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Modification of physicochemical and mechanical properties of shellac by partial hydrolysis

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Abstract

The shellac was modified by partial hydrolysis with 2.0% (w/w) NaOH for different times. The hydrolysed shellac was then evaluated for physicochemical and film properties in comparison with native shellac. The tablets coated with native and hydrolysed shellac were also evaluated. The results demonstrated that acid value (AV) of shellac increased with prolongation of hydrolysis time. The solubility of shellac in buffer solution (pH $\leq$ 7) gradually increased with increasing hydrolysis time. The films prepared from hydrolysed shellac were more flexible and soft than those prepared from native shellac. The increasing of flexibility was correlated with the increasing of soft resin in shellac. The water vapor permeability of hydrolysed shellac film was lower than that of native shellac film. The higher acid permeability of the tablet coated with hydrolysed shellac was observed. In ethanol-based film coating, shellac had lower solubility and thus lower drug dissolution from coated tablets was observed. In ammonia-based film coating, the solubility of shellac was improved higher nearby pH 7.0 by an ammonium neutralisation method because of forming well-soluble salts, thereby higher drug dissolution was obtained. Partial hydrolysis provided modified shellac, which is more effective for ammonium salt formation, thus very higher drug dissolution was achieved in the ammonia-based coated tablets.

Keywords: Shellac; Enteric polymer; Coating; Films; Hydrolysis

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1. Introduction

Shellac is a natural polymer of animal origin secreted by the lac insect, which parasitically grows on some types of tree in China, India and Thailand. Due to excellent film forming and protective properties, it is widely used in food industry, paint industry and a less extent in pharmaceutical industry. The shellac has been used for sealing, glossing and enteric coating of pharmaceutical products, while the use of shellac as an enteric coating material has greatly declined. Problems associated with shellac are batch-to-batch variation, need of organic solvent, less stability and

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less solubility in alkaline pH of intestine, comparing to synthetic and semi-synthetic enteric polymers, e.g. polyacrylates, cellulose derivatives (Banker and Agyilirah, 1999; Müller and Krause, 2001). During a past few decades, several attempts have been made to clarify and to solve these problems. Wang et al. (1999) reported the slight variations of chemical constituents of shellac between sources from India and Thailand, and the variation among samples from the same country was not observed. The batch-to-batch variation was related to bleaching process. Severe change of shellac properties was observed by using sodium hypochlorite while it was not clearly observed by using activated charcoal. The aqueous coating systems of shellac were introduced to avoid using organic solvent (Chang et al., 1990; Müller and Krause, 2001). Recently, the stabilisation method of shellac was reported. Specht et al. (1998) demonstrated that application of shellac from aqueous solution of alkali salts showed better stability than the application from ethanolic solution. However, the solubility problem is not yet solved. Shellac does not dissolve in solution at pH below 7. Since the pH in proximal region of small intestine is between 3.8 and 6.9, failure of shellac coated tablet to disintegrate is still the major problem.

The carboxyl group in the molecule governs the enteric properties of all enteric polymers. As pH increases, the acid-salt equilibrium shifts to formation of the ionised form with increasing water solubility. Thus, the pH in which enteric polymer dissolved is controlled by the K_a and the amount of carboxyl group. Kokubo et al. (1997) developed the enteric polymer that dissolved at lower pH by increasing number of carboxyl group with trimelletic and maleic acid. Since shellac consists mainly of a mixture of esters (chemical structure is shown in Fig. 1), hydrolysis or alkali treatment of esters should be a simple approach to increase a number of free carboxyl groups.

The aim of the present study was to increase the solubility of shellac by alkali-treatment process and to study the effect of alkali treatment on the physicochemical and mechanical properties of shellac.

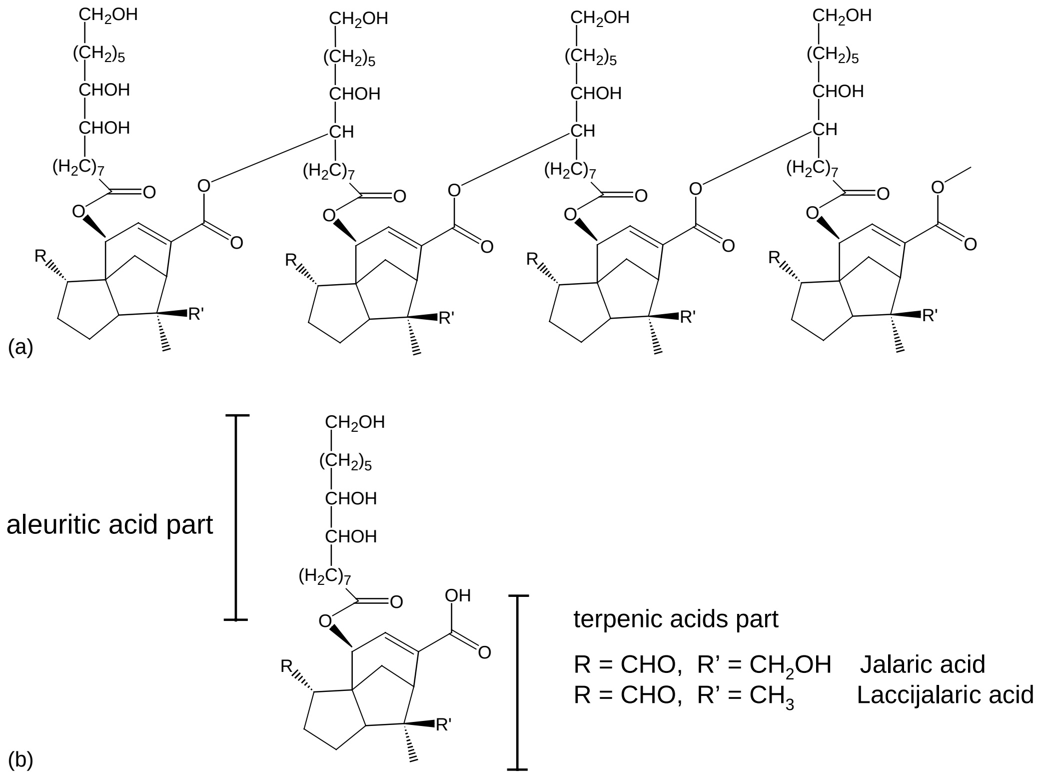

Fig. 1. Chemical structure of shellac. Polyesters (a), single esters (b).

2. Materials and methods

2.1. Materials

Shellac was kindly supplied from Union Shellac Part., Ltd. (Bangkok, Thailand). All other reagents were of reagent grade.

2.2. Methods

2.2.1. Alkali-treatment process

Shellac was finely ground and screened through 40-mesh screen. A 200 g of ground shellac was dissolved in 1800 g of 2% (w/w) sodium hydroxide solution and kept at 30±1 °C for 8, 15, 30, 60 and 120 min. The mixtures were then neutralised with 2N sulfuric acid, washed with excess water and dried at 25 °C.

2.2.2. Determination of acid value, saponification value and ester value

Acid value (AV) and saponification value (SV) were determined by titration according to the method described in the USP XXIII. The end point was determined by potentiometric titration instead of using color indicator due to dark color of shellac. The ester value (EV) was determined by subtraction of SV with AV. All measurements were performed in duplicate.

2.2.3. Powder X-ray diffractometry

The powder X-ray diffraction (PXRD) measurements of samples were conducted on a powder X-ray diffractometer (Rigaku, Miniflex, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA and scanning speed 4°/min.

2.2.4. Preparation of films

Aqueous solutions of native shellac or hydrolysed shellac were prepared by neutralisation with 28% (w/w) ammonium hydroxide and adjusted so that the solid concentration was 15% by weight and pH was in the range of 7–8. The solutions were poured onto polytetrafluoroethylene plate and allowed to evaporate at 50 °C. The drying conditions were carefully controlled for all samples. The films were peeled off and stabilised in a desiccator at room temperature 12 h prior to testing.

2.2.5. FT-IR spectroscopy

Fourier transformed infrared (FT-IR) spectroscopy was used to characterize films and to confirm the presence of ammonium in films after drying. The films of native shellac and hydrolysed shellac were pulverised, blended with KBr and compressed. The measurements on prepared films were carried out using a FT-IR spectrophotometer (Nicolet, Magna 750, USA).

2.2.6. pH-solubility profile of films

The solubility was determined by measuring the weight loss of film (Wu et al., 1997). The film was cut in 1 cm × 1 cm and placed in the USP disintegration apparatus. The obtained film was tested in simulated gastric fluid (SGF) for 2 h and then transferred to buffer at various pH for 2 h. The resulted film was dried at 41 °C for 24 h, and weighed to determine percent dissolved.

2.2.7. Mechanical properties of films

Maximum stress and strain at maximum stress of films were measured by a material testing apparatus (Llyod, LR 50K, UK). The prepared films were measured for thickness, cut into a dumbbell shape with the gauge length of 25 mm and extended at the rate of 20 mm/min. At least five measurements were conducted.

2.2.8. Determination of soft resin and hard resin of shellac

The isolation of hard and soft resins in shellac was adapted from method described by Khurana et al. (1970). Native shellac or hydrolysed shellac (20.0 g) was stirred with distilled water (150 ml) for 15 min, the aqueous part was decanted and the process of washing was repeated six times. The washed shellac was dried at room temperature and then thoroughly dispersed in 78% ethanol (80 ml) with stirring for 30 min. The alcohol insoluble matter was again treated with two further portions of 78% ethanol (30 and 20 ml). The total alcohol extract was concentrated under reduced pressure to one-fifth of its volume. The concentrate was cooled and slowly diluted with ether (250 ml) with vigorous stirring. The precipitate was removed, washed with ether (50 ml × 3) and soxhleted about 24 h to finally yield the insoluble portion as ‘hard resin’. The total ether extract and washing were combined and the solvent was flashed off. The residue was dissolved in chloroform (45 ml) and filtered. The chloroform part was extracted with 15% (w/v) sodium carbonate (25 ml × 6). The alkali extract was acidified with diluted phosphoric acid (1:1) and extracted with the ethyl acetate (50 ml × 5). The ethyl acetate extract was combined and the solvent was removed to give a 'soft resin'. Percentage of soft resin was calculated by dividing the amount of soft resin with total amount of soft and hard resins.

2.2.9. *Water vapor permeability of film*

An adapted permeation cell for water vapor permeation (WVP) study was used according to method described in the Annual Book of ASTM Standards (ASTM, 1989). The cell consisted of a glass bottle, filled with dried granular calcium chloride, and a cap with an opened circular hole of 3–4 cm in diameter. The prepared film with an exposed area of 800–1000 mm^2 was placed inside the cap and then sealed tightly. The cell was then kept in a cabinet at 40 °C, 75% RH. The weight change was recorded periodically. The WVP coefficient of at least six cells for all films was then calculated using the following formula. WVP coefficient $= (W \times t)/(A \times \Delta P)$, where W was the amount of water permeated through the film in mg/h, t was the thickness of film (mm), A was the area of the exposed film (mm^2) and ΔP was the vapor pressure difference (mmHg).

2.2.10. *Preparation of coated tablet*

A single punch machine with biconvex 13-mm punch was used for preparing of paracetamol tablet. The composition of the tablet was as follows: paracetamol 10%, Avicel PH102 30%, Tablettose 59% and magnesium stearate 1% by weight. The core tablets were coated in a film coating apparatus (Narongkarnchang, Rama-cota 18, Thailand). The coating materials of shellac and hydrolysed shellac were prepared in two categories for comparison purpose: ethanol-based and ammonia-based solutions. The formula of ethanol-based solution was as follows: shellac (or alkali-treated shellac) 8%, talcum 1.6%, triacetin 0.4% and ethanol 95% by weight. The composition of ammonia-based solution was the same as ethanol-based solution, except the ammonia, in the amount equivalent to acid value, was used to dissolve shellac sample and the sufficient water was added to make 100% by weight. The coating level of polymer was 5.0–5.2 mg/cm^2 (calculated from weight gained of polymer divided by total surface area of core tablet). The coating conditions were as follow: tablet weight 2500 g, inlet air temperature 48–50 °C (38–40 °C for ethanol-based solution), spray rate 8 g/min and spray pressure 1.5 bar (1.0 bar for ethanol-based solution).

2.2.11. *Evaluation of coated tablet*

Dissolution of paracetamol was determined according to USP XXIII, with apparatus II, method A (Erweka, DT 70, Germany). The rotating speed was 50 rpm. The dissolution was conducted in 0.1N hydrochloric acid for 2 h, followed by a phosphate buffer with a pH of 6.80. Samples were periodically withdrawn and paracetamol was assayed.

3. Results and discussion

3.1. *Effect of alkali treatment on AV and EV of shellac*

Since polyester chain of shellac was prone to hydrolyze and a limited solubility of shellac in acid medium was observed, partial hydrolysis with alkali-treatment process was used to modify shellac properties. The condition of alkali treatment was set up so that complete hydrolysis did not occurred within 2 h. The effect of alkali treatment on AV and EV of shellac are shown in Fig. 2. Acid value increased with prolonged alkali-treatment time. The results

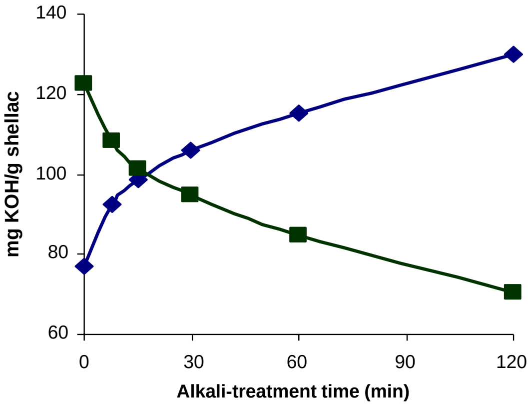

Fig. 2. Effect of alkali-treatment time on acid value and ester value of shellac. (◆) Acid value; (■) ester value.

suggested that the ester bonds were broken down to free carboxyl group during alkali treatment. Since the AV was affected by both the ionization constant (pK_a) and the amount of free carboxylic acid, predominant factors should be clarified by determining pK_a from potentiometric titration curves. The pK_a of native shellac, 8, 15, 30 and 60 min hydrolysed shellac were not significantly different, i.e. 6.7, 6.7, 6.8, 6.7 and 6.5, respectively. The increase in AV should be the results of an increase in free carboxyl groups having relatively the same pK_a. Davis et al. (1986) reported that enteric polymers, including polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP, HP-50) and cellulose acetate phthalate (CAP) had lower pK_a values of 4.9, 4.2 and 4.5, respectively. These explained the lower aqueous solubility of shellac, compared to other enteric polymers.

It was noted that different hydrolysis rate was observed in Fig. 2. The higher hydrolysis rate was observed at initial period, followed by a slow hydrolysis rate. Two reasons were assumed for explanation. The first assumption was the different hydrolysis rate at ester bonds. Shellac demonstrated various ester bonds; e.g. ester linked between carboxyl group of aleuritic acid and hydroxyl group of terpenic acid, and ester linked between carboxyl group of terpenic acids and hydroxyl group of aleuritic acid; which might possess different bond strength or steric hindrance. Secondly, we assumed that native shellac might contain amorphous and crystalline region as previously observed in some polymers, e.g. cellulose (Fan et al., 1987). The high hydrolysis rate would expect to occur in the loose, amorphous region. However, the second assumption proved to be incorrect since clear diffraction peak due to crystalline part was not observed in the powder X-ray diffractogram of native shellac. In the case of shellac, different ester bonds should be a more possible explanation for different hydrolysis rate.

3.2. Properties of free films

Since ammonium could be lost from carboxylic binding site as observed in ammoniated film of enteric polymer, e.g. cellulose acetate phthalate (Béchard and Levy, 1995), preliminary study employing FT-IR measurement was conducted to ensure the presence of ammonium in shellac film. As shown in Table 1, the relative peak intensity of N–H bending at 1556 cm^{-1} due to ammonium ion was constant after drying at temperature not higher than 60 °C for 24 h and markedly decreased after drying at 80 °C. In addition, the relative peak intensity due to ammonium slightly decreased after storage at 40 °C for 3 month. The result suggested that ammonium was fairly bound to carboxyl group of shellac and the high temperature should be avoided during drying process.

Table 1
Absorbance ratio of IR peak at 1556 and 1714 cm^{-1} of native shellac prepared and stored at various conditions

Conditions	A_{1556}/A_{1714} (cm^{-1})
Drying at 50 °C for 24 h	0.228 ± 0.004
Drying at 60 °C for 24 h	0.216 ± 0.003
Drying at 80 °C for 24 h	0.136 ± 0.046
Drying at 100 °C for 24 h	0.036 ± 0.009
Ageing at 40 °C for 2 weeks	0.230 ± 0.061
Ageing at 40 °C for 1 month	0.215 ± 0.015
Ageing at 40 °C for 2 months	0.228 ± 0.019
Ageing at 40 °C for 3 months	0.165 ± 0.009

FT-IR peaks at 1556 and 1714 cm^{-1} were due to N–H bending of ammonium ion and C=O stretching of shellac, respectively.

To study the effect of hydrolysis time on film properties, native shellac and hydrolysed shellac were comparatively evaluated for physicochemical and mechanical properties of film. Fig. 3 demonstrates the pH-solubility profiles of shellac samples after alkali treatment for different times. All shellac samples were completely dissolved at pH more than 7.0, whereas the films were partially dissolved at pH 7.0 and lower. The percent dissolved of films increased as hydrolysis

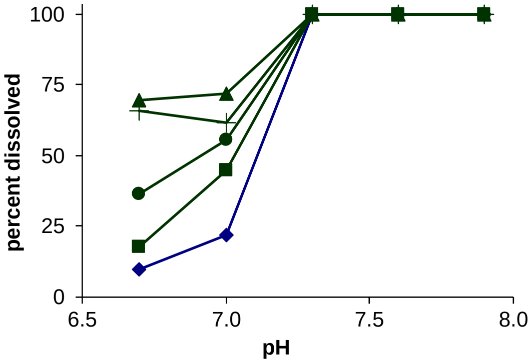

Fig. 3. pH-solubility profiles of native shellac and hydrolysed shellac after alkali treatment for different times. (◆) Native shellac; (■) 15-min hydrolysed shellac; (●) 30-min hydrolysed shellac; (—+—) 60-min hydrolysed shellac; (▲) 120-min hydrolysed shellac.

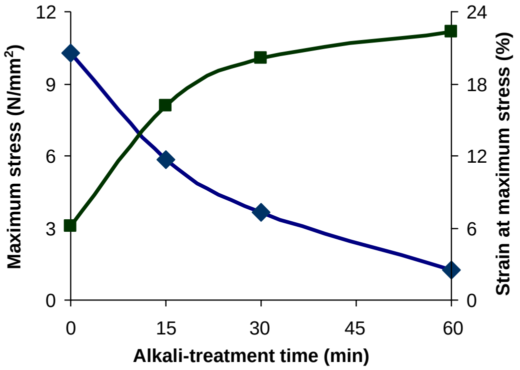

Fig. 4. Mechanical properties of film prepared from native shellac and hydrolysed shellac after alkali treatment for different times. (◆) Maximum stress; (■) strain at maximum stress.

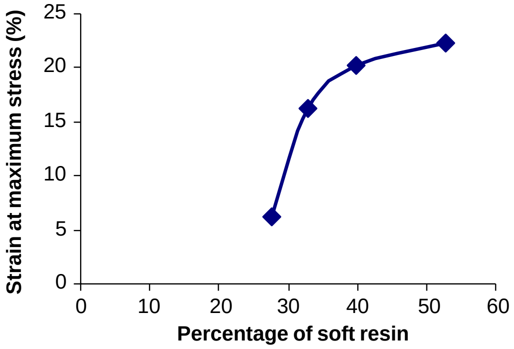

Fig. 5. Relationship between percentage of soft resin and strain at maximum stress of native and hydrolysed shellac.

time increased, especially at the first 15 min. The increased solubility well corresponded with an increase in the AV (Fig. 2), suggesting the solubility increment by ionization of more carboxyl groups.

Fig. 4 illustrates the stress and strain curves of shellac after alkali treatment for different times. The maximum stress of shellac film decreased whereas the strain increased with alkali-treatment time. It was known that mechanical properties of film could be altered depending on the MW of polymer. Generally, the lower MW of polymer demonstrated lower stress and strain as compared with the higher one. For examples, hydroxypropyl methyl cellulose phthalate (HPMCP, HP 55S) which had average MW of 33,000 could produce tougher film, comparing to HP 55 having average MW of 20,000 (Banker and Agyilirah, 1999). Extruded product prepared from hydrolysed starch, having shorter amylose chain, demonstrated the lower stress and strain (Soest et al., 1996). The result suggested that hydrolysis of polyester backbone produced shellac having lower MW and decreased the stress of shellac film. However, the explanation was not agreed with the increment of strain of film prepared from hydrolysed shellac.

Native shellac consisted of a major constituent of hard resin and a minor constituent of soft resin. The hard resin comprised polyesters that served as a backbone of shellac while the soft resin contained mixture of single esters (Upadhye et al., 1970; Singh et al., 1974). The plasticising effect of small ester, e.g. glyceryl triacetate, ester of citric acids, in shellac was clearly well known whereas the role of single ester in shellac was not clarified. Fig. 5 demonstrated the relationship between the percentage of soft resin and the strain of film. The higher strain was observed as amount of soft resin increased. The result suggested that soft resin containing single esters should be a factor contributing to an increase in strain. Therefore, it should be concluded that the hydrolysis of backbone and the increasing amount of single esters affected the mechanical properties of shellac films.

The important characteristic of shellac film is a low WVP, compared to other enteric polymers (Banker and Agyilirah, 1999). Since the hydrolysis process affected molecular structure of polymer and changed mechanical properties of film, we also determined the effect of hydrolysis on WVP of shellac. As illustrated in Fig. 6, WVP coefficient of hydrolysed shellac was lower than that of native shellac. The WVP coefficient significantly decreased after 15-min hydrolysis and slightly decreased after 30- and 60-min hydrolysis. The results suggested that WVP was not dependent on soft characteristic of hydrolysed shellac, but the change of WVP should be related with other factors. Water vapor permeability was dependent on the number of available polar groups (–OH, –COOH) that polymer possessed as exemplified by glucomannan. The increase in polar groups should promote intermolecular interaction through hydrogen bonding, which led to the formation of highly structured matrix thereby impeding diffusion of water vapor (Cheng et al., 2002). The more available polar group of hydrolysed shellac might promote molecular interaction in the same way. However, other

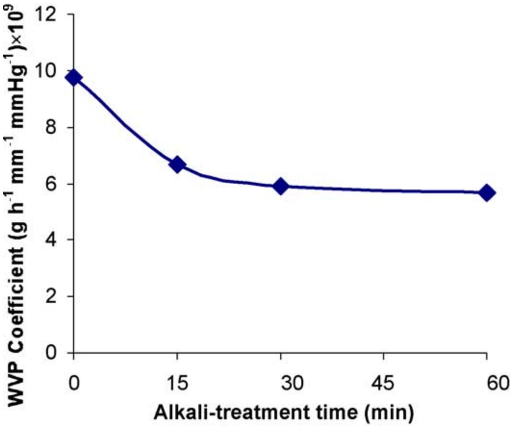

Fig. 6. Water vapor permeability (WVP) coefficients of native shellac and hydrolysed shellac after alkali treatment for different times.

factors, e.g. effect of hydrolysis products on WVP, should be further clarified.

3.3. Properties of coated tablets

To develop alkali-treated shellac as an alternative enteric polymer, paracetamol tablets were coated with native or hydrolysed shellac. The evaluation of enteric properties of coated tablets was carried out. The coating level of polymer of all shellac samples were fixed in the range of 5.0–5.2 mg/cm^2 to produce coated tablets which could withstand the disintegration test in SGF for more than 1 h.

The percent released of paracetamol from coated tablets in 0.1N HCl during 2 h is illustrated in Fig. 7. The ethanol-based coated tablets showed slightly higher percent released as compared to ammonia-based coated tablets. The results suggested that changing from free acid into ammonium salt had little effect on the acid permeability of shellac. In contrast, hydrolysis time showed pronounced effect on the acid permeability of shellac. The percent released were 0.19 (Fig. 7a) and 0.60 (Fig. 7b) for tablets coated with native shellac and 8-min hydrolysed shellac in ethanol-based solution. For ammonia-based solution, the percent released from coated tablets were 0.12 (Fig. 7c), 0.29 (Fig. 7d) and 1.32 (Fig. 7e) for native shellac, 8-min and 15-min hydrolysed shellac, respectively. The tablets coated with 30-min hydrolysed shellac failed to pass the disintegration test in SGF, suggesting non-enteric properties of 30-min hydrolysed shellac. As reported earlier, the acid permeability was influenced by properties of coating materials, coating conditions and added excipients (Breitkreutz, 2000; Flösser et al., 2000; Scheiffele et al., 1998). Since the last two factors were controlled in the study, property of shellac was the only parameter involved with the acid permeability. The higher solubility of hydrolysed shellac should increase the acid permeability of coated tablets.

Fig. 8 shows the release profiles of paracetamol tablets coated with native and hydrolysed shellac. Minimal release of drug was observed in the first

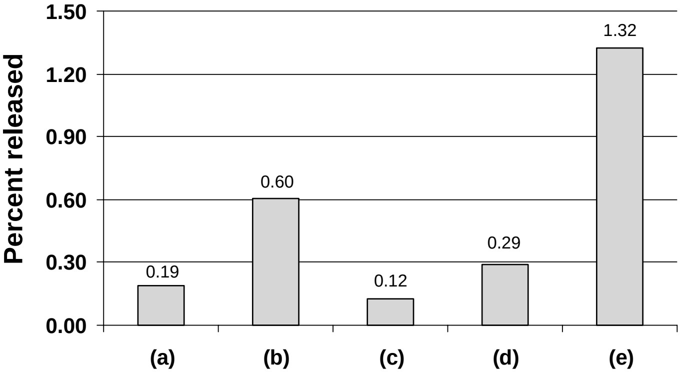

Fig. 7. Percent released of paracetamol in 0.1N HCl from tablets coated with native and hydrolysed shellac after dissolution for 120 min. (a) Native shellac, ethanol; (b) 8-min hydrolysed shellac, ethanol; (c) native shellac, ammonia; (d) 8-min hydrolysed shellac, ammonia; (e) 15-min hydrolysed shellac, ammonia.

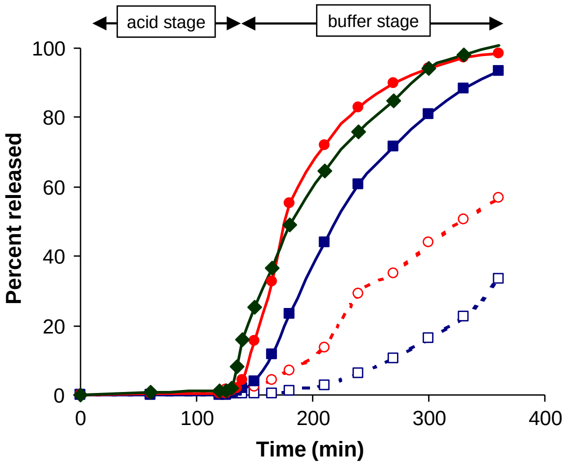

Fig. 8. Release profiles of paracetamol tablets coated with native and hydrolysed shellac. (☐) Native shellac, ethanol; (○) 8-min hydrolysed shellac, ethanol;(■) native shellac, ammonia; (●) 8-min hydrolysed shellac, ammonium; (◆) 15-min hydrolysed shellac, ammonium.

2 h in 0.1N HCl. In pH 6.8 phosphate buffer, the percent released of drug from the ammonia-based coated tablet was markedly faster than that from the ethanol-based coated tablet. The lower dissolution of drug from the ethanol-based coated tablets was attributed to the low solubility of shellac in water at pH 7.0 and lower. Most of the free carboxyl groups of shellac could form ammonium salts under the film preparation in ammonium hydroxide solution at 50 °C as previously discussed in Section 3.2. It was, therefore, expected that the formation of ammonium salts took place in the ammonia-based film coating operated at around 50 °C. Therefore, the solubility of shellac could be improved nearby pH 7.0 by an ammonium neutralisation method in film coating because of forming the well-soluble salts. This could enhance hydration of the films and the subsequent drug release. In addition, the tablet coated with hydrolysed shellac revealed faster drug release as compared to native shellac. Partial hydrolysis of shellac caused an increment in free carboxyl group for ammonium salt formation. Thus, it was very effective in improvement of the solubility of the shellac films by ammonium neutralisation method, resulting in higher drug release.

4. Conclusion

Changes in the mechanical and physicochemical properties of shellac were observed by partial hydrolysis. The change of film flexibility should be related to hydrolysis of polyesters chain and the presence of single esters. With the increased amount of free carboxyl group of shellac by partial hydrolysis, the solubility of shellac was enhanced nearby to pH 7.0 and the hydrolysed shellac obtained was more effective for ammonium salt formation in ammonia-based film coating, resulting in higher drug release. Therefore, it could be concluded that alkali-treatment process should be the simple approach for modifying shellac that possessed better enteric properties.

Acknowledgements

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