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International Journal of Pharmaceutics 198 (2000) 97–111

international journal of pharmaceutics

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Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablet

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Received 28 April 1999; received in revised form 1 September 1999; accepted 7 December 1999

Abstract

Chitosan citrate solution containing 25% w/w propylene glycol was prepared and tested for its compatibility with some water soluble anionic dyes. The immiscibility between erythrosine, ponceau 4R, sunset yellow or tartrazine solutions and chitosan citrate solution was evident. The Fourier transform-infrared spectra revealed charged interaction between anionic dye and chitosan. Brilliant blue and green FS at concentration of 0.02–1.00% w/w polymer could be miscible with chitosan citrate solution due to the decrease in charge interaction by the positive charge on molecule of brilliant blue, which was also the composition in green FS. Propranolol HCl tablets coated with these colored film-coating solutions exhibited good appearance and no color migration. Drug dissolution from coated tablets was pH dependent, corresponding to the ability of chitosan to protonate in the medium. Color incorporation slightly retarded drug dissolution in acidic medium. Drug dissolved from coated tablet colored with brilliant blue was faster than from that colored with green FS. This was because brilliant blue had positive charge and more SO_3H groups on its molecular structure, and exhibited higher water solubility. Accelerated condition could alter dissolution characteristics, and the $Td + t_0$ value from curve fitting between the dissolution profiles and Weibull equation was increased. However, drug dissolution from freshly prepared coated tablets, coated tablets after exposure to accelerated condition and after storage at room temperature for 12 months conformed to the monograph in USP XXIII.

Keywords: Chitosan citrate; Film former; Coated tablet; Water-soluble anionic dye; Compatibility

1. Introduction

Chitosan is a bio-polysaccharide derived from chitin, a polymer from bio-waste of shellfish industry. It can also be manufactured by artificial culturing, thus it has the possibility to be further mass produced by biotechnological techniques (Yokoi et al., 1998). Due to high biocompatibility, biodegradability and low toxicity, this substance has been officially approved as a food additive by

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PII: S0378-5173(99)00460-3

Japanese Ministry of Health and Welfare (Hirano et al., 1988; Weiner, 1992). The reported hypolipidemic and hypocholesterolemic activities of chitosan further attribute to the potential use of this cellulose-like biopolymer. The main structure of chitosan is similar to cellulose, thus it is possible to be applied as a film former like other cellulosic matter.

The investigation of chitosan citrate as a hydrocolloidal matrix material (Nigalaye et al., 1990; Adusumilli and Bolton, 1991) and as the wall of a microcapsule (Lin and Lin, 1992) has been previously reported. However, the utilization of chitosan citrate as a film former for tablet coating has not previously been investigated. Due to the volatile nature of commonly used acetic acid for dissolving chitosan, the solubility property of prepared film was possibly altered after long-term storage (Demarger-Andre and Domard, 1994). Therefore, chitosan citrate has more potential use as a stable film coat. Usually, pharmaceutical coatings contain colorant to provide distinctive color and elegance to the coated tablets (Radebaugh, 1988). The most brilliant coloring agents are anionic dyes, such as certified Food, Drug and Cosmetic (FD&C) or Drug and Cosmetic (D&C) dyes (Goldemberg, 1983). While in acidic solution, the amino groups in glucosamine units on chitosan can convert to protonated form. Hence, the compatibility and possibility of coloring the chitosan citrate film-coating solution with commonly used anionic dyes were of interest.

Prillig (1969) investigated the effect of colorants on the solubility characteristics of cellulose polymers. Coating layers containing various FD&C and D&C colors showed retardation effects on the disintegration and dissolution rate of riboflavin-coated tablet. Therefore, the effect of these dyes on the dissolution behavior of propranolol HCl from chitosan citrate film-coated tablets was investigated in this study. Additionally, the effect of storage conditions on physical properties of coated tablets was assessed to indicate the potential utilization of this film component as coating material.

2. Materials and methods

2.1. Materials

Chitosan (molecular weight, 40 000 Da; % deacetylation, $85.91 + 0.75$) supplied by G.T. Chemical Co. was passed through sieve No. 80 mesh before use. Citric acid and propylene glycol were obtained from Srichand United Dispensary Co. (Bangkok, Thailand). Water-soluble dyes (brilliant blue, C.I. No. 42090; erythrosine, C.I. No. 45430; green FS, a mixture of brilliant blue and tartrazine of 12 and 88% by weight, respectively; ponceau 4R, C.I. No. 16255; sunset yellow, C.I. No. 15985; and tartrazine, C.I. No. 19140) were purchased from Government Pharmaceutical Organization (Bangkok, Thailand). Propranolol hydrochloride was purchased from China National Chemicals Imp. & Exp. Corp. (China). Lactose hydrous (Wyndale, Hawera, New Zealand), polyvinyl pyrrolidone K30 (GAF, Singapore), cross-linked carboxymethylcellulose sodium (Ac-Di-Sol®) (FMC Corp., USA) and magnesium stearate (Lek Pharm and Chem Work, Yugoslavia) were utilized as tablet excipients. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Compatibility of chitosan citrate solution with water-soluble dyes

The 5% w/w chitosan solution was prepared by dissolving chitosan powder in citric acid solution (mole ratio glucosamine unit of chitosan: citric acid 1:1.2) with constant stirring for 14 h and then filtering through polyester cloth. Each 1% w/w dye solution was mixed with chitosan citrate solution to obtain the final dye concentration of 0.02–1.00% w/w based on chitosan. The physical appearance of the mixtures was visually observed.

Precipitated matter, if any, was then evaluated with a Fourier transform-infrared (FT-IR) spectrometer (Spectrum 2000; Perkin-Elmer, Bucks, England) by the KBr disc method. Primarily, the precipitated matter was washed with deionized water several times until the color in the filtrate disappeared, subsequently rinsed with absolute methanol and then dried at 60°C for 2 h. The

FT-IR spectra of chitosan and the corresponding colorant to the precipitated matter were analyzed.

2.2.2. Preparation and evaluation of cast film

The cast films of about 80 μm thickness were obtained by evaporating the coating solution on a glass petri dish at 60°C for 6 h. Physical appearances such as color, transparency, glossiness, precipitation, stickiness, flexibility and bleeding were visually examined. Differential scanning calorimetry (DSC) curves of dye, plasticized chitosan citrate film with and without dye were recorded by a DSC analyzer (model DSC 7; Perkin Elmer, CT, USA). Prior to measurement, the cast films were cut and then ground with a small vibrating mill (Shimadzu vibrating mill; Kyoto, Japan). Each test specimen was encapsulated in a pierced lid aluminium pan before tested. A heating rate of 10°C/min and a temperature range of 40–400°C were chosen for scanning. FT-IR spectra of these cast films were also recorded.

2.2.3. Tablet preparation, coating and evaluation

The core tablets containing model drug, propranolol hydrochloride and other additives (Table 1) were prepared as followed. The granules containing propranolol hydrochloride, lactose and Ac-Di-Sol® were produced by wet granulation method. Ethanolic PVP K30 solution was utilized as binder. The wet mass was screened through sieve No.18 mesh prior to drying at 60°C for 1 h. The dry granules were screened through an oscillating granulator (Viuheng Engineering, Bangkok, Thailand) with sieve No.18 mesh. The obtained granules were then mixed with magnesium stearate in a V-shape blender (Kan Seng Lee Machinery Ltd., Bangkok, Thailand) for 5 min.

Table 1
The composition of the propranolol HCl core tablet

Substance	mg/tablet
Propranolol HCl	40
Lactose	233
PVP K30	12
Ac-Di-Sol®	9
Magnesium stearate	6
Total	300

Lubricated granules were compressed into 300 mg tablets using a biconcave punch 8.6 mm in diameter on a single punch tableting machine (Yieheng Engineering, Bangkok, Thailand). The compression force was controlled in order to obtain the tablet hardness of 8 ± 1 Kp.

Film coating components were prepared by dissolving the required plasticizer, propylene glycol, at the concentration of 25% w/w (based on chitosan) in chitosan citrate solution for 30 min before coating. A batch size of 500 g core tablets was coated with coating formulation using conventional coating pan-spray method in a coating pan (Fuji, Electric, Japan) coupling with an air-atomized spray nozzle (Uni Glatt Laboratory unit, Hamburg, Germany). The coating solution was applied with intermittent spray at a spray rate of 7.5 ml/min. The atomizing air pressure was 2 bars and the drying temperature was 60°C. The coating level was 3% w/w based on chitosan. The coated tablets were kept in a desiccator before evaluation.

The surface topography and cross-section of coated tablets were studied under a scanning electron microscope (JSM-T220A; Jeol, Tokyo, Japan). Hardness of coated tablets was measured with a hardness tester (Erweka TBH 30; Milford, Germany). Disintegration of coated tablets was performed using standard USP testing method without disk by a disintegration apparatus (Erweka GmbH ZT31; Milford, Germany). The immersion fluid used was deionized water and the temperature was maintained at 37 ± 1°C.

The drug dissolution studies were based on the USP XXIII using dissolution apparatus 1 (Hanson Research model SR2, California, USA) at 100 rpm and 37°C. Dilute HCl acid (1 in 100) solution of pH 1.2 was used as dissolution fluid. The drug dissolution was also performed in phosphate buffer (pH 6.8). A portion of dissolution medium at various time intervals was assayed spectrophotometrically (Milton Roy, Spectronic 3000 Array, USA) at the wavelength of 290 nm. The amount of drug dissolution was then calculated from absorbance–concentration calibration curve. Six tablets of each formulation were determined.

The effect of storage conditions on drug dissolution in dilute HCl solution (pH 1.2) was also

Table 2
Miscibility between water-soluble dye solutions and chitosan citrate solution

Dye	Concentration of dye solution (% w/w chitosan)				
	0.02	0.05	0.20	0.50	1.00
Brilliant blue	Readily miscible	Readily miscible	Readily miscible	Readily miscible	Miscible
Erythrosine	Colloid like	Colloid like	Colloid like	Colloid like	Colloid like
Green FS	Readily miscible	Readily miscible	Miscible	Miscible	Miscible
Ponceau 4R	Miscible	Precipitate	Precipitate	Precipitate	Precipitate
Sunset yellow	Precipitate	Precipitate	Precipitate	Precipitate	Precipitate
Tartrazine	Miscible	Precipitate	Precipitate	Precipitate	Precipitate

undertaken. The coated tablets were tested after storage in sealed amble bottle at 45°C in 75% relative humidity (RH) atmosphere for 7 and 30 days, and after direct exposure to 45 °C in 75% RH atmosphere for 7 days. The prepared tablets after 12 months storage at room temperature were retested on hardness, disintegration time and drug dissolution.

2.2.4. Dissolution profile fitting

Fitting the experimental dissolution data to the mathematical expression, the Weibull equation, was performed by using a nonlinear computer programme, SCIENTIST (MicroMath Scientific Software, UT, USA). The equation was

$$F(t) = 1 - \exp\{-[(t - t_0)/\mathrm{Td}]^{\beta}\}$$

where $F(t)$ is the fraction of drug dissolved at time t, Td denotes a scale parameter, β was the shape parameter, t_0 was the lag time and $\mathrm{Td} + t_0$ was the time when 63.2% was dissolved. The statistical parameter of the coefficient of determination was used to indicate the degree of goodness of curve fitting.

3. Results and discussion

3.1. Compatibility of chitosan citrate solution with water-soluble dyes

The 5% w/w chitosan in citric acid solution had a pH value of 2.96. This solution containing 25% propylene glycol as plasticizer was yellowish. It was found that brilliant blue and green FS could readily dissolve in this solution at the concentration of 0.02–1.00% w/w, providing brilliant and distinctive color, while precipitated matter obviously appeared after mixing chitosan citrate solution and ponceau 4R or tartrazine at the concentration of more than 0.02% w/w.

Sunset yellow solution was also unable to be miscible with chitosan citrate solution at concentrations between 0.02 and 1.00% w/w. After mixing, insoluble matter suddenly appeared. Also, colloid-like characteristics were found in the mixture of erythrosine at every concentration and chitosan citrate solution. These results are summarized in Table 2.

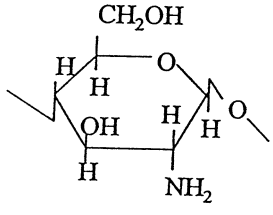
The presence of the insoluble matter was attributed to the charge interaction between anionic dye molecules and the NH_3^+ group in glucosamine units on the chitosan chain. This evidence was also found in the preparation of the microcapsule by complex coacervation using polycationic and polyanionic polymers. The domain mechanism of insoluble wall forming was the electrostatic interaction between protonated amino groups on the chitosan chain and the negative charge of polyanionic polymer (Ritthidej and Tiyaboonchai, 1997). Maghami and Roberts (1988) investigated the adsorption of anionic dyes on chitosan and found that under acidic and in equilibrium conditions, there was a 1:1 stoichiometric interaction between acid groups on the dyes and protonated amine groups of chitosan.

The structures of water-soluble anionic dyes and glucosamine unit of chitosan are illustrated in Fig. 1. In acidic solution, the acidic group (COOH) on the erythrosine molecule was mostly

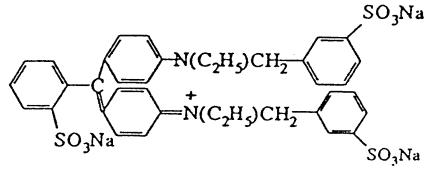
in nonionized form, with solubility less than the SO_3H group of other dyes. Also, the partial transformation to the leuco form in acid solution would alter this dye to colorless matter (Parrott, 1971), hence the colloid-like characteristic observed after mixing, while the charge interaction would be involved in cases of mixing chitosan citrate and other anionic dyes. Incompatibility of sunset yellow with chitosan solution was found. Ponceau 4R and tartrazine solutions showed poorly compatibility, as presented in Table 2. Thus, this interaction depended on the concentration and physicochemical characteristic of colorant.

Good compatibility between chitosan citrate solution and brilliant blue at concentrations of 0.02–1.00% w/w was interesting. The presence of positive charge on a molecule of brilliant blue and its influence, especially in an acidic environment, might provide enough repulsion force to decrease the charge interaction between sulfonate groups of dye and protonated amine groups of chitosan. Because of the presence of positive charge on its structure and the high water solubility (200 g/l) (Rowe, 1984), the tolerance of brilliant blue to coagulate with chitosan was higher than that of other dyes. The water solubilities of erythrosine, ponceau 4R, sunset yellow and tartrazine are 70, 140, 120 and 140 g/l, respectively (Rowe, 1984). The greater amount of this auxochrome (SO_3H) present, a greater solubility of colorant was found (Noonan, 1975).

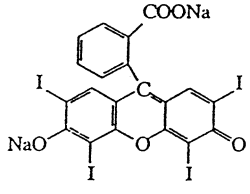
Green FS, the combined color between brilliant blue and tartrazine of 12 and 88% by weight, respectively, remained miscible with chitosan solution at concentrations up to 1.00% w/w. This result was rather surprising; however, the degree of miscibility of green FS was less than that of brilliant blue, as presented in Table 2. Brilliant blue and green FS could be readily miscible with



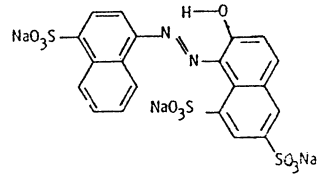
Glucosamine unit



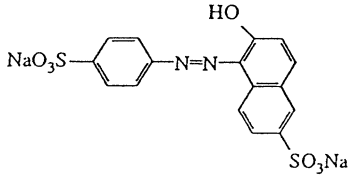
Brilliant blue



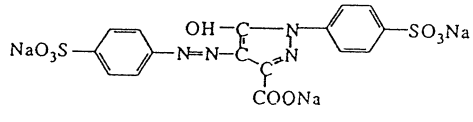
Erythrosine



Ponceau 4R



Sunset yellow



Tartrazine

Fig. 1. The chemical structures of water-soluble dyes and the glucosamine unit.

plasticized chitosan citrate solution at concentrations of 0.02–0.50 and 0.02–0.05% w/w, respectively. It was believed that the presence of brilliant blue as a component in green FS could induce the miscibility between tartrazine and chitosan. The color concentration of brilliant blue and green FS in chitosan citrate solution exhibited high enough tinctorial strength to apply for pharmaceuticals and cosmetic products. This preliminary study showed that these two colorant solutions could be miscible with chitosan citrate solution and provide brilliant color.

The insoluble matter obtained after mixing chitosan citrate solution and sunset yellow solution was selected to be analysed with FT-IR spectroscopy. The FT-IR spectra of chitosan, sunset yellow and this insoluble matter are depicted in Fig. 2.

The FT-IR spectrum of chitosan powder showed the NH_2 deformation peak and amide I band at 1595 and 1655 cm^{-1}, respectively. The broad band of O–H stretching was centered at 3450 cm^{-1}, and the C–H stretching bands were found at 2914 and 2850 cm^{-1}. Additionally, the peak indicating skeletal vibration involving the C–O stretching of C_6 primary alcohol was found at 1070 cm^{-1} (Demarger-Andre and Domard, 1994), and the peaks around 1170–1114 cm^{-1} indicate C–O–C stretching (Colthup et al., 1975).

Sunset yellow, which was an azo dye in the form of aromatic sulfonic acid salt, exhibited four bands at 1253, 1186, 1118 and 1031 cm^{-1}, indicating three SO and one S-phenyl vibrations in FT-IR spectrum, whereas the N=N bands of azo aromatic compound were detected at 1380 and 1495 cm^{-1}, and the N=N stretching appeared at 1574 cm^{-1}. The bands of C=C stretching in aromatic ring occurred at 1623 cm^{-1}, and the peaks of O–H stretching on aromatic ring were found at 3399 and 3510 cm^{-1} (Colthup et al., 1975).

The FT-IR spectrum of water-insoluble matter precipitated after mixing chitosan citrate solution and sunset yellow solution showed the dominant peaks of both chitosan and sunset yellow, such as the C–H stretching band and broad C–O–C stretching band of chitosan, and the N=N band and SO and S-phenyl vibrating bands of sunset yellow. The decrease in intensity of three SO and S-phenyl vibrations interacting bands of dye, and the NH_2 deformation peak of chitosan was found. This result demonstrated that this anionic dye reacted with chitosan due to possibly electrostatic interaction between the sulfonate group on the dye molecule and the protonated amino group on the chitosan chain. This type of bonding was claimed as one of the main causes of interaction between polymer and dye (Prillig, 1969; Slark and Hadgett, 1998). Utilization of chitosan to improve dyeability of prepared cotton was reported by Shin and Yoo (1998), and they also noted that higher dye uptake was obtained in acidic conditions than in alkaline conditions. Therefore, chitosan in citric acid solution could interact with sunset yellow or other anionic dyes. Nevertheless, no water-insoluble matter appeared after adding excess amount of brilliant blue solution in chitosan solution for analysis with FT-IR spectroscopy.

3.2. Cast film evaluation

The noncolored and colored cast films were easily peeled off from the petri dish. They were glossy, transparent and flexible. Neither precipitation nor bleeding was found. Tinctorial strength of colored cast films was increased as the amount of brilliant blue or green FS was increased.

The endothermic and exothermic peaks from DSC curves of brilliant blue powder, plasticized chitosan citrate film and plasticized chitosan citrate film colored with brilliant blue at the concentration of 0.5% w/w based on chitosan are illustrated in Fig. 3. The endothermic peak, appearing at nearly 100°C, of brilliant blue powder was associated with the loss of water, and the exothermic peak at 291°C was the degradation temperature of this dye. The plasticized chitosan citrate film exhibited the endothermic peak at 175.5°C, which was related to the melting point of this mixture, and the degradation temperature appeared at 354.0°C. The endothermic and exothermic peaks of colored film appearing at 175.17 and 352.17°C, respectively, nearly matched those of noncolored film. Therefore, there was no new peak or significant peak shift observed in the thermogram of colored film. It was also found

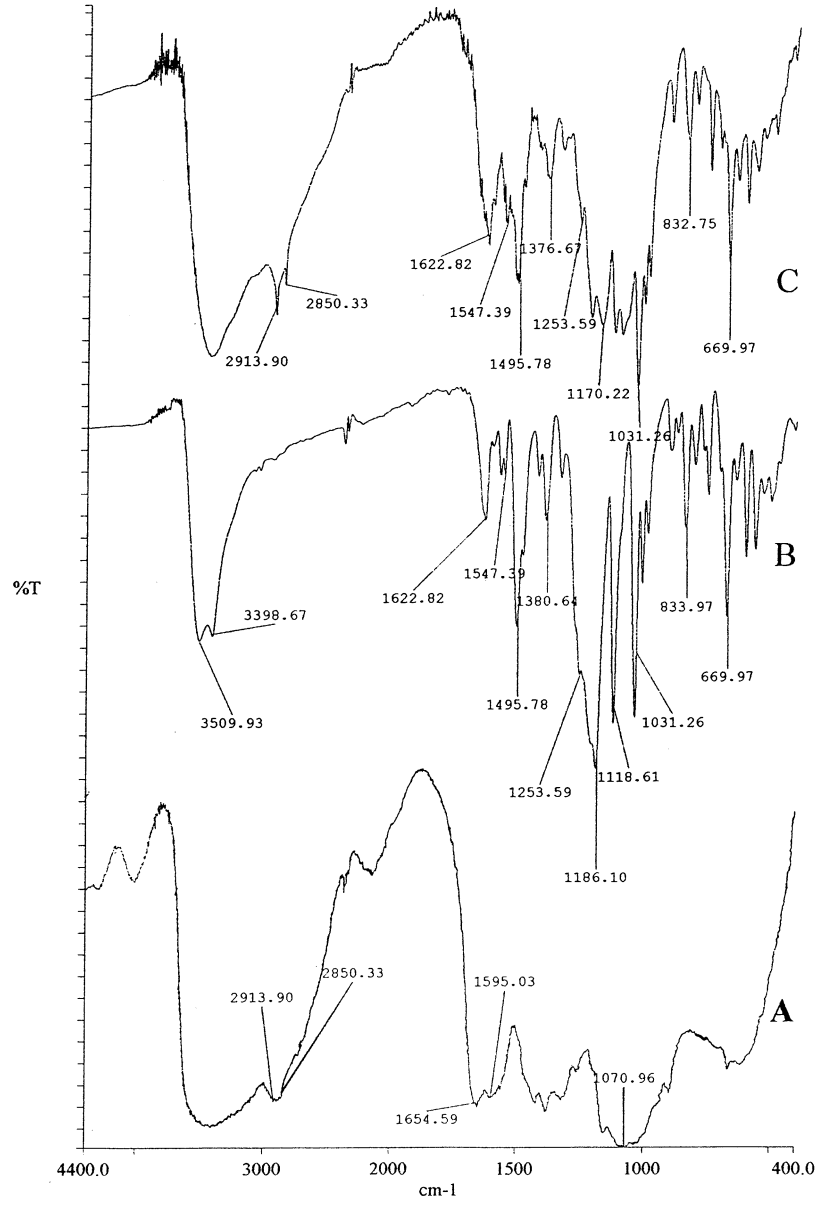


Fig. 2. FT-IR spectra of (A) chitosan; (B) sunset yellow and (C) water-insoluble matter after mixing chitosan citrate solution and sunset yellow solution.

that the peak of brilliant blue did not appear in this film, thus the brilliant blue incorporated at this concentration was miscible with plasticized chitosan citrate film. However, it should be considered that the amount of brilliant blue was very small in the test specimen, so the DSC study might be unable to detect the alteration in this study.

The broad endothermic peak at about 175°C was not attributed to only evaporation of propylene glycol, of which the boiling point was 188°C (Rowe, 1984), but also to the melting point of

chitosan citrate, since the broad endothermic peak of unplasticized chitosan citrate (unshown) was obviously found at this region having the peak at 172.9°C.

There was no new peak or peak shift occurring in the FT-IR spectra (unshown) of these cast films, although the concentration of brilliant blue was increased, indicating that the interaction between chitosan citrate and brilliant blue was scarce.

3.3. Tablet coating and evaluation

3.3.1. Physical appearance

Chitosan film-coated tablets produced by the aqueous polymeric coating technique could be

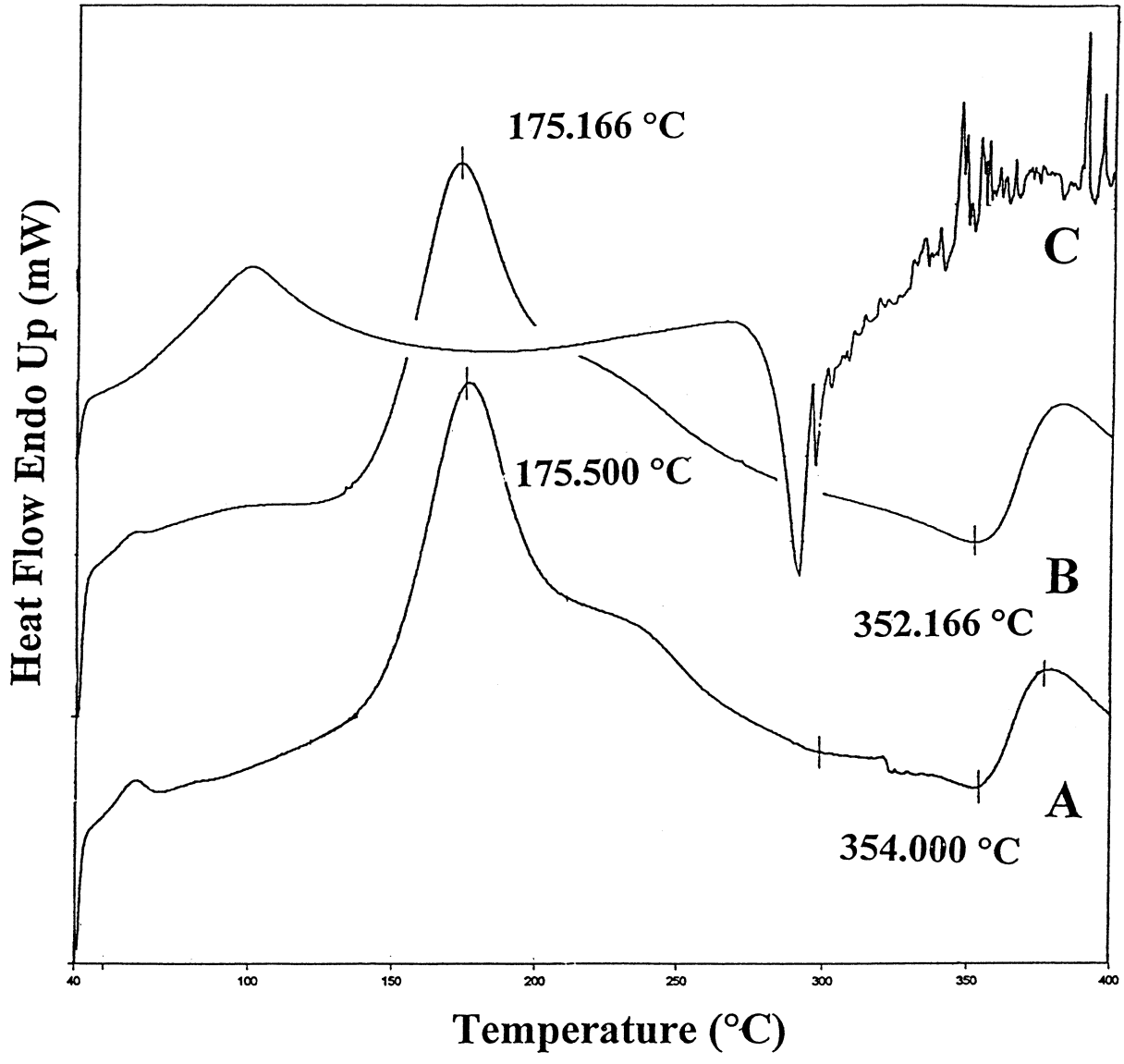


Fig. 3. DSC thermograms of (A) plasticized chitosan citrate film; (B) plasticized chitosan citrate film with brilliant blue 0.5% w/w of polymer and (C) brilliant blue.

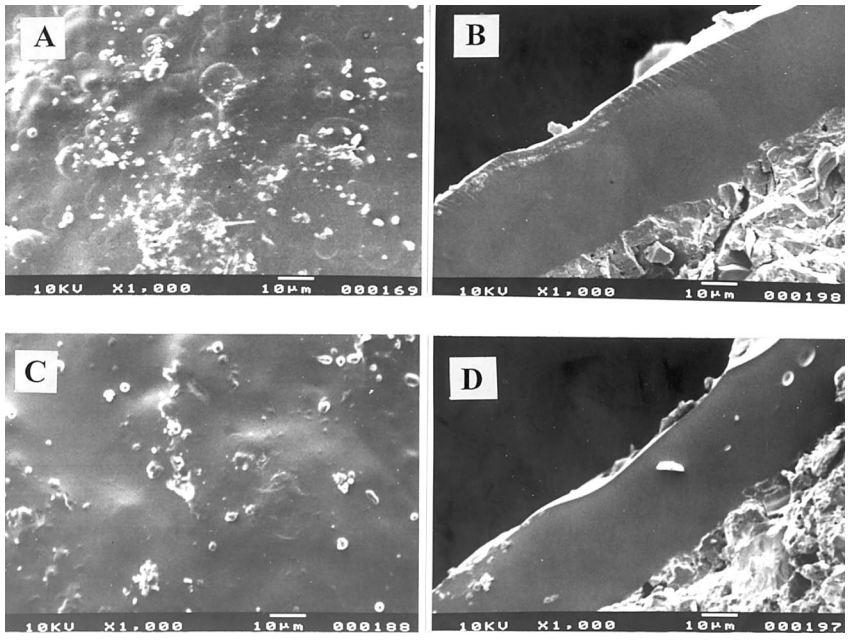


Fig. 4. Scanning electron micrographs of a tablet coated with plasticized chitosan citrate film, (A) surface area and (B) cross-section, and a tablet coated with plasticized chitosan citrate film colored with brilliant blue 0.5% w/w of polymer, (C) surface area and (D) cross-section.

easily prepared without any sophisticate equipment. Hence, this would also be better than the conventional organic-based coating technique, which caused a polluted environment and was toxic to humans. After coating, the plasticized, coated tablets were rather yellowish and glossy. The surface of colored coated tablets exhibited smooth and uniform color dispersed within the film. Color migration was not observed on the surface. This satisfactory appearance came from the partial ionic bond between polymer and colorant; hence, the movement of color molecule owing to the evaporation of solvent during coating process was minimized. In addition, these two colorants could mask the undesired color of chitosan citrate film coat.

Photomicrographs from scanning electron microscopy showed the rather smooth surface of tablet coated with chitosan citrate film plasticized with propylene glycol 25% (Fig. 4A). The cross-section, as shown in Fig. 4B, illustrated that the film coat was homogeneous and was well attached onto the core tablet. The film characteristic of tablets coated with plasticized chitosan citrate film colored with brilliant blue or green FS was similar to that of the former. The surface topography and cross-section of a tablet coated with this plasticized chitosan citrate film colored with brilliant blue 0.5% are shown in Fig. 4C,D, respectively. The film coat was rather smooth and well attached onto the core tablet, and there was no defect found on coated tablets.

The hardness of coated tablets is presented in Table 3. The hardnesses of both noncolored and colored coated tablets were similar. It was shown that the hardness was not much changed after exposure to accelerated conditions, but slightly decreased after storage at room temperature for 12 months.

3.3.2. Disintegration time

The disintegration times of coated tablets were less than 10 min, except those of coated tablets after direct exposure to accelerated condition, which were extended to more than 30 min. This result is presented in Table 3.

3.3.3. Drug dissolution

The drug dissolution from freshly prepared coated tablets both in dilute hydrochloric acid (pH 1.2) and phosphate buffer (pH 6.8) is graphically displayed in Fig. 5, part 1. Core tablets exhibited the highest drug dissolution at each time interval and the dissolution profile in dilute hydrochloric acid (pH 1.2) was similar to that in phosphate buffer (pH 6.8). This demonstrated that the drug dissolution from the core tablet was not affected by the dissolution media.

The drug dissolution from coated tablets was slower than that of core tablets. Especially, the dissolution in phosphate buffer (pH 6.8) was much slower than that in acidic medium. This result showed that the pH of medium affected the drug dissolution from chitosan citrate film-coated tablets. In acidic medium, chitosan could be protonated and subsequently solubilized. However, the protonation of amino groups, and the hydrogen bonding between the hydroxyl group on the chitosan chain and that on the water molecule, caused hydration and swelling of the film coat prior to the dissolution. The hydration and gel-forming properties of chitosan in the acid environment have been reported by Nigalaye et al. (1990). Thus, the drug dissolution was slightly retarded by the hydrated film and the drug dissolution was slower than that of core tablet. As a polyelectrolyte polymer, chitosan having a pK_a of about 6.5 was unlikely to protonate in phosphate buffer (pH 6.8). However, citric acid incorporated in coated film could enhance the penetration of water and induce the hydration of coated film, and the drug dissolution could occur but more slowly than that in acidic medium. The increase in the solubility coefficient of hydroxy propyl methylcellulose film by addition of citric acid has been reported, and this evidence was attributed to the nonpolymeric nature and multiple hydrophilic groups of citric acid that could enhance the moisture affinity of polymeric film (Okhamafe and York, 1988). Similarly, commonly used film former, Eudragit®E, also a cationic polymer, could dissolve in water with salt formation upon addition of one to three equivalents of organic or inorganic acids. Suitable acid components were citric acid and sodium dihydrogen phosphate (Bauer et al., 1998).

The dye incorporation slightly retarded the drug dissolution in acidic medium. Since the electrostatic charged interaction between anionic groups of dye and protonated amino groups of chitosan occurred, the remaining protonated amino groups that were ready for dissolving were decreased. Thus, the retardation of drug dissolution was evident. However, because of the higher hydration efficiency of chitosan citrate film, the effect of dye binding to retard the dissolution was minute. This higher hydration and solubility came from the high water penetration and the more acidic environment induced by citric acid.

In contrast, the dissolution from colored film-coated tablet was apparently faster than that of noncolored film-coated tablet in phosphate buffer (pH 6.8), as depicted in Fig. 5, part 1. In this

Table 3
The hardness ($n = 10$) and disintegration time ($n = 6$) of tablets coated with plasticized chitosan citrate film colored with different dyes[a]

Storage condition	Hardness (Kp)			Disintegration time (min)		
	Non-colored	Brilliant blue	Green FS	Non-colored	Brilliant blue	Green FS
A	21.37 ± 2.20	18.46 ± 2.89	17.82 ± 2.85	8.43 ± 0.42	9.88 ± 1.08	7.80 ± 0.51
B	21.15 ± 2.91	17.98 ± 3.15	17.86 ± 2.32	5.70 ± 0.54	5.42 ± 0.67	6.46 ± 0.96
C	18.28 ± 3.46	20.00 ± 2.51	17.37 ± 2.71	9.23 ± 0.46	9.07 ± 0.52	8.77 ± 0.47
D	21.37 ± 2.20	20.71 ± 1.41	18.39 ± 2.20	>30	>30	>30
E	17.72 ± 2.09	15.77 ± 3.78	13.78 ± 2.32	7.94 ± 0.71	7.76 ± 0.40	7.50 ± 0.39

[a] A, freshly prepared; B and C, after being kept in a bottle and in accelerated conditions for 7 and 30 days, respectively; D, after direct exposure to accelerated condition for 7 days; and E, after storage at room temperature for 12 months.

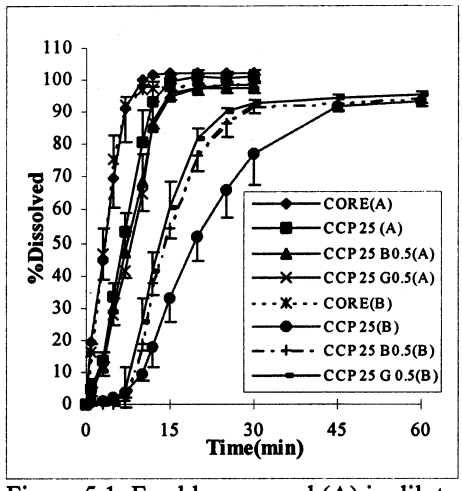


Figure 5.1. Freshly prepared (A) in dilute HCl acid and (B) in phosphate buffer pH 6.8.

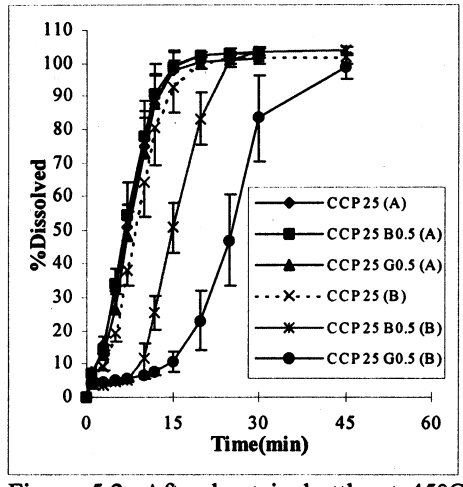


Figure 5.2. After kept in bottle at 45°C 75%RH for (A) 1 week and (B) 1 month.

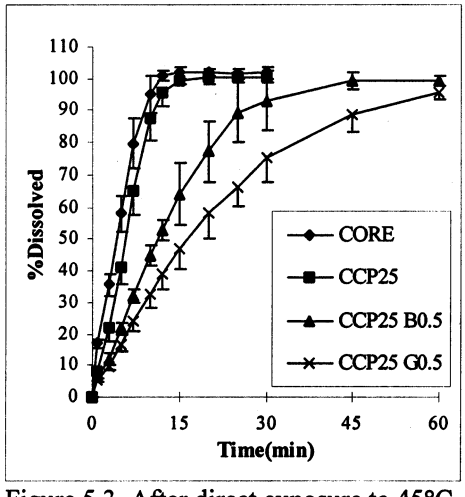


Figure 5.3. After direct exposure to 45°C 75% RH for 1 week.

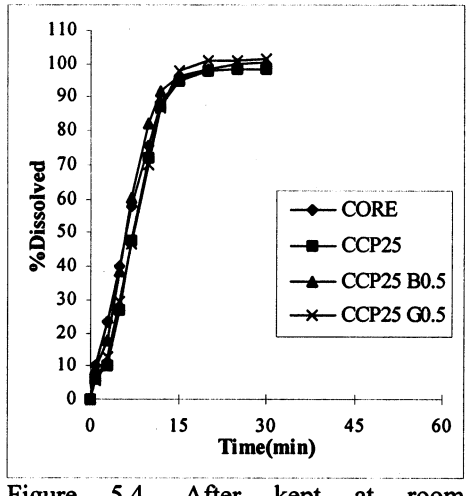


Figure 5.4. After kept at room temperature for 1 year.

Fig. 5. The dissolution profiles of propranolol HCl from the core tablet and tablets coated with plasticized chitosan citrate film (CCP25), and tablets coated with plasticized chitosan citrate film colored with brilliant blue 0.5% w/w of polymer (CCP25 B0.5) and green FS 0.5% w/w of polymer (CCP25 G0.5) ($n = 6$). Part 1, Freshly prepared (A) in dilute HCl acid and (B) in phosphate buffer (pH 6.8); part 2, after being kept in a bottle at 45°C, 75%RH, for (A) 1 week and (B) 1 month; part 3, after direct exposure to 45°C, 75% RH, for 1 week; part 4, after being kept at room temperatur for 1 year.

environment, the anionic dye molecule could be easily ionized and could promote film hydration. This result was attributed to the decline in the dye-binding capacity of chitosan above its pK_a, as mentioned by Knorr (1983) who tested dye binding of chitosan and FD&C Red No. 40. Shin and Yoo (1998) also noted that dye uptake of chitosan obtained in acidic environment was greater than in alkaline environment. Hence, the drug dissolution in phosphate buffer (pH 6.8) from colored film-coated tablets was faster than noncolored film-coated tablet.

The effect of storage conditions on drug dissolution in dilute hydrochloric acid (pH 1.2) was investigated (Fig. 5, parts 2–4). It was found that there was no apparent change in drug dissolution of coated tablets after they were kept in a sealed amble bottle at 45°C, 75% RH, for 7 days, as presented in Fig. 5, part 2. The effect of dye incorporation on the retardation of drug dissolution could be not found. After longer storage at 45°C, 75%RH, for 1 month, the dominantly slower drug dissolution was observed, especially in case of colored coated tablets. Film-coated tablets colored with green FS exhibited slower drug dissolution than that of coated tablets colored with brilliant blue.

This result was more obvious when coated tablets were directly exposed to the presented conditions, as illustrated in Fig. 5, part 3. The retardation of disintegration and dissolution of drug release from gelatin capsule after exposure accelerated condition has been previously published, and the proposed mechanism for this evidence was the cross-linking between amino groups of gelatin and carbonyl substances resulting in the insolubility of capsule shell (Adesunloye and Stach, 1998). The cross-linking of cellulose has in recent years been reported to be focused on the utilization of multifunctional carboxylic acids to replace the traditional aldehyde based reagents (Yang and Wang, 1997; Jegal and Lee, 1999). Thus, the cross-linking between amino groups on chitosan chains and carboxyl groups on citric acid under accelerated conditions could possibly retard the disintegration and drug dissolution of coated tablets. The more extensive exposure to the accelerated environment possibly enhanced the degree of cross-linking. Therefore, the direct exposure to the accelerated condition could retard the drug dissolution from film-coated tablets more than those after storage in a sealed amble bottle under accelerated conditions for 1 month and 1 week, respectively. Because the outside moisture could gradually permeate through the plastic cap of the bottle, the longer storage under rather high temperature (45°C) resulted in the greater degree of alteration. Due to the high solubility and high amount of SO_3H group of brilliant blue, the drug dissolution was still faster than that of coated tablets colored with green FS. Coated tablets after exposure to accelerated condition still exhibited the drug dissolution conforming to the monograph in USP XXIII, which was not less than 75% of drug dissolved in 30 min. The influence of ageing for 1 year on drug dissolution was investigated. It was found that the dissolution profiles were not much altered from freshly prepared coated tablets, as shown in Fig. 5, part 4, except for the drug dissolution from the core tablet, which was slightly slower. All aged tablets exhibited drug dissolution that conformed to the monograph in USP XXIII and reached the plateau stage of dissolution at 15 min.

3.4. Dissolution profile fitting

Fitting each experimental drug dissolution profile to the Weibull function provided high coefficients of determination, as shown in Table 4. This result indicated that the fitting was successful. This mathematical equation was an expression for a cumulative probability distribution but had proved applicable for fitting the dissolution profiles in general (Jorgensen and Jacobsen, 1992). The release profiles of enteric-coated tablets and pellets (Odegardstuen et al., 1991) or microcapsules (Racz et al., 1997) could be described and compared by using the Weibull function. Td values representing the time of 63.2% drug dissolved are shown in Table 4. It was found that long storage in accelerated conditions or direct exposure accelerated conditions would increase the Td value from the dissolution profile of colored coated tablets. Using the green FS as coloring agent could enhance Td values greater than using the brilliant blue. This indicated that the partial ionic bond of chitosan-green FS was greater than that of chitosan-brilliant blue. All dissolution profiles of freshly prepared and 12 month-aged coated tablets had a sigmoidal form, represented by $\beta > 1$ (Table 4). The description about shape parameter, β, was noted by Racz et al. (1997). The β value obviously decreased in dissolution profiles of tablets coated with film plasticized with propylene glycol and colored with brilliant blue or green FS after direct exposure to accelerated condition, especially in the latter case.

Table 4
β value, $Td + t_0$ and coefficient of determination from data fitting to Weibull equation of dissolution profiles of tablets coated with plasticized chitosan citrate film colored with different dyes[a]

Storage condition	β value			$Td + t_0$ (min)			Coefficient of variation		
	Non-colored	Brilliant blue	Green FS	Non-colored	Brilliant blue	Green FS	Non-colored	Brilliant blue	Green FS
A	1.8028 ± 0.0798	1.8059 ± 0.0954	1.8851 ± 0.0712	7.88 ± 0.85	8.86 ± 0.87	9.15 ± 0.13	0.9950 ± 0.0018	0.9934 ± 0.0031	0.9880 ± 0.0053
B	1.7829 ± 0.1928	1.8056 ± 0.1586	1.84676 ± 0.1034	8.28 ± 0.63	8.78 ± 0.77	8.49 ± 0.94	0.9927 ± 0.0077	0.9942 ± 0.0018	0.9926 ± 0.0035
C	1.9990 ± 0.1855	1.5110 ± 0.0240	2.1136 ± 0.0765	9.98 ± 1.33	16.67 ± 0.95	26.85 ± 2.09	0.9974 ± 0.0014	0.9947 ± 0.0041	0.9684 ± 0.0256
D	1.8041 ± 0.1285	1.3124 ± 0.1251	1.1652 ± 0.0532	6.82 ± 0.78	14.68 ± 1.68	20.93 ± 2.47	0.9951 ± 0.0025	0.9932 ± 0.0043	0.9946 ± 0.0029
E	1.9922 ± 0.1293	1.898 ± 0.2535	1.7826 ± 0.1140	8.36 ± 1.27	7.48 ± 1.16	8.82 ± 0.52	0.9967 ± 0.0018	0.9931 ± 0.0065	0.9925 ± 0.0343

[a] A, freshly prepared; B and C, after being kept in a bottle and in accelerated conditions for 7 and 30 days, respectively; D, after direct exposure to accelerated condition for 7 days; and E, after storage at room temperature for 12 months ($n = 6$).

By comparison, using a statistical unpaired t-test, the Td value of freshly prepared coated tablets was not significantly different from that of 12 month-aged coated tablets of each individual coating formula ($P > 0.02$).

4. Conclusions

The occurrence of insoluble matter after mixing indicated the incompatibility between chitosan citrate solution and anionic dyes erythrosine, ponceau 4R, sunset yellow and tartrazine, whereas green FS and brilliant blue at concentrations of 0.02–1.00% w/w of polymer could be miscible with this polymeric solution and could provide tinctorial strength high enough for coloring film coating. The high water solubility of brilliant blue and the influence of positive charge on its molecule, especially in acidic environment, might possibly decrease the charge interaction between sulfonate groups of dye and protonated amine groups of chitosan. The presence of brilliant blue as a component in green FS should induce the miscibility of tartrazine and chitosan citrate solution. The analysis with FT-IR and DSC techniques revealed that there was no interaction between brilliant blue and chitosan.

Satisfactory characteristics of chitosan citrate film-coated tablets were obtained. No color migration appeared. The film coated onto the core tablet was smooth, homogeneous and well attached. However, the dissolution of propranolol HCl from coated tablets was pH dependent. The drug dissolution in dilute hydrochloric acid (pH 1.2) was faster than that in phosphate buffer (pH 6.8). The drug dissolution in latter was retarded due to the unprotonated nature of chitosan, whereas in acidic medium, chitosan could be easily protonated and then solubilized. Because the solubility of anionic dyes was pH dependent, color incorporation slightly inhibited or enhanced drug dissolution in dilute hydrochloric acid (pH 1.2) or phosphate buffer (pH 6.8), respectively.

The retardation of disintegration and drug dissolution of these coated tablets was evident after exposure accelerated conditions but not in the case of 1-year storage at room temperature. Brilliant blue was more suitable than green FS for coloring the plasticized chitosan citrate film because its effect on retardation of disintegration and drug dissolution was less than that of green FS. The cross-linking between amino groups on chitosan chains and carboxyl groups on citric acid under accelerated conditions might be the cause of film property alteration.

Acknowledgements

The authors wish to express appreciation for the research grant from the Cooperative Research Project Between Thailand and Japan (NRCT-JSPS).

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