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RESEARCH PAPER

Effect of Anionic Water-Soluble Dyes on Film Coating Properties of Chitosan Acetate

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ABSTRACT

Solution of chitosan in dilute acetic acid was prepared to have an apparent viscosity of 125 mPa s and mixed with solution of anionic water-soluble dye. The effects of concentration and type of dye and molecular weight and percentage deacetylation of chitosan on their miscibility and physical stability were investigated. High concentration of dye and high molecular weight and percentage deacetylation of chitosan resulted in precipitation or colloidal dispersion due to ionic interaction between dye and the polymer. The effect was more prominent upon storage. The miscibility of dye and the polymer depended on the molecular configuration and ionic group in the dye molecule. It was ranked brilliant blue ≅ green FS > fast green > ponceau SX ≅ sunset yellow > erythrosine ≅ tartrazin > indigo carmine. Solutions of low molecular weight chitosan with and without green FS were then used as coating formulations onto propranolol hydrochloride core tablets. There was no color migration on coated tablets even after storage for 1 year. Disintegration and drug dissolution from tablets coated with colored film were slightly slower than those from tablets coated with plain film and core tablet, respectively. This was corresponding to the results of swelling and dissolution of cast films. However, all tablets conformed to the specification in monograph of USP XXIV.

Key Words: Anionic water-soluble dyes; Chitosan acetate; Film coated tablet.

INTRODUCTION

Polymeric film coating is increasingly popular since aqueous polymeric film coating formulations have been commercially available.[1] Moreover, the dissolution of drug from coated tablet could be regulated as fast or extended release depending on the type of the polymeric material. Chitosan acetate

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film was reported to be poorly soluble under accelerated conditions[2] and became insoluble after moist heat treatment.[3] Addition of magnesium stearate or talcum to chitosan acetate film and thereafter top-coated with an enteric-soluble polymer onto triamcinolone tablets was reported to exhibit extended release of drug upto 4 hr in basic medium.[4] Although moist heat treatment to propranolol hydrochloride tablets coated with chitosan acetate film containing magnesium stearate and triacetin could successfully extend the release of drug to 24 hr, these coated tablets were found to have unfavorable color.[5]

Coloration to pharmaceutical preparations is mainly to provide distinctive identification and elegance of the product. It can also mask unpleasant color. The main advantage of soluble dyes over lakes is the more elegance of the product. However, migration of color is more prominent. Most water-soluble dyes commonly used in pharmaceuticals and cosmetics are sodium salt of anionic dye molecules.[6] Interaction of these dyes and the cationic polymer was reported.[7]

Precipitation or colloidal dispersion was observed after incorporation of various anionic water-soluble dyes to chitosan citrate film coating solution except briliant blue and green FS.[7]

The objective of this study was therefore to investigate the possibility of using anionic water-soluble dye to mask the discoloration of chitosan acetate film. The miscibility of chitosan acetate solution with eight water-soluble anionic dyes both after preparation and storage at room temperature for 1 week was determined. The effect of molecular weight and concentration of chitosan and the concentration of dye on their miscibility was also studied. Chitosan solution with selected dye was then coated onto propranolol hydrochloride tablets. The migration of color was assessed. The hardness, disintegration, and dissolution of these coated tablets were evaluated and compared with those of coated tablets without dye and core tablets. Physicochemical properties of colored chitosan acetate film were also compared to those of film without dye.

MATERIALS AND METHOD

Materials

Three grades of chitosan, chitosan L, M, and H (lot number UCPL-LO1, UCPL-MO1, and UCPL-HO1, respectively), were supplied by Unicord Public Company, Thailand. The polymeric flakes were pulverized with a Fitz mill (Kan Seng Lee Factory Ltd., Thailand) and passed through a 80-mesh sieve prior to use. Eight water-soluble anionic dyes—brilliant blue (C.I. No.42090), erythrosine (C.I. No. 45430), fast green (C.I. No. 42053), indigo carmine (C.I. No. 73015), ponceau SX (C.I. No. 14700), sunset yellow (C.I. No. 15985), tartrazine (C.I. No. 19140), and green FS (a mixture of brilliant blue and tartrazine of 12 and 88% by weight, respectively)—were purchased from the Government Pharmaceutical Organization, Thailand. Propranolol hydrochloride (lot number 850602, China National Chemical Imp. Exp. Corp., China) was used as a model drug. Lactose hydrous (Wyndale, Hawera, New Zealand), PVP K30 (GAF, Singapore), cross-linked CMC (Ac-Di-Sol®) (FMC Corp., USA), and magnesium stearate (Lek Pharm. and Chem. Work, Yugoslavia) were used as tablet excipients. All other reagents were of analytical or AR grade.

Determination of Physicochemical Characteristics of Chitosan Powder

Molecular Weight and Percentage Deacetylation

Chitosan solutions were prepared to have concentrations of 0.025–0.500% w/w by dissolving the polymer in the solution of 0.2 M glacial acetic acid and 0.1 M sodium acetate. The density of chitosan acetate solution was determined with a pycnometer. The relative viscosity was then obtained by using an Oswald viscometer. The molecular weight was subsequently calculated by using the Mark-Houwink equation ($\eta = KM_V^a$, where the proportionality constant, $K = 1.8 \times 10^{-3}\,\mathrm{cm^3/g}$ and the shape factor, $a = 0.93$).[8] The percentage of deacetylation of chitosan was determined according to Haynes'colloidal titration method.[9] Each chitosan powder was undertaken in triplicate.

IR Spectroscopy

The FT-IR spectrum of chitosan was obtained from a Fourier transform infrared (FT-IR) spectrophotometer (Spectrum 2000, Model SP2000, Perkin Elmer, USA). The measurement was made by the KBr disc method.

Thermal Property

The melting thermogram of chitosan was recorded with a differential thermal analyzer (Model DT-30, Shimmadzu, Japan). The heating rate was 10°C/min. The sensitivity was ±50 μv at the temperature of 30–250°C.

Compatibitlity of Chitosan Solution and Water-Soluble Dyes

Chitosan L, M, and H were individually dissolved in 1% w/w acetic acid to obtain the concentrations between 0.5 and 5.0% w/w. Each solution was filtered through a polyester cloth to discard insoluble matter. The viscosity of each solution was determined by using a viscometer (Haake Mass-Technik, Germany). The concentration vs. viscosity profile of each grade of chitosan was plotted to determine the concentration that would provide a viscosity of 125 mPa s. Polymeric solution of this viscosity was reported to be optimal for spraying onto tablet.[1] The solutions of chitosan L, M, and H of such concentrations were then prepared as aforementioned. The pH of each solution was also determined by using a pH meter (Model PHI32, Beckman Instrument, USA). The experiment was done in triplicate.

The coloring agents, brilliant blue, erythrosine, fast green, green FS, indigo carmine, ponceau SX, sunset yellow, and tartrazine, were separately dissolved in deionized water to obtain a concentration of 1% w/w. The dye solution was then diluted with each optimal chitosan solution to have the dye concentrations of 0.001, 0.01, 0.025, and 0.05% w/w. The physical compatibility of the mixture was visually observed both initially and after storage at room temperature for 1 week.

Preparation and Evaluation of Propranolol Hydrochloride Coated Tablets

The composition of propranolol hydrochloride core tablet is listed in Table 1. The process of preparation was previously described.[7] Chitosan acetate film solutions with and without selected dye were then individually coated onto the core tablets to increase the tablet weight by 1.5%.

The hardness of coated tablets was determined by using a hardness tester (Scheuniger Model 2E/205, Switzerland) and compared with that of core tablets. The disintegration of tablet was performed under standard USP testing method by using a disintegration apparatus (Hanson Research Model QC-21, USA). Deionized water was used as disintegration medium and maintained at 37 ± 1°C. Dissolution study was performed according to the monograph of USP XXIII. Dissolution apparatus and medium were as previously described.[7] Samples were withdrawn and spectrophotographically assayed (Spectronic 2000, Bausch and Lomb, USA) at the wavelength of 289 nm. The time for 75% drug dissolved was then obtained from the percentage drug dissolved–time profile.

Table 1. The composition of propranolol hydrochloride core tablet.

Ingredients	Amount (mg/tablet)
Propranolol hydrochloride	40.0
Lactose	195.0
PVP K30	7.5
Ac-Di-Sol®	7.5
Magnesium stearate	2.5

Preparation and Evaluation of Chitosan Acetate Free Films

Chitosan acetate films with and without selected dye were prepared by casting method. The polymeric solution was dried at 60°C for 24 hr to have a thickness of about 50–60 μm. A film of $2.5 \times 2.5\,cm^2$ was placed in a vacuum desiccator for 1 week, prior to initial weight (W_0). The film was immersed in deionized water for 5 min, removed of excess water with filter paper and weighed (W_1). After drying in an oven at 60°C for 24 hr the film was reweighed (W_2). The swelling index and the percentage of film dissolution were then obtained by the equations

$$\text{Swelling index} = (W_1 - W_2)/W_2 \quad (1)$$

$$\%\ \text{film dissolution} = (W_0 - W_2)/W_0 \times 100 \quad (2)$$

RESULTS AND DISCUSSION

Determination of Physicochemical Characteristics of Chitosan Powder

Table 2 lists some physicochemical characteristics of chitosan powder. It could be seen that the

Table 2. Physicochemical characteristics, peak height ratio at $1150/3480\,cm^{-1}$ from FT-IR spectra, and endothermic peak temperature from DSC thermogram of chitosan.

Chitosan	MW (Daltons)	% deacetylation[a]	Peak height ratio	Endothermic peak temperature (°C)
L	46167.61	82.25 ± 0.35	0.288	165.0
M	48054.96	63.54 ± 1.26	0.325	171.0
H	58204.40	77.12 ± 1.26	0.416	181.0

[a]Mean ± S.D. of three determinations.

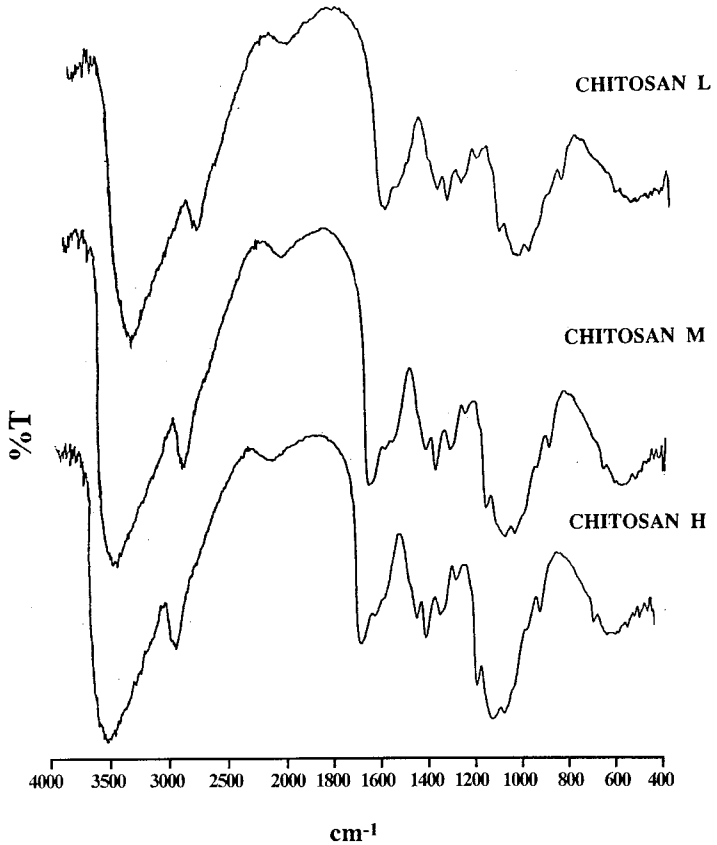

Figure 1. FT-IR spectra of chitosan L, M, and H.

calculated molecular weight of chitosan L was the lowest, followed by those of chitosan M and H, respectively. This result corresponded to the results from the FT-IR spectra of chitosan L, M, and H as shown in Fig. 1 and the endothermic peak temperature from DSC thermogram. Since the peak at the wavelength of $1140–1170\,cm^{-1}$ in the FT-IR spectra indicated the ether linkage or β-linkage of glucosamine unit, while that at $3480\,cm^{-1}$ indicated the hydroxy group, higher peak height ratio at $1150/3480\,cm^{-1}$ would indicate higher molecular weight of the polymer.[10] Moreover, polymer of lower molecualr weight required lower energy to change its chemical structure or physical state.[11] Chitosan L correspondingly exhibited the lowest endothermic peak temperature followed by chitosan M and H, respectively. The percentage deacetylation was ranked chitosan L > H > M.

The apparent viscosity of chitosan solution of each grade was plotted against its concentration as illustrated in Fig. 2. It was graphically shown that chitosan H exhibited the steepest curve, followed by chitosan M and L, respectively. The apparent viscosity of 125 mPa s, which was optimal

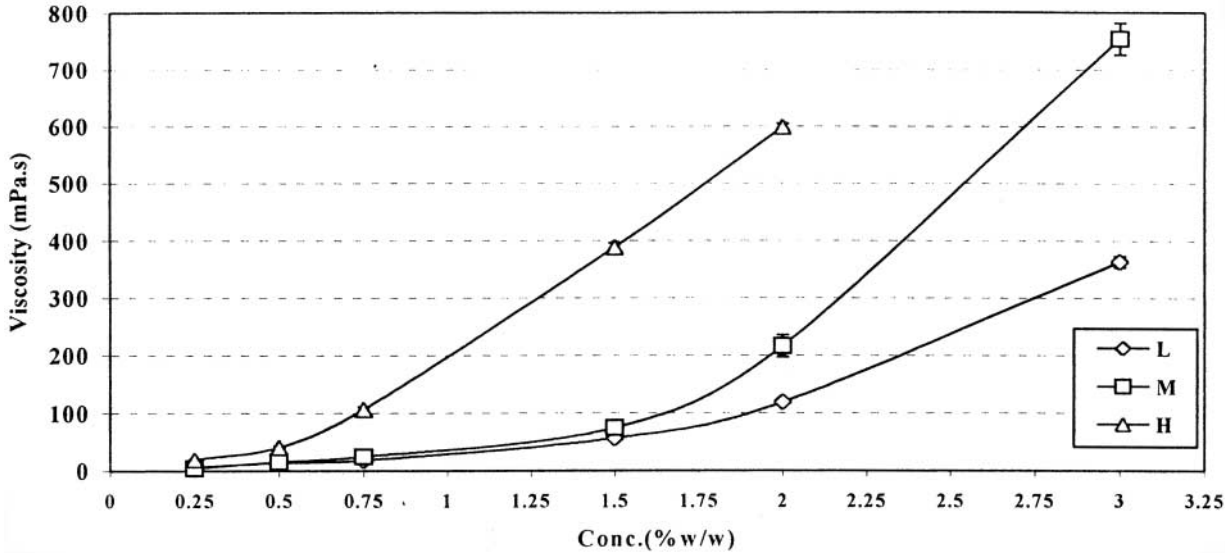

Figure 2. Apparent viscosities of chitosan L, M, and H solutions at different concentrations.

for film coating, could be obtained at the concentration of 2.025, 1.750, and 0.825% w/w of chitosan L, M, and H, respectively. At these concentrations, the prepared chitosan solutions exhibited pH of 5.04 ± 0.02, 4.74 ± 0.03, and 4.37 ± 0.01, respectively.

Compatibility of Chitosan Solution and Water-Soluble Dyes

Table 3 shows the physical compatibility of mixture of various dyes and chitosan solution. It could be noted that at low dye concentration of 0.001% w/w, all anionic dyes were miscible with chitosan acetate solution except indigo carmine, which mixture with chitosan M solution instantly precipitated. After storage for 1 week, the color of indigo carmine gradually faded. Moreover, precipitation also occurred in mixture of both erythrosine and tartrazine in chitosan H solution. Increasing the concentration of dye to 0.01% w/w resulted in instant precipitation in all chitosan solutions except green FS, brilliant blue, and fast green. Precipitation retained even after storage for 1 week. At this concentration, erythrosine formed colloid with chitosan solutions. After storage, its mixture with chitosan M and H solutions precipitated. At dye concentrations of 0.025 and 0.05% w/w, only green FS and brilliant blue were miscible with chitosan acetate solution.

Theoretically, precipitation occurred due to the interaction of opposite charge between anionic dye and cationic glucosamine on the polymer chain. However, at low dye concentration, there were few anionic dye molecules to react with ammonium (NH^{3+}) on glucosamine unit of chitosan chain. Available free ammonium group could substantially react with acidic medium, which resulted in miscible mixture. The molecular configuration and ionic group in the dye molecule seemed to play a prominent role in compatibility. Brilliant blue is a highly water-soluble dye. It has positive charge on its molecule that consequently could cause repulsion between its molecule and cationic chitosan molecule. The compatibility was also supported by the low pH of the dye solution, which was close to the pH of chitosan solution. The pH values of various 1% w/v dye solutions were reported[12] and are also listed in Table 3. Fast green had water solubility, pH range, and chemical structure similar to brilliant blue as shown in Fig. 3.[13] However, the repulsion between fast green and chitosan was less favored. This was due to the transposition of sulfophenyl group to its positive charge in the molecule of fast green, whereas in briliant blue, the sulfophenyl group was in the cis-position.

Erythrosine and sunset yellow were reported to precipitate with chitosan citrate solution even at diluted concentration of 0.001% w/w.[7] The incompatibility was due to the lower pH of chitosan citrate solution of only 2.96. The higher pH of chitosan acetate solution at 4.3–5.0 indicated less amount of

Table 3. Physical compatibility of mixture of chitosan acetate solution and various dyes.

		Concentration of dye (% w/w)							
		0.001		0.01		0.025		0.05	
Dye	Chitosan	A	B	A	B	A	B	A	B
Brilliant blue	L	—	—	—	—	—	—	—	—
(4.9–5.6)[a]	M	—	—	—	—	—	—	—	—
	H	—	—	—	—	—	—	—	—
Erythrosine	L	—	—	c	c	p	p	p	p
(7.7)[a]	M	—	—	c	p	p	p	p	p
	H	—	p	c	p	p	p	p	p
Fast green	L	—	—	—	—	p	p	p	p
(4.2–5.8)[a]	M	—	—	—	—	p	p	p	p
	H	—	—	—	—	p	p	p	p
Green FS	L	—	—	—	—	—	—	—	—
	M	—	—	—	—	—	—	—	—
	H	—	—	—	—	—	—	—	—
Indigo carmine	L	—	f	p	p	p	p	p	p
(8.5)[a]	M	p	f	p	p	p	p	p	p
	H	—	f	p	p	p	p	p	p
Ponceau SX	L	—	—	p	p	p	p	p	p
(6.4)[a]	M	—	—	p	p	p	p	p	p
	H	—	—	p	p	p	p	p	p
Sunset yellow	L	—	—	p	p	p	p	p	p
(6.6)[a]	M	—	—	p	p	p	p	p	p
	H	—	—	p	p	p	p	p	p
Tartrazine	L	—	—	p	p	p	p	p	p
(6.8)[a]	M	—	—	p	p	p	p	p	p
	H	—	p	p	p	p	p	p	p

Note: A, B = at time 0 and 7 days, respectively. —, c, f, p = clear solution, colloid-like, fade and precipitation, respectively.
[a]pH of 1% w/v solution.

available cationic glucosamine unit. Therefore, less electrostatic interaction with anionic dye would result. The FT-IR spectra of sunset yellow and precipitate from the mixture of sunset yellow and chitosan solution are shown in Fig. 4. The peaks at the wave numbers of 1253, 1190, and 1119, and 1035 cm^{-1} indicated three SO and *S*-phenyl vibration bands of sunset yellow. It could be seen that the peak intensity at these wave numbers from the spectra of the precipitate was less than that from the dye alone. This indicated that there was an interaction between sunset yellow and chitosan acetate.

Indigo carmine exhibited low water solubility of 16 g/L.[14] Its pH was the highest among tested dyes indicating the highest degree of anionic charge. Therefore, interaction between this dye and chitosan was more prominent than other dyes. Moreover, this dye is very sensitive to acid and light.[15] Redox reaction could turn this dye into colorless molecule even at low concentration. The chemical structure of this dye is also shown in Fig. 3.

Chitosan of higher percentage deacetylation had more available cationic ammonium group. It would have higher degree of interaction with anionic dye. In addition, the concentration of chitosan solution would also regulate the total amount of free ammonium group. This would reflect the ionization or the pH of the solution. Chitosan of lower molecular weight exhibited higher pH value. This indicated that it had lesser amount of cationic molecules. In contrast, chitosan of higher molecular weight had longer chain length, thus was bulkier. Therefore, precipitation would be of higher degree when the polymer interacted with anionic dyes. It was noted that the molecular weight of polymer played more important role in the miscibility than the degree of deacetylation. Moreover, the result of incompatibility was more prominent after 1-week

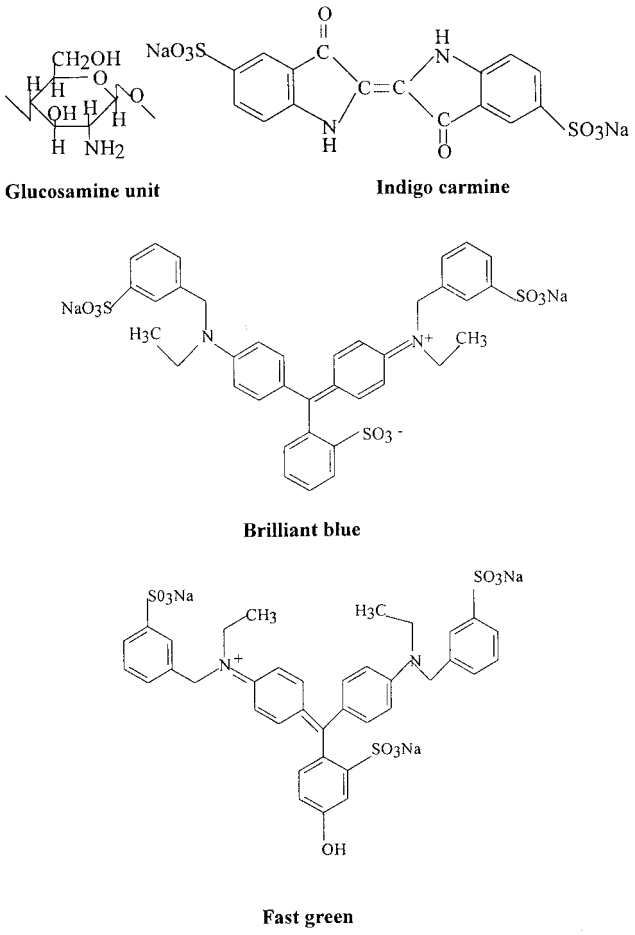

Figure 3. Chemical structures of glucosamine unit of chitosan and water-soluble dyes.

storage. This indicated that time was essentially required in order to reach equilibrium. The ionic interaction was obviously time dependent.

Preparation and Evaluation of Propranolol Hydrochloride Coated Tablets and Chitosan Acetate Free Films

Because of providing miscible solution with higher pH, chitosan L 2.025% w/w in 1% w/w glacial acetic acid containing 0.025% w/w green FS was selected as coating solution onto propranolol hydrochloride tablets and compared with that without the coloring agent. The appearance of coated tablets was satisfactorily smooth and glossy. Those coated without green FS were slightly yellowish due to the color of chitosan, whereas coated tablets with green FS were uniformly greenish. There was no migration of color on the tablets even after storage for 1 year. This was obviously due to the attractive force between ionic charge of dye and polymer molecule during evaporation of water in film coating process.

Table 4 shows some physicochemical properties of propranolol hydrochloride tablets and chitosan acetate free films. The hardness of coated tablets was higher than that of core tablets. Addition of dye in the coating formulation had minute effect on the hardness of coated tablets. Improvement of the mechanical strength of the tablet due to film coating was notified.[16] An increase in breaking load of tablet by existence of polymeric film coat might be due to the ability of film coat to promote stress distribution over the tablet, its ability to fill in surface irregularities of core, and its intrinsic strength to resist breakage.[17] The disintegration time and time for 75% drug dissolved ($T_{75\%}$) from coated tablets with green FS were longer than those from coated tablets without dye. As expected, core

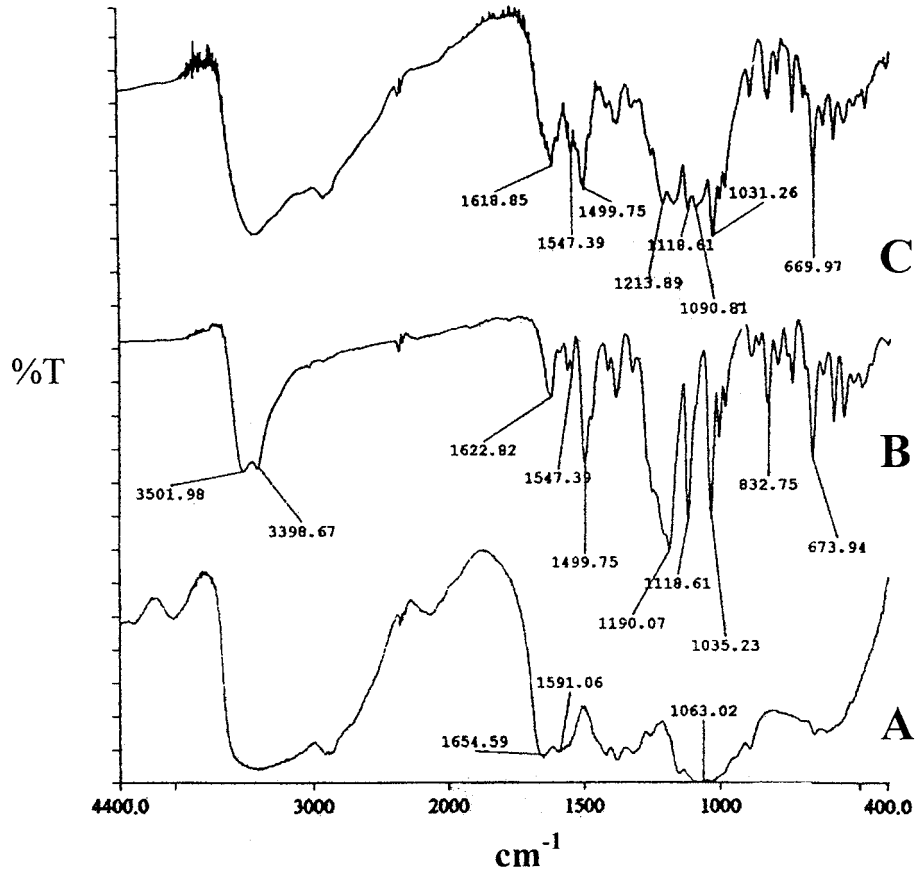

Figure 4. FT-IR spectra of (A) chitosan, (B) sunset yellow, and (C) water-insoluble matter after mixing solutions of chitosan acetate and sunset yellow.

Table 4. Physicochemical properties of propranolol hydrochloride core and coated tablets and chitosan acetate free films with and without green FS.

Properties	Core	Chitosan acetate	Chitosan acetate with green FS
Tablets			
Hardness (Kp)[a]	7.29 ± 0.66	11.34 ± 1.09	10.18 ± 0.63
Disintegration time (sec)[b]	113.8 ± 10.7	171.7 ± 12.1	234.8 ± 24.4
$T_{75\%}$ (min)[c]	4.97 ± 0.38[b]	7.60 ± 0.56[c]	8.47 ± 0.46[c]
Free films			
Thickness (μm)[d]		54.8 ± 3.56	60.27 ± 4.74
Swelling index[c]		3.08 ± 0.74	2.49 ± 0.23
Film dissolution (%)[c]		29.54 ± 2.55	22.12 ± 1.01

[a, b, c, d]Mean ± S.D. from 10, 6, 3, and 5 determinations, respectively.

tablets disintegrated and dissolved faster than coated tablets.

The dissolution profiles of propranolol hydrochloride coated tablets compared with those of core tablets are illustrated in Fig. 5. It was clearly seen that the slopes of drug release from core tablet and coated tablet without coloring agent were graphically paralleled. Film coating could only extend the release due to the lag time or time for the film to dissolve completely. Initially, chitosan film would swell after

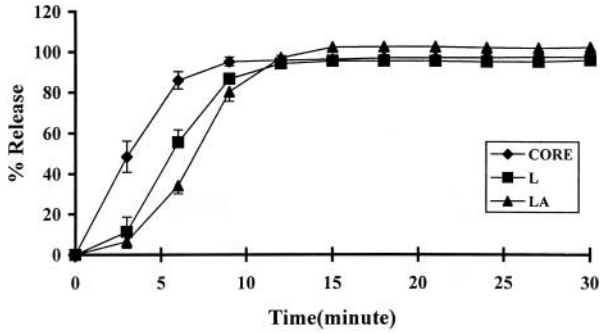

Figure 5. Dissolution profile of propranolol HCl from core and film coated tablets without (L) and with (LA) green FS.

immersion into dissolution medium and form gel surrounding the core tablet. At this stage, some drug could diffuse from coated tablets through gel barrier. After the gel layer completely dissolved, the drug would release according to the concentration gradient between core tablet and the medium. Addition of green FS into the film formulation decreased the drug release. Sulfonate group of brilliant blue and tartrazine of the dye would interact with protonated amino group of chitosan.

The properties of chitosan acetate free films as listed in Table 4 showed that the swelling index and the percentage dissolution of free films with green FS after immersion in deionized water for 5 min were less than those of films without dye even though their film thickness was comparable. Therefore, the hydration or swelling of film coated onto tablet in dissolution medium was expected to decrease when adding green FS into the film formulation. The dissolution of these colored film coatings would subsequently be slower. Prillig[18] reported the slower disintegration and release of drug when adding water-soluble dye to film coating solution of hydroxypropyl cellulose and sodium ethylcellulose sulfate. The mechanisms were also proposed. However, the release of propranolol hydrochloride and the disintegration time of coated tablets, with and without green FS, conformed to the specification of USP XXIV that the dissolved drug was not less than 75% within 30 min and the tablet was disintegrated within 30 min.

CONCLUSIONS

Ionic interaction between positive charge of amino group on chitosan molecule and negative charge on chemical structure of water-soluble dye resulted in incompatibility shown as precipitation. This phenomenon was more prominent when increasing the concentration of both agents. Anionic dyes with high water solubility, high stability, and low pH value, such as briliant blue and green FS, at the concentration between 0.001–0.05% w/w, could be miscible with chitosan acetate solution. Solution of low molecular weight chitosan colored with green FS could be coated onto propranolol hydrochloride tablet. The film-coated tablets were glossy with satifactory color. The coloring agent could mask the discoloration of chitosan film coated tablets. Their disintegration and dissolution conformed to the official compendia. No migration of color was observed after storage for 1 year.

REFERENCES

1. Seitz, J.A. Aqueous film coating. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York and Basel, 1990; Vol. 1, 337–349.
2. Lim, L.Y.; Wan, L.S.C. Heat treatment of chitosan film. Drug Dev. Ind. Pharm. **1995**, *21* (7), 839–846.
3. Lim, L.Y.; Khor, E.; Ling, C.E. Effect of dry heat and saturated steam on the physical properties of chitosan. J. Biomed. Mater. Res. **1999**, *48* (2), 111–116.
4. Yamada, A. Sustained Release Tablet. J. Patent 4-264021, 1992.
5. Ritthidej, G.C.; Phaechamud, T.; Koizumi, T. Additives in moist-heat-treated chitosan acetate films: a method to extend the release of propranolol HCl coated tablets. STP Pharma Sciences **2000**, *10* (1), 112–119.
6. Goldemberg, R. Colorants for drug tablets and capsules. Drug Cosmet. Ind. **1982**, *133*, 44–46.
7. Phaechamud, T.; Koizumi, T.; Ritthidej, G.C. Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablet. Int. J. Pharm. **2000**, *198*, 97–111.
8. Qurahi, M.T.; Blair, H.S.; Allen, S.J. Studies on modified chitosan membranes. II. Dialysis of low molecular weight metabolites. J. Appl. Poly. Sci. **1992**, *46*, 263–269.
9. Hayes, E.R. Characterization of Chitosan II: The Determination of the Degree of Acetylation and Chitin. In Proceedings of the 1st International Conference on Chitin/Chitosan, Boston; Muzzarelli, R.A., Pariser, E.R., Eds.; MIT SG 78 7, 1978, 406–420.

10. Ritthidej, G.C.; Chomto, P.; Pummangura, S.; Menasveta, P. Chitin and chitosan as disintegrant in paracetamol tablet. Drug Dev. Ind. Pharm. **1994**, *20* (13), 2109–2134.
11. Alonso, I.G.; Peniche-Covas, C.; Nieto, J.M. Determination of the degree of acetylation of chitin and chitosan by thermal analysis. I. Thermal Analysis **1983**, *28*, 189–193.
12. Dale, J.K.; Booth, R.E. Compounding and dispensing information. In *Dispensing of Medication*, 8th Ed.; Hoover, J.E., Ed.; Mack Publishing Company: Easton, Pennsylvania, 1976; 330–634.
13. Marmion, D.M. Certified colors. In *Handbook of U.S. Colorants for Foods*; Marmion, D.M., Ed.; John Wiley & Sons: New York, 1979; 28–73.
14. Bauer, K.H.; Lehman, K.; Osterwald, H.P.; Rothgang, G. Raw materials. In *Coated Pharmaceutical Dosage Forms*; Bauer, K.H., Lehmann, K., Osterwald, H.P., Rothgang, G., Eds.; Medpharm Gmbh Scientific Publishers: Stuttgart, Germany, 1998; 217–261.
15. Walter, W. *Handbook of Organic Chemistry*; Translated by Douglas Lloyed. Prentice Hall Europe: Hertfordshire, England, 1996; 726–726.
16. Lehtola, V.H.; Heinamaki, J.T.; Nikupaavo, P.; Vliruusi, J.K. Effect of some excipients and compression pressure on the adhesion of aqueous-based hydroxypropyl methyl cellulose film coating to tablet surface. Drug Dev. Ind. Pharm. **1995**, *21* (12), 1365–1375.
17. Fell, J.T.; Rowe, R.C.; Newton, J.M. The mehanical strength of film-coated tablets. J. Pharm. Pharmacol. **1978**, *31*, 69–92.
18. Prillig, E.B. Effect of colorants on the solubility of modified cellulose polymers. J. Pharm. Sci. **1969**, *58* (10), 1245–1249.