JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

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J Pharm Biomed Sci 2015; 05(05): 372-379.

Journal of Pharmaceutical and Biomedical Sciences (***J Pharm Biomed Sci.***), **Member journal. Committee on Publication ethics (COPE) and Journal donation project (JDP).**

PBMS
Journal of Pharmaceutical and Biomedical Sciences

ISSN NO- 2230 – 7885
CODEN JPBSCT
NLM Title: J Pharm Biomed Sci.

Research article

Influence of Composition and Physical Aging Treatment on Properties of Free Ethyl Cellulose Film

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Article citation:
R Luo, X Luo, N Sun, Y Pu, P Wang, D Ran, et al. Influence of composition and physical aging treatment on properties of free ethyl cellulose film. *J Pharm Biomed Sci.* 2015; 05(05):372-379. Available at www.jpbms.info

ABSTRACT:
Film coating by insoluble polymer materials is one of the most commonly used methods to control drug release in sustained and controlled release preparations. The composition, aging process and the stability of coating film significantly affect the drug release behavior. Ethyl cellulose (EC), a derivative of cellulose insoluble in water, is widely used as film coating material to realize sustained and controlled release. In this work, the properties of free EC film, including mechanical properties, water uptake and water vapor transmission (WVT), were investigated for different film composition after treatment under different aging and storage condition. As the concentration of plasticizers in the film increased, the tensile strength descended with a raise of elongation at breakage. Compared with the domestic EC films, imported EC films had a smaller tensile strength and higher elongation at breakage. The water uptake and WVT capacity decreased with the extension of aging time while increased with the enhancement of plasticizer concentration. The imported EC films showed a generally less water uptake and WVT capacity than domestic EC films. With the extension of aging time, the tensile strength of the films prepared with different plasticizers increased while the elongation at breakage decreased. The water uptake and WVT of the films was reduced as well. The sort and concentration of plasticizers, the sort of EC and the aging time had a great impact on the properties of free EC films. The preparations coated with imported EC may be stable than those with domestic EC.

KEYWORDS: Ethyl cellulose film; Plasticizer; Aging time; Mechanical properties; Water uptake; Water vapor transmission.

INTRODUCTION
Film coating is a technique to cover the solid preparation with a layer of polymer coating materials, which aims to achieve the optimal therapeutic effect of drugs. The advantages of coating include light-proof, moisture-proof, masking the poor odor of drugs, separating incompatible ingredients and controlling position, rate and extent of drug release. Film coating trends to be used more and more widely because of its good stability and high coating efficacy[1]. From the mid-20th century, film coating have become a continuous interest in the aspect of

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ournal of Pharmaceutical and Biomedical Sciences
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membrane-controlling sustained release preparations. Coating materials, such as ethyl cellulose (EC) and acrylic resins of Eudragit RS/RL/NE series, which cannot be dissolved in water and whole physiological pH range, were commonly used. This study is dedicated to investigate the properties of EC film.

EC is a kind of water-insoluble polymer material, which can be dissolved in many organic solvent and usually applied in membrane-controlling sustained release preparations. However, dynamic mechanical analysis of film showed that EC itself was not suitable for film coating because of its low flexibility and low elongation with high stress[2]. Scientists always focused on optimizing the formulation of EC film by using suitable plasticizer or mixing with coating materials. The influence of plasticizer is essential to enhance film-forming characteristic, workability and serviceability of the coatings[3]. Bodmeier R et al. investigated how the plasticizers distributed in polymers through changing the ratio and detecting the concentration of plasticizers[4]. Kuang CC. et al. certified that the plasticizer could decrease the glass transition temperature of film, which indicated that the film can turn softer with appropriate plasticizer so that can resist more mechanical force[5]. On the other hand, other polymers were reported to be blended into EC film to satisfy specific drug delivery systems. Karrout Y.'s study showed that Nutriose (a water-soluble, branched dextrin) and EC complex film was a highly promising film coating materials for advanced drug delivery systems allowing for colon targeting[6]. Fan TY. et al. reported that tablets with EC/Eudragit L as coating film generated a pulsatile release of drug rapidly after a predetermined lag time of about 3-h in intestine rather than in stomach[7].

However, referring to the influence of aging condition on film properties, only a few studies were related. Guo JH et al. found that the creep compliance of EC latex films decreased with aging time, and the film forming temperature had no effect on the mechanical properties within the range of 60 °C to 100 °C [8]. Muschert S et al. studied about aqueous polymer dispersions for the preparation of controlled-release film coatings. They compared two curing methods for ethylcellulose:poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer) film coatings and found that 2h dynamic curing at 57 °C and relative humidity of 15% assured stable film structure in the case of theophylline matrix cores coated with 15% ethylcellulose : PVA-PEG graft copolymer 85:15 [9].

Although kinds of formulation of EC film coating were investigated and employed, the property research of free EC film was still not complete and comprehensive until now, especially under different physical aging and storage conditions. In this study, in order to provide more reference for EC coating, properties of free EC films made of different composition and treated for different aging time were investigated through detecting their mechanical property, water uptake and water vapor transmission (WVT).

MATERIAL AND METHODS

MATERIALS

Domestic Ethyl Cellulose (EC) was purchased from Shantai Cellulose Co. Ltd (Guangdong, China). Imported Ethyl Cellulose (EC) was from Shanghai Colorcon Company (China). Dibutyl Sebacate (DBS) and Triethyl Citrate (TEC) were supplied from Aladdin Chemistry Co. Ltd (Shanghai, China). Diethyl o-Phthalate (DEP) was from Damao Chemical Reagent Factory (Tianjin, China). All other reagents were of analytical grade.

PREPARATION OF FREE FILMS

The free films were prepared by plate casting method based on different formulation by changing the sort and concentration of plasticizers and the sort of EC. After dissolving completely, appropriate amount of EC solution was poured into a plate and subsequently dried to remove solvent. Then the free films were removed off the plate and dried again at 50 °C for physical aging of different time. Ultimately, the smooth homogeneous free films were tested for mechanical properties and capacity of water uptake and water vapor transmission (WVT).

MECHANICAL PROPERTIES EVALUATION

According to national standards[10], the prepared free films were cut into 11cm×1cm rectangular pieces and measured the thickness. The mechanical properties test was performed with electronic universal testing machine (AG-1, Shimadzu Corporation, Japan). The testing conditions were listed in Tab.1 and the load - displacement curve will be recorded.

Table 1. Tensile test condition

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Temperature (°C)	Tensile Speed (mm/min)	Film Length (mm)	Film Width (mm)
25±1	10	50	10

$$\text{Tensile strenght(Mpa)} = \frac{Force_{max(n)}}{Film\ width(mm)\ X\ Film\ thickness(mm)}$$

$$\text{Elongation on breakage(\%)} = \frac{Stroke(mm)}{Film\ lenght\ (mm)} \times 100\ \%$$

WATER VAPOR TRANSMISSION (WVT) TEST

According to the Desiccant Method[11], appropriate amount of anhydrous calcium chloride was added as desiccant into volumetric flask and then the flask was sealed with different free EC films for test. The samples were weighed (W1) before putting them into a desiccator. The desiccator was kept at 25 °C and the relative humidity (RH) in it was 75% by adding saturated sodium chloride solution at the bottom of the desiccator. After a set interval, the weight (W_2) of the volumetric flask was measured. WVT was calculated by the following formula.

$$WVT = \frac{(W2 - W1)}{t \times A}$$

Where W_1 and W_2 is the weight before and after the test, t is the set interval for test, and A represents the film area for test.

WATER UPTAKE TEST

According to the national standards[12], the water uptake were determined by precisely weighing the free films before (W_0) and after (W_1) immersing them into distilled water for a set interval at room temperature. The excessive water on the films surface was carefully removed before weighing. Then the wet films were dried to constant weight (W_2). Again, take another pieces of the same films and weigh them before (W_3) and after (W_4) directly drying them to constant weight. The water uptake was calculated by the following formula.

$$\%\ \text{water uptake} = \frac{W_1 - W_2 - W_0 \times \frac{W_3 - W_4}{W_3}}{W_0} \times 100$$

RESULTS AND DISCUSSION

Influence of Plasticizer Sort and Aging Time on Properties of Free EC Films

Free EC films were prepared with domestic EC by using different plasticizers, including DEP, DBS, and TEC. The films were treated with different aging time. The results of mechanical properties, water uptake and WVT were illustrated in Fig. 1 and Fig. 2.

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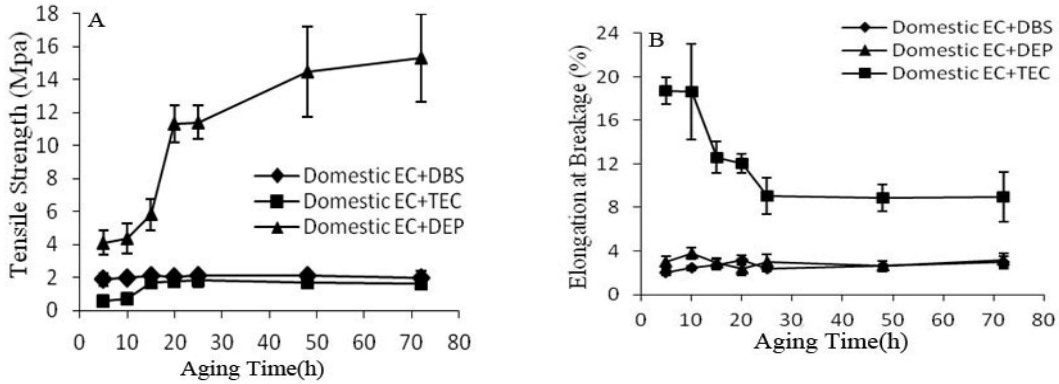

Figure 1. Influence of different plasticizers on mechanical properties of domestic EC films treated for different aging time (mean ± S.D., n = 3. A-tensile strength, B-elongation at breakage).

When a polymer remains under its glass transitional temperature for a long time, the elongation at breakage of the polymer will be weaker and the polymer will change from ductile to brittle, which is called physical aging phenomenon. These changes on mechanical properties are related to the temperature and time, which, on the microscopic level, are strongly dependent on the mobility of molecular chains[13]. As the results shown in Fig. 1, the mechanical properties of EC films were affected differently by aging time and the sort of plasticizer. As the aging time increased, the tensile strength showed a tendency of increase to different extent for the films prepared by different plasticizer, while the enlongation at breakage displayed an opposite change. The films prepared by DEP exhibited a great augmentation in tensile strength and those by TEC showed a distinct drop in enlongation at breakage with the extension of aging time. Both the tensile strength and enlongation at breakage became somewhat steady after 24h aging. The EC films prepared with DEP had the highest tensile strength about 2-7 folds of that with other two plasticizers at different aging time. The EC films prepared with TEC was the most ductile with a steady enlongation around 3 folds as much as that with DBS and DEP after 24 h aging.

Tensile strength is the greatest longitudinal stress a sample can bear without tearing apart, which represents the film's rigidity. The stronger the tensile strength is the harder and more brittle the films will be. The elongation at breakage describes the ductility of the film. Higher the elongation value, softer the films. The films of low enlongation are not easy to be deformed. Aging is a process transforming the EC film (amorphous polymer) from unstable to stable. If the film structure turns more stable with the increase of aging time, the intermolecular interaction of EC film is more intensive so that the mobility of molecular chains is restricted, thus resulting in the increase of tensile strength (Fig. 1A) while the decrease of enlongation at breakage (Fig. 1B).

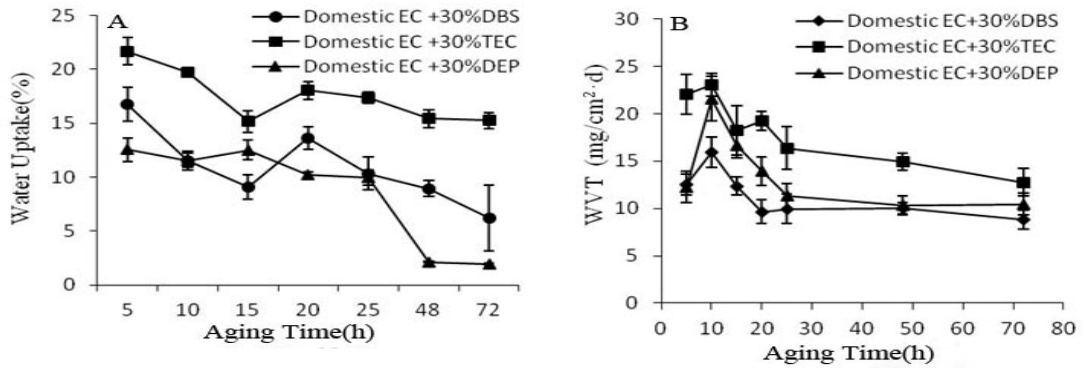

Figure 2. Effect of different plasticizers on water uptake (A) and WVT (B) of domestic EC films treated for different aging time (mean ± S.D., n = 3.).

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As shown in Fig. 2A, the aging time increase made the percentage of water uptake of EC films reduced as a whole. This could be attributed to the solubility of plasticizer and the structure of film[5]. EC is insoluble in water, if the plasticizer is dissolved out from the film, fractures may be produced on the film, which may enhance the possibility for water molecules entering into the film. As the aging time increased, the interaction intensity between EC molecules as well as that between EC and plasticizer molecules also increased. Tight structure provided less room for water molecule, and less plasticizer was able to be dissolve out, resulting in a descending of water uptake. In addition, the solubility of TEC was 57 g/L (25 °C), which was the highest among three plasticizers. Therefore, the water uptake of EC film prepared with TEC was larger than that with DBS and DEP.

The WVT of domestic EC films had a similar trend as their water uptake (Fig. 2B). Through aging, the structure of film became tighter and less pores and gaps were left, which reduced the WVT capacity of films. TEC had a high enlongation at breakage and could prepare ductile films, which suggested good mobility between molecules might exist in the films. The lowest strength tensile of films prepared with TEC indicated the weakest intermolecular action and the least tight structure. Additionally with the best solubility in three plasticizers, the EC films prepared with TEC might react with water molecules easily to enlarge the space in the film. Due to all these reasons, the EC films prepared with TEC showed the largest WVT capacity. Furthermore, the films with 5h aging showed a less WVT value than those with 10h aging. Compared with 10h aging, it was possible that the solvent had not been evaporated completely after 5h aging. The residual solvent left in the films might prevent the permeation of water vapor. After 25h aging, the WVT value of films became stable with little change.

INFLUENCE OF PLASTICIZER CONCENTRATION ON PROPERTIES OF FREE EC FILMS

The free films were prepared with domestic EC by using different concentrations of DEP in 15%, 20%, 25%, 30% and 35% (w/w) to the amount of EC, respectively. The concentration of DEP slightly affected the mechanical properties of EC films within 15%-30% (Fig. 3). With the increase of plasticizer concentration exceeded 30%, both the tensile strength and the elongation at breakage changed dramatically. It is well-known that EC itself is a kind of brittle material, which is not suitable for film coating. Plasticizer is of relative low molecular weight and can be embed into EC molecular chains, blocking the interaction of EC molecules[14]. Therefore, the EC film with plasticizer becomes flexible and it is more difficult to rupture.

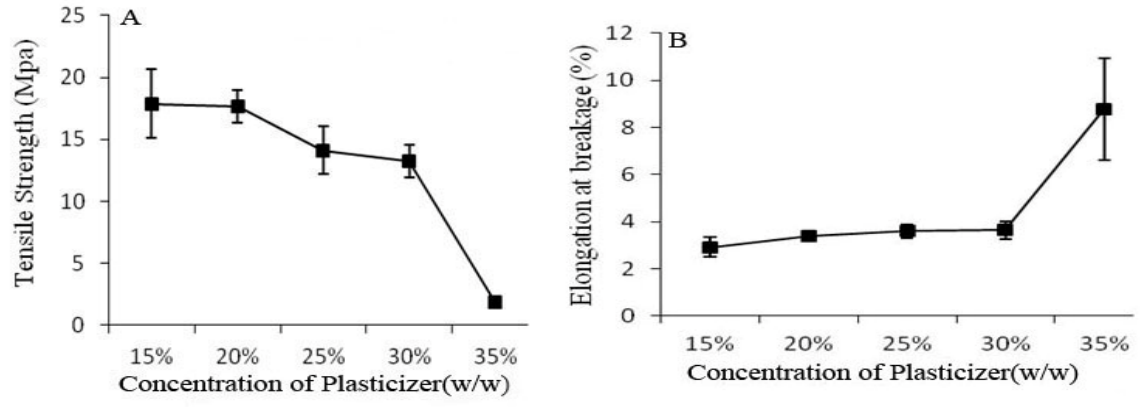

Figure 3. Influence of plasticizer concentration on mechanical properties of domestic EC films (mean ± S.D., n = 3. A-tensile strength, B-elongation at breakage).

The results of water uptake and WVT of films prepared with different concentrations of plasticizer were shown in Fig. 4. Based on the mechanical properties, it was found that the films turned less tight in structure and ductile as the concentration of plasticizer increased, which tended to increase the gaps and improve the intermolecular mobility of films. In the films of

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ISSN NO- 2230 – 7885
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high DEP, more plasticizer molecules could combine with the water molecules to facilitate water uptake. Similarly, in WVT test, the number of water molecules binding to EC film from the vapor also increased with the concentration enhancement of plasticizer. The increasing water molecules, likely also acting as a kind of plasticizer, would further improve the mobility of EC molecular chains, which help more water molecules pass through the film to achieve a high WVT capacity.

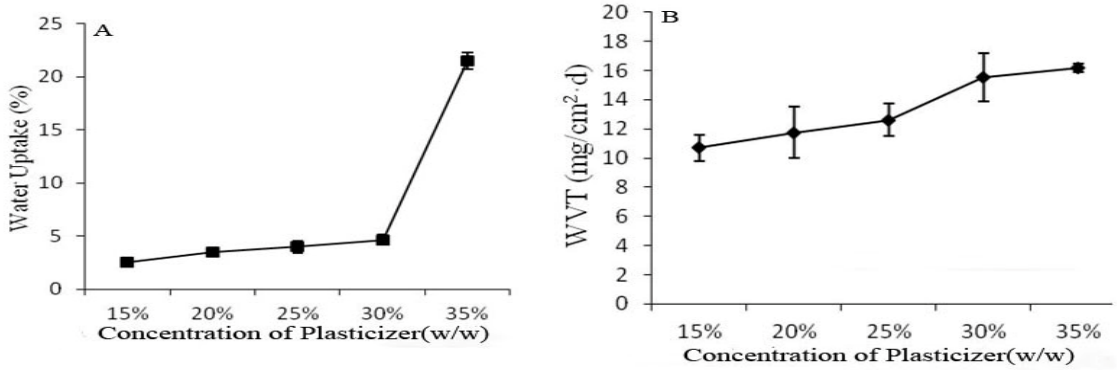

Figure 4. Effect of plasticizer concentration on water uptake (A) and WVT (B) of domestic EC films (mean ± S.D., n = 3).

INFLUENCE OF EC SORT ON PROPERTIES OF FREE EC FILMS

The free films were prepared with domestic and imported EC, respectively. DEP was use as plasticizer and the films were treated with different aging time. As it was shown in Fig. 5, compared with the imported EC film, domestic EC film had a stronger tensile strength and a smaller elongation at breakage. However, in the range from 15h to 25h of aging, the stability of elongation at breakage of imported EC was better than domestic EC. According to Student's T-test, there was a significant difference between imported and domestic EC films treated with same aging time in tensile strength and elongation at breakage, respectively ($p < 0.05$).

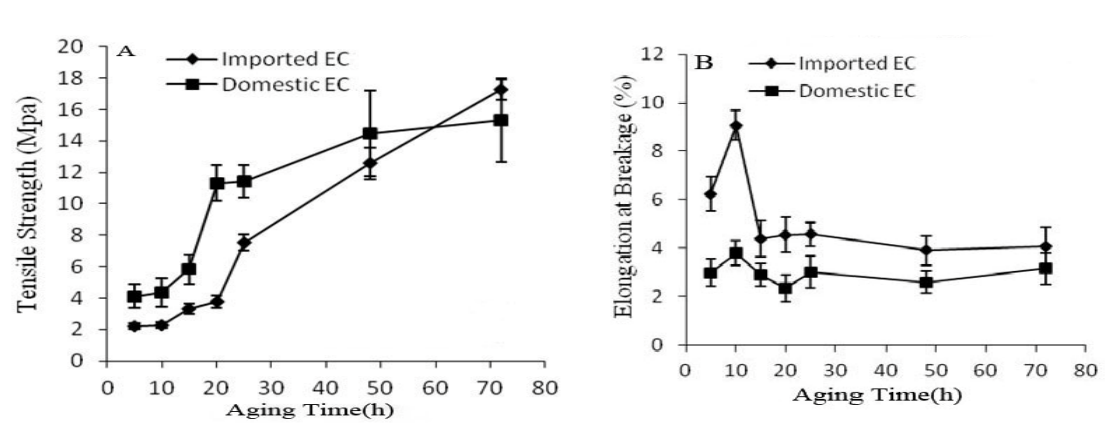

Figure 5. Influence of EC sort on mechanical properties of free films treated for different aging time (mean ± S.D., n = 3. A-tensile strength, B-elongation at breakage).

As the results showed in Fig. 6, different water uptake and WVT capacity was observed in these two kinds of EC films with similar changing trend with the extension of aging time. However, when aging time was longer than 20h, the imported EC films have better stability than domestic EC films, which was consistent with the results of mechanical properties.

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ISSN NO- 2230 – 7885
CODEN JPBSCT
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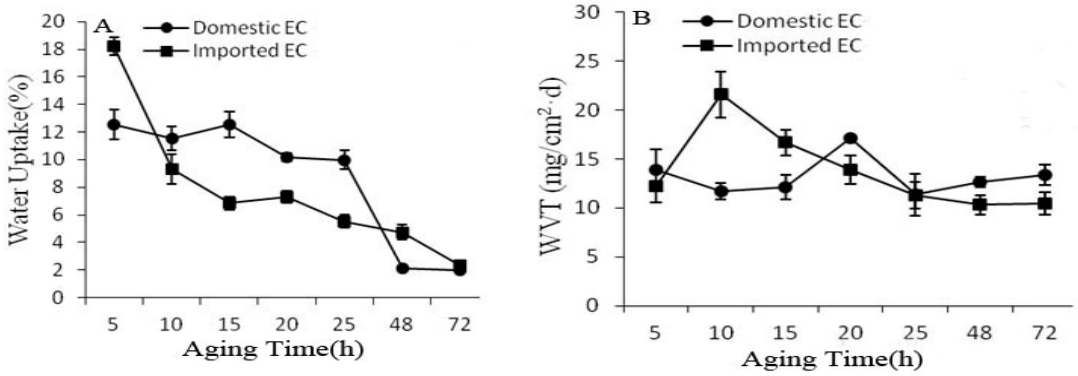

Figure 6. Effect of EC sort on water uptake (A) and WVT (B) of free films treated for different aging time (mean ± S.D., n = 3).

CONCLUSION

The composition and physical aging time distinctly affected the mechanical properties, water uptake and WVT capacity of free EC films. All these three properties distinctly influence the drug release behaviour in preparations coated with EC, which may determine whether the expected sustained and controlled release target can be accomplished. In order to prepare the coating films matching different drug release design, both rigidity and ductility should be considered. Among three plasticizers, it was found that the tensile strength of EC films prepared with TEC or DBS were much weaker than those with DEP although TEC indicated better plasticizing effect to produce softer and ductile films. The imported EC showed stabled properties than domestic EC with higher flexibility. The relative lower water uptake and WVT indicated that imported EC had a better effect of sustained release and moisture-proof in application. The film coating prepared by using imported EC and DEP may have better quality and an aging time of 25h was preferred.

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Statement of Originality of work: The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and that each author believes that the manuscript represents honest and original work.

Source of funding: This research was supported by the Guangzhou science and technology project (2013J4400061) to LI Sha and the Guangzhou Liwan District science and technology project (20134415049) to LI Sha.

Competing interest / Conflict of interest: The author(s) have no competing interests for financial support, publication of this research, patents and royalties through this collaborative research. All authors were equally involved in discussed research work. There is no financial conflict with the subject matter discussed in the manuscript.

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