CHAPTER IV

PREPARATION OF CHITIN WHISKER/PLURONIC THERMAL RESPONSIVE GEL FOR INJECTABLE DRUG DELIVERY SYSTEM

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4.1 Abstract

Pluronic F-127 (PF-127), a triblock copolymer of polyethylene oxide-polypropylene oxide-polyethylene oxide, is a thermal-responsive polymer that can change from sol to gel at an elevated temperature. Regarding to this property, PF-127 has been investigated as a carrier for an injectable drug delivery system. However, the stability of PF-127 gel under the physiological conditions is poor. Chitin whisker, a nanofibrillar form of chitin, with content varying from 0.4 % to 7 %, was added to PF-127 solution at room temperature and then incubated at 37 °C to allow gel formation. The stability of PF-127 gel was evaluated in terms of weight loss. From the result of weight loss, the stability of pluronic gel was increased with increasing the chitin whisker content. The increase in gel stability might be due to the physical interactions between the pluronic micelles and chitin whisker. The release characteristic of various types of dyes and insulin protein, used as the model drug for the chitin whisker-incorporated PF-127 gel having different chitin whisker ratios, was investigated as a function of releasing time for the purpose of drug carrier applications.

Keywords: Pluronic; Chitin whisker; Thermal responsive gel; Injectable drug

4.2 Introduction

Drug administration is an introduction of a drug into an appropriate part of the body during a required period with a specific amount of drug. It is necessary that the drug concentration in the blood is maintained at a level that provides the highest

therapy and the lowest toxicity. There are three main routes of drug administration: topical, oral and parenteral administration. For the topical system, a drug is applied directly to a surface area of the body, which has a limitation to only small drug molecules that are small enough to penetrate through skin. The oral administration refers to a route of drug administration that involves the digestive tract. However, the oral administration has some limitations on poor drug absorption and degradation of drug in acidic environment. In case of the parenteral system, a drug is introduced into the body through the blood circulation which consequently provides an effective therapy.

In recent years, biodegradable polymers, especially natural polymers, have received more attention in biomedical applications. Natural polymers are attractive in this area due to their biocompatibility, biodegradability, and non-toxicity. Furthermore, natural polymers derive from renewable sources which can be obtained in a large supply. Chitin, poly (β-(1-4)-*N*-acetyl-D-glucosamine), is a polysaccharide that has been found in various natural sources such as the shells of crustaceans, the cuticles of insects and the cell wall of fungi (Jayakumar *et* al., 2010). In commercial production of chitin, chitin is mainly prepared from the shells of crustaceans such as crabs and shrimps which are readily available as wastes from seafood industries.

Chitin whisker, or chitin in the form of crystalline nanofibrils, is obtained by acid hydrolysis of chitin. Chitin whisker has been investigated as reinforcement in several materials (Paillet *et* al., 2001). When chitin whisker has been used in composites, the improvement of the mechanical properties (Sriupayo *et* al., 2005) and dimensional stability of the composites (Wongpanit *et* al., 2007) have been reported.

Pluronic or Poloxamer is a triblock copolymer of polyethylene oxide-polypropylene oxide-polyethylene oxide. Pluronic is commercially available in series with the difference in molecular weight. Pluronic F127 has a molecular weight of 11,500, 70-79% of which is accounted for by the hydrophilic ethylene oxide portion. Pluronic F127 is a thermo-responsive polymer that changes from sol to gel at an elevated temperature. According to this property, pluronic F127 has been investigated as a carrier for injectable drug delivery system. In addition, pluronic F127 in aqueous solutions exhibits reversible thermal gelation at a concentration

between 20 and 30% (w/w). The thermo-responsive behavior of pluronic was hypothesized to be caused by entropically driven hydrophobic interactions between polypropylene blocks of pluronic chains. When the temperature of an aqueous solution of pluronic F127 is increased, the copolymer molecules aggregate into spherical micelles, which contain a dehydrated polypropylene oxide core and an outer shell of hydrated polyethylene oxide. The micelles of pluronic F127 in an aqueous environment have been shown to be suitable for the incorporation of both hydrophilic and hydrophobic drugs and to prolong drug release.

In this study, chitin whisker-incorporate pluronic F127 composite gel with different chitin whisker content was prepared in order to obtain thermal-responsive gel for being used as a carrier for injectable drug delivery system. The release characteristic of chitin whisker-incorporated pluronic F127 composite gel was investigated by using cationic dye, anionic dye and insulin as model drugs. The effects of chitin whisker content, releasing time, initial dye concentration, and type of dye on the releasing behavior of model drugs was determined. Moreover, the effect of chitin whisker on the gel stability was also evaluated.

4.3 Experiment

4.3.1 Materials and chemicals

Chitin whisker was prepared from the shells of *Metapenaeus dobsoni* shrimp, which were kindly provided by Surapon Foods Public Co., Ltd. (Thailand). Analytical grade hydrochloric acid (HCl) and sodium hydroxide (NaOH) pellets were purchased from RCI Labscan Limited (Thailand). Pluronic F-127 and phosphate-buffered saline (PBS) were purchased from Sigma Aldrich and dialysis tube for drug release was purchased from Spectrum Laboratories (spectra), which has a molecular weight cutoff of 3,500 Da. Methylene blue C.I. 52015 (UNILAB), methyl orange C.I. 13025 (LABCHEM) and insulin were used as the model compounds.

4.3.2 Preparation of chitin

Chitin was prepared from shrimp shell by decalcification and deproteinization to remove calcium carbonate and protein, respectively. These

processes were carried out according to the procedure described by Shimahara and Takigushi, (1988). To prepare chitin, shrimp shells were first cleaned and dried under sunlight for a few days. Then, chitin was ground into small pieces. 1 kg of dried shrimp shells was immersed in 10 liters of a 1 N HCl solution with occasional stirring at room temperature for 2 days. The acidic solution was changed daily. The decalcified shrimp shells were subsequently neutralized by distilled water and dried at 60 °C for 48 hours. The decalcified shrimp shells were further deproteinized in a 4 % w/v NaOH solution at a ratio of NaOH solution to shrimp shells of 10:1 with continuous stirring at 80 °C for 4 hours. The obtained chitin was filtered, neutralized by distilled water, and dried at 60 °C in a convective oven for 24 hours.

4.3.3 Preparation of chitin whisker (CTW) suspension

Chitin whisker suspension was prepared by acid hydrolysis based on the method of Dufresne *et* al., (2001, 2002, 2003). Chitin flakes were hydrolyzed with 3N HCl, which the ratio of chitin to HCl was 1 g of chitin to 30 ml of HCl, under vigorous stirring at 104°C for 6 hours. The suspension was later diluted with distilled water, followed by centrifugation at 10,000 rpm for 10 minutes. This process was repeated for three times to remove HCl. Afterward, the suspension was dialyzed in distilled water until neutral. The dispersion of chitin whiskers in the suspension was accomplished by ultrasonication for 10 minutes. The suspension was stored in a refrigerator before use.

4.3.4 Preparation of pluronic solution and pluronic/chitin whisker composite gel

Pluronic solution was prepared by Schmolka's cold method (Schmolka, 1972). Briefly, an appropriate amount of the pluronic copolymer was slowly added into cold distilled water with constant agitation using magnetic stirrer. After that the solution was kept in a refrigerator for at least 24 hours to ensure complete dissolution. Then the pluronic solution was mixed with chitin whisker suspension by varying the weight ratio of chitin whisker to pluronic. The pluronic/chitin whisker suspension was incubated at 37 °C to induce gel formation.

4.3.5 Characterization of pluronic/CTW composite gel

Chemical structures of chitin and chitin whisker were determined by FTIR. The morphology of CTW was observed by TEM. The CTW suspension were dilute with distilled water into the concentration at 0.006 %w/v. The samples were prepared by air-drying the particles onto a carbon-coated copper grid and air-dried. The morphology of composite gel was observed by SEM. Sample solutions were dropped onto foil, followed by drying in convection oven. After that, dry samples were placed onto stubs, coated with platinum using a JEOL JFC-1100 sputtering device. For the stability of composite gel, The samples were then dried in convection oven and measured the weight remaining after immersion in PBS solution pH 7.4 at 37 °C. The gel stability of samples in wet state was also evaluated in term of weight remaining by the following equations:

$$\text{Weight remaining (\%)} = 100 - \{[\frac{(W_0 - W_t)}{W_0}] \times 100\} \qquad (1)$$

where W_0 is original dry weight and W_t is the weight of the dry gel after incubation for a given time period (Nsereko and Amiji, 2002).

4.3.6 Preparation of dye solutions and evaluation of model drug release characteristics

The dyes used in this study were methylene blue, a cationic dye, and methyl orange, an anionic dye. The dye stock solutions were prepared by dissolving dyes in distilled water to the concentration of 1000 mg/l. Consequently, the dye stock was diluted to the desired initial dye concentrations. The pluronic/chitin whisker composite gel was added 0.5 ml of dye solutions at low temperature to prepare the sample. The *in vitro* release studies were carried out in 100 ml of phosphate buffer saline (PBS) solution pH 7.4 at 37 °C. A 1 ml of release media was taken out at a specific time interval and replaced with the same volume of fresh media. The concentrations of dye solutions were determined by the UV-VIS Spectrophotometer. A system having two separated compartments was used to study the release of drug from the gels as shown in Figure 4.1, (Paavola *et* al., 1997). In this system, cellulose membrane, with the molecular weight cut off equal to 3500 Da, was used to separate

the gel in the donor compartment from the PBS solution. The area of the membrane was 4.90 cm^2 and the PBS solution in the acceptor compartment was stirred with a magnetic bar at 250 rpm. The release behaviors of dyes from dye solution, neat pluronic gel, and pluronic/chitin whisker composite gels containing in the donor compartment were evaluated. The solutions in the acceptor compartment were taken to determine the released dye concentrations at the specific time interval until 72 hours.

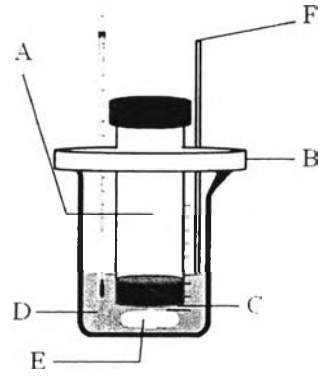

Figure 4.1 Experimental set-up for the dye release measurement. A : Glass cylinder (donor compartment) ; B : Plexiglass cover ; C : Membrane ; D : PBS solution (acceptor compartment) ; E : Stirring magnetic ; F : Sampling port.

4.4 Results and discussion

4.4.1 Characterization of chitin whisker

4.4.1.1 Yields Production

In general, chitin from animals occurs associated with other elements, such as lipids, calcium carbonate, proteins and pigments so the shrimp shells were treated with chemicals to extract chitin. The shrimp shells were first cleaned and treated with HCl and NaOH to remove calcium and proteins, respectively. Demineralization occurs according to the following reaction (Belgacem *et* al., 2008):

$$CaCO_3 + HCl \rightarrow CO_2 + CaCl_2 + H_2O$$

Afterwards, chitin was crushed to be the small flakes for use in chitin whisker preparation. The yields of chitin and chitin whisker production was represented in Table 4.1.

Table 4.1 Yields of chitin and chitin whisker production

Substances	Dry Weight (g)
Shrimp shells	100
Demineralized shrimp shells	45.00
Chitin	30.83
Chitin whisker	15.04

4.4.1.2 Characterization of chitin and chitin whisker

FT-IR spectra of chitin and chitin whisker are depicted in Figure 4.2. The amide I bands at 1655 cm^{-1} (sometimes together with the amide I band at 1630 cm^{-1}) or the amide II band at 1560 cm^{-1} are used as the characteristic band(s) of *N*-acetylation. In general, the characteristic bands of chitin are the OH stretching band at 3450 cm^{-1}, the C-H stretching band at 2870–2880 cm^{-1}, the $-CH_2$ bending centered at 1420 cm^{-1}, the amide III band at 1315–1320 cm^{-1}, the anti-symmetric stretching of the C-O-C bridge at around 1160 cm^{-1}, the skeletal vibrations involving the C-O-C stretching bands at 1070 or 1030 cm^{-1} and the band at 897 cm^{-1} (C-O-C bridge as well as glycosidic linkage). In Figure 2, the peak at 1540 cm^{-1}corresponding to protein could not be seen, indicating the effective removal of protein from chitin (Brugnerotto *et* al., 2001). In addition, the characteristic peaks of amide I (–CONH–) were observed at 1660 and 1621 cm^{-1} (amide I bands; singly H-bonded and doubly H-bonded, respectively) and peak of amide II was at 1558 cm^{-1}. The degree of deacetylation (%DD) of chitin and chitin whisker were determined by following the method of Sannan *et* al., 1977 which estimates %DD from the ratio of the absorbance of amide II band at 1550 cm^{-1} and C-H band at 2878 cm^{-1}. In this study, %DD of chitin and chitin whisker were found to be 34 % and 38 %, respectively.

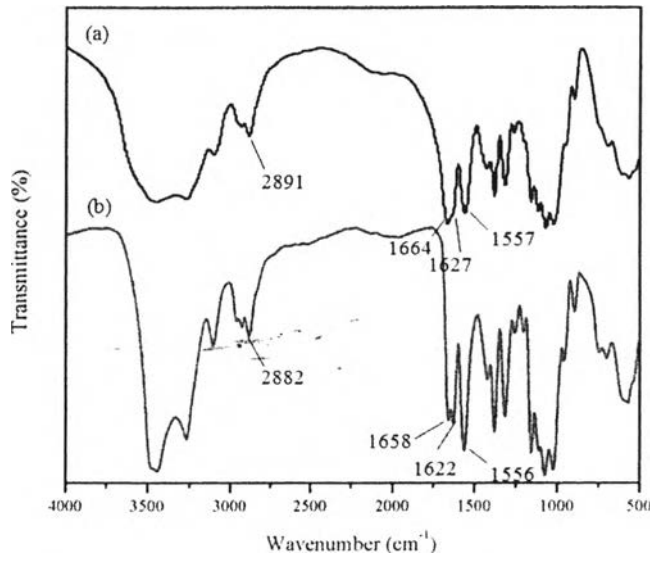

Figure 4.2 FT-IR spectra of (a) chitin and (b) chitin whisker.

TEM image of chitin whisker is shown in Figure 4.3. It can be seen that the individual chitin whisker has a rod-shaped structure. The protonation of the amino groups ($-NH_3^+$) in chitin after acid hydrolysis using hydrochloric acid resulted in positive charges appearing at the surfaces of chitin whisker. Hence, the repulsion forces of these cationic charges led to the stable colloidal suspension of chitin whisker in water (Marchessault *et* al., 1959). The chloride ions (Cl^-) from HCl did not play important role on charges because chloride ions were easily eliminated by washing with distilled water for several times (Akira *et* al., 1999).

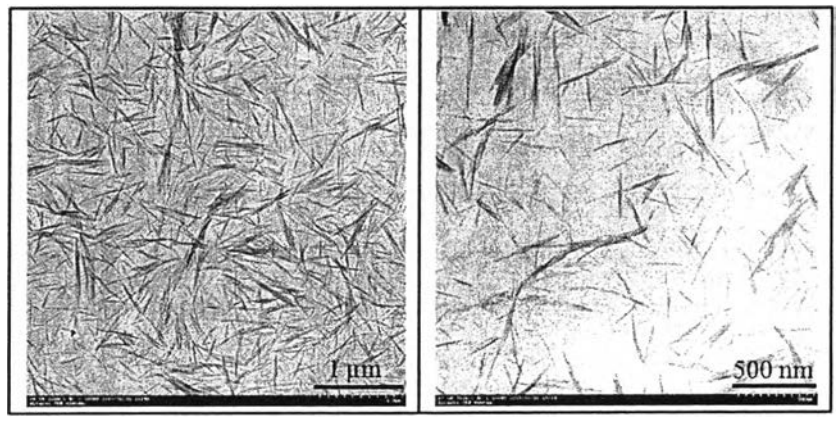

Figure 4.3 TEM images of a dilute chitin whisker suspension 0.006 %w/v at the magnification of (a) 4000X and (b) 7000X.

Figure 4.4 is shows the distribution of the histrogram graph of chitin whisker from 115 representatives of chitin whisker fibrils. The length of chitin whiskers ranged from 300 to 730 nm while the width ranged from 20 to 70 nm. The average length and width of chitin whiskers were about 468 and 39 nm, respectively. The average length to width ratio (L/d) of chitin whisker was about 12.

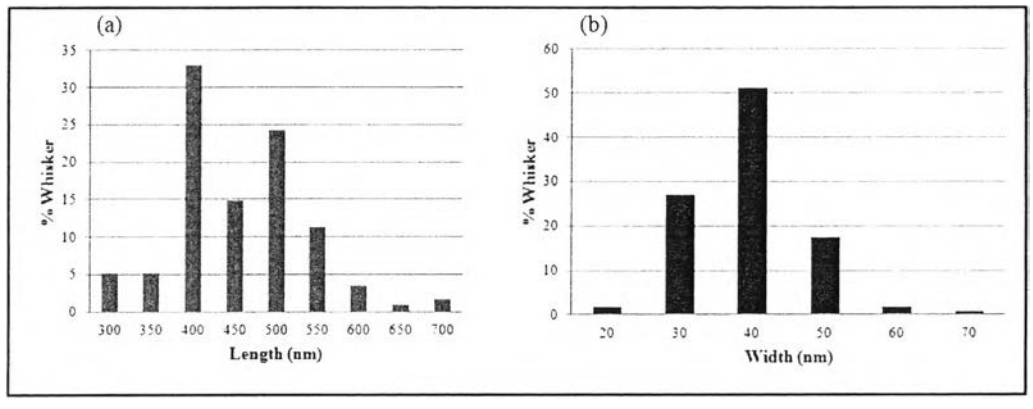

Figure 4.4 Histrogram showing the length and the width distribution of chitin whiskers.

4.4.2 Characterization of pluronic solution

The property of pluronic solution study in term of sol-gel phase transition in the difference of temperature. The pluronic in water was observed by vial tilting method as shown in Figure 4.5. Each of pluronic solution was varied with different concentrations. The gel state was determined by inverting the vial. If the solution did not flow in 1 min, it was called gel phase. The transparent flow liquid was called sol phase. With the increasing in temperature to 37 °C, the solution of 20 and 25 % of pluronic solution change from sol phase at 5 °C to gel phase at 37 °C. The formation of the gel was appeared from the hydrophobic core of polypropylene block is partially dehydrated, causing the micelle to be more rigid and partial entanglement between micelles occur. Finally, the pluronic structure form into 3-dimentional structure of the gel.

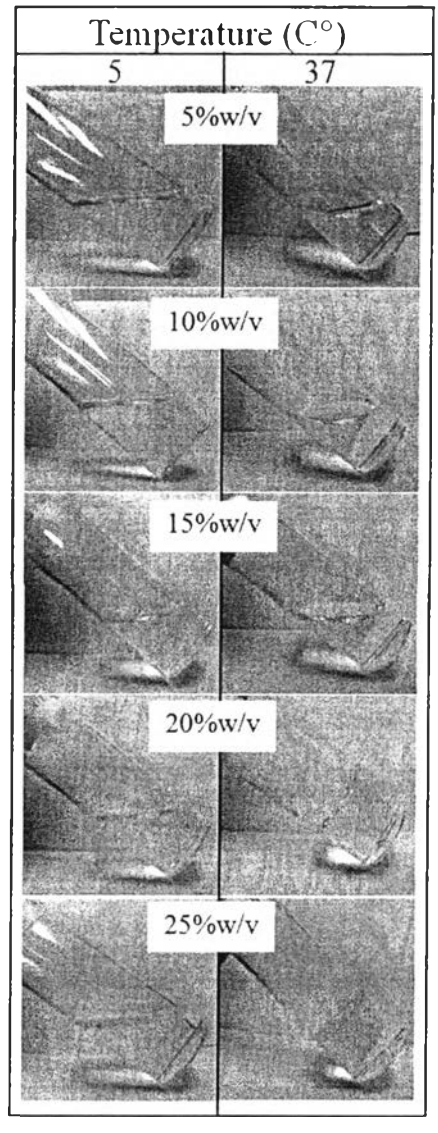

Figure 4.5 The appearance of pluronic solution with the various concentrations after incubated at different temperatures.

4.4.3 Characterization of pluronic/CTW composite gel

For the characterization of the pluronic/CTW composite gel, from Figure 4.6 shows the weight remaining after incubated in PBS solution for 6 hours and 12 hours. The result shows that the weight remaining of composite gel increase when the content of chitin whisker increase. Furthermore, the increasing of weight remaining indicates about the stability of the gel. The stability of the gel increase with the chitin whisker increase due to the reinforcement of the chitin whisker in the

composite gel and the physical interactions between the pluronic micelles and chitin whisker. Moreover, the incubation time increase from 6 hours to 12 hours resulting in the decreasing values of the weight remaining.

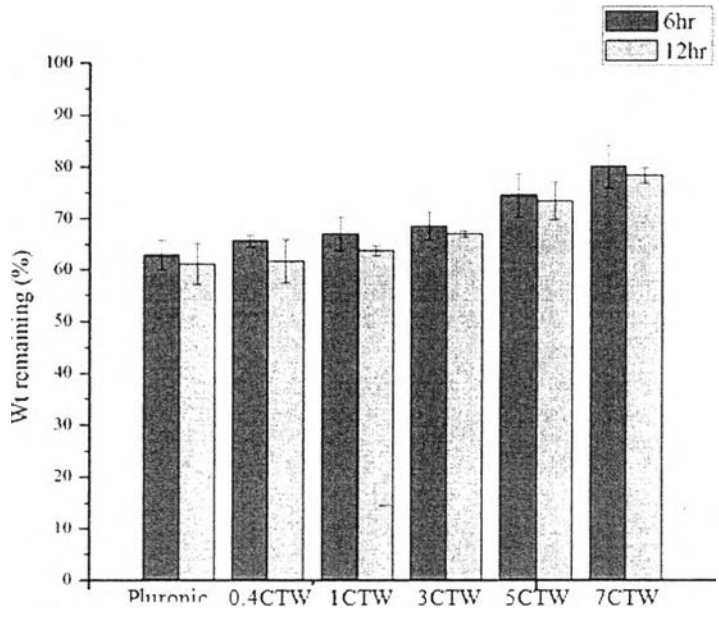

Figure 4.6 The percentage of weight remaining of composite gel after incubated in PBS, 37 °C for 6 hr and 12 hr.

SEM images surface of pluronic/chitin whisker composite gel at different ratios is show in Figure 4.7. The increasing of chitin whisker content also increases the roughness into the surface of composite gel.

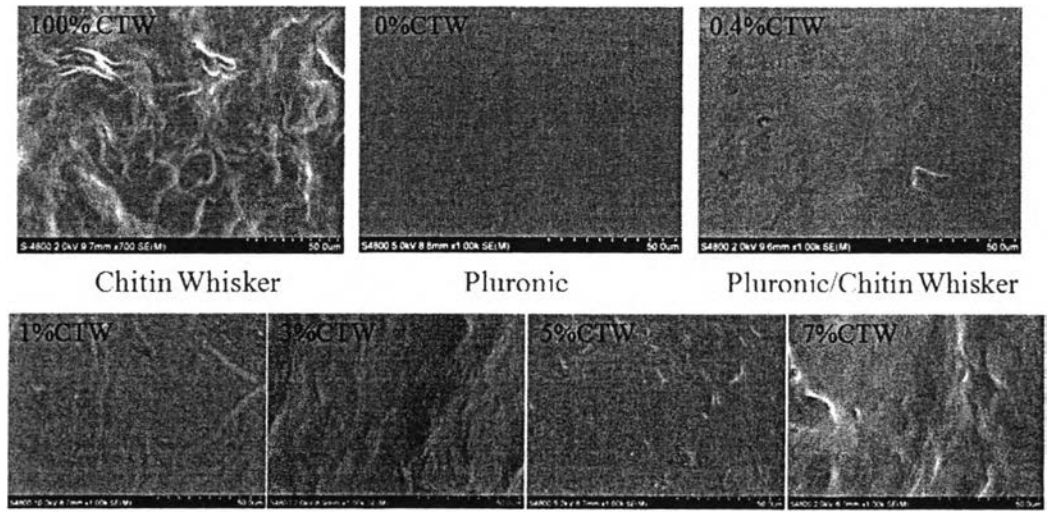

Figure 4.7 SEM images of surface of Pluronic/Chitin Whisker composite gel at different ratios.

From the drug testing of the pluronic/CTW composite gel, show the graph plotting between the cumulative drug release and the releasing time. The comparison of percent cumulative release of pure methylene blue (MB) solution, MB in neat pluronic gel and MB in pluronic/chitin whisker gel with different chitin whisker content varying from 0.4% to 7% is shown in Figure 4.8. It was found that the pure MB solution had the highest release rate due to the burst release of MB and had a cumulative release close to 100 % within 16 hours. Since the neat pluronic gel gradually changed to solution under the studied condition, the percent cumulative release of almost 100% was eventually obtained. The change from gel to solution of the neat pluronic gel occurred due to the diffusion of the buffer solution from the acceptor compartment to the donor compartment resulting in diluting pluronic concentration to lower than the critical value for the gelation of pluronic. Furthermore, the neat pluronic gel had a slower release rate than that of the pure MB solution. This is because of the time required for the diffusion of methylene blue from the pluronic gel to the solution outside. Compared with the neat pluronic gel, the incorporation of chitin whisker into pluronic gel could slow down the release rate of MB. It was found that the percent cumulative release of pluronic/chitin whisker

gel with any chitin whisker content were in the range of 50% to 70% that was much lower than that of the neat pluronic gel. This might be caused by the interaction of MB and chitin whisker, resulting in better gel stability and consequently leading to a lower releasing amount of MB from the pluronic/chitin whisker gel. Moreover, The increasing of chitin whisker contents induces to the increasing of the stability of composite gel. These result is conform to the result of weight remaining. Notice in the lower cumulative release while the chitin whisker increasing. The dye of MB is the representative of cationic drug molecule for study the releasing behavior of the drug. Moreover, In this research had been studied in various types of model drugs. The methyl orange, is the anionic dye, used as the representative of anionic drug.

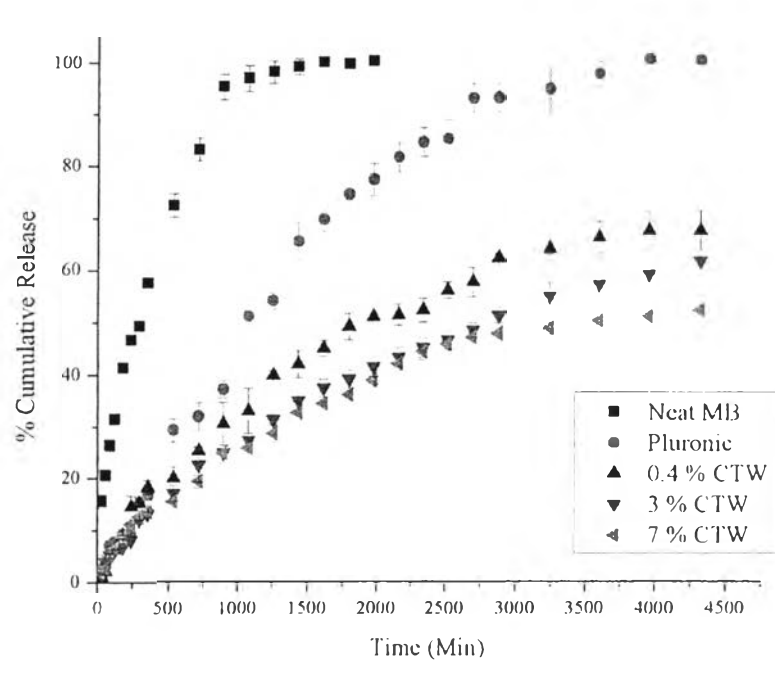

Figure 4.8 The cumulative release of 1000 mg/l of methylene blue solution, methylene blue in neat pluronic and methylene blue in pluronic/chitin whisker composite gel as a function of releasing time and chitin whisker content.

After decrease the initial concentration of MB from 1000 mg/l to 500 mg/l, the cumulative release of lower initial concentration MB (Figure 4.9) shows the higher drug release rate as compared with the higher initial concentration of MB.

Because the more MB molecules in the system, the more interactions of MB with the matrix.

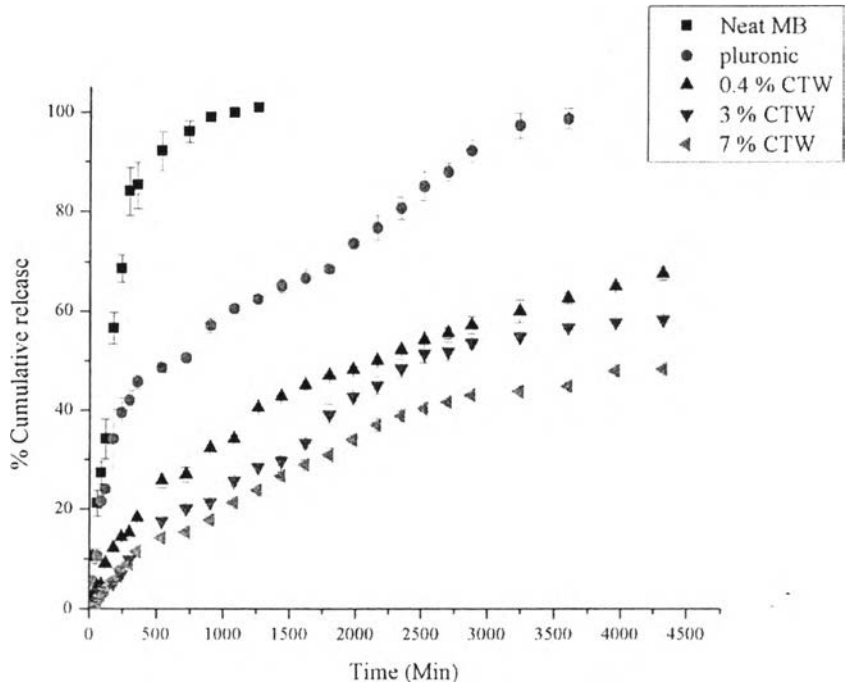

Figure 4.9 The cumulative release of 500 mg/l of methylene blue solution, methylene blue in neat pluronic and methylene blue in pluronic/chitin whisker composite gel as a function of releasing time and chitin whisker content.

From the Figure 4.10, it can be seen that the releasing graph is similar to MB release graph. The pure MO solution had the highest release rate due to the burst release of MO and had a cumulative release close to 100 % within 24 hours. The neat pluronic gel had a slower release rate than the pure MO solution. The incorporation of chitin whisker into pluronic gel could slow down the release rate of MO. It was found that the percent cumulative release of pluronic/chitin whisker gel with any chitin whisker content were in the range of 15% to 25% that was much lower than the neat pluronic gel due to the interaction of MO and chitin whisker and lower than in case of MB release. Chitin whisker present positive charge of amino groups ($-NH_3^+$) on the surface of the crystallites and interact with negative charge of MO molecules more than MB molecules (Positive charge), resulting from the protonation of amino groups (Marchessault *et* al., 1959). The interaction between MB and chitin

whisker is repulsion force and the interaction between MO and chitin whisker is attractive force or ionic interaction from the negative charge and positive charge. By the way, in case of the neat pluronic. The percent cumulative release of MO is lower than MB. It might be the hydrogen bonding from the molecule of MO. MO have 3 oxygen atoms in each molecule. Consequently, the MO molecule had a higher chance to forming hydrogen bonding with pluronic copolymer.

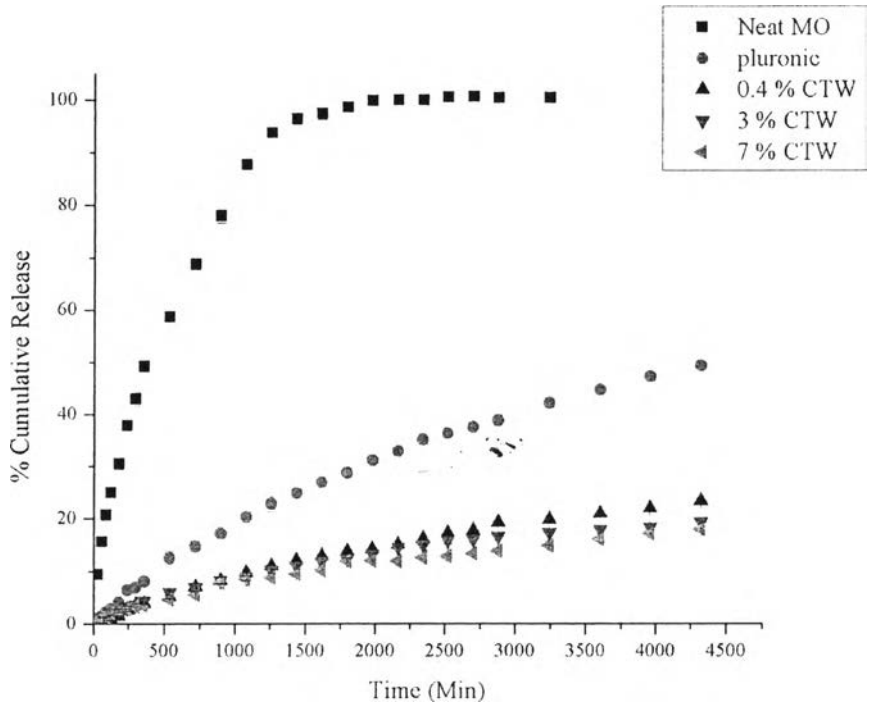

Figure 4.10 The cumulative release of 1000 mg/l of methyl orange solution, methyl orange in neat pluronic and methyl orange in pluronic/chitin whisker composite gel as a function of releasing time and chitin whisker content.

Figure 4.11 shows the cumulative release of MO when reduce the initial concentration of MO into 500 mg/l. The result shows that the release profile had the same trend with 1000 mg/l of initial concentration of MO. The burst release of neat dye, the lower percent cumulative release of MO from the matrix after incorporated with chitin whisker. The more content of chitin whisker from 0.4%, 3% until 7%, respectively, it also prolong release and has a slower releasing rate of dye.

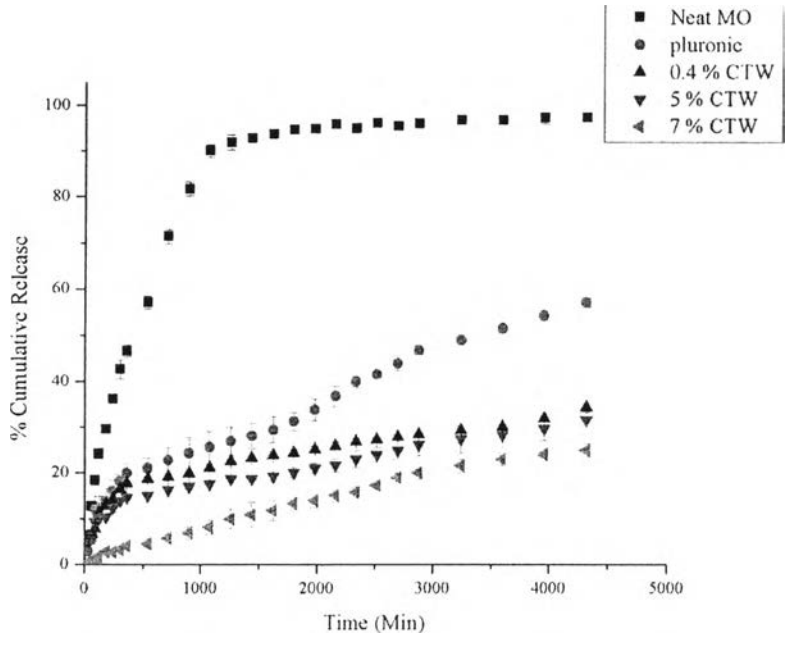

Figure 4.11 The cumulative release of methyl orange solution at 500 mg/l, methyl orange in neat pluronic and methyl orange in pluronic/chitin whisker composite gel as a function of releasing time and chitin whisker content.

From the protein release. Insulin, the drug for the diabetes treatment, as the representative of the protein drug that shows the releasing characteristic in the Figure 4.12. The result shows the cumulative release of neat insulin had a highest drug release rate more than insulin in pluronic solution and the incorporated with chitin whisker had also improve the drug release of insulin as the same as in case of model of dyes release. The percentage of insulin cumulative release had a lower value than the dye system because the molecular weight of insulin has a higher molecular weight more than both of MO and MB. Possibly because of the result of the formation of intermolecular hydrogen bonds between amino group of chitin whisker and the carboxyl group of insulin. Moreover, due to the presence of COO^- on insulin molecules and NH^{3+}on chitin whiskers, the electrostatic interaction between the chitin whiskers and the insulin molecules might be also occur.

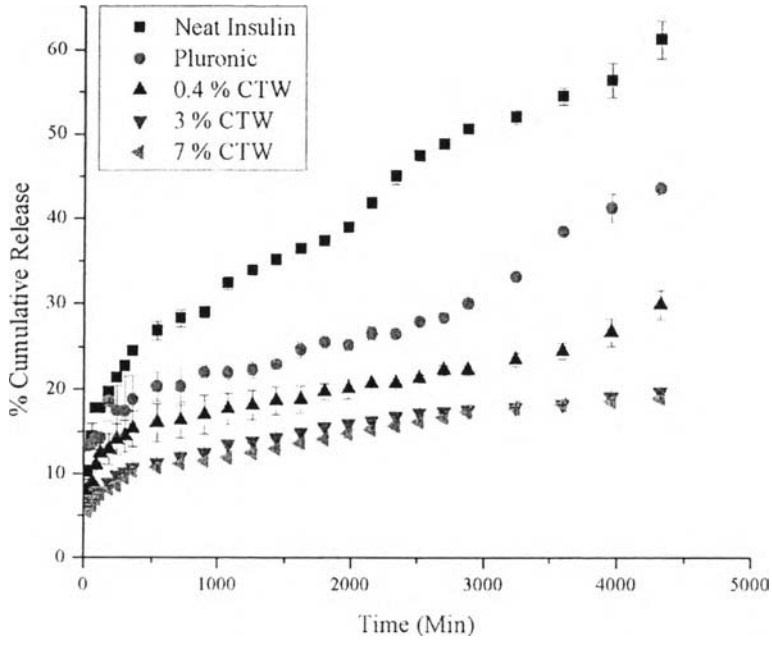

Figure 4.12 The cumulative release of 20 unit/l of insulin in pluronic/chitin whisker composite gel with various chitin whisker contents as a function of releasing time.

The increasing concentration of insulin has a lower percent cumulative release as shown in Figure 4.13. It shows that the higher concentration of insulin had more interaction in the matrix more than the lower concentration. Indicating that the higher concentration of insulin might be occur the interaction between drug molecule and the matrix. From the structure of insulin, both amino groups and carboxyl groups can increase the oppotunities to forming the intermolecular hydrogen bond between insulin and matrix.

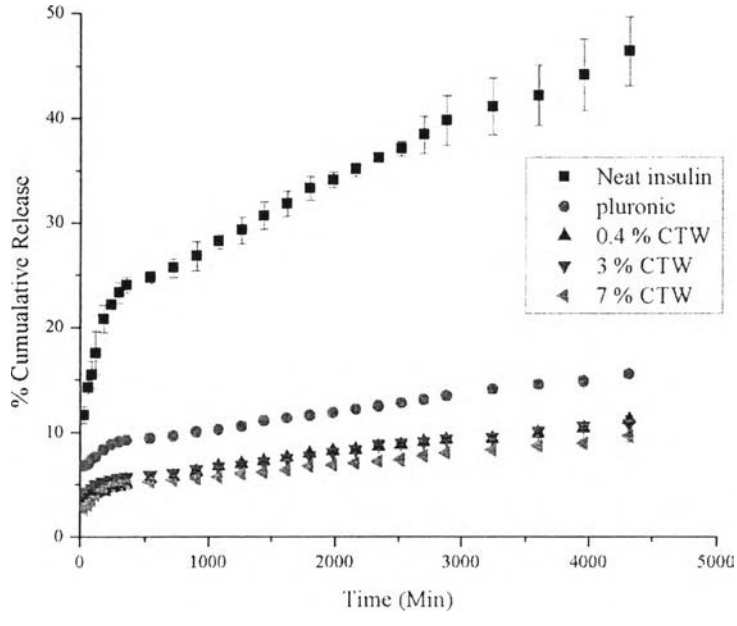

Figure 4.13 The cumulative release of 40 unit/l of Insulin in pluronic/chitin whisker composite gel with various chitin whisker contents as a function of releasing time.

The releasing rate of model drug from the composite gel of pluronic/chitin whisker was determined by linear regression analysis. The zero order rates constant was obtained from the slope of straight line describing the releasing rate which related with the concentration of model drug. As shown in Figure 4.14a, the amount of releasing model drug at various times of MB dye from 30 to 240 min. The cumulative dye release graph show the initial releasing rate from the initial straight line. The initial releasing rate of neat of MB and pluronic were 0.2803 and 0.1639, respectively. Compared with the incorporating of chitin whisker, the initial releasing rate of 0.4% CTW/pluronic was 0.592, while 3% and 7% of chitin whisker were 0.282 and 0.231, respectively. The releasing together with the correlation coefficient (R^2) was 0.991, 0.954, 0.962, 0.974, and 0.929 respectively. The releasing rate of MB decreased with increasing chitin whisker content. The higher content of chitin whisker exhibit slower down released. For MO dye as shown in Figure 4.14b, The initial releasing rate of neat of MO and pluronic were 0.119 and 0.0545, respectively.

Compared with the incorporating of chitin whisker, the initial releasing rate of 0.4%, 3% and 7% of CTW in pluronic were 0.0365, 0.0273 and 0.0106, respectively. The correlation coefficient (R^2) was 0.972, 0.938, 0.959, 0.931, and 0.958 respectively.

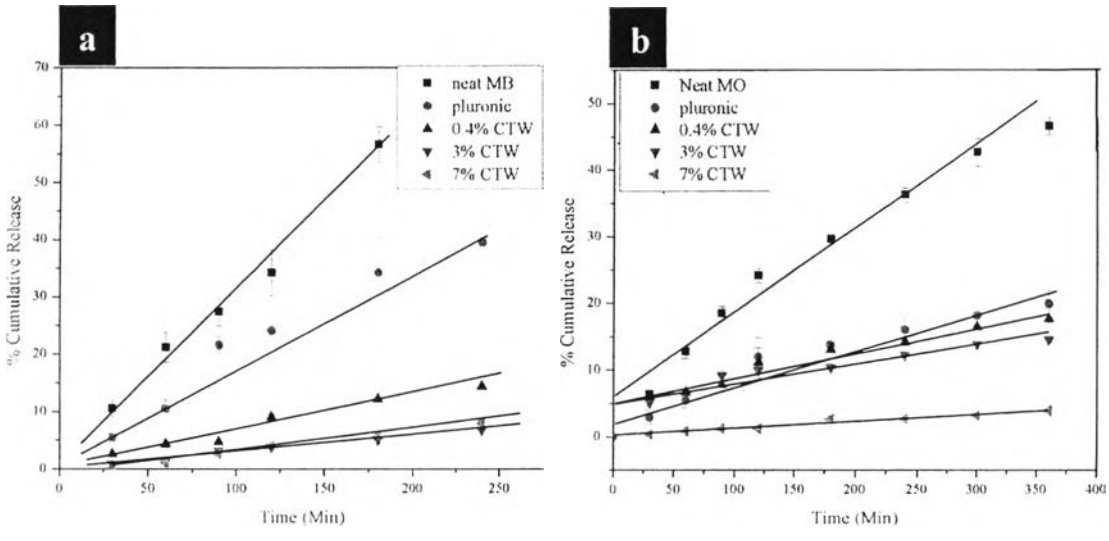

Figure 4.14 The releasing rate of (a) MB and (b) MO of the model drug release from composite gel.

The mechanism of model drug released was investigated by Korsmeyer-Peppus model. The relationship between the amount of model drug released at time t (M_t) and the amount of model drug release at time infinite (M_∞) can be expressed by Korsmeyer-Peppus equation, as follows: $M_t/M_\infty = kt^n$. The n value is a diffusion release exponent which indicating of the releasing mechanism. The releasing mechanism can be defined as Fickian, non-Fickian (anomalous), linear (zero order), and super case II transport when n is equal to 0.5, $0.5<n<1.0$, $n=1$ and $n>1$, respectively (Korsmeyer, 1983). From the plotted between $\ln(M_t/M_\infty)$ and ln time for determined the n values, The n values of neat MB and pluronic were 0.868 and 0.859 and the n values of composite gel incorporated chitin whisker having chitin whisker content ranged from 0.4%, 3%, and 7% were 0.814, 0.982 and 0.932, respectively. The correlation coefficient (R^2) was 0.991, 0.953, 0.967, 0.985, 0.989, respectively. The n values of composite gel of any chitin whisker contents were identified as non-Fickian (Anomalous transport) mechanism which is superposition of both

phenomena of diffusion controlled and swelling controlled release. The dye release mechanism divided into 2 paths. Some of dyes in the sample exhibit the diffusion controlled release because the difference in MB concentration between composite gel and in PBS buffer solution. Therefore, the dye in composite gel with high concentration inside exhibites the burst release of MB into the PBS buffer medium. And some of dyes released by gel swelling. However, The n value of MO dye system was also in the case of Anomalous transport which is the superposition of both phenomena (diffusion controlled and swelling controlled release). This may be due to the amount of dye incorporation in sample is quite low, so the releasing mechanism cannot occur only through the diffusion mechanism by the difference in concentration gradient of dye between inside and outside of the composite gel. Thus, the releasing mechanism was controlled by using both and diffusion controlled and swelling controlled release.

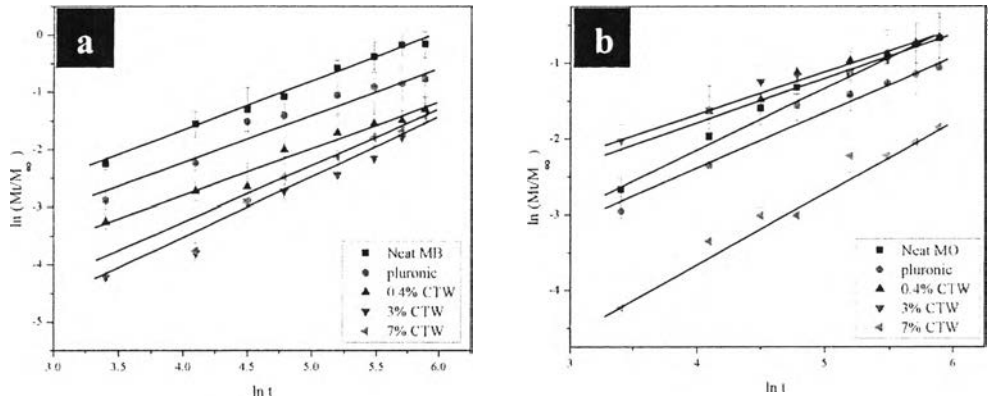

Figure 4.18 Korsmeyer-Peppus model of mechanism of (a) MB release and (b) MO release.

4.5 Conclusions

The incorporation of chitin whisker into the pluronic gel resulted in the improvement in gel stability and slow release of the model drugs by the interaction between polar functional groups of chitin whiskers and model drugs. In conclusion, pluronic/chitin whisker composite gels showed a potential to be used as a carrier for injection drug delivery system for the purpose of prolongation of the drug release and the improvement in the efficiency of the medical therapy.

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