 μm (RSD 5%).

T_g of different blended membranes with various plasticizers

The tan δ/temperature curves for the films of EC, CS, and the blends of EC with CS containing various plasticizers are shown in Figure 4(a–h). Figure 4(a) showed T_g of EC was 144.12°C, with a relative sharp transition, while Figure 4(b) displayed T_g of CS was 140.05°C, with a broad peak. We could not obtain the T_g curve of the blended film of EC and CS without a plasticizer because of the fragility of the film. If a plasticizer can insert the chains of a polymer effectively, it can weaken the attractive strength among the chains and enhance the flexibility of the chains, thus T_g of the polymer will be dropped. Figure 4(c–h) showed that there were two T_g peaks in all curves for EC and CS, respectively, indicating that those plasticizers could reduce the T_g of EC or CS. We proposed that most of water-soluble plasticizer (i.e., glycerol, TR, DES, and DMP) could go into the chains of CS, resulting in significant T_g dropping of CS, while most of water-insoluble plasticizer (i.e., DEP and DBP) inserted the chains of EC, leading to T_g dropping of EC. Among them, DBP seemed to have the highest plasticizing efficiency, causing the lowest T_g (39.9°C) for EC of the blended film. Films plasticized by PG did not undergo DMTA determination for the high fragility.

Mechanical properties of dry and wet films

Besides T_g, tensile strength (T), elongation (%), and elastic modulus (E) are always utilized to evaluate compatibility and effectiveness of plasticizers with polymeric films. Rowe[15] thought that using only one kind of aforementioned parameters could not show the mechanical properties of coating films completely. He has verified through experiments that the T/E value had significant relationship with quality of films, i.e., the less T/E value, the more flaws were in the films. So, T/E value was employed in the present study to assess the function of each plasticizer in the films (Table I). The results showed that mechanical properties of the dry films (EC/CS equals to 20/6 v/v) with various plasticizers had significant differences. Among them, the films with TR had the highest T/E, which indicated that film coating systems in dry state plasticized by TR might have the most promising intensity and toughness to resist the damage in the process of package, shipment, and storage.

However, the wet films exhibited quite different mechanical properties from the dry films. In the wetted films, there was hydroplasticization caused by water, which was one reason for the lower T of the wetted films compared with the dry ones. The dry films with glycerol, PG, DES, TR, and DMP, respectively, all had higher T and lower E than the corresponding wet films so that T/E values of dry films were much higher than those of the wet ones. On the contrary, the films involving DEP and DBP, respectively, had both higher T and E in dry state than in wet state, and the T/E values of their wet films were all higher than those of dry films. The reason might be that in wet state, the chains of the two polymers were more expanding, leading to easy insert of the plasticizers. If the plasticizer was water-insoluble, more of it could insert between the chains of EC, causing the improvement of the mechanical properties of the blending films in wet state. If not, the quick dissolution of the plasticizer could cause the instability of the blending films. Additionally, the lower the water solubility of plasticizer, the higher T/E of corresponding wet membrane. (The water solubility order is glycerol > PG > TR > DES > DMP > DEP > DBP.) Although the mechanical properties of dry films with water-soluble plasticizers were good enough for coating films, they would become more fragile after hydration, leading to decrease of film mechanical stability in wet state.

Dissolution of each plasticizer from the blended films and water absorption of the films

The blended films were composed of EC and CS solution in ratio of 20/6 v/v containing various plasticizers (3% w/w). Because CS only can dissolve in pH < 6.5 solution and EC is a hydrophobic polymer, in PBS of pH 6.8, both CS and EC cannot dissolve and they have no influence on the detection of the plasticizer concentration. The results have showed that different plasticizer types had different dissolution rate. After 24 h dissolution, the concentration of DBP was nearly intact within the wet membranes. The remaining concentration order of the plasticizers after 24 h dissolution in the study was DBP > DEP > DMP > DES > TR > PG > glycerol, which was reverse to their solubility order in water (Table II).

Water absorption of each membrane after 24 h dissolution of dry films showed significant relevance with the dissolution rate of the plasticizer. Observed under an optical microscope (Fig. 5), the blended film with glycerol had many micropores that were occupied by dissolution medium, resulting in higher water uptake. Meanwhile, the morphology of blended film with water-insoluble plasticizer DBP was still smooth

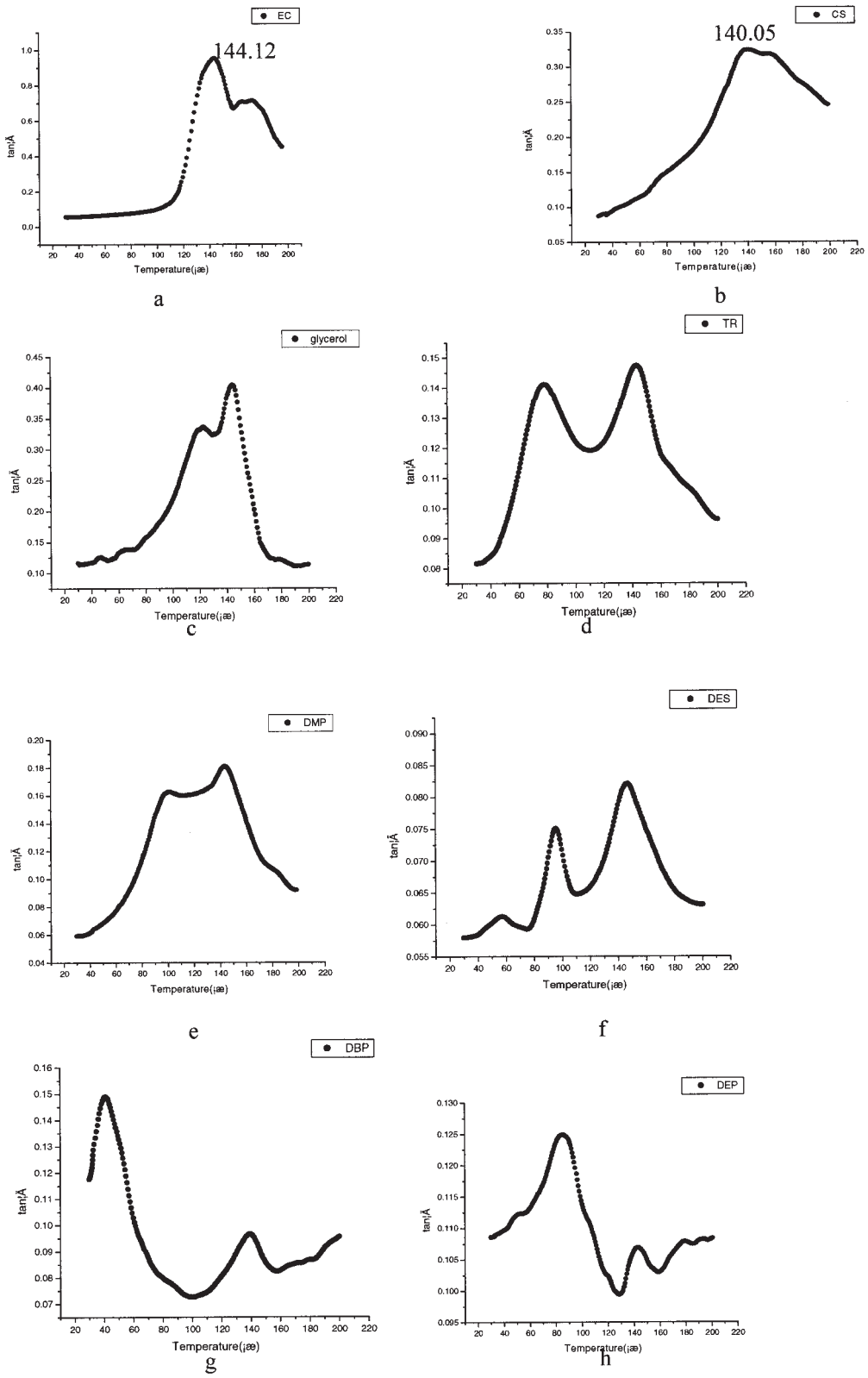

Figure 4 DMTA thermograms of pure EC (a), CS (b), and their blending films in ratio of 20:6 (v/v) with 3% (w/w) different plasticizers, (c) glycerol, (d) TR, (e) DMP, (f) DES, (g) DBP, and (h) DEP.

and compact with lower water uptake. Therefore, it could be further deduced that because of the micropores caused by dissolution of water-soluble plasticizer in the blending films, the mechanical properties of the blending films with water-soluble plasticizers could be impaired greatly in wet state.

TABLE I
Mechanical Property of the Blending Films of EC and CS in Ratio of 20 : 6 (v/v) with 3% (w/w) Various Plasticizers in Both Dry and Wet States

Plasticizer	*T* (mPa)	Elongation (%)	*E* (mPa)	*T/E*
Glycerol				
Dry	0.30 ± 0.20	10.93 ± 0.20	0.91 ± 0.20	0.34
Wet	0.08 ± 0.15	2.45 ± 0.30	1.26 ± 0.10	0.063
PG				
Dry	0.41 ± 0.10	3.70 ± 0.16	0.85 ± 0.20	0.48
Wet	0.13 ± 0.10	8.40 ± 0.15	1.76 ± 0.15	0.074
DMP				
Dry	5.67 ± 020	2.65 ± 0.50	6.15 ± 0.30	0.94
Wet	1.64 ± 0.30	3.88 ± 0.30	6.78 ± 0.20	0.24
DEP				
Dry	3.97 ± 0.14	3.00 ± 0.20	4.36 ± 0.18	0.91
Wet	2.97 ± 0.15	3.02 ± 0.20	2.70 ± 0.21	1.1
DBP				
Dry	3.16 ± 0.20	3.73 ± 0.20	3.90 ± 0.17	0.81
Wet	3.01 ± 0.20	8.00 ± 0.12	2.51 ± 0.11	1.2
TR				
Dry	4.54 ± 0.10	1.02 ± 0.18	4.31 ± 0.12	1.05
Wet	1.47 ± 0.10	1.59 ± 0.10	8.67 ± 0.15	0.17
DES				
Dry	3.29 ± 0.10	0.91 ± 0.22	8.96 ± 0.14	0.37
Wet	2.09 ± 0.20	1.59 ± 0.20	10.45 ± 0.15	0.20

TMPP release from the coated pellets

The dissolution profiles of the pellets coated with EC and CS (20/6 v/v) plasticized by different plasticizers are shown in Figure 6. It can be found that TMPP release rate speeds up with increasing water-solubility of these plasticizers. It further proved the micropore formation in the films with water-soluble plasticizers in solvents. It could be inferred that the blended films plasticized by higher water solubility plasticizers may have quicker drug release rate. According to the study by another author,[16] two mechanisms for the release of TMPP from such a system could be proposed: (a) transport of TMPP through a hydrated swollen film and (b) transport of TMPP through a network of capillaries filled with dissolution media. Before the water-soluble component (CS) is still retained within the matrix, the former mechanism is the major process. If CS is leached out of the matrix, the latter one is applicable. Meanwhile, if the plasticizer is water-soluble, it can enhance the drug release by the two mechanisms significantly because of its quick dissolution to form micropores, while those water-insoluble plasticizers has little effect on the drug release from the pellets, leading to the similarity in the dissolution profiles of TMPP pellets coated with the blended film plasticized by DBP and DEP, respectively.

TABLE II
Water Absorption of Each Membrane after 24 h Dissolution of Dry Films

Plasticizer	*C* (%) Dry	*C* (%) Wet	Loss (%)	Water absorption (%)
Glycerol	99.3 ± 0.4	12.2 ± 0.6	87.1	25.9
PG	99.5 ± 0.1	28.9 ± 0.7	70.6	10.4
DMP	100.8 ± 0.6	70.8 ± 0.2	31.0	6.75
DEP	99.6 ± 0.3	80.2 ± 0.2	18.9	4.22
DBP	99.7 ± 0.4	98.0 ± 0.4	1.71	3.98
TR	99.5 ± 0.5	32.2 ± 0.2	67.3	8.72
DES	100.4 ± 0.2	58.0 ± 0.2	42.4	7.22

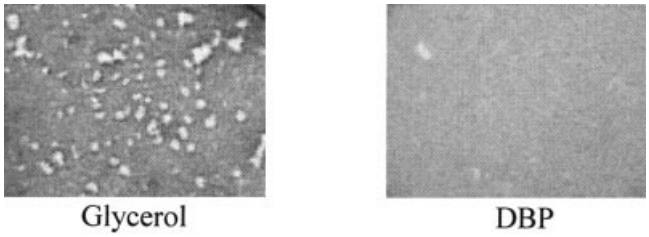

Figure 5 Optical microscopes of the blending films with glycerol (left) and DBP (right) after 24 h dissolution in PBS (pH 6.8)(magnification × 200).

CONCLUSIONS

Because of the absence of great intermolecular interactions between EC and CS, the blended membranes of EC and CS showed morphologies of nucleation and phase separation, which were affected greatly by the ratio of EC and CS, the type of plasticizer, and the film thickness. There was a turning point in the various ratios of EC and CS with different plasticizers. When CS concentration was increased from the point, the viscosity of the blended solution gradually decreased, and the morphologies of the blending films became more homogeneous.

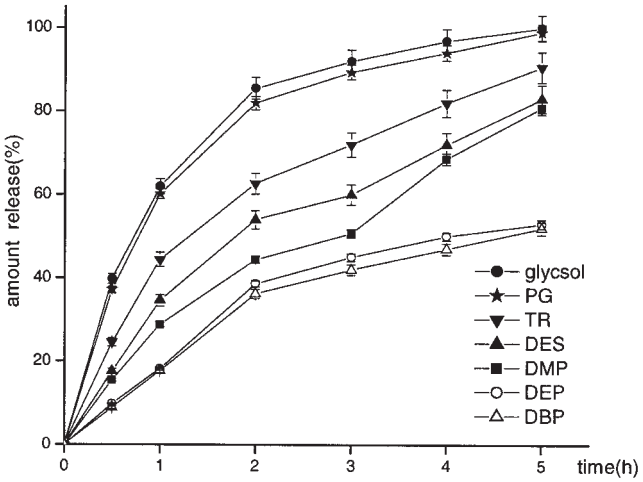

Figure 6 The dissolution profiles of TMPP pellets coated with EC and CS (20 : 6 v/v) plasticized by various plasticizers (3% w/w).

The best ratio range of EC/CS was below 20/6 with all the tested plasticizers. The blended films showed different morphology characters when they were plasticized by various plasticizers. The results of T_g determination tests showed that the plasticizers all had excellent compatibility with the blended films by inserting the chains of either EC or CS decided by the solubility of the plasticizers and DBP had the highest efficiency of plasticization leading to the lowest of T_g of EC. To be stable in wet state, especially in the case of high osmotic pressure from core tablets or pellets, the blended films with a plasticizer should be pliable and tough enough in both dry and wet state. The blended films in wet state plasticized by DBP had the highest *T/E* value (1.2), showing the best stability in wet state. The results of the plasticizers dissolution rate and TMPP release test also indicated that the water-insoluble plasticizer (such as DBP) might be more suitable to the blended films of EC and CS than water-soluble ones.

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