Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 352 (2008) 66–73
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of poly(styrene-alt-maleic anhydride)–ethanol as enteric coating material

Xiaolin Lai [a,b,*], Chengdong Sun [a,b], Hua Tian [a,b], Wenjun Zhao [a], Lin Gao [a]

[a] *Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Science, Urumchi 830011, China*
[b] *The Graduate School of Chinese Academy of Science, Beijing 100049, China*

Received 11 June 2007; received in revised form 28 August 2007; accepted 13 October 2007
Available online 22 October 2007

Abstract

This study aims at evaluating the potential of SMA–ethanol as enteric coating polymer for erythromycin tablets. SMA–ethanol was synthesized and characterized for physicochemical properties, molecular weight and thermal analysis. Free films were prepared by adding different kinds and amounts of plasticizers, the film surface topography was determined by a SEM, the tensile strength, water vapor transmission rate and moisture absorption were also tested to choose the most promising film. DBP was proved to be the most suitable plasticizer with a best using amount of 20%, such polymer films had low vapor transmission rate and low moisture absorption which were very important to an enteric coating material. The polymer was further characterized for film coating by evaluating the release of erythromycin tablets in vitro, tablets coated with SMA–ethanol can satisfy the drug release requests of USP when the film weight gains were between 4 and 6%; tablets coated with both a subcoat and the polymer showed excellent gastro-resistance, less than 0.2% drug release occurred even with weight gains as less as 2% after 2 h exposure to acid (pH 1), while over 90% drug release occurred in pH 6.8 sodium phosphate buffer within 45 min, regardless of weight gains of coating material, moreover, we confirmed that the application of a subcoat could decrease the amount of required coating polymer. In conclusion, the potential use of SMA–ethanol as enteric coating material was demonstrated.

Keywords: SMA–ethanol; Enteric coating; Erythromycin tablets

1. Introduction

Recently, polymer systems that undergo phase transition in response to external stimuli such as changes in temperature and pH value have attracted much attention. Such polymers could be used in drug delivery system, for example, they could be used as enteric coating materials whose main function is to help the drug pass through the stomach intactly but only release their contents on reaching the small intestine.

Nowadays, the available polymers for enteric coating include shellac, CAP, CAT, PVAP, methacrylic acid copolymers, HPMCP and HPMCAS. Shellac is produced from a purified resinous secretion of the insect Laccifer lacca. It can be modified to meet certain specifications. In the past shellac was used widely in a variety of applications, especially as a sealer coat prior to sugar coating, enteric coating, or modified release coating. Due to its many drawbacks including inconsistent supply, variation in quality (common with a natural product), and stability problems associated with an increase in disintegration and dissolution times upon storage, shellac is not often used in coating today. Partial hydrolysis of shellac can improve the flexibility and lower the water vapor permeability, but the acid permeability is higher than native shellac (Limmatvapirat et al., 2004). Considering its dissolution in intestinal fluids is too slow, addition

Abbreviations: SMA, styrene-maleic anhydride; CAP, cellulose acetate phthalate; CAT, cellulose acetate trimellitate; PVAP, polyvinyl acetate phthalate; USP, united states pharmacopoeia; HPMCP, hydroxypropyl methylcellulose phthalate; HPMCAS, hydroxypropyl methyl cellulose acetate succinate; DOP, dopamine (3,4-dihydroxyphenethylamine); NCS, neocarzinostatin; BPO, dibenzoyl peroxide; DBP, dibutyl phthalate; PEG, polyethylene glycol; TBC, tributyll citrate; PMMA, poly(methyl methacrylate); HPMC, hydroxypropyl methyl cellulose; MEK, methyl ethyl ketone; TEA, triethylamine; GPC, gel permeation chromatography; DSC, differential scanning calorimetry; TG, thermogravimetric analysis; SEM, scanning electron microscopy; WVT, water vapor transmission.

* Corresponding author at: No.40-1, South of Beijing Road, Urumchi 830011, China. Tel.: +86 991 3835675; fax: +86 991 3835675.
E-mail address: xiaolin_lai@yahoo.com.cn (X. Lai).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.10.011

of pore-formers, such as organic acids and hydrophilic polymers can improve the disintegration of shellac (Pearnchob et al., 2004). CAP is a white, free-flowing powder with a slight odor of acetic acid. According to USP specifications, CAP should contain 21.5–26.0% (w/w) acetyl content and 30.0–36.0% (w/w) phthalyl content. The USP also requires a maximum limit on the quantity of free acid and loss on drying or water content since both parameters can accelerate hydrolysis of CAP. Additionally, due to its chemical composition, CAP is unstable upon storage (common with a phthalate-based enteric coating polymer). CAT polymer has similar structure and properties to CAP polymer, and it has an additional carboxylic acid group on the aromatic ring, dissolves at a pH of 5.5. To obtain the best enteric coating results from aqueous processing, ammoniated solutions of CAT in water are recommended. PVAP as an enteric coating material should contain 55–62% (w/w) phthalate specified by the USP. The final polymer composition is also controlled by a viscosity specification and a limit of 5% water content. The feature of PVAP is that it can be dissolved in a pH value of 4.5–5.0, so it can be used in front-end drug delivery system of small intestine. Compared with CAP, PVAP is less susceptible to hydrolysis, which minimizes or limits the content of free phthalic acid and other free acids. Methacrylic acid copolymers contain free carboxylic acid groups, and therefore they can be used for enteric coating purposes by forming salts with alkalis. Methacrylic acid copolymers are soluble at pH values greater than 5.5, and they can be dissolved in different parts of the small intestine by varying the composition. Due to their convenient application and good stability, methacrylic acid copolymers become the most popular enteric coating material. HPMCP characteristics, particularly at the pH where dissolution occurs, are determined by the degree of substitution of the three substituent groups (i.e. methoxy, hydroxypropoxy, and carboxybenzoyl). Basically, this polymer is prepared from phthalic acid-treated HPMC. It is unstable upon storage, and the phthalic ester groups could be partly cleaved after 11 months storage even without the influence of enzymes (Thoma and Bechtold, 1999). HPMCAS is produced from the esterification of HPMC with acetic anhydride and succinic acid. It is insoluble in water, but soluble in alkaline media, and it also has good thermal stability but poor water permeation resistant ability. Open storage at elevated temperatures and humidity can cause changes in the surface structure of HPMCAS coatings. The potential use of HACS (high amylose corn starch) as food grade enteric coating material was demonstrated, but additional work must be done to overcome the problem of coating cracking (Dimantov et al., 2004).

To sum up, the amount of enteric coating polymers is less and some of them have a few drawbacks. Comparing with their increasing applications, the choice of enteric coating materials is quite limited, and therefore it is necessary to develop new enteric coating materials which have good quality and low cost. International Conference on Harmonisation (ICH) is advocating new excipient development, and an excipient testing strategy is under consideration which will reduce the difficulty of new excipient development (Baldrick, 2000).

Poly (styrene-*co*-maleic anhydride) (SMA) is a synthetic copolymer with interesting features from both the chemical and the biological points of view. It has been used as interior parts or instrument panel in vehicle, adhesives, dispersant and food packaging listed by FDA, etc. In recent years, its applications in pharmaceutics have gradually aroused our attention. Lots of work has been done for its application as a non-occlusive male contraceptive from toxicity, histological changes, teratogenic potential evaluation to clinical trial (Sethi et al., 1989, 1990a,b; Guha et al., 1998). SMA is the most successful synthetic polyfunctional polymer in bioconjugation (Veronese and Morpurgo, 1999), for example, SMA-DOP is a more stable form of dopamine (Kalcic et al., 1996), SMA–AP may be a bactericidal material by itself and its bactericidal activity may last for a fairly long period of time under neutral conditions (Jeonga et al., 2002), and the conjugation of SMA with NCS (a potent but very toxic antitumor protein) causes an increase of the NCS plasma half-life and a decrease of its toxicity(Maeda, 2001). It also can form a microcapsule by interfacial polycondensation or complex coacervation (Shulkin et al., 2002). In our study, we discovered that the esterification derivatives of SMA with aliphatic alcohol were pH-sensitive, such polymers could be dissolved in the slightly alkaline conditions while precipitation occurred in a acidic environment. The purpose of this paper is to evaluate the potential of SMA–ethanol as an enteric coating material.

2. Materials and methods

2.1. Materials

Monomeric styrene was freed from phenolic inhibitors by shaking twice with 10% sodium hydroxide solution, washed three times with distilled water, dried over calcium chloride and distilled into a receiver under reduced pressure of nitrogen. It was stored in a refrigerator until required. Maleic anhydride and BPO were both purified by recrystallization in chloroform and dried to constant in vacuum at 50 °C, stored in a desiccator until required.

Erythromycin was chosen as the model drug (Fluka, Switzerland), DBP, PEG600, PEG6000 and TBC were chosen as plasticizers and were reagent grade, HPMC was used as the subcoat coating material (Colorcon, Shanghai, China). All the other chemicals were of analytical grade and purchased locally.

2.2. Synthesis of polymer

SMA was prepared by a traditional solution polymerization, 200 ml of distilled toluene, 10.4 g (0.1 mol) of destabilized styrene, 9.8 g (0.1 mol) of pure maleic anhydride, and 0.2 g (0.8 mmol) of BPO was placed in a 500 ml four-necked flask, fitted with stirrer, thermometer, reflux condenser and inlet of nitrogen, and stirred at room temperature until a clear solution was obtained. The reaction mixture was continuously stirred and heated to 80 °C on a water bath, the copolymer gradually precipitated, after 3 h the mixture was cooled, the white solid polymer filtered off and dried to constant weight in vacuum at 60 °C. The polymer was redissolved in MEK and precipitated in methanol.

TEA is attempted as the catalyst in the esterification reaction of SMA for the first time, 60 ml of THF, 2.0 g (0.01 mol) of SMA

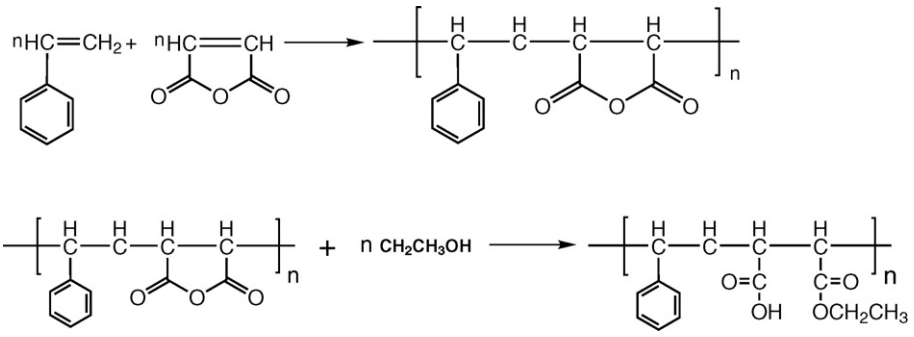

Fig. 1. Reaction equations of the synthesis of SMA and SMA–ethanol.

were placed in a 250 ml three-necked flask, fitted with stirrer, thermometer and reflux condenser, and stirred at room temperature until a clear solution was obtained, then 4.7 ml (0.08 mol) of ethanol and 0.3 ml redistilled TEA were added by dropping. The reaction mixture was continuously stirred and heated to 65 °C for 6 h, the samples were precipitated in petroleum ether. Fig. 1 shows both the reaction equations.

2.3. Characterization of SMA–ethanol

2.3.1. Structure

The structure was characterized by FT-IR spectroscopy (BLO-RAD FTS165, USA) and H-NMR (INOVA-400, Varian, USA).

2.3.2. Molecular weight

The molecular weight of the SMA was determined by gel permeation chromatography (WATERS150-CALC, USA) relative to narrow disperse polystyrene standards, and using tetrahydrofunan as mobile phase, the molecular weight of SMA–ethanol can be calculated according to the esterification degree.

2.3.3. Acid value

About 1 g (with the precision of 0.0001 g) polymer was dissolved in 70 ml 95% ethanol, then the solution was titrated by 0.2N KOH standard solution with phenolphthalein as the indicator.

2.3.4. Thermal analysis

The glass transition temperature (T_g) was determined by a differential scanning calorimetry (NETZSCH DSC-204, Germany). Approximately, 10 mg of the sample was placed in an aluminium pan and scanned over a temperature range of 25–600 °C at the rate of 10 °C/min. Samples were scanned in triplicates. The moisture content was expressed as the percent of weight loss and was determined by thermogravimetric analysis (NETZSCH TG-204, Germany).

2.3.5. Solubility

0.5 g of material and 20 ml solvent was placed in an airtight vial and agitated at about 25 °C for 4 h, the samples were considered to be soluble if a single phase, clear, gel-free solution was observed.

2.3.6. PH-sensitive value

Free films were prepared from SMA–ethanol (method can be seen in Section 2.4), cut this films to 3 mm × 3 mm fragments, placed 20 mg such films to several tubes, each of them was filled with buffer solution of different pH value. Shaking these tubes in a shaker under the temperature of 37 °C, 2 h later, the lowest pH value of complete dissolution was defined as the pH-sensitive value.

2.4. Free film preparation and characterization

2.4.1. Film preparation

The polymer was dissolved in 95% ethanol to obtain a 8% (w/w) solution, homogeneously mixed with different amounts of the plasticizers. Each mixture was cast on PMMA film holders and dried for 24 h at 40 °C and 50% RH. After 24 h drying, a polymeric film with 0.070 ± 0.005 mm thickness (determined by a graduate microscope) was obtained.

2.4.2. Screen test for SMA–ethanol free films

For choosing the most promising film, the peel test, transparency and flexibility were determined. The surface topography of each film was determined using a SEM (KYKY-2800B SEM, Beijing, China).

2.4.3. Mechanical properties test

The folding endurance, bursting strength and tensile strength were measured using paper testers. The folding endurance was measured as the number of folds which the polymer film would withstand before failure, under controlled tension, using a folding endurance tester (FET-135, Hangzhou, China). Bursting strength is the ability of a film to resist damage, when force is evenly applied perpendicularly to the surface of the film, measured with a bursting strength tester (BSM-6000, Hangzhou, China). Tensile strength was measured as the maximum tension the film can withstand without tearing using a tensile strength tester (TTM-500, Hangzhou, China).

2.4.4. Water vapor transmission rate studies

Films were cut into appropriate dimensions and mounted on a permeation cell containing saturated salt solution (excess salt) of potassium acetate, potassium carbonate, sodium chloride and potassium nitrate to provide relative humidity (RH) conditions of

23, 43, 75 and 93%, respectively (Patel et al., 1964). The charged cell were weighed and placed in pre-equilibrated desiccators maintained at 0% RH. The cells were reweighed at the end of 24 h. The amount of water transmitted through the film was given by the weight loss of assembled cell. The WVTR was computed using Utsumi's equation (Utsumi et al., 1961) taking the film thickness into consideration as shown below.

$$Q = \frac{WL}{S}$$

where W, L, S were gram of water transmitted per 24 h, film thickness (cm) and surface area (cm^2), respectively, Q is water vapor transmission (g cm/(cm^2 24 h)).

2.4.5. Moisture absorption by free films

Films were cut into 25 mm × 10 mm strips. The strips were transferred to a Petri dish and transferred to glass desiccators maintained at controlled relative humidity of 23, 43, 75 and 93%, respectively. The relative humidity in the chamber was controlled by the use of different saturated solutions containing excess solute. The film specimens were accurately weighed, placed in relative humidity chambers, removed and weighed again at the end of 14 days (Satturwar et al., 2004). Increase or decrease in weight and changes in physical appearance were then observed. Percent moisture absorption was calculated by using the formula:

$$\text{percent moisture absorption} = \frac{a-b}{a}$$

where a is the weight of conditioned film and b is the initial weight of film.

2.5. Tablet coating

Erythromycin was chosen as the model drug to assess the enteric integrity of SMA–ethanol films. Erythromycin tablets were compressed over plain punches. Tablet physical parameters such as weight, hardness and thickness were measured. Tablet thickness was determined with a precision of ±0.001 mm using a micrometer. Considering erythromycin can be dissolved in ethanol (solvent used in coating) which would cause the erythromycin diffusion with the volatilization of ethanol, the release of tablets coated with both a subcoat (2% HPMC) and the polymer was also evaluated. Both of the tablets with and without a subcoat were coated at 2, 4, 6, 8 and 10% theoretical film weight gains using process parameters shown in Table 1. The plasticizer was chosen according to the film test result, physical evaluation of films sprayed onto erythromycin tablets was performed by SEM.

Table 1
Film coating process parameters

Parameters	Value
Batch size	200 g
Inlet temperature	60 °C
Spray rate	2–3 g/min
Atomizing pressure	0.1 MPa
Pan speed	16 rpm
Outlet temperature	40–45 °C
Drying	10 min at 2 rpm, heat on

Table 2
Physicochemical properties of SMA–ethanol

Parameters	Value
Appearance	White powder
Molecular weight (Mw)	15,356
Polydispersity	1.83
Acid value (mg of KOH)	249.06
T_g (°C) (by DSC)	208
Moisture (by TG)	6.15%

Using this methodology, coated erythromycin delayed-release tablets were placed into dissolution apparatus (RC-8D, Tianjin, China) and were stirred at 100 rpm in dissolution vessels containing 1000 ml of a 0.1N HCl solution. After 2 h, 5 ml samples were collected from the dissolution vessels and the amount of drug released was determined at 486 nm (UV–vis Spectrophotometer, PGENRAL-T6, Beijing, China). The tablets were then transferred into 1000 ml of a pH 6.8 sodium phosphate buffer and the amount of drug released was measured using 5 ml samples removed without replacement after 15, 30, 45 and 60 min. Amounts of erythromycin were determined in comparison with a standard solution having a known concentration in the same medium.

3. Results and discussion

3.1. SMA–ethanol

The SMA–ethanol was synthesized and characterized in the present study, the polymer is a kind of white powder, whose molecular weight is 15356 with a narrow distribution of 1.83. SMA–ethanol has lower acid value as compared to SMA (acid value = 480.00) due to the esterification of anhydride, and the T_g

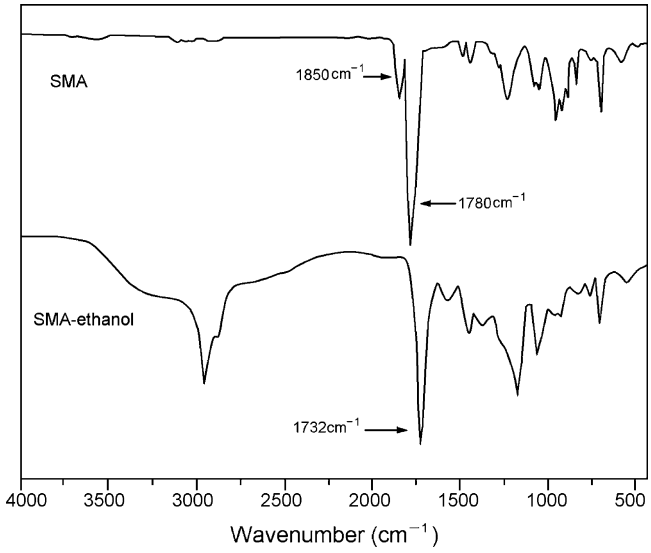

Fig. 2. FT-IR of SMA and SMA–ethanol.

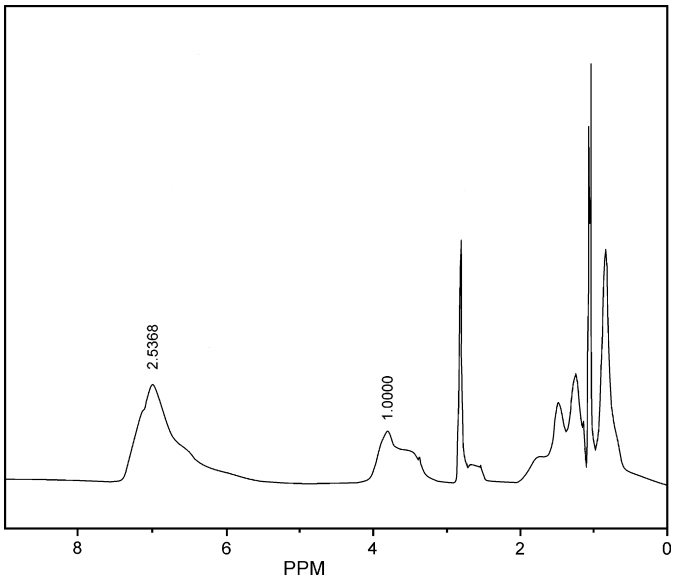

Fig. 3. HNMR of SMA–ethanol.

Table 3
Solubility of SMA–ethanol in solvents

Solvent	Polarity	Solubility
Petroleum ether	0.01	Insoluble
Carbon tetrachloride	1.60	Insoluble
Toluene	2.40	Insoluble
Ethyl ether	2.90	Insoluble
Tetrahydrofuran	4.20	Soluble
Ethanol	4.30	Soluble
Acetone	5.40	Soluble
Methanol	6.60	Soluble
Dimethyl sulfoxide	7.20	Soluble
Water	10.20	Insoluble

is lower than SMA ($T_g = 231\ ^\circ C$) which indicated that it is more flexible after conjugating. The physicochemical properties are shown in Table 2.

The IR spectra of the polymer shows bands at 1850 and 1780 cm^{-1} corresponding to the antisymmetric and symmetric C=O stretch, the resulting SMA–ethanol conjugate did not contain any unreacted maleic anhydride units, as shown in Fig. 2, thereby indicating that the ring-opening reaction of the maleic anhydride unit with ethanol was complete. The integral ratio of phenyl (5H) to the methylene protons (2H) bonded directly to

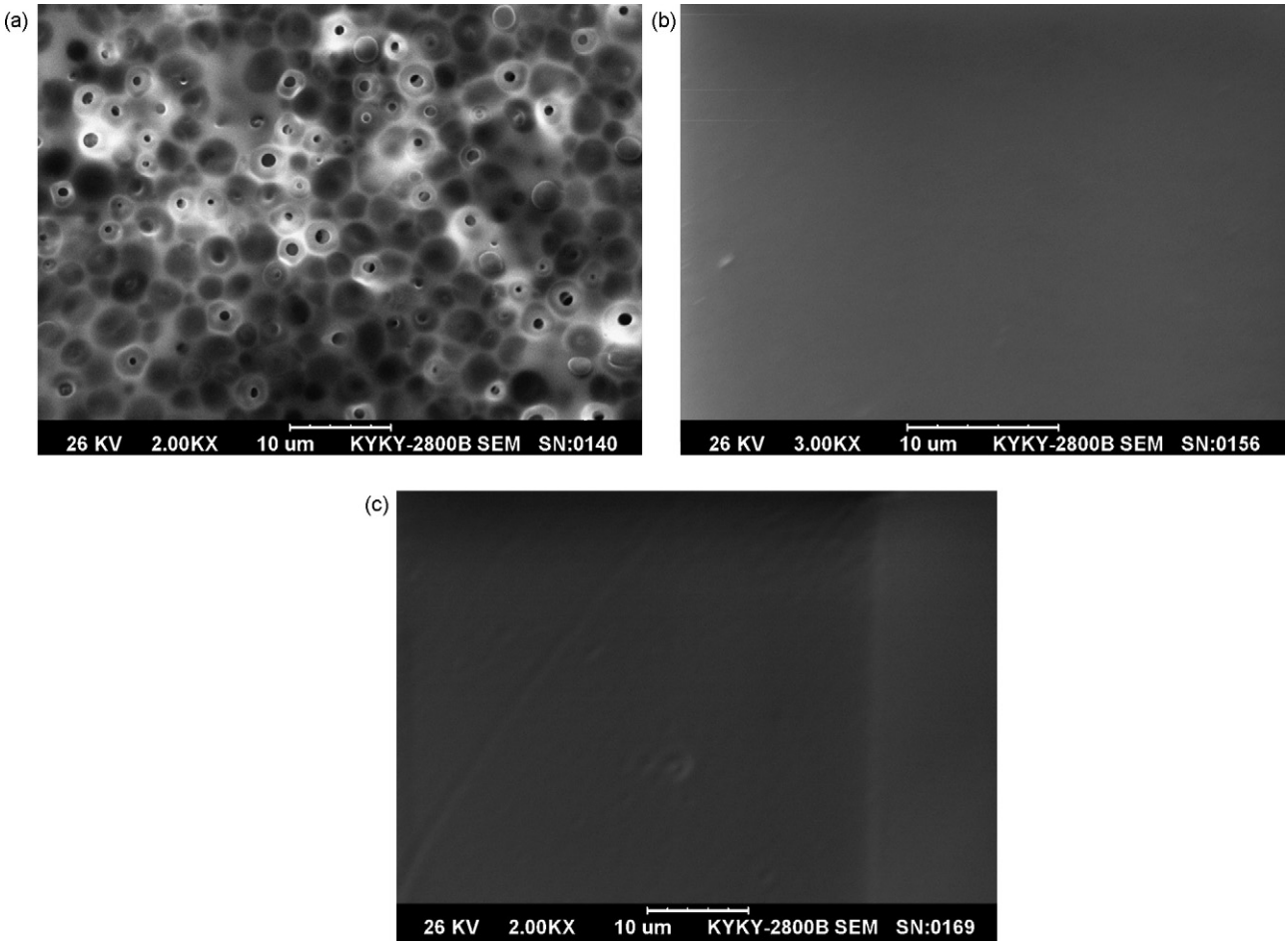

Fig. 4. (a) SEM of film plasticized with 20% TBC, (b) SEM of SMA–ethanol plasticized with 20% PEG600 and (c) SEM of SMA–ethanol plasticized with 20% DBP.

Table 4
The screen test results of SMA–ethanol films plasticized with different kinds and amounts of plasticizers

	DEP				PEG600				PEG6000				TBC			
	5%	10%	15%	20%	5%	10%	15%	20%	5%	10%	15%	20%	5%	10%	15%	20%
Complete peel	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Transparency	++	++	++	++	++	++	++	++	++	++	++	++	×	×	×	×
Flexibility	+	+	+	+	+	+	+	+	×	×	×	×	+	+	+	+

(++) Good; (+) may be used; (×) poor.

oxygen atom of the ester group was about 5:2 (Fig. 3). This result indicated the fact that SMA is an alternating copolymer, and the esterification degree of SMA–ethanol is 50%. With such a degree of esterification, the surface properties could be markedly enhanced (Dana et al., 1998).

A study of relative solubility was carried out in different solvents and pH solutions. SMA–ethanol can be dissolved in THF, acetone, ethanol, etc., as shown in Table 3, on the other side, its solubility improves with the increase in the pH value of the buffer solution: pH value under 6.0, insoluble; pH value between 6.0 and 6.4, swollen; pH value above 6.4, soluble. So the pH-sensitive value of SMA–ethanol is defined as 6.4. Varying the reacting time could gain a series of products of different degree of esterification and pH-sensitive value, such polymers can be dissolved in different parts of the small intestine, and relative research will be reported in another paper.

3.2. SMA–ethanol free film

The film test result of the compatibility of SMA–ethanol films with different types and amounts of plasticizers is shown in Table 4. The result indicated that DBP and PEG600 were suitable plasticizers for SMA, however, films plasticized with PEG6000 had poor flexibility for its high molecular weight, nonuniformity and haziness was observed in films plasticized with TBC for its poor compatibility with the polymer, phase separation or precipitation occurred along with solvent volatilization. From the table we could also found that the minimum level of plasticiz-

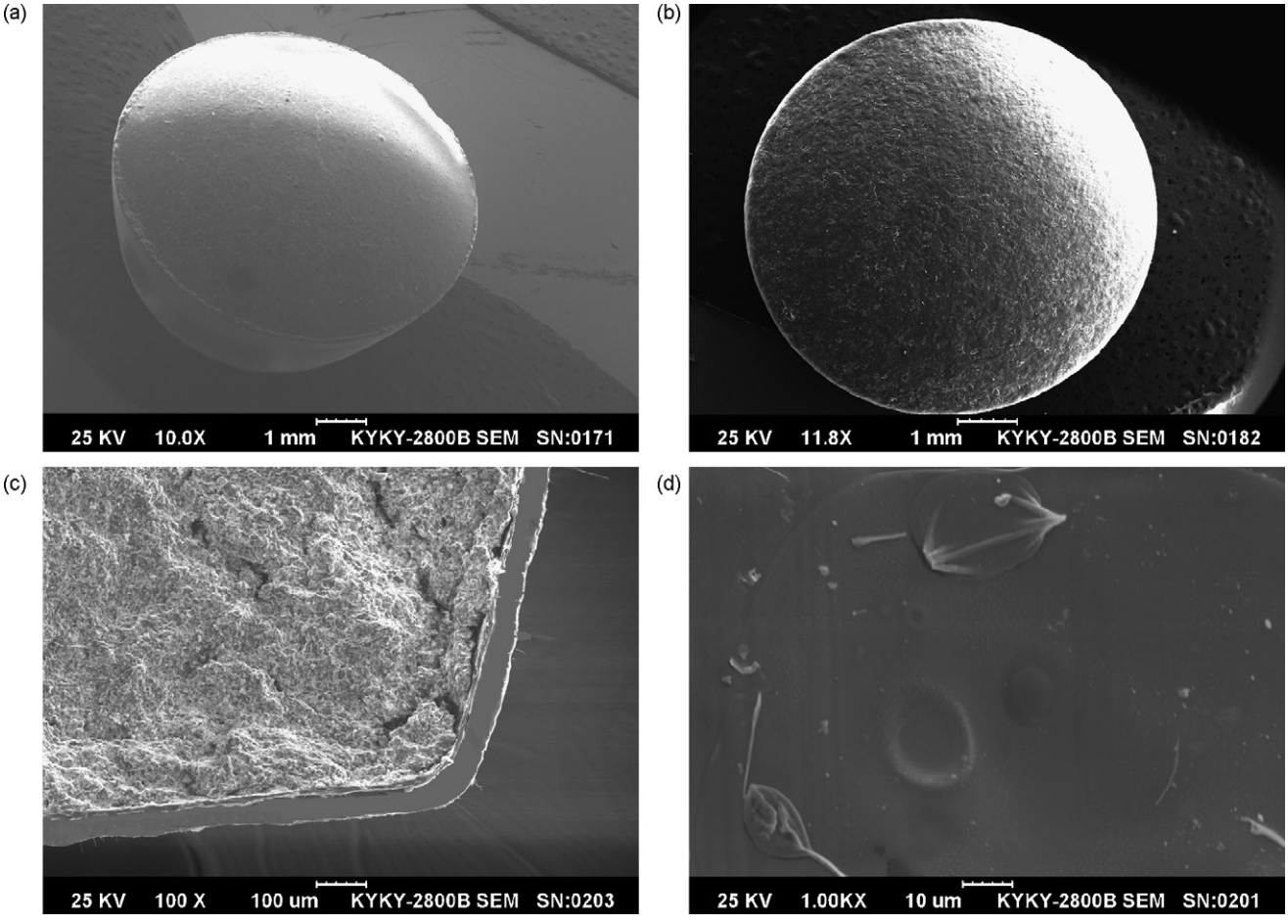

Fig. 5. (a) SEM of uncoated erythromycin tablet, (b) SEM of coated erythromycin tablet, (c) SEM of coated tablet cross-section and (d) SEM of coated tablet surface.

Table 5
Mechanical properties of free films plasticized with different plasticizers

Mechanical properties	TBC (20%)	PEG600 (20%)	DBP (20%)
Folding endurance	1	2	2
Bursting strength (kPa)	53	57	60
Tensile strength (kn/m)	4	6	7

Each value is mean ± S.D. of four determination.

Table 6
Results of WVT rate and moisture absorption percent

	Relative humidity (%)			
	23	43	75	93
WVT Rate (g cm/(cm^2 24 h))	2.47×10^{-5}	4.46×10^{-5}	5.92×10^{-5}	6.98×10^{-5}
Moisture absorption (%)	0.19	0.45	0.87	2.29

ers that provided good film formations was 20% weights (based on SMA–ethanol). The surface topography of the SMA–ethanol film plasticized with the higher concentration of TBC appeared porous, whereas the surface topography of the films plasticized with PEG600 and DBP was uniform and smooth, as shown in Fig. 4, the mechanical properties test result, as shown in Table 5, indicated that the films plasticized with DBP had the best properties from all sides of view, which confirmed the conclusion described earlier. So DBP was chosen as the plasticizer in later film tests and tablet coating, its amount is 20% (weight, based on SMA–ethanol).

The results of WVT rate and moisture absorption are shown in Table 6. The rate of WVT was low even at high humidity, which indicated the strong moisture resistance of the film. Increase in RH increased the moisture absorption, but even at high RH of 93%, the free films showed low moisture absorption with slight change in their physical appearance.

3.3. Tablet coating

The core tablet weight, hardness and thickness were found to be 130 ± 2 mg (mean ± S.D.), 5.90 ± 0.5 kg and 6.93 ± 0.02 mm, respectively. The tablet surface area as determined from punch drawing and tablet thickness was 1.08 cm^2. SEM of the uncoated tablets, coated tablets and the cross-section showing distinct core-coat regions and the surface of coated tablets are shown in Fig. 5. At a high magnification, the cross-section of coated tablets showed distinct uniform layers of coating material and erythromycin, the film coat displayed

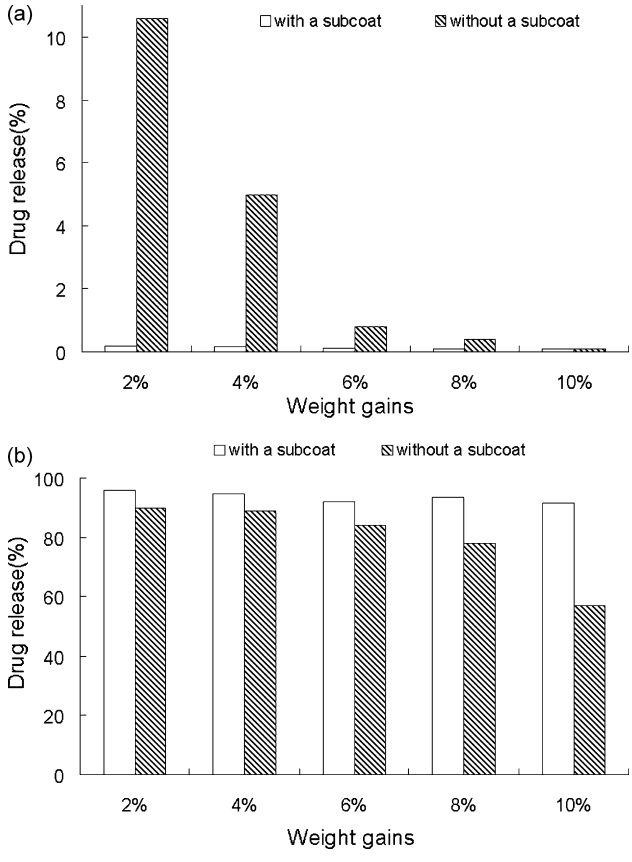

Fig. 6. (a) Drug release in pH 1 media in 2 h and (b) drug release in pH 6.8 buffer solution in 45 min.

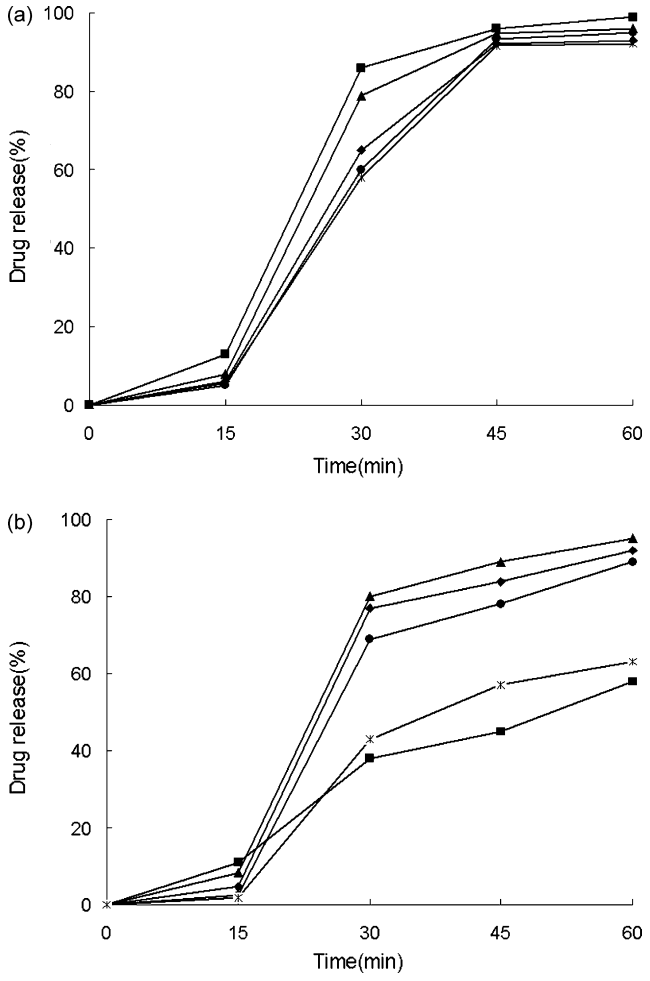

Fig. 7. (a) Drug release of tablets (with a subcoat) in pH 6.8 buffer solution. Weight gains: (■) 2%, (▲) 4%, (□) 6%, (●) 8% and (*) 10%. (b) Drug release of tablets (without a subcoat) in pH 6.8 buffer solution. Weight gains: (■) 2%, (▲) 4%, (□) 6%, (●) 8% and (*) 10%.

smooth and uniform features. At still higher magnification (1000×), the surface of the coated tablets appeared smooth and homogenous and no sign of cracking.

The core tablets released 95.2 ± 4.6%(S.D., $n = 6$) erythromycin after 30 min in acid, showing that the drug was readily available from the formulation. Figs. 6 and 7 show the drug release profiles of tablets in different buffer solution and time. From the figures we can find that tablets coated with SMA–ethanol can satisfy the drug release requests of USP when the film weight gains were between 4 and 6%, film coating levels of less than 4% resulted in failures in the acid integrity testing due to the incomplete coverage, especially at tablet edges, while film coating levels of more than 6% caused the incomplete release of the tablets, which may be caused by the diffusion of erythromycin into the coating film. On the other hand, tablets coated with both a subcoat and the polymer showed excellent gastro-resistance, less than 0.2% drug release occurred even with weight gains as less as 2% after 2 h exposure to acid (pH 1), while over 90% drug release occurred in pH 6.8 sodium phosphate buffer within 45 min, regardless of weight gains of coating material. Therefore, we confirm the application of a subcoat, which smoothes the core surface and reduce the affection of the coating solvent to the core tablet decreased the amount of gastro-resistant coating polymer required.

4. Conclusions

SMA–ethanol was successfully synthesized by reacting SMA with ethanol, and a monoesterification polymer was obtained. It has shown good film forming property with potential for delayed drug release from coated dosage forms. DBP has been proved to be a suitable plasticizer in improving film forming property and tablets coating. The coating test showed that the erythromycin tablets coated with SMA–ethanol could successfully resist the simulated gastric juice for 2 h while the drug contents released thoroughly in the simulated intestinal juice. Therefore, SMA–ethanol has the potential as an enteric coating material, but further study (such as toxicity study) should be done before it comes to actual use.

Acknowledgements

The authors express their sincere thanks to the Western Light Programs of the Chinese Academy of Sciences for the financial assistance and to Dr. Danhong Yang for assistance with the experiments.

References

Baldrick, P., 2000. Pharmaceutical excipient development: the need for preclinical guidance. Regul. Toxicol. Pharm. 32, 210–218.

Dana, M., Villenave, J.J., Montaudon, E., 1998. Correlation entre architecture moleculaire et adhesion thermodynamique: copolymeres (anhydride maleique-*co*-styrene) modifies. Eur. Polym. J. 34, 1309–1313.

Dimantov, A., Greenberg, M., Kesselman, E., Shimoni, E., 2004. Study of high amylose corn starch as food grade enteric coating in a microcapsule model system. Innovative Food Sci. Emer. Technol. 5, 93–100.

Guha, S.K., Singh, G., Srivastava, A., Das, H.C., Bhardwaj, J.C., Mathur, V., Koul, V., Malhotra, R.L., Das, S.K., 1998. Two-year clinical efficacy trial with dose variations of a vas deferens injectable contraceptive for the male. Contraception 58, 165–174.

Jeonga, J.-H., Byounb, Y.-S., Leea, Y.-S., 2002. Poly(styrene-alt-maleic anhydride)-4-aminophenol conjugate synthesis and antibacterial activity. React. Funct. Polym. 50, 257–263.

Kalcic, I., Zorc, B., Butula, I., 1996. Macromolecular prodrugs. Polymer-dopamine conjugates. Int. J. Pharm. 4, S109.

Limmatvapirat, S., Limmatvapirat, C., Luangtana-anan, M., Nunthanid, J., Oguchi, T., Tozuka, Y., Yamamoto, K., Puttipipatkhachorn, S., 2004. Modification of physicochemical and mechanical properties of shellac by partial hydrolysis. Int. J. Pharm. 278, 41–49.

Maeda, H., 2001. SMANCS and polymer-conjugated macromolecular drugs: advantages in cancer chemotherapy. Adv. Drug Deliver Rev. 46, 169–185.

Patel, M., Patel, J.M., Lemberger, A.P., 1964. Water vapour permeation of selected cellulose ester films. J. Pharm. Sci. 53, 286–290.

Pearnchob, N., Dashevsky, A., Bodmeier, R., 2004. Improvement in the disintegration of shellac-coated soft gelatin capsules in simulated intestinal fluid. J. Control Release 94, 313–321.

Satturwar, P.M., Fulzele, S.V., Panyam, J., Mandaogade, P.M., Mundhada, D.R., Gogte, B.B., Labhasetwar, V., Dorle, A.K., 2004. Evaluation of new rosin derivatives for pharmaceutical coating. Int. J. Pharm. 270, 27–36.

Sethi, N., Board, Path., Srivastava, R.K., Singh, R.K., 1989. Safety evaluation of a male injectable antifertility agent, styrene maleic anhydride, in rats. Contraception 39, 217–226.

Sethi, N., Srivastava, R.K., Singh, R.K., 1990a. Histological changes in the vas deferens of rats after injection of a new male antifertility agent "SMA" and its reversibility. Contraception 41, 333–339.

Sethi, N., Srivastava, R.K., Singh, R.K., 1990b. Male mediated teratogenic potential evaluation of new antifertility compound SMA in rabbit. Contraception 42, 215–223.

Shulkin, A., Stover, H.D.H., 2002. Microcapsules from styrene-maleic anhydride copolymers: study of morphology and release behavior. J. Membr. Sci. 209, 433–444.

Thoma, K., Bechtold, K., 1999. Influence of aqueous coatings on the stability of enteric coated pellets and tablets. Eur. J. Pharm. Biopharm. 47, 39–50.

Utsumi, I., Ida, T., Takahashi, T., Sugimoto, N., 1961. Water vapour transmission properties of polymeric materials. J. Pharm. Sci. 50, 592–597.

Veronese, F.M., Morpurgo, M., 1999. Bioconjugation in pharmaceutical chemistry. IL Farmaco 54, 497–516.