CHARPTER III

DISCUSSION AND CONCLUSIONS

Part I

Chitosan Solutions and Cast Films

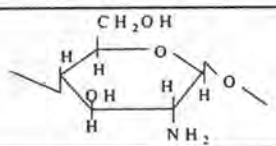
Physical Characteristics of Chitosan Solutions

Chitosan powder could easily dissolve in acetic, citric, formic, glycolic, lactic, malic and propionic acid solutions. The solubility of chitosan in these carboxylic aqueous media was considerably advantage in that noxious organic solvent was not included in processing. These organic acids are classified to be harmless. Some of them are edible or to be the degradation product in human body. Moreover the pH's of the all obtained chitosan solutions were not too acidulous. The rank of pH's of chitosan solutions using different acids was directly related to that of the pKa of the corresponding carboxylic acids as showed in Table *79*. Because of high dissociation ability of citric and malic acid used, the pH of these solutions were lower than that of the others. The structure and some physicochemical properties of carboxylic acids used in this study are also shown in Table *79*.

The viscosity's of solutions were quite stable in the range of 104.28 to 138.12 cps. At 24 hours, the viscosity of solutions using citric or malic acid was rather lower than that of the others. Since citric and malic have higher M.W. than other acids, thus they had to be used in higher amount. Due to the high aqueous solubility, these two acids were likely to use the water molecule to dissolve themselves, thus it was difficult for chitosan molecule to recoil itself in water and that the viscosity of these solutions was lower. All obtained chitosan solutions were not too viscous. Therefore, they were suitable for many applications.

Generally, the solubility of chitosan depends on the balance between the electrostatic repulsion coming from the protonated amine groups and the hydrogen bonding from amino groups on polymeric chain. As a polyelectrolyte polymer, chitosan is a weak polybase with a pKa of 6.5. In acidic environment, the amino groups on chitosan molecule is protonated and solubilized, and then formed an ionic pair with carboxylate ions. Citric and malic acid which are triacid and biacid respectively, at mole ratio acid: glucosamine unit less than 1.2:1 these acids could not dissolve chitosan powder. The requirement of slightly greater of acid than glucosamine unit came from the complexity of chitosan since commercial chitosan composes of two ranges of copolymers, containing the two monomer residue, anhydro-D-glucosamine and anhydro-N-acetyl-D-glucosamine and generally the former is the predominant component in chitosan.

Table 79 Some physicochemical properties of carboxylic acids and chitosan.

Acid	M.W.	bp (°c)	mp (°c)	pK_a	Chemical Structure
Acetic	60.06	118.2		4.76	CH_3COOH
Citric	192.12		153.0	3.15, 4.78, 6.40	H_2C –COOH | HO –C –COOH | H_2C –COOH
Formic	46.03	100.5		3.75	HCOOH
Glycolic	76.05		80	3.83	HO –CH_2 –COOH
Lactic	90.08	122	17	3.86	COOH | H C –OH | CH_3
Malic	134.09		131-133	3.4, 5.1	COOH | HO –CH | CH_2 | COOH
Propionic	74.08	141.1		4.87	CH_3–CH_2–COOH
Chitosan	161.16			6.3 - 7	

Chitosan used for this study had 85.91% deacetylation. In addition the more bulky and steric hindrance of malic and citric acids which made them difficult to protonate the amino groups and unfold the polymeric chain in solution.

Physicochemical Characteristics of Chitosan Cast Films

Chitosan could evidently act as filmable material due to its glycosidic linkage like cellulose. It exhibited good film forming capability. However, chitosan citrate and malate films were slightly brittle which was likely because of the solid state of both acids. The water sorption of chitosan films decreased proportionally with the increasing pH of medium. All freshly prepared chitosan films , films after kept in vacuum and the films after drying at 60°C could be easily dissolved in deionized water and HCl buffer pH 1.2 solution. The high swelling of free films was observed before softened and eventually dissolved. Chitosan propionate film took longer time to dissolve than the others as also detected by Austin (1986) who tried to prepare free flowing chitosan powder by spray drying technique.

Since the type and ionization behavior of the hydrophilic functional groups of chitosan and organic acids played an important role on water sorption and dissolution in different environment pH's, the presence of hydroxyl group on molecule of organic acids affected the water sorption and dissolution of the moist heat treated films. As a consequence, the larger amorphous regions and the greater hydrophilic functional groups, the higher was the water sorption. Thus, chitosan films prepared by using glycolic, lactic, malic and citric acids after treatment had these values higher than those of films which were prepared by using acetic, formic and propionic acid. Whereas the longer moist heat treatment and an increase or longer of acyl group or lower amount of hydroxyl group in acid molecule would decrease in %ws and dissolution of treated film as found that these values of treated chitosan propionate films were less than chitosan acetate and formate films respectively. The water sorption capacity of the polymer was probably determined by the nature of functional groups of the polymer. The highest hydrate capacity were possessed by the hydroxyl, amide and ester group meanwhile that of the =C-, $-CH_2-$, $-CH_3$ and $-C_6H_5$ functional groups were several orders of magnitude lower (Belokurova, Koifman and Romanova, 1996).

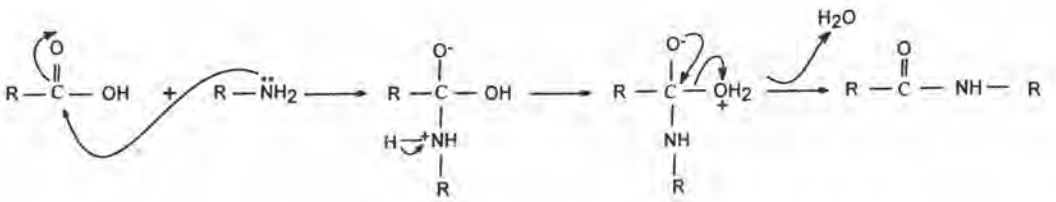
Water sorption and dissolution of treated chitosan film, were also depended on the pH of immersion fluids because the protonation of the remaining amino group on chitosan did not occur in the pH higher than the pKa of chitosan. Due to the decrease in the remained amino groups, the pH dependent of water sorption and dissolution tended to be minimized after longer moist heat treatment. Owing to the complex formation between chitosan and phosphate ion by the binding of phosphate to amine group as reported by Remunan-Lopez and Bodmeier (1997) and Knaul, Hudson and Creker (1999), the weight after immersion in phosphate buffer and drying was slightly increased.

The FT-IR spectra absorption characteristics of freshly chitosan salts was attributed to the electrostatic interaction between protonated amino groups and carboxylate ions. The conversion of chitosan from salt form to neutral form after neutralization could be detected from FT-IR spectra and powder X-ray diffractograms.

The increase in peak intensity at 1655 cm^{-1} after moist heat treatment indicated that there was amide formation. The protonated amino group and carboxylate ions could react at elevated temperature. As the catalyst, water in atmosphere of 75% RH was absorbed into chitosan film and promoted extensive ionization of amino and carboxylic groups to readily react with each other. During drying the progressive regeneration of amide linkage was formed and water molecule was eliminated as by-product. This proposed mechanism is presented in Figure *238*. Kubota et al. (1993) claimed that upon amino group on chitosan chain only N-acetylation with some crosslinking agents could be formed in the presence of water. The decrease of hydrophilic groups after amidation led to the decrease in %ws and dissolution of treated films in three mediums and related to the alteration to insoluble form of chitosan films.

The disappearance or regression of carbonyl peak of pure carboxylic acid in FT-IR spectra was related to ionic formation between ammonium and carboxylate ion of freshly prepared films and further amidation occurrence after moist heat treatment. In case of polycarboxylic acids, malic and citric acid, the unreacted carbonyl peak after moist heat treatment came from the remained carbonyl groups on their structure. The increase in degree of crystallinity of films such as chitosan lactate and glycolate films after moist heat treatment would also decrease the film dissolution. Roth et al.(1988) reported that lactic acid could be formed such intramolecular and intermolecular condensation depended on the concentration and temperature, and Brophy and Deasy (1988) also reported that lactic and glycolic acids could be polymerized by condensation. Consequently, this reaction was the cause of the crystallinity increasing and decreasing in %ws and dissolution of these two treated films. Chitosan glycolate, formate, lactate, malate and citrate films would also have amide formation, however, their FT-IR absorption characteristic was difficult to detect the chemical change due to their broad band interfering the interesting peaks.

Vacuum and dry heat at low temperature of 60°C did not markedly affect the physicochemical properties, since the FT-IR absorption was not changed. Whereas dry heat at 130°C promoted the esterification in treated chitosan acetate, citrate and propionate films. The occurrence of shoulder peak at 1741 cm^{-1} appeared in FT-IR spectra of treated chitosan acetate and propionate films indicated the formation of esterification. Generally, the peak at 1080 cm^{-1} in FT-IR spectra of polysaccharide was skeletal vibration involving the C-O stretching of C_6 primary alcohol (Demarger-Andre and Domard, 1994). Thus the lower of $A1080_{cm-1}$ /$A3450_{cm-1}$ ratio could be useful to indicate the formation of esterification. $A1080_{cm-1}$ /$A3450_{cm-1}$ ratio of each film is listed in Table *80*. The decrease of this absorption ratio when using the temperature at 130°C was observed. All peak intensities of chitosan citrate were decreased after exposure to dry air at 130°C . This result should be related to an occurrence of an ester formation. Additionally, the multiple ester crosslinking might be occurred from polycarboxylic nature of citric acid by bonding to the adjacent carbon of chitosan backbone especially at CH_2OH group of C_6 of glucosamine unit. Crosslink formation could be found if two acid groups on the same citric molecule reacted with two different chitosan chain. Thus, %ws and dissolution of chitosan citrate film after dried heat exposure were very low. However, due to the difficulty of homogeneous esterification reaction in solid state, their films were very brittle and disintegrated during water sorption test. After exposure to the



R-NH_2 = Glucosamine unit

Figure 238. Proposed mechanism of amide formation between chitosan and carboxylic acid.

Table 80 Peak ratio (A1080/3450) from FT-IR studies of different chitosan films after different treatment .

Time (hr)	Chitosan Film			
	Acetate	Citrate	Formate	Propionate
freshly prepared	0.544	0.677	0.882	0.630
vacuum 168 hrs	0.401	0.653	0.707	0.563
60°C 168 hrs	0.447	0.707	0.526	0.468
60°C 360 hrs	0.431	0.295	0.552	0.782
130°C 5 hrs	0.314	0.217	0.672	0.370
130°C 9 hrs	0.245	0.200	0.587	0.514
130°C 12 hrs	0.321	0.135	0.507	0.263

temperature at 130°C, chitosan formate showed the amide band at 1670 cm^{-1}. No presence of carbonyl band over the wave number of 1700 cm^{-1} indicated that no ester was formed, however it was found that $A1080_{cm-1}$ /$A3450_{cm-1}$ ratio was slightly decreased. Chitosan formate was therefore not undergone as great degree of esterification. Boiling point of formic acid (bp.=100.5°C) is lower than that of the other acids used as presented in Table 79 and therefore it is likely to be volatile before esterification.

The diffraction characteristic of chitosan powder composed of a large reflection at about 20° 2θ and a minor reflection at 10.6° 2θ is the pattern of chitosan derived from chitin. Ogawa (1991) had proposed chitosan into three forms: non-crystalline, hydrated crystalline and anhydrous crystalline. The hydrated crystalline structure shows one of reflection at 10.4° 2θ and anhydrous crystalline structure shows one of reflection at 15° 2 θ. Hence the chitosan used in this study was hydrate form and there was no the presence of anhydrous crystalline in treated chitosan films. Robert (1994) claimed that an anhydrous crystalline form did not form salt with acids and it was not soluble in dilute aqueous acids.

By comparison, the difference in diffractogram of pure solid acids, physical mixtures and cast films signified that the film formation altered the lattice structure of both chitosan and acids. Several diffraction patterns of chitosan salts were found, depending on acid used. The crystallinity of salt form was less than neutral form of chitosan powder. The physical mixture between chitosan and solid acids showed the combination signal peak of the two compounds, however the proportion of peak intensity of solid acids in physical mixture was changed indicated that the two compounds could interact in physical mixture, especially between chitosan and glycolic acid. Diffraction pattern of chitosan films using different acids had different characteristic. This indicated that type of acid played a significant role in the formation of crystalline structure.

An alteration of diffractograms after moist heat treatment, especially the apparent enhancement of crystallinity of chitosan lactate and propionate films was corresponding to the decrease in %ws and dissolution. Crystallinity inhibited the absorption of water molecules so that the %ws and dissolution were decreased with increasing the crystallinity. Amide formation might alter lattice structure of chitosan salt film, and condensation reaction of lactic acid in chitosan lactate film might induce an increase crystallinity and regress of %ws and dissolution of moist heat treated films. Intramolecular and intermolecular condensation of lactic acid was reported by Roth et al. (1988) and Brophy and Deasy (1988).

The regression of the intensity of minor reflection of chitosan acetate and formate at 11.8° 2θ and 12.4° 2θ respectively after dry heat at 60°C for 168 and 360 hours should be related to the decrease in acid in polymeric film. This minor reflection should be related to the presence of acid or N-acyl functionality in polymeric film. High volatility of these acids was related to the lower intensity of the minor reflection. The result also found in case of using lactic and propionic acid but not in case of using glycolic acid. However, the disappearance of reflection at 11.2° 2θ of chitosan malate films after moist heat treatment was found. Neutralised chitosan films showing the diffraction pattern similar to chitosan powder indicated there was a conversion from chitosan salt to neutral form.

No anhydrous crystalline structure was found in this study since there was no presence of reflection at 15° 2θ. Therefore film insolubility was not due to an anhydrous formation. Demarger-Andre and Domard (1994) noted that anhydrous form was rather difficult to obtain especially if salt form existed but could only be obtained after complete elimination of water. However, cooling down to room temperature led to simultaneously recovery of water again.

From the analyses of DSC curves, the exothermic peak appearing at temperature of 306.9°C of chitosan powder was the decomposition temperature associated to the first stage of pyrolysis, when dehydration and depolymerization of deacetylated and acetylated units of chitosan occurred as described by Peniche-Covas and Arguelles-Monal (1993). The exposure of chitosan powder to moist heat for 12 to 360 hours did not markedly affect the decomposition temperature. The peak shift and new peak presented in DSC curves of physical mixtures between chitosan and solid acids indicated that there was partial interaction between chitosan and acids in solid state. This result was corresponding to the change in powder X-ray diffractogram as aforementioned. This partial interaction was possibly promoted from the moisture which was absorbed during mixing the two substrates before DSC measurement.

Apart from the case of chitosan citrate and malate films, chitosan films were less stable than chitosan powder due to their lower degradation temperatures than chitosan powder as also reported by Lim and Wan (1995) who investigated on chitosan acetate film. Although chitosan films still had a high decomposition temperature, their thermal properties were changed by heat. The shift to the higher degradation temperature of moist heat treated films compared to the degradation temperature of freshly prepared film signified that covalent linkage between carboxylic acid and chitosan was more stable than ionic bond in salt form. However it was still lower than that of chitosan powder. Chitosan formate could only form amidation not further to esterification since high temperature (during heat supplied in DSC measurement) would accelerate the volatility of formic acid before ester formation therefore the endothermic peak of reaction at about 160 °C was occurred which was lower than that of the other films.

Since the esterification of chitosan citrate film during heat supply in DSC test was occurred easier than chitosan malate film due to more carboxylic group on molecule of citric acid, thus the endothermic peak of chitosan citrate occurred at lower temperature than that of chitosan malate film. These moist heat treated films had exothermic peak at temperature slightly less than those of freshly prepared films. This showed that the long exposure to heat supplied during DSC test, an ester was formed, and the more break down of polymeric chain might also be occurred. The latter evidence was also supported from the more brittleness of films after dry heat treatment at 130°C water sorption test. The higher disintegration to small fragments was found after immersion of longer exposure to dry heat of chitosan films. Crosslinking two chitosan chains with two ester bonds on the same citric or malic molecules resulted in its higher exothermic temperature or higher decomposition temperature than the other films. The crosslinking of cellulose in recent years focused on the multifunctional carboxylic acids to replace the traditional aldehyde based reagents was reported (Yang and Wang, 1997; Rattanawaleedirojn, 1997).

Since heat treated chitosan salt films could not completely dissolve in aqueous or usual solvent, hence, it could not be able to use solution ^{1}H NMR or ^{13}C NMR spectroscopy for analysis. Solid state ^{13}C NMR spectroscopy could characterize a molecular level of polymers in their functional state. The resolution of solid state NMR is less than that for solution, however it has been shown that much useful information can be analyzed by this technique (Bovey and Mirau, 1996).

The ionically bound acetate groups from acetic acid were washed out from sample and the sample was converted to chitosan since the spectra of neutralized chitosan salt film was similar to that of chitosan powder. Additionally, solid state ^{13}C NMR provided evidence of the N-acylate further changing to N-acyl derivative after longer moist heat treatment on chitosan acetate and propionate due to the slight increase in peak intensity at 23 and 173 ppm. The enhancement of peak intensity was also observed in case of using the dry heat treatment at 130°C for 9 hours which showed more evidence than moist heat treatment. This result was corresponding to the report of Ackah (1996) and Toffey (1996), however, this investigation concentrated only on the dry heat treatment.

The shift to higher wavelength from UV-VIS absorption test of chitosan citrate, glycolate, lactate and malate films after heat treatment were greater than that of chitosan acetate, formate and propionate films. Therefore the rate of yellowing of film depended on type of chitosan salt too. This observation might be useful to apply this material for contact lens or other uv-light protect products due to its still optical clarity. The yellow discoloration of the treated film might be the result of the Maillard reaction between NH_2 and OH groups as claimed by Lim, Khor and Koo (1998) who found this characteristic of chitosan film upon γ-irradiation.

Effect of Additives on Cast Film Characteristics

1. Plasticizer

Due to the solid state nature of incorporated acids, citric and malic acids, chitosan citrate and malate films were less flexible than chitosan acetate and propionate films. Practically the plasticizer is the important component affecting mechanical properties of polymeric films. To modify mechanical properties of chitosan film, many type of plasticizers were employed for this purpose. Usually, the plasticizer had to be blended uniformly and homogeneously with polymer. An addition of glycerin and propylene glycol could produce satisfactory physical appearance film since they were transparent and had no precipitation or bleeding. In contrast, PEG400, PEG1540, PEG6000, triacetin or triethyl citrate seemed not suitable for plasticizing chitosan films because there was phase separation after they were incorporated into chitosan films.

Microscopic nature of plasticized chitosan film was performed to support and gain further insight into the compatibility and incompatibility between polymeric salts and plasticizers. Chitosan citrate and chitosan propionate films which were intended to utilize as representatives for films to produce fast and extended release coated tablets

were selected for this investigation. This also confirmed the good compatibility between chitosan salt and glycerin or propylene glycol. Whereas the incompatibility between chitosan salt and many plasticizers: PEG 400, 1450, 6000, triacetin and triethyl citrate were obviously seen. Degree of phase separation depended on the level of plasticizer incorporation. The more increase amount of plasticizer, the greater was the degree of phase separation. PEG 400 and triethyl citrate also had been reported to be incompatible with chitosan glutamate (Remunan-Lopez and Bodmeier, 1996). The compatibility between PVA and propylene glycol and glycerin, and leaching of PEG400 from PVA film was also detected by Lim and Wan (1994). They also claimed that PEG400 molecule that was seven times larger in size than glycerol molecule had a tendency to be rejected from the crystal lattice of PVA film. This suggestion might be the cause of phase separation of PEG 400, 1450 and 6000 from these chitosan films. Additionally, owing to rather hydrophobic nature of triacetin and triethyl citrate than propylene glycol and glycerin, they were poorly compatible with chitosan.

No significant plastic deformation from stress-strain curve prior to breakage of unplasticized chitosan citrate film and chitosan citrate film incorporated with PEG6000 indicated that there was the limit of mobility of molecules due to the particular boundary and the formation of internal crack which further promoted crack propagation and had brittle fracture occurrence. The initial steep slop rising to a break or failure point at relatively low strain was detected in this brittle composite. This mechanical behavior had been described by Wang et al. (1997). Because of the brittleness and phase separation of cast film after incorporation of PEG 6000, this substance was not suitable plasticizer for chitosan film. Limited compatibility between high molecular weight PEG and HPMC film had been reported by Aulton, Houghtonand and Wells (1985). They claimed that the evidence was due to PEG crystallinity and low entropy of mixing for polymer. The amount of plasticizers, propylene glycol and glycerin, had direct influence on the fracture characteristic by providing ductile property for chitosan citrate and chitosan malate films.

The addition of glycerin and propylene glycol could shift the fracture behavior of chitosan citrate and malate films from brittle to ductile characteristic by increasing maximum percent stain and minimizing the Young's modulus and stress at break. This was due to the alteration of polymeric matrix from a glassy to a rubbery state from plasticizing effect. An introduction of plasticizer promoted ductile fracture owing to a decrease in the intermolecular force along polymeric chain and thereafter the motion of polymeric chains was enhanced as described by Wang et al. (1997). Since glycerin and propylene glycol at concentration of 25% provided relatively high value of toughness, good physical appearance and apparently physical compatibility, they were selected as suitable plasticizers for chitosan film.

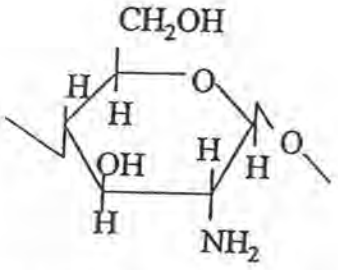
The high toughness of films plasticized with propylene glycol was due to the still remaining high stress at break and slight decrease in Young's modulus and slight increase in maximum percent strain. The decrement in the toughness of cast film plasticized with low concentration propylene glycol should be come form the antiplasticizing effect as reported by many investigators (Guo, 1993; Wang et al., 1997). This phenomenon was attributed to the immobilization of polymer chains or molecules by hydrogen bonding, Van der Waal's forces and steric hindrance with the plasticizer molecules (Guo, 1993, 1994; Wan et al. 1997). The reduction in the mobility of polymer

segments was attributed to the result of the formation of hydrogen bonds between -OH-, -CONH- and -COO- groups of the polymers and also the possible formation of aggregates (clusters) from water molecules (Belokurova, Koifman and Romanova, 1996). Thus the movement of chitosan chains in composite was more restricted.

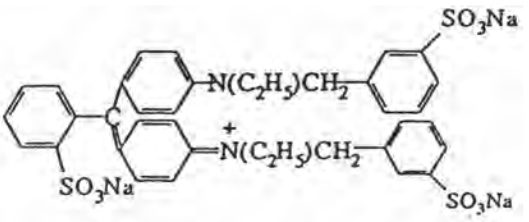
2. Colorant

Chitosan citrate solution containing propylene glycol was further investigated its compatibility with water soluble dye since an addition of propylene glycol affected the drug release characteristic of coated tablets after direct exposure accelerated condition less than that of glycerin and chitosan citrate film was less pH sensitive than chitosan malate film. The presence of insoluble matter after mixing most anionic dyes solutions and chitosan citrate solution containing propylene glycol was attributed to the charge interaction between anionic dye molecules and $-NH^{3+}$ groups on chitosan chain and thereafter the insoluble matter was appeared after mixing these two solutions. This interaction was also found in case of microcapsule preparation by complex coacervation using polycationic and polyanionic polymers. The domain mechanism of insoluble wall forming was the electrostatic charge between protonated amino group on chitosan chain and the negative charged of polyanionic polymer (Ritthidej and Tiyaboonchai,1997). Natural polyanionic polymers could react with chitosan and the electrostatic interaction between COO^- or SO^{3-} and NH^{3+} was claimed as the major force behind complex formation (Mireles et al., 1991). The electrostatic charge or hydrogen bonding were claimed as the main cause of interaction between polymer and dye (Slark and Hadgett, 1988; Prillig, 1969). Utilization of chitosan to improve dyeability of prepared cotton was reported by Shin and Yoo (1998). They also noted that higher dye uptake was obtained in acidic condition than in alkaline condition. Therefore chitosan in citric acid solution could possibly interact with anionic dyes. The research on an equilibrium adsorption of anionic dyes on chitosan under acidic environment investigated by Maghami and Robert (1988) demonstrated that there was a 1:1 stoichiometric interaction of sufonate groups on mono-, di- and trisulfonated dyes with protonated amino groups of chitosan. The removal of anionic dyes by chitosan from solution was undertaken by the precipitation/flocculation process and it also manifested that this process was directly proportional to the charge on anionic dye ion (Robert, 1994). The presence of some colorants such as FD&C Red No. 3 and FD&C Red No. 40 was also mentioned as the cause of alteration the configurational properties of gelatin and rendering its insolubility (Adesunloye and Stack, 1998). Hence the negatively charged dye molecules could be possibly interacted with the positively charge chitosan chain. The degree of this interaction was different depended on physicochemical properties of color.

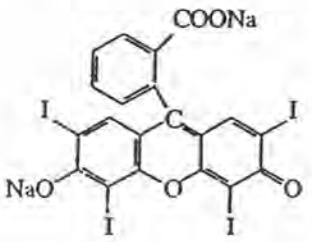
In acidic solution, acidic group (COOH) on erythrosine molecule as depicted in Figure *239* was mostly in nonionized form which the solubility was less than SO_3H group of other dyes. Also the partial transformation to the leuco form in acid solution would alter this dye to colorless matter (Parrott, 1971; Prasertvithayakarn, 1993) and the remained ionized erythrosine molecules could potentially be reacted with protonated amino groups on chitosan, thus the colloid like was observed after mixing. The charge interaction could be occurred between chitosan and other dyes (sunset yellow, ponceau 4 R and tartrazine) since the presence of precipitated matter was also detected. The



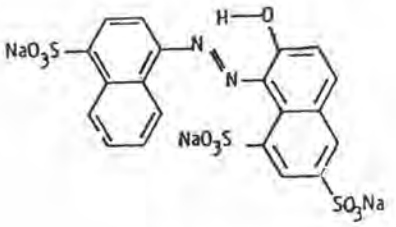
Glucosamine unit



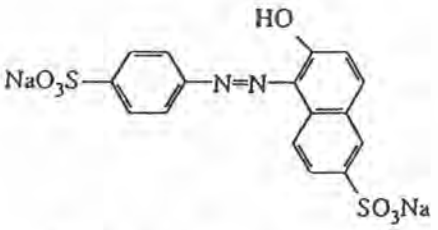
Brilliant blue



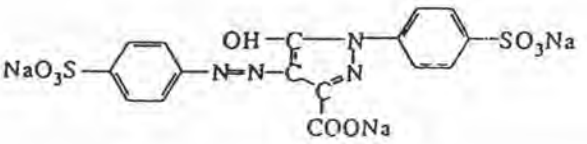
Erythrosine



Ponceau 4R



Sunset yellow



Tartrazine

Figure 239 The chemical structures of water soluble dyes and glucosamine unit.

presence of positive charge on molecule of brilliant blue and its influence especially in acidic environment might provide enough repulsion force to decrease the charge interaction between sulfonate groups of dye and protonated amine groups of chitosan. Owing to the presence of positive charge on structure and high water solubility (200 g litre^{-1}) at 25°C (Goldemberg,1983) and also high amount of SO_3H group (3 groups) of brilliant blue, the tolerance to coagulate with chitosan should be higher than other dyes. Generally, the more amount of this auxochrome (SO_3H) resulted in the high solubility of color, and also the efficiency for ionization of SO_3H auxochrome was higher than that of -COOH and -OH respectively (Noonan, 1975; Prasertvithayakarn, 1993). The water solubility's of erythrosine, ponceau 4R, sunset yellow and tartrazine are 70, 140, 120 and 140 g litre^{-1}, respectively (Rowe, 1984).

Green FS, the combined color between brilliant blue and tartrazine (in ratio 3:22) remained to be miscible with chitosan solution at concentration 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. Brilliant blue and green FS could be readily miscible with plasticized chitosan citrate solution at concentration of 0.02-0.50 and 0.02-0.05 % w/w respectively. It was believed that the presence of brilliant blue as component in green FS could induce the miscibility between tartrazine and chitosan. The concentration of brilliant blue and green FS in chitosan citrate solution exhibited high tinctorial strength enough 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. Color incorporation slightly decreased mechanical properties of plasticized chitosan film. Brilliant blue and green FS were selected for coloring chitosan citrate.

3. Pigment and Another Solid Additive

Satisfactory physical appearances after coloring chitosan citrate films (plasticized with propylene glycol at concentration of 25% w/w of polymer) with brilliant blue and green FS was obtained since they were still glossy and moderate flexible and transparent, neither bleeding nor precipitation was evident due to the compatibilty of these materials. Because of plate-like particle, talcum enhanced the film glossiness but spherical-shaped titanium dioxide decreased this satisfactory characteristic as the amount of pigments was increased respectively. Owing to very high reflectance at visible and ultraviolet wavelengths (Brittain, 1994), titanium dioxide could effectively provide whiteness for chitosan films than talcum. In addition, the extremely high reflective index of titanium dioxide to scatter light, chitosan films pigmented with this material was totally opaque.

An appraisal of research works found that no certain characteristic could completely describe the tensile behavior of pigment-filled materials since there were deficiencies addressing pigment-polymer interactions (Gibson, Rowe and White, 1988 a; Nielsen and Landel, 1994). Frequently, the tensile strength of pigment-filled material was reduced but in certain cases the pigment enhanced the strength of the composite. This was attributed to the nature and quality of interaction between the pigment and polymeric composite. The more reason for this complicate force and failure behavior of pigment-filled polymer was not only due to the existence of local inhomogeneity in polymer, but

also several possible failure modes that were closely related to interfacial strength, deweting, stress concentration at the interface, and relative brittle or ductile nature of the solid additive and polymer (Gau and Tsou, 1999).

Since titanium dioxide, being spherical, has greater surface area several times than talcum and thus it has potentially greater available surface area for titanium dioxide-polymer interaction, and electrostatic charges of titanium dioxide can produce in dry state (Ritter, 1973). The influence negative particle surface of titanium dioxide on polymer had been notified by Li et al. (1999). Some investigators reported that the internal stress was highest in the formulation containing titanium dioxide compared with those containing either calcium carbonate or talcum. This evidence might be due to platy structure of talcum arranged in specimen resulting in a restraint of volume shrinkage parallel to the plane of the coating as mentioned by Rowe (1981). Therefore the decrease in mechanical properties of plasticized chitosan citrate film as the amount of titanium dioxide was increased was apparent and this result was also found in case of incorporation with talcum but degree of lowering these mechanical properties was less than an incorporation of titanium dioxide and % strain and toughness after adding talcum were still higher than unpigmented cast film. Characterization of the talcum deposition in HPMC film by using ion beam etching revealed that the large particles of talcum tended to lie flat in the plane whereas the small talcum particles were more randomly oriented (Gibson, Rowe and White, 1988 a). The orientation of talcum in the direction of applied stress could provide the higher level of reinforcement. The report that talcum had the ability to align during fabrication could produce a anisotropic reinforcement for polymer had been proposed (De and White, 1996; Radosta and Trivedi, 1987). Particulate of pigment tended to yield lower bound values and long oriented pigment tended to yield greater bound values of modulus while short and randomly oriented pigment tended to yield intermediate values (Dokbua, 1994). From the model prediction of crack propagation, polymeric film containing red iron oxide of 0.5 μm particle size had calculated crack velocities lower than those containing titanium dioxide of 0.25 μm particle size (Rowe, Rowe and Robert, 1994). Therefore the decline in mechanical strength of chitosan film containing high level of titanium dioxide was greater than that containing high level of talcum. Due to polar in nature of talcum and titanium dioxide, some bond especially the dipole-dipole interaction will be occurred between the pigment and polymer. In other word, incorporation of pigment in the film caused discontinuities in the polymeric net work and poor adhesion between pigment and polymeric matrix especially at high level of pigment loading, and thus the film strength was decreased (Okhamafe and York, 1984, 1985 a; Stricker, Bruch and Mulhaupt, 1997) and the dewetting also became more evident as the concentration of filler was increased as notified by Nielsen and Landel, 1994. In case of addition of talcum, this was the rare instance where fillers introduced additional crazing, and perhaps at the same time acted as stopper to crack growth and thereafter the mechanical properties was greater than that of the unfilled polymeric film. The enhancement of elongation at break of rubber due to addition of carbon back had been reported (Nielsen and Landel, 1994). The pigment treated with silane coupling agent appeared to react with both the polymer and the pigment surface and thus the treated pigment often provided composite with increased tensile strength (Nielsen and Landel, 1994).

Pigment-polymer interaction was claimed as the cause of the less influence of low concentration of titanium dioxide and lake pigment on mechanical properties of HPMC film (Gibson, Rowe and White, 1988 a). The film containing pigment which had a larger proportion of loosely bond water such aluminum lake might cause plasticization of the matrix by the loosely bond water, which would decrease the Young's modulus (Gibson, Rowe and White, 1988 a). The reduction of Young's modulus of HPMC film due to incorporation of titanium dioxide was detected and it was suggested that there was a strong evidence of specific interactions between HPMC and titanium dioxide and thus adsorption of polymer onto the pigment particles might be occurred (Gibson, Rowe and White, 1988 b). The negative particle surface of titanium dioxide might possibly interact with positive charge on chitosan and thus the mechanical properties were improved. The tensile strength improvement of poly (ester-urethane) by addition of silicate fillers probably due to the interactions (hydrogen bonding) between silicate (Aktisil®) and hydroxyl end groups of polymer was reported by Hiljanen-Vainio, Heino and Seppala, 1998. The increase in elongation at break of poly propylene by the presence of titanium dioxide was also reported by Burke, Young and Stanford, 1993. The examination of the necked surfaces of tensile specimens found the voids around pigment particles, with occasional fibrils of polymer still attached to pigment particles, thus debonding of particles and fibrillation of the polymeric matrix appeared to aid the necking process, making the polymer more extensible (Burke, Young and Stanford, 1993). These aforementioned especially the chitosan-pigment bonding might be the cause of rather high mechanical strength of chitosan citrate film incorporated with low amount of pigment.

Basically an increase in the values of elastic modulus was corresponding with increment of internal stress or pigment-polymer interaction (Rowe, 1982; Tjong and Li, 1997; and Hiljanen-Vainio, Heino, Seppala, 1998). When the amount of pigment was raised, Young's modulus was invariably enhanced due to an increase in the stiffness or rigidity of the polymeric phase after incorporation of hard, rigid pigment particles. By comparison at the same concentration, the Young's modulus of chitosan film pigmented with talcum was higher than that of film pigmented with titanium dioxide. Okhamafe and York (1985 a) also found that internal stress appeared to be greater in the presence of plate-like talcum compared with spherical titanium dioxide where the pigment-polymer interaction played important role on the titanium dioxide loaded film. Okhamafe and York (1985 a) and Bauer et al. (1998) claimed that the hydrodynamic effect of plate-like talcum on Young's modulus was greater than that of spherical titanium dioxide in view of larger shape factor of plate-like talcum.

Partial ionic bond between chitosan and dye molecules, possibly reduced the hydrophilic groups of chitosan citrate film, therefore the moisture sorption was slightly decreased. Talcum decreased moisture sorption of pigmented chitosan citrate film more obviously than titanium dioxide. This effect came from the embedded platy-shaped pigment particles in the polymeric film which reduced the more hydrophilic surface of polymer to contact the moisture. The sorption of vapors by a composite containing a nonsorbing filler were reduced in proportion to the volume fraction of the filler had been reported (Dokbua, 1994).

Effect of Acid and Heat Treatment on Cast Film Characteristics

Because there was the different interaction between chitosan and acids in solution, and thus during film fabrication the chitosan molecules had distinctive spatial configuration, the mechanical properties of various chitosan salt films was distinctive as aforementioned by Kienzle-Sterzer, Rodmigue-Sanchez and Rha (1982) who compared this characteristic of neutralized chitosan films prepared from acetic and propionic acids. From X-ray diffraction measurement of Yamamoto et al. (1997) and Kawada et al. (1998) revealed that chain conformation of chitosan in crystal depended on the kinds of aqueous acid solutions which utilized as solvent for film fabrication. From aforementioned X-ray diffraction (Part I) also confirmed that diffraction pattern was different depended on different salt forms of chitosan. Additionally, because of the solid state nature and high M.W. of citric and malic acids, the amount of acid loading was rather high and thereby these two acids had a tendency to interfere the closeness or linkage between polymeric chains and thus the mechanical properties of chitosan films in these salt forms were lower than those of chitosan acetate, formate and propionate films. The decrease in puncture strength and modulus at break of chitosan citrate film as amount of citric acid was increased was reported by some authors (Remunan-Lopez and Bodmeier, 1996).

Due to the relaxation of the chitosan acetate, formate, malate and propionate films to the utilized stress during tension testing, the plastic deformation was detected in their stress-strain profiles as there was a yield point followed by a plateau which escalated to an increasing stress to the stress peak and exhibited the proportionally small increase in stress at higher displacements

The toughness and maximum percent strain were more regressed as the duration of moist heat treatment was longer because there was the reduction of film extensibility as well as the portion of profiles representing plasticity property of chitosan films was more decreased. This study found that the rate of decrement in toughness and maximum percent strain of chitosan acetate during initial moist heat treatment was slower than that of chitosan propionate and vice versa after treatment longer than 36 hours. The rearrangement of network structure after moist heat treatment might contribute to the loss of film ductility. This postulation was corresponding to the alteration of physicochemical properties of chitosan salt film after treatment as aforementioned. Ageing of unplasticied HPMC films at 37°C and 75%RH impaired the mechanical properties of these films owing to the lowering of the molecular order had been published by Okhamafe and York, 1986.

Part II

Chitosan Film Coated Tablets

Physical Appearances

Coated tablets using chitosan as film former could be prepared by unsophisticated process and without the utilization of organic solvent. Unplasticized and plasticized film coated tablets using chitosan citrate and chitosan malate films were off-white and glossy. The minute friability of coated tablets was due to the ability of film to protect the core tablet from abrasion during friability test. The surprisingly negative value of %friability of some coated tablets was attributed to the moisture sorption during friability test. The weight variation and uniformity of dosage unit of core and coated tablets conformed the limit of USP XXIII. From the assay by HPLC method, there was the good stability of propranolol HCl in coated tablets after moist heat treatment, exposure accelerated condition or ageing at room temperature. Color migration was not found in coated tablets using chitosan film colored with brilliant blue or green FS 0.5%. Usually, water soluble dyes were added at concentration less than 1% and if they were not sufficiently absorbed by substrate, they would potentially migrate and cause a mottled surface (Bauer et al., 1998). No presence of color migration in chitosan film should be come from the partial ionic bond between chitosan and dye, hence the movement of small dye molecule owing to the evaporation of solvent in coating process was minimized. The incorporation of hydrophobic substance such as castor oil and rather hydrophobic substances such as diethyl phthalate and triacetin could ostensibly minimize the roughness of chitosan acetate film containing magnesium stearate, whereas hydrophilic plasticizer such as propylene glycol could not. This result related to the efficiency of these hydrophobic plasticizers to promote the continuous film which contained hydrophobic additive such as magnesium stearate. Owing to very high reflectance at visible and ultraviolet wavelengths (Brittain, 1994), titanium dioxide could effectively provide whiteness for chitosan film coated tablets. Due to the extremely high reflective index of titanium dioxide and its efficiency to scatter light, chitosan films pigmented with this material was totally opaque.

The coloration of coated tablets was intensified from yellowish to brown with increasing the temperature, %RH or duration of heat treatment. The yellow discoloration of the heat treated films might be the result of the Maillard reaction between NH_2 and OH groups as mentioned by Lim and Khor (1999) and Lim et al.(1998).

Adhesion Properties

An enhancement of coating level of chitosan citrate film resulted in stronger adhesion. This result was corresponding to that of Felton and McGinity (1996) who investigated the adhesion between Eudragit L30 D-55 film and tablet surface. The result clearly demonstrated that the addition of glycerin into chitosan citrate film apparently

enhanced the adhesion greater than that of propylene glycol, however this effect was not seen in case of chitosan malate film coated tablet. The greater adhesion when hydrophilic plasticizers were added into polymer film was corresponding to the result of Felton and McGinity (1997). From the adhesion theory, it indicated that the main role in adhesion is played by polar groups, i.e. orientation, electrostatic, hydrogen, induction and other forces rather than dispersion force (Koryagin, 1997). Felton and McGinity (1997) found that greater adhesion was found when hydrophilic plasticizer was incorporated into film prepared from Eudragit L30 D55 compared to the hydrophobic plasticizer, nevertheless the authors did not explain the reason of this evidence. Huntspherger (1967) and Wang et al. (1997) mentioned that plasticizer could act as adhesion promoter by providing better wetting of polymer on the substrate and consequently eliminating interfacial continuities. The decline of adhesion between Eudragit L30 D-55 film and tablet surface was found as the surface of tablet became more hydrophobic through an addition of wax (hydrogenated castor oil) to tablet component (Felton and McGinity, 1996). While Iida et al. (1992) reported that the contact area between glass bead and polymer film was increased when the polymer film became softened by the sorbed water. Hence an addition of hydrophilic plasticizer such as glycerin and propylene glycol which were hygroscopic in nature to chitosan film would promote the moisture sorption and soften the film coat and subsequently enhanced the film adhesion to tablet surface.

The addition of pigment did not markedly affected to the film adhesion to tablet surface. Except, tablets coated with colored film pigmented with talcum 45% showed the greater values of average peeling strength and energy to break point than those of other pigmented film. Okhamafe and York (1995 b) claimed that adhesion would be decreased when a pigment increased the internal stress of the film faster than it increased the strength of the film-tablet interface and vice versa. A poor adhesion between film and tablet surface was due to a high internal stress in the film coat which the Young's modulus was proportioned of internal stress (Lehtola et al., 1995 b). This suggestion was not corresponding to the result of this study since tablets coated with films pigmented with titanium dioxide exhibited the lower energy to break point than those using talcum. However, the reduction of adhesion of HPMC film after an addition of 10% w/w of titanium dioxide was reported by Fisher and Rowe (1976). An addition of high level of titanium dioxide might diminish the peeling strength since the embedded high surface area of pigment particle between the polymer film and core surface interfered the bond of polar groups of the film and shielded them from the core surface as mentioned by Nadkarni et al. (1975). The polymer chains which firmly attached to the pigment surface might increase the internal stress within polymer matrix resulting in reduction of adhesion to substrate (Hegedus and Kamel, 1993). Thus owing to the bonding between titanium dioxide and chitosan, the adhesion of film onto core surface was reduced.

By comparison, at coating level of 3% w/w of polymer, the values of average peeling strength, modulus and energy to break point measured from tablet coated with chitosan acetate film were extensively less than those tablets coated with chitosan citrate film and chitosan malate film. Because high tensile strength of chitosan acetate film as found from mechanical test of cast film, this high internal stress resulted in the considerable decline in adhesion properties. The failure of the adhesive bond because of the high cohesive nature of substrate had been proposed (Koryagin, 1997). The internal stress caused the coating to be less flexible and to fail its adhesiveness when external

force was applied during adhesion test (Hegedus and Kamel, 1993). The evidence from topography study also obviously demonstrated that the film coat of chitosan acetate loosely adhered on core surface. This evidence was more obvious in the case of chitosan acetate film containing magnesium stearate. The decrement of film adhesion due to the enhancement of hydrophobic lubricant, magnesium stearate, but in core tablet had been disclosed (Lehtola et al., 1995 a). Whereas film coat of chitosan citrate seemed greater tightly adhere on core surface than that of chitosan malate. Conventionally, after wetting and penetration of the core tablet surface by the coating solution, adhesion of the viscous solution to the outer layer of the coated tablet was occurred. Consequently, the gelled film collapsed during further drying and adhered to the tablet surface. From SEM photomicrographs, they clearly manifested that the composite of chitosan citrate was likely to more penetrate into tablet surface than that of chitosan malate. The more increase in coating level of chitosan acetate, the less was the adhesion to core surface. This trends in this result was the same as that reported by Rowe (1978, 1980) and Lehtola et al. (1995 a) who found the decrease in measured adhesion when increasing film thickness. A poor adhesion between chitosan acetate film coat and tablet surface might be come from the high internal stress in film coat as the film was thicker as mentioned by Lehtola et al. (1995 a) who investigated the adhesion of HPMC film. However, Rowe (1978) mentioned that there was diverse results about effect of film thickness on adhesion property and these apparently anomalous results were due to the differences in the stress distribution within film during testing and also depended on the test method. The gradual and slow peeling rate was chosen for this study in order to reduced elastic deformation of the film. This suggestion was notified by Nadkarni, et al. (1975).

Hardness

Because of higher strength and toughness of chitosan acetate film than chitosan malate and chitosan citrate films, this resulted in the higher hardness of tablets coated with chitosan acetate film than those of tablets coated with chitosan malate and chitosan citrate films respectively. An increase in coating level would enhance the strength of film coat, hence the hardness of chitosan film coated tablet was more increased. From the comparison between hardness of tablets before and after film peeling, this undoubtedly implied that coating level of chitosan film more influenced on hardness of coated tablets. Improvement of the mechanical strength of the tablet due to film coating was notified by Lehtola et al., 1995 a. 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 diameter by acting as padding material, due to its ability to fill in surface irregularities of core reducing the possibility of fracture and due to its intrinsic strength to resist breakage by acting as a tough envelope (Fell, Rowe and Newton, 1978). The incorporation of additives in chitosan citrate film did not considerably alter the hardness of coated tablets. This might be due to these film coats was not thick enough to affect on hardness of coated tablet. While an incorporation of magnesium stearate, talcum and titanium dioxide caused discontinuities in polymeric net work and thus might reduce the strength of chitosan acetate film and thereafter the hardness of tablets coated with pigment-filled film was lower than those of tablets coated with pigment-free film. Due to the softness and its unctuous characteristic of magnesium stearate, the hardness of tablets coated with chitosan acetate containing this material was less than that of tablets coated

with film containing talcum or titanium dioxide. This evidence possibly also came from the transformation of magnesium stearate molecule during film coating process. Plasticizers enhanced the motion of polymeric chain and decreased the film strength and therefore the hardness of tablets coated with chitosan acetate film containing plasticizers was less than that of tablets coated with unplasticized film. This characteristic was also found in case of addition of urea to coating composite since there was the decline of hardness of coated tablets especially at higher loading of this substance.

Disintegration Time

Because of the gel forming property of chitosan film, the greater amount of film coat would provide the thicker gel layer around core tablet before its dissolution and this evidence resulted in longer disintegration time in deionized water. As barrier for water penetration, the film coat from chitosan prolonged the disintegration time of coated tablets. The thicker of this barrier as the coating level was increased, the longer was the disintegration time of film coated tablets. Due to the higher film solubility of chitosan citrate, the disintegration time of tablets coated with this films was less than that of tablets coated with chitosan malate. Plasticized film coated tablets exhibited slightly longer disintegration time than that of unplasticized film coated tablets. An incorporation of pigment caused the discontinuities in polymeric network and thus the disintegration time of tablets coated with pigmented film was shorten. As discussed in Part I, the chitosan salt films were changed to insoluble form after heat treatment thus the disintegration time of treated film coated tablets mostly was lengthen.

Physicochemical Characteristics of Film Peeled off from Coated Tablets

An interaction between chitosan citrate and propylene glycol, brilliant blue, talcum and titanium dioxide was scarce since the prominent peaks in FT-IR spectra did not shift. In addition, cast film and film peeled off from coated tablets had the same pattern of FT-IR spectra. This result demonstrated that coating process did not alter the film characteristic.

Because the formation of the magnesium salt of stearic acid occurred at the carbonyl end of the molecules as illustrated in Figure *240,* the differences between the obtained absorption spectra of stearic acid and magnesium stearate are mainly due to the alteration of the absorption bonds associated with the carbonyl group. The shift from 1703 cm^{-1} to 1615-1540 cm^{-1} was due to the alteration of the carbonyl stretch, indicating that the carbonyl groups had changed from an unionized to an ionized state in forming the magnesium salt of stearic acid (Ertel and Carstensen, 1988 a). There were the peaks shifted to the higher wavelength (from 1655 to 1635 cm^{-1} and 1559 to 1543 cm^{-1}) after incorporation magnesium stearate in chitosan acetate film. This evidence might be the ionic interaction between protonated amino groups on chitosan and carbonyl group of stearic acid liberated from magnesium stearate molecule. While the longer duration of moist heat treatment, the sharper of shoulder peak of C=O stretching was found in

chitosan film containing magnesium stearate 45%. This evidence was also seen in film containing castor oil indicating to the amide formation.

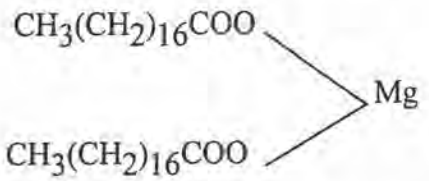


Figure 240 The structure of magnesium stearate

FT-IR spectra of magnesium stearate after dispersion in dilute acetic acid revealed that stearate could be liberated from magnesium stearate. However, main FT-IR peaks of stearic acid especially the dominant at about 1703 cm^{-1} did not appear in spectra of chitosan film containing magnesium stearate both prior and after moist heat treatment. Therefore, the breakdown product of magnesium stearate molecule, stearic acid, containing carbonyl group in its structure could interact with protonated amino group on chitosan by electrostatic charge and further amide formation after moist heat treatment. This suggestion was corresponding to the above result that there were the peaks shifted to the longer wavelength and the evidence of sharper shoulder peak of C=O stretching. The peak shift to the longer wavelength of C=O stretching of acetamido groups was due to the alteration of environment or geometrical arrangement of this group by an introducing of stearate molecules. Some investigations also indicated that chitosan had cooperative effect in the binding with fatty acids and plasma membrane of various plant cells (Domard and Demarger-Andre, 1991). From the conductometric measurement, only electrostatic interaction was occurred between chitosan and fatty acids such as undecylenic acid or butyric acid in dilute solution. Some anionic surfactant, dodecyl sulfate in form of sodium salt, showed a tendency to bind with chitosan in solution (Wei and Hudson, 1991). The positive charge of chitosan had ability to chemically bond with negatively charged lipids, fats and bile acids, thus there is a product used as dietary fiber. Also because of this lipid entrapment property, chitosan has hypocholesterolemic action.

Plasticizers could enhance the amorphous phase of chitosan citrate and malate films in powder X-ray diffraction study. This evidence might be due to crystallization disturbance of chitosan in the blend state as mentioned by Arvanitoyanis et al. (1997) who found the reduction in percentage crystallinity in the mixture composed of chitosan and sorbitol or sucrose. An increased amount of pigments (talc and TiO_2) would provide the higher intense of diffraction peak of these pigments. No crystalline structure change due to addition of these pigments into chitosan film was evident since the prominent peaks of talcum and titanium dioxide was not shifted. The pigments should be dispersed in chitosan citrate, and still showed their diffraction pattern.

Magnesium stearate utilized in this study exhibited the diffraction pattern of dihydrate form as described its characteristic by Ertel and Carstensen (1988 a,b). Conventionally, the diffractogram of the dihydrate or trihydrate magnesium stearate exhibit several distinct peaks while in the case of the anhydrate, there is main single broad peak. The alterations in the angle of inclination of the hydrocarbon chains related to the plain of the magnesium atom head groups brought about by the incorporation of water

into or the loss of water from the crystal lattice (Ertel and Carstensen, 1988 a). The more enhancement amount of magnesium stearate, the intensity of dominant peak of this material especially at about 5°2θ was more increased and there was the more sharper of peak at 23.5°2θ. The sharper dominant peaks of urea were also seen after incorporation of urea in the film, especially, at high concentration. The evidence of stearic which was breakdown product from magnesium stearate after dispersion in dilute acetic acid was also detected in powder X-ray diffractograms. Because of no appearance of diffraction pattern of free stearic acid in chitosan film containing magnesium stearate, the liberated stearic acid molecules had potential to further interact with protonated amino groups of chitosan.

There was no new peak or significant peak shift in the thermogram of colored film. It was also found that the peak of brilliant blue did not appear in this film, thus the brilliant blue incorporated at 0.5% was miscible with plasticized chitosan citrate film. An incorporation of pigment (talcum and titanium dioxide) at concentration of 30%w/w in plasticized and colored chitosan citrate film did not alter the DSC thermogram, this evidence indicated that both talcum and titanium dioxide did not change the thermal properties of plasticized and colored chitosan citrate film. There was no the evidence indicated that talcum or titanium dioxide affected the thermal characteristic of chitosan films. Talcum is presented as to be inert to most chemical reagents and rather thermal stable substance which exhibits an endothermic peak in DTA thermogram at approximately 950-975°C (Patton, 1973). This thermal event is attributed to decomposition of the talcum to $MgSiO_3$, SiO_2 and water. The chemical inert nature of talcum is attributed to its structurally nature. The structure of talcum comprises a brucite ($MgO.H_2O$) sheet sandwiched between two silica (SiO_2) sheets. Their planes are superimposed on each other indefinitely and due to their electrically neutral, adjacent talcum planes are held together only by weak secondary forces such as Van der Waals force (Lin and Peck, 1994; Patton, 1973).

The interest of incorporating titanium dioxide in chitosan film was due to this material was almost totally opaque. Titanium dioxide is extremely stable. This material shows to react at high temperature (melting point 1850°C for rutile polymorph). This exceptional stability is due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions and also due to the screening of the titanium dioxide by six oxygen ions in crystal structure (Kampfer, 1973). The melting points of anatase and brookite polymorphs have not been established since these polymorphs convert to the rutile phase at elevated temperature (Brittain, 1994).

DSC analyses of chitosan acetate film containing magnesium stearate at concentration of 45% w/w showed that there was no endothermic peak of magnesium stearate but the new endothermic peak was appeared at 83.3°C. This characteristic was also seen in film containing magnesium stearate combined with castor oil, and film containing magnesium stearate, castor oil and urea. The new endothermic peak should not be the characteristic of hydrate form of magnesium stearate since the endothermic peak representing the loss of water from dihydrate and trihydrate magnesium stearate occurred at about 104°C and 89°C respectively as reported by Ertel and Carstensen, 1988 a, b). Additionally, the endothermic peak should not occur from urea since the melting temperature of urea appears at 132.7°C and on further heating it decomposes to biuret,

ammonia and cyanuric acid (Windholz, 1983). DSC study revealed that magnesium stearate could be broken down after dispersion in dilute acetic acid and this result was corresponding to the evidence in FT-IR and powder X-ray diffraction studies. Lim and Wan,1998 also found that magnesium stearate was converted to stearic acid (DSC analysis data) during preparation of chitosan microsphere by an emulsification-coacervation technique. Since there was no occurrence of stearic endothermic peaks in diffractograms of chitosan acetate film that containing magnesium stearate, the liberated stearate chains had to be linked with protonated amino groups.

From the thermal studies of mixtures between magnesium stearate with other substance investigated by using DSC ostensibly demonstrated that acidic drugs: ibuprofen (Khan et al., 1995), ketoprofen (Mura et al., 1995; Botha and Lotter, 1989), ascorbic acid (Botha, De Preez and Lotter, 1986) and nalidixic acid (El-Shattawy, 1984) could form an eutectic mixture with magnesium stearate. The occurrence of new endothermic peak at lower temperature than magnesium stearate or drug was claimed that this signified the eutectic formation. However, from the above studies in view point of the alteration of magnesium stearate not drugs it could be observed that the transition endotherm at about 120°C of magnesium stearate in prepared mixture had been obliterated. This evidence could be detected, though the tested specimen was ground mixture. While the mixture between magnesium stearate and other non-acid substances which exhibited an alteration in DSC thermogram was remarked. Nevertheless, this alteration was not dominant such as slight shift of decomposition temperature. These substances were included : cephalexin (El-Shattawy, Kildsig and Peck, 1982 a), albendazole and closantel (Malan, de Villier and Lotter, 1997), diphenhydramine HCl (Botha, De Preez and Lotter, 1986), erythromycin (El-Shattawy, Kilgsig and Peck, 1982 b), ampicillin (El-Shattawy, 1982). The appraisal of these research works clearly demonstrated that magnesium stearate was potentially broken down after mixing with acidic substances since there was the disappearance of endothermic peak of magnesium stearate.

Drug Release Study

1. Fast Release

Drug release from tablets coated with chitosan citrate and chitosan malate films in basic medium dominantly delayed than that in acidic medium. This result indicated that the pH of medium affected drug release from chitosan film coated tablets. In acidic medium, amino groups in chitosan film were extensively protonated and facilitated the passage of water into polymeric film and then chitosan films were subsequently solubilized. Nevertheless the protonation of free amino groups and the hydrogen bonding between hydroxyl groups on chitosan chain and water molecules caused hydration and swelling of the coated film prior to the dissolution of the coat, therefore the drug release was slightly retarded by the hydrated film and the release was slower than that of core tablet. The hydration and gel forming properties of chitosan in the presence of citric acid in matrix formulations had been reported by Nigalaye, Adusumilli and Bolton (1990). In phosphate buffer pH 6.8 which pH was above pKa of chitosan, where protonation of amino groups in chitosan films was not favorable, low swelling and dissolution of film coat was occurred. Therefore the retardation of drug release due to longer lag period was

more obviously evident and was more obviously seen as the coating level was increased. However citric acid incorporated in film coat could enhance the water absorption, induce the hydration and dissolution of film coat, and finally the drug release could be occurred but slowered than that in acidic medium. The increase in solubility coefficient of HPMC film by addition of citric acid had been reported and this evidence was attributed to the non-polymeric nature and multiple hydrophilic groups of citric acid that could enhance the moisture affinity of polymeric film (Okhamafe and York, 1988). Since at the same mole ratio of glucosamine: acid was utilized, the amount of acids used was different due to the different in their molecular weight. At the same coating level based on %w/w of polymeric salt, the chitosan malate film composed of higher amount of chitosan greater than that of chitosan citrate because molecular weight of citric acid is greater than malic acid. Therefore, due to the higher amount of chitosan in chitosan malate film than in chitosan citrate film, the drug release of the chitosan malate film coated tablets was dominantly slower, particularly in basic environment.

Chitosan is an acid soluble polymeric matter, therefore at the same amount of polymer in chitosan citrate and malate films chitosan could solubilize at nearly the same extent in acid dissolution fluid since both citric and malic acids were the high water soluble substances. Whereas solubility of chitosan salt films in basic dissolution medium was depended on the solubility of acid utilized since chitosan is naturally unprotonated in basic environment. The high amount of citric and its more hydrophilic carboxylic groups might promote the acidic environment and hydration of chitosan citrate film resulting in the partial film solubility in basic medium. Therefore the drug liberation from tablets coated with chitosan citrate film was not as enormously retarded as that of tablets coated with chitosan malate film. This could be concluded that chitosan citrate was less pH dependent than chitosan malate. An addition of propylene glycol affected drug release of coated tablets after exposure accelerated condition less than glycerin.

Due to the fast dissolution of chitosan citrate plasticized with propylene glycol in acid medium, no obvious difference in release characteristic by varying amount of propylene glycol loading was found. However the more decrease molecular order and probably enhance chain mobility in chitosan film by the more addition of propylene glycol, the more faster was the drug release in basic medium. This suggestion was corresponding to the evidence from powder X-ray diffraction study which amorphous phase of chitosan citrate was more increase after addition of plasticizer. Enlargement and facility of drug diffusion by addition of plasticizer in HPMC film was also reported by Okhmafe and York (1983).

Because of the electrostatic charged interaction between anionic groups of dye and protonated amino groups on chitosan especially in acidic medium, thereby the remained protonated amino groups which were readily for dissolving were decreased. Thus retardation of drug release was occurred. However owing to the high hydration efficiency of chitosan citrate film, the effect of dye binding to retard the release in acid medium was minute. This higher hydration and solubility of chitosan came from the high water penetration of this film and the more acidic surrounding induced by citric acid. In basic environment, the anionic dye molecule could be easily ionized and could promote the film hydration, thus the drug release from colored film coated tablets was faster than non-colored film coated tablets. This result was also attributed to the decline in the dye-

binding capacity of chitosan above its pKa as mentioned by Knorr (1983) who tested dye binding between chitosan and FD&C Red. 40. Shin and Yoo (1998) also noted that higher dye uptake of chitosan was obtained in acidic environment than in alkaline environment.

The longer storage or direct exposure to accelerated condition altered the chitosan citrate and malate films to be less soluble thus the dominantly slower drug release in dilute HCl solution was detected, especially in case of colored coated tablets. Anionic molecules of tartrazine that is the component of green FS had tendency to react with protonated amino groups greater than brilliant blue thus film coated tablets colored with green FS exhibited slower drug release than that of coated tablet colored with brilliant blue. Due to the high amount of SO_3H group and high water solubility and the presence of positive charge in molecule of brilliant blue, the drug release was still faster than that of coated tablets colored with Green FS. Under accelerated condition, gelatin capsule exhibited the retardation of disintegration and dissolution which proposed mechanism for this evidence was the crosslinking between amino groups of gelatin and carbonyl substances especially aldehyde resulting in the insolubility of capsule shell (Adesunloye and Stach, 1998). This study also demonstrated that when glycine and citric acid were present in gelatin capsule formulation, crosslinking of the gelatin capsule was prevented. An addition of citric acid into chitosan microsphere prepared by glutaraldehyde crosslinking increased the formation of a water-soluble gel and release rate of phenobarbitone (Al-Helw et al., 1998). The temperature of storage and the environment may result in complex effect of drug release behavior was mentioned by Wood (1984). 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. The more extensive exposure to the accelerated environment possibly enhanced the degree of alteration. Therefore, the direct exposure to accelerated condition could retard the drug dissolution from film coated tablets greater than those after storage in sealed amble bottle under accelerated condition for one month and one week respectively. Freshly prepared coated tablets or non-colored or colored coated tablets after exposure accelerated condition exhibited the drug release passed the criteria based on USP XXIII which not less than 75% of drug was dissolved in 30 minutes. All coated tablets after storage at room temperature for one year exhibited the drug release conformed to the monograph of USP XXIII.

Discontinuity of chitosan citrate film due to filled pigment which would disrupt the gel-forming property of chitosan in acid medium, thus the drug liberation was slightly enhanced. Effect of film additive in increasing release rate of coated product has been reported and accounted (Parker, Peck and Banker, 1974; Porter, 1982; Chang and Hsiao, 1989; Wan and Lai, 1993; Bauer et al., 1998). Poor or insufficient pigment-polymer interaction tended to induce the void formation at pigment-polymer interface which could facilitate the drug diffusion (Okhamafe and York, 1987). Spherical titanium dioxide might increase permeability because of their hydrophilic surfaces as well as the missing barrier effect (Maul and Schmidt, 1995). However, in basic medium, chitosan was likely to be insoluble, thus the filled pigments acted as barrier and retarded water penetration and thus drug release was slower. However the higher amount of talcum could promote discontinuity in chitosan citrate film and thus there was the disruption of barrier effect of chitosan and the drug release was faster. The retardation of drug release of pigmented

coated tablets after exposure accelerated condition was also remarkably occurred. While the drug release profiles of coated tablets after kept at room temperature for one year were similar to those of freshly prepared coated tablets and all formula conformed to the monograph of USP XXIII. Thus drug release from tablets coated with chitosan citrate and malate as coating material was sensitive to the environment of storage condition especially humidity and moisture whereas the aging at the room temperature did not affect to the release behavior of these coated tablets with or without film additives. This soluble and rapidly disintegrating properties of chitosan citrate film coating seemed to be potentially utilized for finishing, color identification or stability improvement. Similarly, commonly used film former for pharmaceuticals, Eudragit® E100 (polybutyl methacrylate/(2-dimethylaminoethyl) methacrylate/methyl methacrylate), also a cationic polymer, could dissolve in water with salt formation upon addition of 1 to 3 equivalents of organic or inorganic acids. Suitable acid components were citric acid and sodium dihydrogen phosphate (Bauer et al., 1998). Brilliant blue which was less affected to release behavior of chitosan citrate than green FS and provided enough tinctorial strength for coloring and product identification. Addition propylene glycol and low amount of talcum could improve mechanical properties and provide the desired glossiness. The talcum would also reduce the moisture permeability of the coating, thus aiding the stability of core component. The good adhesion property of chitosan citrate film to tablet surface would possibly reduce the occurrence of logo bridging.

2. Extended Release

The thicker of hydrated film as coating level of chitosan acetate film was increased resulted in the longer lag time in release profiles of freshly prepared film coated tablets. Lag effect could be minimized by addition of glycerin which could enhance film hydrophilicity and thereafter the film hydration and solubility. Glycerin also enhanced the release rate and also shorten the lag time of drug release from these coated tablets in basic medium. The enhancement of water penetration into core tablet due to an addition of hydrophilic plasticizer in film coat had been notified (Rangaiah, Chattaraj and Das, 1997). Basically, administration of oral sustained release dosage form has to pass the stomach before movement further to the next gastrointestinal part, hence the product must withstand and control drug release in both acid and basic environment of gastrointestinal tract. Freshly prepared chitosan film coated tablets could effectively control drug release in basic medium while exhibited extensively fast release in acid medium. Therefore it was difficult and seemed impossible to use this film as the barrier for oral sustained release product extended to 24 hours. Nevertheless due to the effectiveness for control medicament in basic environment, it may repeat to coat chitosan film coated tablet with enteric coating film former to prolong the release both in acidic and basic environment but this method was not included in this present research.

Because of brittleness of unplasticized and plasticized chitosan acetate and chitosan propionate film after heat treatment, these treated coated tablets could not extend drug release. Thermal treatment virtually altered the mechanical properties as previously mentioned in Part I. Owing to the potential removal of plasticizer during heat treatment, the remainder was less than to plasticize the polymer. The hydrophilic nature of these plasticizers might not able to plasticize the less hydrophilic treated polymeric film. The

loss of plasticizer due to its evaporation during drying has been reported (Skultety, 1984; Arwidsson, et al., 1991; Hutchings et al., 1994; Singh and Khan, 1997; Frohoff-Hulsmann, Schmitz and Lippold, 1999). Virtually, low molecular weight plasticizers did not satisfy for long term storage on account of their higher volatility, caused in loss of plasticizing effect with time and consequently an increase in the rigidity and brittleness of the film (Zhurarleva et al., 1997 a, b). Castor oil at concentration of 15% could not promote the prolongation of release since the low amount of this plasticizer might be less than to effectively plasticize treated chitosan film. Nevertheless it could not be incorporated at greater amount due to its phase separation. By visual observation during dissolution test, it clearly demonstrated that after heat treatment film coat of chitosan propionate was more brittle and yellowish than that of chitosan acetate. Thus an ongoing study selected chitosan acetate film for further prepared the extended released film coated tablets.

Owing to acid soluble property of chitosan film, an incorporation of talcum and titanium dioxide could not significantly prolong drug release since the film coated tablets had to previously pass acid stage whereas an incorporation of magnesium stearate slightly retarded drug release. The electrostatic charge interaction between protonated amino groups on chitosan and stearate molecules from magnesium stearate resulting in retardation of dissolution of film coat that containing magnesium stearate. Magnesium stearate was claimed as auxiliary lubricant in plastic fabrication (Flick, 1986). Stearate salts such as calcium stearate has been reported to also utilize as plasticizer for paper coating (Lower, 1996 a) and to enhance ageing and heat resistance and employ as non-toxic stabilizer against heat and light for polyvinyl chlorides (Lower, 1996 b). Butyl stearate can be utilized as plasticizer in coating such as enamels, lacquers, dopes and wire insulating varnishes. It is a primary plasticizer for rubbers, chlorinated rubber and cellulose ethers and acetate. It can be incorporated into many plastics as a supplementary lubricant/plasticizer, improving water resistance (Lower, 1982). For this study, the stearic acid after coupled with chitosan might provide the plasticizing effect for chitosan films especially after moist heat treatment thus the treated films still remained their integrity during dissolution test. Additionally the hydrophobic nature of stearate could inhibit hydration of polymeric film and drug release. Magnesium stearate is described as an inert or nuisance material and is classified as unhazardous under normal condition of use by the department of Transportation Regulation (The Pharmaceutical Society of Great Britain, 1986). Magnesium stearate was also recommended as filler in film coating (Okhamafe and York, 1985; Thoennes and McCurdy, 1989). Chetty and Dangor (1994) and Govender, Dangor and Chetty (1995) produced diethylpropion HCl coated pellet and salbutamol sulphate coated pellets respectively using a combination of Eudragit RS and magnesium stearate as stable film coat that controlled drug release as desired. This material was applied as coating material for isoprenaline HCl particles by using dry coating technique (Yoshizawa and Koishi, 1990). A slower in vitro release of salbutamol from pellet coated with Eudragit RS 30D was demonstrated with higher concentration of magnesium stearate(Govender, Dangor and Chetty, 1995). These studies also claimed that magnesium stearate exhibited an inhibitory effect on the rate of drug release due to its hydrophobicity which inhibited hydration of polymeric membrane and thereafter retarded the release.

An incorporation of plasticizer in chitosan acetate film containing magnesium stearate 45% obviously prolonged drug release. This evidence might relate to the effect of incorporated plasticizers on reducing the electrostatic repulsion of protonated amino groups and thus reducing the film hydration. The decrease in the permeability to water and water soluble agent due to an introducing hydrophobic plasticizer such as dibutyl sebacate in ethylcellulose film had been reported by Appel and Zentner, 1991. Because of high hydrophobic nature, castor oil could retard water penetration and film hydration and effectively prolong drug release greater than the other plasticizers. This effect of castor oil was attributed to the formation of a more continuous film as seen in SEM photomicrographs especially after moist heat treatment. This evidence might be due to the efficiency of rather long molecule of castor oil to penetrate through chitosan and stearate chains. Long chained dibutyl sebacate and acetylated monoglyceride molecules was recently reported that they could penetrate the polymeric chains of ethyl cellulose better than the more spherical triethyl citrate, triacetin and diethyl phthalate molecules (Hyppola, Huddson and Sundholm, 1996). Simultaneous interpenetrating polymer networks prepared from methylmethacrylate and castor oil was also reported (Bui, Liu and Legault, 1996). The introduction of castor oil in chitosan acetate for preparation of polyurethane-chitosan interpenetrating polymer networks had been notified by Gong et al. (1998). During preparation of Semi-IPNs using interchange reaction between the castor oil and poly(ethylene terephthalate), the copolymer formed by bond interchange affected miscibility by reducing the phase separation (Barrett, 1992).

Dry heat treatment at 60°C could promote the removal of acetic acid from film coat and thus reducing the chitosan in acetate salt form. Due to the less hydrophilic of free amino groups of chitosan than amine salt, its solubility was also decreased and thus drug release from coated tablets was also slower, however the desired extended drug release did not attain. Another underlying mechanism of drug release retardation by dry heat treatment was curing effect and thus more continuity of film coat was attained and thereafter the drug liberation was slower. The decrease in release rate of drug from coated formulations after curing at elevated temperature had been notified (Wan and Lin, 1992; Guma, Kale and Morris, 1997).

Longer or higher temperature and %RH of moist heat treatment could greater prolong drug release due to the more extensive promotion of amide linkage formation. An amide formation after moist heat treatment changed film to insoluble form and this acted as controlled membrane for drug release. As aforementioned, carbonyl group of sterate chains could react with protonated amino group on chitosan chains and further amide formation after moist heat treatment. Therefore treated chitosan acetate film containing magnesium stearate was greater effective to prolong drug release than that of film containing talcum or titanium dioxide. The high efficiency of talcum to prolong drug release than titanium dioxide might be due to the platy nature of talcum particles. Platelet-shaped filler had tendency to align parallel to the substrate surface and thus build a rooftile-like barrier and reduced the penetration of dissolution media. The reduction of drug release from coated preparations by addition of platelet-shaped fillers had been reported (Maul and Schmidt, 1995; 1997; Aoki et al. 1998). Ion beam etching was usually utilized and informed that large talcum particles tended to lie in the plane of HPMC film coat whereas the small particles were more randomly oriented (Gibson, Rowe and White, 1988a). The investigation for study effect of filler on property of

polypropylene revealed that talcum particles oriented parallel to the surface of prepared product (Lisy, 1993). The decrease in water vapor transmission of film fabricated with the mixture of HPMC and ethyl cellulose as increasing the talcum loading had been noted (Parker, Peck and Banker, 1974). Effect of moist heat treatment was more dominant than dry heat on prolongation of drug release. The moisture could induce more homogeneous of amide formation. Usually, the rate and extent of the thermal reactions were increased in the presence of moisture. The change of physical properties of chitosan was accelerated in the presence of saturated steam has been recently reported (Lim, Khor and Ling, 1999).

Effect of castor oil on enhancement the efficiency of moist heat treated chitosan acetate film containing magnesium stearate to extend drug release should be similar to the case of its effect on freshly prepared coated tablet. However, this thermal treatment possibly induced the more extensive penetration of castor oil through chitosan and stearate chains. The more decrease in release rate of propranolol HCl from ethylcellulose coated pellets by addition of plasticizer had been mentioned (Hutchings and Sakr, 1994). Nature of plasticizing effect of anisole and fluorocarbon oil was responsible for opposite trends in compatibility and effectiveness for PVA film. The heat ageing process could be promoted by migration of these plasticizers. Additionally, the retention potentially depended on the composite of their processing properties with time and the durability of the product because of their low volatility (Zhuravleva, Laktionov and Treneva, 1997). Swierz-Motysia (1996) mentioned that there was the necessary for auxiliary agent comprised primarily plasticizers which provided the plastic with required elasticity and stabilizers to prevent breakdown of the polymer at elevated temperature. The only stabilizers authorized by the European Pharmacopoeia for medical applications were non-toxic calcium-zinc stabilizers. There were usually Ca/Za salts of higher fatty acids, such as stearates, laurates or mixtures of them. Therefore the low volatile plasticizer like castor oil combined with magnesium stearate could effectively plasticize moist heat treated chitosan film and promote the prolongation of drug release.

Propranolol HCl, a basic drug with a pKa of 9.45, should be greater soluble in acidic environment than in neutral and alkaline environment respectively. However this anticipation was not found, the drug solubility in deionized water was greater than that in acid and basic dissolution fluids respectively. The decline of solubility in HCl buffer pH 1.2 was attributed to the common-ion (chloride) effect, which provided an unexpected trend in solubility of this medicament in the presence of chloride ion in this acidic medium. This evidence was also noted by Rekhi et al.(1989).

The drug release from moist heat treated CA M45 CAS15 and CA M45 CAS15 U5 coated tablets exhibited pH dependent behavior. Drug release from these coated tablets was more enormously prolonged in basic medium than in acid medium. Drug release could be completely depleted in acid medium at 24 hours whereas maximum % drug release in basic medium was about 90% at 36 hours. The drug release from coated product that depended on drug solubility had been reported by Shah et al. (1994) and Ragnarsson et al. (1992) who investigated the release of cilazapril from beadlets coated with Surelease. Apart from the effect of pH on drug solubility and thereafter on the drug release, this dominant effect should be also come from the effect of pH on the alteration of permeability of chitosan film. The mutual repulsion of remaining cationic protonated

amine groups of chitosan film in acidic medium could promote pore formation, subsequently the dissolution fluid diffused through the film coat along with protonated amino groups. However, pore could not be detected on scanning electron micrographs, perhaps the pores were very small or during drying before tested the swollen film would be collapsed and thus the pore size was more decreased. An increase in the release of diffusant from the donor to receptor part when cation content in acrylate-methacrylate copolymer was increased had been reported (Narisawa et al. 1991; Hariharan and Peppas, 1996). Phares, Johnson and Swarbrick (1995) studied the drug transport across Nylon 610 films and claimed that water diffused through the membrane of microcapsule along with diamine molecules of Nylon 610 through microcapsule. The transport of various diffusants through network of methacrylate cationic copolymers which was pH dependent was also reported by Hariharan and Peppas (1996). Referring to the water uptake of coated tablet during dissolution test, the treated film coat could imbibe of aqueous fluid. This uptake data indicated the hydration of polymeric film and thus the presence of water-filled within the wet film structure. An increase in the porosity of latex film after exposed to the aqueous medium was reported by other investigators (Chainey, Wilkinson and Hearn, 1985). The swelling of film coated tablet during dissolution test and the collapsed structure of dry state was visually observed and corresponded to the above mentioned. The effect of pH on drug solubility should be greater affected to drug release than film hydration since the drug release was fastest in deionized water which drug solubility was greatest whereas chitosan film hydration should be less than that tested in acid medium.

An appraisal of research works indicated that it was important to consider or include the osmotic pumping mechanism when elucidation release characteristics of membrane coated preparation was performed (Kelbert and Bechard, 1992; Lindstedt et al., 1989). Recently, the fabrication of osmotic devices has not required a drilled exit passageway by using laser beam or drilling by small screw since the incorporated pore-forming agent in membrane could provide the microporous structure after immersion in aqueous extraction medium and thereafter the encapsulated drug could be liberated. Osmotic pressure could be developed within the coated tablet from encapsulated water soluble drug and other excipients. Assessment of drug release pattern in dissolution fluids which were different in osmotic pressure was the convenient method to evaluate the release mechanism (Rekhi et al., 1995; Narisawa et al. 1997). From the study of the effect of osmolality of dissolution fluids on drug release behavior clearly demonstrated that drug release was decreased as the osmotic pressure difference was decreased, however drug solubility was also decreased as the osmotic pressure difference was decreased. The osmotic pressure might indirectly enhance the drug release from the tablets coated with treated chitosan film, since the osmotic pressure could induce the expansion of the coated tablet and result in further pore formation and/or pore enlargement in the hydrated film coating. This suggestion had been mentioned by Li and Peck (1989).

The release profiles exhibited an initial rather long lag time, because the coated tablet had to be wet, absorbed water and water penetrated into core and subsequently solubilized the core material before drug diffusion into extraction medium. The another unsatisfactory characteristic was the incomplete liberation of all encapsulated drug from coated tablet. The lowering coating level did not solve this undesired release characteristic. In order solve these disadvantages, the composition of film coat was

modified by addition of hydrophilic substance. Efficiency of urea to minimize these unsatisfactory release characteristic was greater than HPMC. Urea molecule is small, readily water soluble and uncharged molecule whereas HPMC is water soluble polymer. When film coat exposed to dissolution medium the HPMC chain would be hydrated and form gel and thus the drug would inconveniently diffuse into dissolution medium. Lehmann (1994) claimed that HPMC was not usually regarded as a true pore former. However it could enhance the drug release and shorten the lag time of release profile. An increment of drug permeation through cellulosic membrane by addition of HPMC had been previously reported (Rowe, 1986; Lindstedt et al. 1989; Gilligan and Po, 1991; Shah, 1992). Although the lag period was shorten after addition of high amount of urea, the release rate was also enhanced due to the more penetration of water and facility of drug diffusion. Urea has been claimed as water soluble additive which could increase solubility coefficient of hydrophilic film (Okhamafe and York, 1987). Low amount of urea (5%w/w) loading could provide the desired release characteristic of moist heat treated coated tablet (CA M45 CAS15 U5). This modified coated tablet after moist heat treated for 24 hours could control drug release to 24 hours and the medicament was liberated nearly to 100% and lag time was shorten to about 60 minutes. Technique of incorporation of pore former to shorten the lag period had been proposed by many studies (Chien, 1983; Lindholm et al., 1986; Rowe, 1986; Appel and Zentner, 1991; Lindstedt et al., 1991; Gilligan and Po, 1991; Kelbert and Bechard, 1992; Jensen et al., 1995; Phuapradit et al. , 1995). Because of aqueous soluble property of urea and HPMC, they are likely to be dispersed on a molecular level in chitosan coating composite. When these materials were dissolved and then created the pores within film coat, the pore size would be extremely minute. Therefore, the presence of pores in film coat after dissolution test could not be electromicroscopically detected. This characteristic of film loading with soluble pore forming agent had been mentioned (Porter, 1989). The effect of urea on enhancement of drug release from this tablets coated with treated CA M45 Cas15 film was attributed to the leaching out of it from the film after exposed to dissolution fluid and thus the drug transport was occurred through a network of capillaries which were filled with dissolution fluid.

As well as the temperature and duration of moist heat treatment, the elevation of %RH could promote greater sustainable drug release. This was attributed to the extensive amide formation during moist heat treatment. As the comment from Kubota et al. (1993) who claimed that upon amino group on chitosan chain only N-acetylation with some crosslinking agents could be formed in the presence of water. As the catalyst, water in atmosphere was absorbed into chitosan film and promote extensive ionization of amino and carboxylic groups to readily react with each other. The decrease of hydrophilic groups after amidation related to the alteration to insoluble form of chitosan films.

No presence of lag period in drug release profile from the commercial product, Inderal LA-80, however this product could liberate drug only about 80% at twelfth hour interval while prepared coated tablet could liberate the encapsulated medicament nearly to 100% and had the lag time about 60 minutes. The drug release of both preparations conformed to the criteria of drug release at each time interval as remarked by USP XXIII. The drug release extended to 24 hours could be attained.

The high swelling film coat by visual observation and high % weight increase of freshly prepared CA M45 Cas15 and CA M45 Cas15 U5 coated tablets during dissolution test demonstrated that these film coats were gradually hydrated and swollen in acidic medium due to the protonation of amino groups on chitosan. Electrostatic binding between chitosan and stearate molecules could retard the hydration and thereby the hydration was rather slow and the drug release could be extended. Whereas urea could be leached out from the film coat of CA M45 Cas15 U5 and film solubility could be promoted. Thus the %weight increase of this coated tablet was less than that of CA M45 Cas15. An increase in the solubility coefficient of polymeric film by addition of urea had been notified (Okhamafe and York, 1987).

The % weight increase of coated tablets after moist heat treatment was markedly regressed. This observation related to the decrease in film hydration due to an alteration to insoluble form, and therefore this change in weight during dissolution test was mainly associated to the fluid transfer through film coat of these treated coated tablets. An addition of urea could promote film porosity by its leachable property by solubility, thus the fluid inside coated tablet which should be more viscous than the external extraction medium could penetrate outward through film coat easier than film without an addition of urea. This mention was corresponding to the report that the maximum weight increase of moist heat treated CA M45 Cas 15 U5 was less than that of moist heat treated CA M45 Cas15 coated tablet. However, the hydration of moist heat treated film was also depended on pH of dissolved medium, hence the % weight increase of moist heat treated coated tablets in acid was greater than that in basic medium. Due to the gradual dissolution of drug from core tablet and it subsequently penetrated through film coat into external dissolution medium, therefore % weight increase was gradually decreased to plateau stage.

Part III

Release Model Development and Curve Fitting

1. Fast Release

Based on the promises, this work proposed a mathematical model for drug release from chitosan film coated tablets and compared its applicability to predict the experimental results with the conventional release models. Comparisons of coefficient of determination values revealed that KGT2 model was most applicable for drug release data of tablets coated with aqueous soluble chitosan films. Although curve fitting of most profiles with the weibull equation could provide high coefficient of determination values, this model does not practically indicate the release mechanism. The weibull equation was intentionally derived to provide the information's about the shape of the curve. Whereas the newly derived equation could provide information about the mechanism of the release such as rate of film dissolution and extent of readiness for the drug to penetrate the film.

From curve fitting with KGT2 equation, Tf values could indicate the film dissolution time which was subsequently useful to determine the film dissolution rate. As the coating level was increased, both Tf and lag period were longer. The lag time corresponding to the duration of initial phase was accounted for simply by computerized estimation. Lag period was also longer as coating level was increased due to the more enhancement of path length of film for water penetration. The extent of lag period which was controlled by the amount of coating had been notified by Odegardstuen et al. (1991). The longer extent of film hydration and solubilization as the chitosan film was thicker, the greater was also the Tf value. The film dissolution rate of chitosan citrate was higher than that of chitosan malate and chitosan acetate respectively. This was corresponding to the above previous discussion in drug release study. Because of the protonation and unprotonation nature of chitosan in acid and basic environments respectively, the dissolution of chitosan citrate film in acid medium was faster than that in basic medium. Since surface area of coated tablets to contact with the dissolution medium was enlarged, the dissolution rate of chitosan film had a tendency to increase as the coating level was increased.

The drug release mechanism from aqueous soluble chitosan film coated tablets could be suggested as following steps:

a Hydration and thereafter dissolution of film coat into dissolution medium.
b Dissolution of drug into the permeating solvent
c Diffusion of drug within the permeating solvent
d Partition of drug into remained film coat
e Diffusion of drug across the remained film coat
f Diffusion of drug into the external dissolution medium
g Dissolution of drug from the remained core tablet into dissolution medium
h Diffusion of drug into dissolution medium

The film coating affected the drug release from core tablet by slightly reducing the release rate of drug from remained core tablets. This was attributed to an enhancement of hardness of core tablet after film coating resulting in increase the closeness of core component which retarded the drug release. Hence the more increase in coating level, the more decrease was the drug release rate from remained core tablet. The drug release from remained core tablet also depended on the film dissolution time. The release rate was decreased as the film dissolution time was longer especially that of drug release performed in basic medium. The addition of plasticizer, color and pigment did not alter the release mechanism since the release profiles could successfully fitted with KGT2 equation providing high coefficient of determination.

Due to electrostatic charge interaction between protonated amino groups on chitosan and stearate molecules from magnesium stearate, and the hydrophobic nature of castor oil, these resulted in retardation of film dissolution. Hence, the film dissolution time and film dissolution rate of chitosan acetate film containing magnesium stearate and

castor oil at concentration 45 and 15% respectively in acid medium had a tendency to be slower than those of chitosan acetate and chitosan citrate film coat.

Owing to the complexity of parameter A and B values which there were microparameters as $D(H_O-R_O)/Df\ k\ H_O$ and $D\ a/\ Df\ k\ H_O$ respectively, the prediction of drug release behavior by A and B was rather unable since D, Df and k had the same tendency to increase or decrease their values in this mass transfer phenomenon. However the ratio of A/B was meaningful and useful to determine the film dissolution time and subsequently the film dissolution rate. The parameter C from curve fitting had a tendency to notably decrease as the film dissolution time was longer. Thus the results seem not agree with model assumption which C should be constant. The reasons for this observation are claimed as followed. C was a complex constant consisting among others, D that was diffusion coefficient of the drug in component filled in the space between the film and remaining core tablet. Additionally inner side/surface of film was dissolved, as well as the outer side/surface, and the film constituents which dissolved from inside could alter the composition and the viscosity of the inner space, and consequently the diffusivity of the drug, D and therefore C value were changed. Basically, the retardation of drug penetration through film coat resulted in the slower drug liberation. The constituents of the film that caused slower drug penetration like magnesium stearate made also the diffusion of the drug in the inner space slower, when the drug was dissolved into that environment. Therefore it could detect the evidence of decrement of the C value as the coating level was increases, the basic medium was utilized as dissolution fluid or there was an addition of magnesium stearate and castor oil in film coat. Additionally, the slow solvent permeation through the thick or less hydrophilic film coat resulted in increase in the viscosity inside that space due to insufficient amount of fluid to solubilize the solid drug and excipients. The decrement of diffusivity of dissolved solute owing to an increasing environmental viscosity had been notified (Bogardus, 1984; Grant and Brittain, 1995). Crank (1975) claimed that diffusion in dilute solution can reasonably be taken as constant, while diffusion in high polymer is markedly on concentration. The viscosity came from both the film coat and core constituent after exposed to the permeating solvent and thereafter filled in the space. Therefore the drug diffusion was decreased and resulted in decrease of D and subsequently C value. As abovementioned, thereupon the C value could provide the informative nature to predict drug release rate from coated tablet. Even though this model did not predict the result exactly, it was the applicable model which provided the informative parameters.

2. Extended release

KGT3 equation was subsequently developed from KGT1 equation by assuming that the film was changed to insoluble form by moist heat treatment. KGT3 equation was the integrated form and the release rate of drug from this device could be expressed as $dF/dt = C / ((1-F)^{-1/3} + (A-1))$. KGT3 seemed similar to Baker-Lonsdale equation (Bodea and Leucuta, 1998) except that the former have the A value [(Ho-Ro)Ds/(Ho.Df)]. Baker and Lonsdale (1974) studied a system of drug release from particle matrix and they found that the drug release rate was expressed as : $3/2\ [1-\{1-(F/F_0)\}^{2/3}]-(F/F_0) = 3CsDt/r^2A$. Cs is the drug solubility, A is the drug loading per unit, r is the radius and D was the diffusion coefficient. Actually, Baker-Lonsdale equation does not assume film at all and

film thickness is zero from the beginning. In other words, KGT3 assumed that film coat was a barrier for drug release, whereas Baker-Lonsdale equation does not assume any barrier out side the spherical matrix. This is the reason why Baker-Lonsdale equation does not contain parameter A.

Although both weibull and KGT3 equations could be fitted by most of release profiles of tablet coated with chitosan acetate containing magnesium stearate or talcum after moist heat treatment, weibull equation did not generally indicate the release mechanism and that it was not subsequently selected for curve fitting. Curve fitting with Higuchi's and zero order equations showed the less goodness-of-fit with release profile of most tablets coated with chitosan film after moist heat treatment, whereas that with KGT3 and first order expressions provided the high coefficient of determination.

The C value is a complex term consisting among others (4π D Ro Cs). D is diffusion coefficient of drug in the content filled in the space between the film and remaining core tablet. There was the evidence of decreasing in C value as the duration of moist heat treatment was longer, or the temperature or %RH of treatment was higher. The C value from curve fitting of drug release from tablet coated with CA M45 after moist heat treatment was less than that of CA Ta45. Additionally, this value was more decreased when there was an incorporation of castor oil into CA M45 film. This study also found that the C value and lag period were decreased and longer respectively when the osmotic pressure of dissolution fluid was increased. From the aforementioned results, it could be concluded that the capacity of permeating medium to penetrate through the treated film coat to dissolve the encapsulated core component depended on the film component and film property after moist heat treatment which affected to the viscosity of surrounding environment of remained core tablet. The permeating solvent entered the polymer, dissolved the drug and enabled the drug in solution out of the coated tablet. Usually, hydrophobic film coat is more effective than the hydrophilic film coat to retard the penetration of permeating solvent. Therefore the more hydrophobic nature by greater extensive amide linkage formation of the treated chitosan film, the slower was the penetration of permeating solvent and thereafter the inside viscosity and drug diffusivity were increased and decreased, respectively. The reduction of diffusion coefficient of diffusant due to an increase in its surrounding viscosity had been reported (Bogardus, 1984; Grant and Brittain, 1995). The diffusivity of drug was strongly affected by the concentration of the liquid and naturally it increased largely when the concentration of liquid was increased (Liu et al., 1988). An increase in osmolality of dissolution fluid also decreased the amount of outer water which would penetrate through the film coat, thus this situation also decreased the drug diffusivity and thereafter the microparameter D in estimate C value in KGT3 equation. The transfer of both dissolved drug and permeating solvent were controlled by transient diffusion. The water permeability of membrane was the primary release-regulating parameter (Lindstedt et al., 1989). An addition of hydrophilic substance such as urea and HPMC which potentially enhanced the influx of permeating medium also increased the C value. The apparent diffusion coefficient of substance was increased with an increase in the amount of hydrophilic additive in ethyl cellulose microcapsule wall had been reported (Vidmar, Jalsenjak and Kondo, 1982). Owing to the cationic repulsion of chitosan film in acid medium which could promote the medium penetration, the C value from curve fitting of drug release in acid medium was higher than that in basic medium.

The relationship between drug solubility or osmotic pressure difference, and C value from curve fitting with KGT3, K from curve fitting with first order equation and lag time of drug release from tablets coated with CA M45 and CA M45 Cas15 films after moist heat treatment at 60°C for 48 and 24 hours respectively are shown in Tables *81* and *82*. The linear relationship between drug solubility or osmotic pressure difference and C value are illustrated in Figures *241* and *242* respectively. It indicated that the C value was depended on the drug solubility and osmotic pressure difference. An increase in drug solubility or osmotic pressure difference could increase the C value with the rather linear relationship. The longer lag time was found as the drug solubility or osmotic pressure difference were decreased as shown in Figures *243* and *244*. This demonstrated that both drug solubility and osmotic pressure difference were very affected the lag time. The lag time was the initial phase where coated tablet was introduced into dissolution fluid, permeating fluid penetrated through the film coat, dissolved the encapsulated drug and built up osmotic pressure. The decreasing in osmotic water influx by increasing the osmotic pressure of dissolution medium could decrease the rate of solvent to dissolve the core component and that the formation of inside osmotic pressure was slower, thus the lag time was prolonged. The abovementioned suggestion also found in case of the release rate (K) from curve fitting with first order was used instead of the C value, except that the relationship between drug solubility or osmotic pressure difference and release rate was the exponential trend as shown in Figures *245* and *246* respectively. The prolongation of lag time owing to a decrease in drug solubility or osmotic pressure difference was also found as illustrated in Figures *243* and *244*. From the abovementioned, the release of propranolol HCl from these coated tablets appeared to be diffusion controlled accompanied by osmotic effect. These combined release kinetic of drug release from reservoir type device had been reported (Lindstedt et al., 1989; Kelbert and Bechard, 1992; Ragnarsson, 1992; Rekhi et al., 1995). Both drug diffusion and osmotic pumping had been reported that they possibly enabled drug transfer through a very low osmotic permeable membrane such as ethyl cellulose (Lindstedt et al.,1989). Iyer et al. (1990) described that the drug diffusion might be caused by the initial hydration of polymeric coating in the dissolution medium, followed by chain relaxation which led to the formation of channels or pores which drug molecules could pass through.

When acid medium was utilized as dissolution medium, due to the protonation nature of remained cationic charge groups under acid environment, the fluid penetration into these film coat was enhanced and the C value was notably increased. The contrary evidence was observed when using basic dissolution medium. The release rate (K) from curve fitting with first order of drug release in acid medium was also obviously higher than that in basic medium.

It could be concluded that the drug liberation from insoluble chitosan film coated tablets appeared by drug molecule first diffusion through space between undissolved core tablet and film coat and dissolving in the film coat at one interface followed by diffusion down a chemical potential gradient and also by osmotic pumping effect across the insoluble film or the rather swollen film and consequently the transport from the second interface into the external dissolution fluid. Such solution-diffusion mechanism is typically observed in the transport of diffusant through hydrophobic membrane materials such as silicone rubber and ethylene vinyl acetate copolymer.

Table 81 Solubility, osmotic pressure difference between dissolution mediums and saturated component of core tablet, C value and lag time from curve fitting with KGT3 equation and release rate (K) and lag time from curve fitting with first order equation of drug release from tablet coated with CA M45 film after moist heat treatment at 60°C for 48 hrs (n=3)

Dissolution fluid	Solubility (mg/ml)	Osmotic pressure difference(atm)	C (E+4)[a]	Lag time (min)[a]	K[b]	Lag time (min)[b]
Deionized water	272.73±1.06	88.95	4.8153+0.5908	57.08+1.00	4.2584+0.5693	17.99+9.53
HCl solution pH 1.2	224.40±0.80	83.51	22.3700+4.5024	61.94+4.28	4.2270+0.3224	77.38+3.81
Phosphate buffer pH 6.8	198.11±4.68	80.73	3.9358+0.5803	191.85+4.59	1.8539+0.0547	167.59+7.37
1.22 m Glucose Solution	143.86±1.38	60.15	3.3725+0.0972	88.12+29.96	1.7276+0.1522	68.52±18.13
2.06 m Glucose Solution	88.18±0.27	45.81	2.1348+0.0997	157.80+31.91	1.0659+0.0914	131.12+31.12
3.13 m Glucose Solution	49.69±0.16	24.26	2.0027+0.1734	324.32+18.45	0.6820+0.0357	343.20+27.98

[a] from curve fitting with KGT3 equation and [b] from curve fitting with first order equation

Table 82 Solubility, osmotic pressure difference between dissolution mediums and saturated component of core tablet, C value and lag time from curve fitting with KGT3 equation and release rate (K) and lag time from curve fitting with first order equation of drug release from tablet coated with CA M45 Cas15 film after moist heat treatment at 60°C for 24 hrs (n=3)

Dissolution fluid	Solubility (mg/ml)	Osmotic pressure difference(atm)	C (E+4)[a]	Lag time (min)[a]	K[b]	Lag time (min)[b]
Deionized water	272.73±1.06	88.95	4.4112+1.0365	74.82+5.76	3.5286+0.7534	14.18+24.34
HCl solution pH1.2	224.40±0.80	83.51	20.9254+8.2774	71.39+9.03	4.3086+0.6623	83.91+10.25
Phosphate buffer pH 6.8	198.11±4.68	80.73	2.2558+0.1217	268.91+45.32	1.4856+0.1798	204.02+28.79
1.22 m Glucose Solution	143.86±1.38	60.15	3.3540+0.0920	125.52+7.42	1.5532+0.0608	107.51+3.68
2.06 m Glucose Solution	88.18±0.27	45.81	2.0409+0.1222	268.33+12.79	0.8246+0.0210	223.83+17.54
3.13 m Glucose Solution	49.69±0.16	24.26	1.9368+0.7907	504.27+44.57	0.5915+0.0223	472.99+54.90

[a] from curve fitting with KGT3 equation and [b] from curve fitting with first order equation

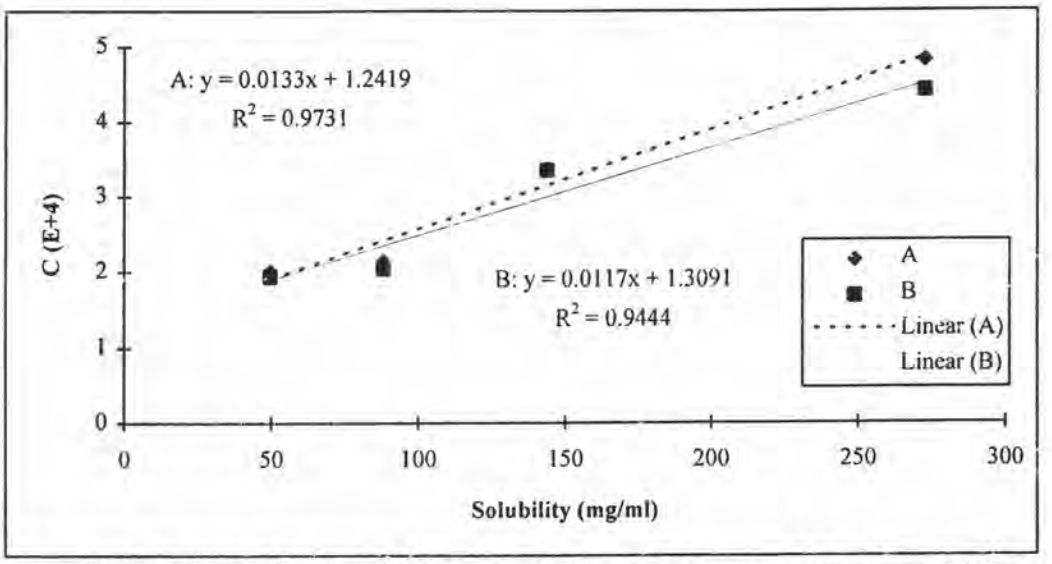


Figure 241 Relationship between drug solubility and C value from curve fitting with KGT3 equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

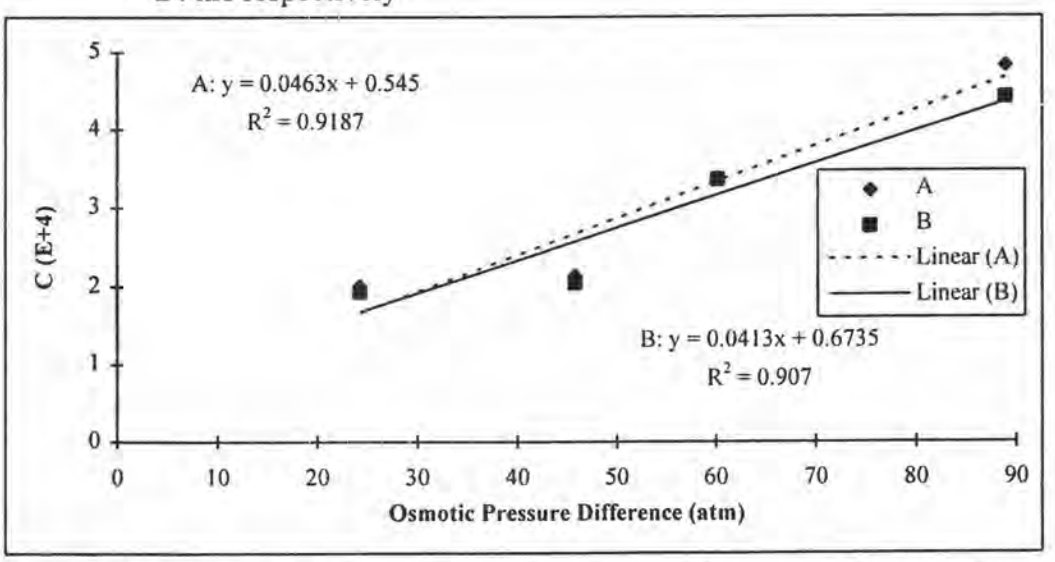


Figure 242 Relationship between osmotic pressure difference and C value from curve fitting with KGT3 equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

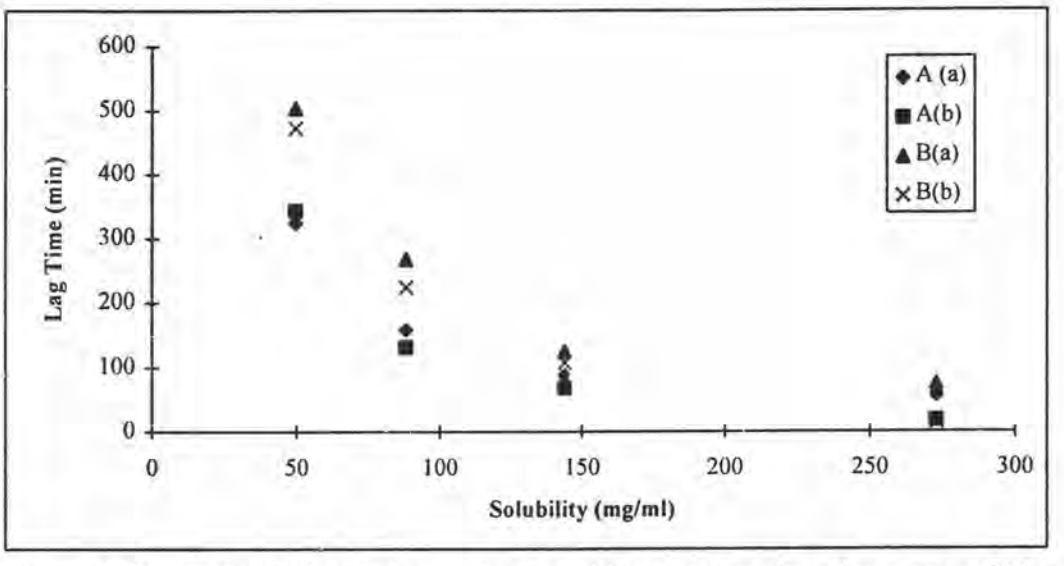


Figure 243 Relationship between drug solubility and lag time from curve fitting with KGT3 (a) and first order (b) equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

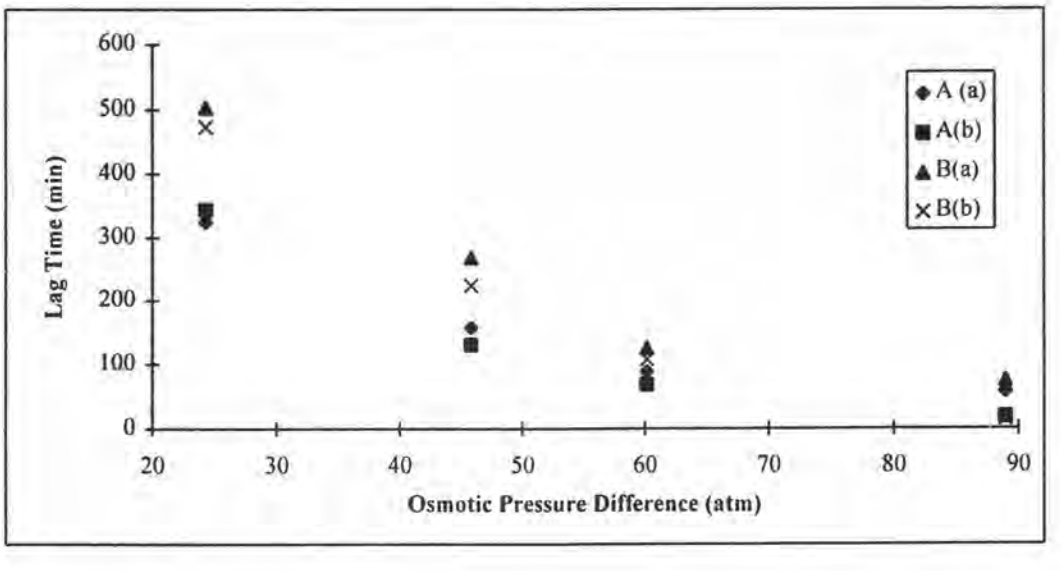


Figure 244 Relationship between osmotic pressure difference and lag time from curve fitting with KGT3 (a) and first order (b) equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

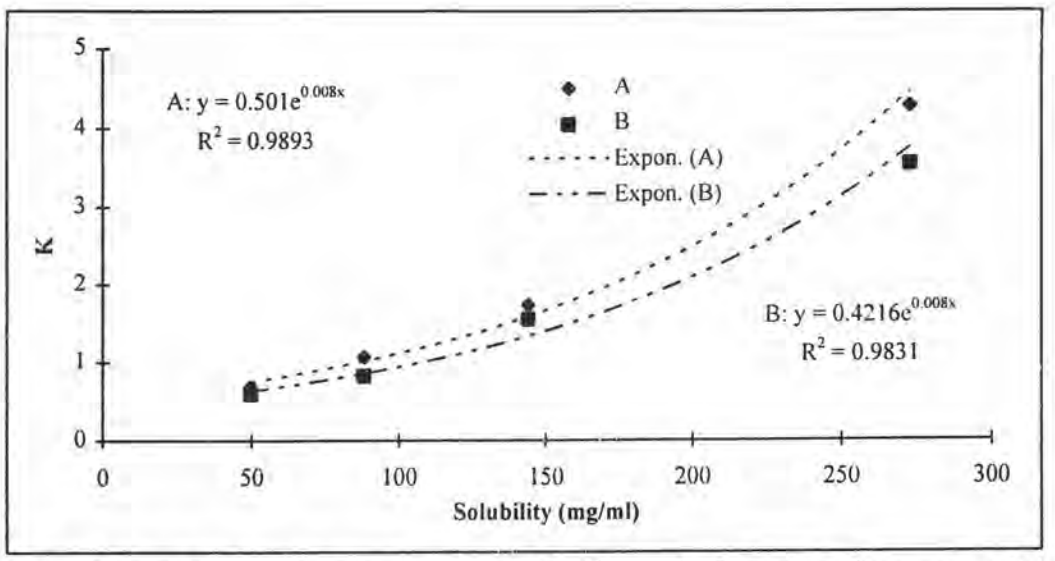


Figure 245 Relationship between drug solubility and release rate from curve fitting with first order equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

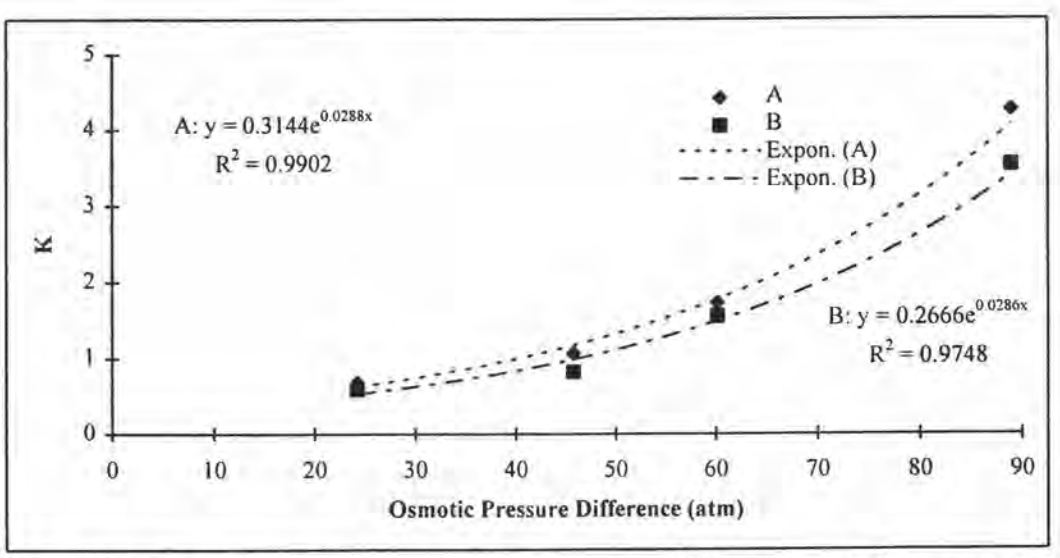


Figure 246 Relationship between osmotic pressure difference and release rate from curve fitting with first order equation of drug release from tablets coated with CA M45 (A) and CA M45 Cas15 (B) film after moist heat treatment at 60°C for 48 and 24 hrs respectively

However the similar mechanism was also responsible for drug permeation through most of the swollen hydrogel membranes (Frohoff-Hulsmann, Schmitz and Lippold, 1999). The latter was obviously found especially in case of the drug release from untreated tablet coated with CA M45 Cas15, CA M45 Cas15 U5 or CA M45 Cas15 HPMC45 films in pH change system. The remained charged groups in cationic network were ionized under acid condition and the resulting repulsion between groups caused the network to expand and thus its permeability was enhanced. It could suggest that additional factors that influenced the drug release from these coated tablets as followed. First, there was the transport of drug through a network of capillaries filled with dissolution fluid created by the leaching out from the film of a water soluble component. And there was the transport of drug through a hydrated network which was due to the ionization nature of film coat. The rate of drug permeation through solution-diffusion membrane was directly proportional to the drug diffusion coefficient in the polymer, Df, and the polymer/solution partition coefficient, k. Unfortunately, the A value was the complex term $(D (H_O-R_O)/Df k H_O)$ which the ratio D/Df k was difficult to predict the drug permeation characteristic since D and Df had the parallel tendency to decrease or increase their values.

Practically, reservoir type delivery system sometimes it may not maintain a saturated reservoir due to either the high drug solubility in the permeating solvent or the limited loading capability in the device. Thus it also found that the release of propranolol HCl which was high water soluble drug through insoluble chitosan film did not follow the zero order kinetic. Even in case where the drug inside device was saturate and therefore, constant thermodynamic activity was established initially, the continued release of drug or the dilution by osmotic water influx could lead to a continuous drop in concentration as time proceeded. This abovementioned was also corresponding to the result of an increasing the coefficient of determination from curve fitting with zero order kinetic when decreasing the osmotic water influx by increasing the osmotic pressure of dissolution medium. KGT3 equation developed from the assumption that there was the drug concentration gradient between the core surface and somewhere in the space between undissolved core tablet and the film coat, thus it was rather successfully fitted by the release profiles. As well as KGT3, the first order expression was also provided the satisfy fit with release data. This was due to concentration dependent release characteristic of drug from these film coated tablets.

Conclusions

Chitosan solutions prepared by dissolving 5% chitosan in acetic, citric, formic, glycolic, lactic, malic and propionic acid solutions at mole ratio acid: glucosamine unit 1.2:1 were not too acidulous and the viscosity was rather stable. These solutions could be fabricated to transparent film by solvent evaporation. After moist heat treatment at 60°C 75%RH, % water sorption and dissolution of chitosan films were decreased more extensively than dry heat at 60°C or 130°C. Both % water sorption and dissolution were pH dependent. These values were greater in HCl buffer pH 1.2 than in deionized water and phosphate buffer pH 6.8 respectively. The longer moist heat treatment or longer of acyl group or lower amount of hydroxyl groups in acid molecule could decrease %water sorption and dissolution. These values after moist heat treatment of chitosan acetate and

chitosan propionate films were relatively low whereas those of chitosan citrate and chitosan malate films were quite high. There was the evidence of amide formation and esterification of chitosan film after moist heat treatment and dry heat treatment at 130°C respectively from FT-IR and solid state ^{13}C NMR studies. The decrease of hydrophilic groups after amidation and esterification led to the decrease in % water sorption and dissolution of heat treated film and related to the alteration to insoluble form of chitosan films. The increase in crystallinity of film such as chitosan lactate and chitosan glycolate films after moist heat treatment related to the decrease in % water sorption and dissolution. No presence of the anhydrous polymorph in heat treated chiosan films, therefore the alteration of hydrate form to anhydrous form was not the cause of insoluble film formation after heat treatment. The evidence from DSC study implied that there was the crosslink between chitosan chain with two ester bonds on the same acid of polyfunctional acid at high temperature. This was corresponded to the evidence of esterification after dry heat treatment at 130°C from FT-IR study.

Glycerin and propylene glycol could be miscible in chitosan films whereas PEG 400, 1450, 600, triacetin and triethyl citrate could not. An introduction of glycerin and propylene glycol promoted ductile fracture and improved mechanical properties of chitosan films. Chitosan cirate and chitosan malate films plasticized with propylene glycol 25% still remained high stress at break and slightly decreased in Young's modulus and slightly increased in maximum percent strain, so these plasticized cast films exhibited the high toughness. Due to charge interaction, incompatibility between anionic water soluble dyes (sunset yellow, tartrazine, erythrosine and ponceau 4R) and chitosan solution was appeared. Good compatibility between chitosan solution and brilliant blue or green FS was owing to the presence of positive charge on structure, high water solubility and high amount of SO_3H group of brilliant blue. Talcum and titanium dioxide were utilized as pigment in chitosan citrate film plasticized with propylene glycol 25%. Low loading of these pigments at 10%, they enhanced mechanical properties of plasticized chitosan citrate film. The lowering mechanical properties of plasticized chitosan citrate film after loading higher amount of titanium dioxide was more obvious than that of talcum. Talcum also decreased the moisture sorption of plasticized chitosan citrate film more obviously than titanium dioxide.

Coated tablets using chitosan as film former were prepared by pan-spraying method which was unsophisticated process and without the utilization of organic solvent. No presence of color migration in plasticized chitosan citrate film coat should be come from the partial ionic bond between chitosan and dye molecules. Film adhesion onto core tablet of chitosan citrate was greater than chitosan malate and chitosan acetate films respectively. The greater film adhesion was evident as the hydrophilic plasticizers, glycerin and propylene glycol, were added into chitosan citrate film. An addition of high level of titanium dioxide diminished the peeling strength and vice versa in case of talcum. The hardness of coated tablets depended on strength and toughness of utilized film, therefore the hardness of tablets coated with chitosan acetate were higher than that coated with chitosan malate and chitosan citrate respectively and an enhancement of coating level enhanced hardness of chitosan film coated tablets. An incorporation of magnesium stearate, talcum and titanium dioxide caused discontinuities in polymeric network and thus might reduced the strength of chitosan acetate film and thereafter the hardness of

tablets. An addition of plasticizers into chitosan acetate film containing magnesium stearate also decreased the hardness of film coated tablet.

Because of the gel forming properties of chitosan film, the greater amount of film coat resulted in longer disintegration time in deionized water. An incorporation of pigment caused the discontinuities in polymeric network and thus the disintegration time of tablets coated with pigmented film was shorten. From FT-IR, powder X-ray diffraction and DSC studies, no interaction between chitosan citrate and propylene glycol, brilliant blue, talcum or titanium dioxide was appeared. Whereas there was the evidence of the interaction between stearates which were liberated from magnesium stearate in acidic environment and protonated amino groups on chitosan in fabricated film coat with further formed amide linkage after moist heat treatment.

The release of propranolol HCl from tablets coated with chitosan citrate and chitosan malate films in basic medium apparently delayed than that in acid medium due to the unprotonation and protonation nature of chitosan in basic and acid environment respectively. The drug release from tablets coated with chitosan citrate film was less pH dependent than coated with chitosan malate film. Because of fast dissolution of chitosan citrate in acid medium, no obvious difference in release characteristic of coated tablets by varying amount of propylene glycol loading in chitosan citrate film was evident. However the more decreased molecular order and probably enhancement of chain mobility in chitosan citrate by more addition of propylene glycol, the faster was the drug release in basic medium. Because of the electrostatic charge interaction between anionic groups of brilliant blue or green FS and protonated amino groups on chitosan especially in acid medium therefore the slight retardation of drug release was occurred, but the anionic dye molecules could be readily ionized and could promote the film hydration, thus the drug release was faster in basic medium. Discontinuity of chitosan citrate film due to filled pigment enhanced drug release in acidic medium. In contrast, in basic medium while chitosan was likely to be insoluble, the filled pigments acted as barrier and retarded water penetration and thus the drug release was slower. However the high amount of talcum could promote discontinuity in chitosan citrate film and thus there was the disruption of barrier effect of chitosan and the drug release was faster.

The retardation of drug release of tablet coated with chitosan citrate films after exposed to accelerated condition was remarkably evident. While the drug release of coated tablets after kept at room temperature for one year were similar to those of freshly prepared and all of them conformed to the monograph of USP XXIII. Thus tablets coated with chitosan citrate or chitosan malate films were sensitive to the accelerated condition whereas aging at room temperature did not affect the drug release of these coated tablets containing or without film additives. Owing to the soluble and rapidly disintegrating properties, good adhesion property, and long term aging stability of chitosan citrate film coats seemed to be potentially utilized this material for finishing, color identification or stability improvement. Brilliant blue which less affected to release behavior of chitosan citrate than green FS could provide enough tinctorial strength for coloring. Addition of propylene glycol 25% and low amount of talcum could improve mechanical properties and provide the desired glossiness and talcum could potentially reduce the moisture sorption of film coat.

Because of brittleness of unplasticized and plasticized chitosan acetate and chitosan propionate films after dry or moist heat treatment, these coated tablets could not extend drug release. By visual observation drug dissolution test, it clearly demonstrated that film coat after moist heat treatment of chitosan propionate was more brittle and yellowish than that of chitosan acetate. Thus other substances were incorporated into chitosan acetate film so as to modify drug release for fabricating sustainable release coated tablet. Moist heat treatment at 60°C was more effective than dry heat at 60°C to prolong drug release of tablets coated with chitosan acetate film containing magnesium stearate, talcum or titanium dioxide. An incorporation of magnesium stearate was more effective than talcum and titanium dioxide to prolong drug release. An addition of castor oil into chitosan acetate film containing magnesium stearate was more effective than that of diethyl phthalate, triacetin and propylene glycol to prolong drug release. This evidence might be due to the efficiency of rather long molecule of castor oil to penetrate through chitosan and stearate chains. Long or higher temperature of moist heat treatment greater prolonged drug release due to the more extensive promotion of amide formation. An amide formation changed the film to insoluble form and this acted as controlled membrane for drug release. There was relationship between osmotic pressure of dissolution fluid or drug solubility and drug release rate or lag time. And in order to shorten lag time of drug release, thus hydrophilic substances, urea and HPMC were added into the chitosan acetate film containing magnesium stearate and castor oil. Apart from the ability to shorten the lag time, an incorporation of urea and HPMC also promoted the drug release nearly up to 100% and urea was more effective than HPMC. The addition of urea at concentration of 5% was suitable to shorten lag time and prolong drug release conformed the monograph USP XXIII. Good stability of this coated tablet after ageing for one year or after exposure accelerated condition was evident.

The mathematical model, KGT2, was developed for the drug release from soluble film coated preparation which the drug was in core material. This model expression was applicable for the drug release from aqueous soluble chitosan film coated tablets. The coefficient of determination was utilized as statistical parameter to indicate the goodness of curve fitting. Because of the protonation and unprotonation nature of chitosan in acid and alkaline environment respectively, the film dissolution time and rate in acid dissolution fluid was faster than that in alkaline medium. From model prediction, the drug release was occurred during film dissolution by the permeating fluid entered to dissolve the encapsulated drug and then the drug molecule gradually diffused through the fluid around remained core tablet and thereafter diffussion and partition through remained film coat into the external dissolution medium. Even though this development model did not predict the result exactly, it was the superior model since the film dissolution time and rate, and also the release rate from remained core tablet after film dissolved could be obtained.

KGT3 equation was sequentially obtained from KGT1 by assuming that the film was changed to insoluble form by moist heat treatment. Most of sustained drug release from coated tablet after moist heat treatment could successfully fit with this equation and first order equation. From model prediction, the drug release through these film coated tablets appeared by dissolved drug molecule first diffusion through space between undissolved core tablet and film coat and dissolving in the film coat and transport through a network of capillaries filled with dissolution fluid by diffusion down a

chemical potential gradient and also by osmotic pumping effect across insoluble film or rather swollen film coat to the external dissolution fluid. The release of drug from these coated tablets appeared to be diffusion controlled accompanied by osmotic effect. The drug release was also pH dependent due to the protonation nature of remained chitosan in acid medium. KGT3 equation developed from the assumption that there was the drug concentration gradient between the core surface and somewhere in the space between undissolved core tablet and film coat, thus it was rather successful fitted by the release profiles. As well as KGT3, curve fitting with first order equation also provided the satisfy fit. This was due to concentration dependent release characteristic of drug release from these film coated tablets.

This investigation indicated that the utilization of chitosan as film former to achieve fast and extended drug release coated tablets was enabled. The properties of chitosan films depended on acid type, film additives and condition of film treatment. KGT2 and KGT3 were developed and they were applicable for drug release from fast and extended release coated tablet using chitosan as film former. These equations should enable to apply for drug release from coated preparations which other film formers were used.