Chapter IV

Discussion and Conclusion

In the presence of two or more macromolecules, the process referred to as complex coacervation is driven by the electrostatic interactive forces between opposite charges of the macromolecule. Microencapsulation by complex coacervation is an uncomplicated process which does not use any elaborate manufacturing equipment. Complex coacervation using aqueous vehicle has advantage of non toxicity to environment. Therefore, in this reserch, microencapsulation was prepared by complex coacervation using aqueous vehicle to formulate indomethacin sustained release preparation. To form microcapsule wall, cationic amine groups of chitosan are capable of interacting with anionic carboxyl groups of CMC or pectin by electrostatic interaction.

1. Preliminary study

The complex coacervation technique of preparing chitosan-CMC and chitosan-pectin microcapsules was to spray CMC or pectin solutions through a nozzle into chitosan solution in order to control small size of droplets. Acetic acid was chosen to dissolve and protonate chitosan polymer. Lin and Lin (1992) found that chitosan microcapsules prepared by using acetic acid as a solvent showed slow release action when compared with other acid solvents such as ascorbic acid and citric acid. The microcapsules prepared with acetic acid was less porous in structure and was swollen in dissolution medium to double in particle size, thus lengthened its diffusion pathway. From the results, varying the process conditions such as

chitosan concentration, CMC or pectin concentration, pH of chitosan solution, temperature of the process, content of hardening agent and hardening time, washing and drying affected the formation of microcapsules.

Concentrations of chitosan solution for preparing of microcapsules were in the range of 0.25-1.0 %w/v while the ranges for concentrations of CMC and pectin solutions were 0.75-1.5 %w/v and 5.0-10.0 %w/v, respectively. The formability of chitosan-CMC microcapsules at CMC concentration 0.5 %w/v did not occur possibly due to the negatively charged density was not enough to form complex coacervation. This result was the same as that reported by Ritthidej and Tiyaboonchai (1995). The microcapsule was not formable when the process had only calcium chloride solution without chitosan reacted with pectin droplet. It was temporary microgel droplets because calcium chloride could cause precipitation reaction with pectin (Montgomery, 1959) and the divalent calcium ions could crosslink the pectin (Bender,1959) hence they could prevent agglomeration of the gelled droplets. However, when spraying pectin solution at concentration of 2.5% w/v into various concentrations of chitosan solution containing calcium chloride 3 gm /gm polymer, clusters of microgel droplets were obtained. The reason was that negatively charged density of pectin was too low to form complex coacervation with positively charged amine groups of chitosan. Therefore, formulation of chitosan-calcium chloride solution with pectin 2.5 %w/v was not the optimum concentration ratio. It was reported that the optimum concentration ratio of polymer to form interpolymer complex could be measured by minimum of viscosity, maximum of turbidity, maximum of coacervate volume, and electrophoresis (Bungenberg de Jong, 1949). In this research, the viscosity of supernatant from interpolymer complex coacervation was less than 10 cps. However, due to the limitations of Brookfield viscometer, the apparent viscosity could not be measured. The optimum

pH for chitosan solution was 4 while the processing temperature should not exceed 15°c. These conditions were used to prepare chitosan-CMC microcapsules by Ritthidej and Tiyaboonchai (1995). The higher processing temperature resulted in the higher interfacial energy hence the microcapsules coalesced to reduce the total interfacial energy of the system (Martin, 1993).

Luzzi and Gerraughty (1967) found that with longer hardening time, the lower glutaraldehyde content could cause more completely crosslinked membrane than at shorter hardening time. The result showed that 0.25 gm glutaral content gave maximum tightening of the microcapsule membrane. Comparison of hardening time in this research between 2 and 3 hours showed no difference in the percentage of drug entrapment, drug recovery and drug release because 2-hour hardening time may be enough to completely crosslinked the membrane or the period of hardening time was not significantly different. Then, 2-hour hardening time and 0.25 gm of glutaraldehyde were chosen to harden microcapsules wall to save time and energy of the process. In addition, Luzzi and Gerraughty (1967) observed that the excess of hardening treatment caused excessively denaturing and cracking of the wall.

In the step of drying, nitrogen gas was used to dry the microcapsules to benefit of moisture resistance. Chitosan-pectin microcapsules were difficult to wash because the microcapsules swelled with water and took longer time for drying to obtain more yield and agglomerate-like microcapsules. The microcapsule agglomerated to clusters probably because the dehydration of the microcapsule was incomplete and water acted as binding material (Peters, Bommel, and Fokkens,1992).

2. Microencapsulation study

For the technique of the complex coacervation using aqueous vehicle, the coating materials are hydrophilic polymers dissolving in aqueous solvent and the core material is hydrophobic to be encapsulated inside.

From this research experiment, CMC or pectin polymer could be dissolved in water to give negatively charged carboxyl group. Chitosan solution is acidic hence the drug to be encapsulated could be weak acid and undissolved in acidic chitosan solution. Therefore, the model drug, indomethcain, which has a pK_a of 4.5 could be achievedly encapsulated by this technique.

Indomethacin microcapsules which failed in recovery process had more coacervate yield hence microcapsules were very close to cause agglomeration. When glutaraldehyde was added to harden the microcapsules, they were deposited in gel like medium. Even when diluted with one-fold volume of water before adding glutaraldehyde to harden at a long period of 6 and 18 hours, the microcapsule was still deposited in gel like medium. The result could be illustrated that the system had more glutaral content of 0.25 gm /gm polymer and took long time to harden for 6 and 18 hours. Eventhough glutaraldehyde content in the formulation was reduced to 0.1 gm /gm polymer, it still formed gel because the hardening process took long time of 18 hours.

Besides the effect of excess glutaraldehyde content and longer time period of hardening time, the excess chitosan molecules remaining in the medium could be crosslinked with the excess glutaraldehyde and turned the medium to be gel.

2.1 Morphology of indomethacin microcapsules

From the optical photomicrographs of chitosan-pectin indomethacin microcapsules, chitosan-pectin microcapsules could encapsulate indomethacin when pectin-indomethacin dispersion was sprayed into chitosan-calcium chloride solution. However, it could be observed that chitosan-pectin indomethacin microcapsules prepared from praparations with calcium chloride 1 gm /gm chitosan showed agglomeration of microcapsules more than preparations with calcium chloride 3 gm. This was possibly due to less content of calcium chloride to precipitate and repulse the microcapsule droplet.

From the optical photomicrographs of microcapsules mounted with water at equal time, it could be observed that chitosan-CMC indomethacin microcapsules had transparent wrinkled wall while chitosan-pectin indomethacin microcapsules had swollen to be transparent wall. This was due to the chitosan-pectin microcapsule wall swelled easier than the chitosan-CMC microcapsule wall. The microcapsule wall with less or without glutaraldehyde was rough, weak and cracking.

Chitosan-pectin microcapsules of preparations with less calcium chloride content or incomplete drying with nitrogen gas fused to be large particle hence they were opaque when mounted with water. Obviously in optical and electron photomicrographs, higher concentration of polymer solution caused thicker wall of the microcapsule because of higher viscosity and more negatively charged density to interact with positively charged amine groups of chitosan.

Moreover, the photographs taken by scanning electron microscope showed that the surface membrane of chitosan-CMC indomethacin microcapsules was smooth to wavy, folding and no pore while chitosan-pectin indomethacin microcapsules was rough, with more thread and heavy crease. This may be resulted from the type of negatively charged polymer since CMC solution was transparent while pectin solution was opaque and sandy. Microcapsule membrane without pore when observed with SEM at x800 magnification could be described that the process was controlled at low temperature and was rapid cooling when droplets of drug-polymer dispersion at room temperature about 25°c were sprayed into 10°c of chitosan solution hence rapid cooling caused to reduce total interfacial energy of the system. It was supported by Deasy (1984) that rapid cooling tended to form a fine pore size which reduced escape of core material. Moreover, the advantage of the process was that higher concentrations of colloids interacted to give thicker wall with reduced porosity (Deasy, 1984).

Traces of indomethacin were found on the surface membrane of some microcapsules because indomethacin was dissolved by isopropanol in the step of washing and remained on microcapsule membrane.

The optical and electron photomicrographs revealed that polymer type, polymer concentration, glutaraldehyde content, calcium chloride content and drying process affected morphology, shape and surface of microcapsule wall.

2.2 Size and size distribution of indomethacin microcapsules

The geometric mean diameters of microcapsules were in the range of 52.48-107.15 and 104.71-281.84 μm for chitosan-CMC and chitosan-pectin

indomethacin microcapsules, respectively. The size of chitosan-CMC indomethacin microcapsules was distributed in the range of 40-291 μm while chitosan-pectin indomethacin microcapsules was of 40-459 μm. It could be found that due to method of spraying colloid by air atomization, the particle size was small and rather uniform. However, the particle size range obtained by this method depended on the air pressure, distance between the orifice of the atomization and the pan, size of orifice and the rate of flow from the infusion pump. These variables were observed by Kwok, Groves and Burgess (1991) that the average particle size decreased with increasing of the air pressure and the viscosity of the colloid and decreasing the infusion rate and the nozzle size.

Moreover, the nozzle and stirring speed influenced the size and size distribution. Nixon and Hasson (1980) illustrated that the faster stirring speeds produced small coacervate droplets and smaller range of size distribution. In contrary to Burgess and Singh (1993), the mean particle diameters and particle size distribution of albumin-acacia coacervate prepared at different stirring speeds did not vary significantly. In this research experiment, the process was stirred by a magnetic stirrer at a speed sufficient to produce a vortex without air bubbles. Obviously, scanning electron photomicrographs confirmed that particle size of chitosan-pectin was larger than chitosan-CMC. This was due to the tendency to agglomerate of microcapsules in the process on drying of chitosan-pectin microcapsules.

The polymer concentration showed some effects on the D_{50} values of the microcapsules. Increasing of the concentration of chitosan solution decreased the D_{50} values especially in chitosan-CMC indomethacin microcapsules. It showed that the lowest D_{50} value was obtained when the concentration of CMC was 1 %

w/v. The reason may be the optimum viscosity and the optimum charged density between the opposite charges of polymers. Burgess and Singh (1993) also found that the higher the viscosity, the lower the interfacial tension, the higher the interfacial charge and the more rigid the interface would be the smaller droplet size. However, it was difficult to discuss the effect of polymer concentration on D_{50} values of the chitosan-pectin microcapsules because there was agglomeration of microcapsules in drying process.

Glutaraldehyde content affected D_{50} value of microcapsules because the glutaraldehyde caused the membrane to tighten and became tortuous (Hou et al., 1989). It could be observed in the preparation of chitosan-CMC indomethacin microcapsules and chitosan-pectin indomethacin microcapsules that increasing of the glutaraldehyde content decreased the D_{50} values.

The diameters of chitosan-CMC indomethacin microcapsules and the chitosan-pectin indomethacin microcapsules using calcium chloride 1 gm /gm chitosan increased with increasing of the drug content. This was due to the surface area of microcapsule was large enough for encapsulating more indomethacin content. The result was in agreement with Milovanovic and Nairn (1986). They found that when the amount of drug increased, the diameter of the microcapsules also tended to increase. On the contrary, D_{50} values of chitosan-pectin microcapsules using calcium chloride 3 gm /gm chitosan or without glutaraldehyde tended to decrease, when the content of indomethacin increased. This might be due to calcium chloride 3 gm /gm chitosan prevent agglomeration of microcapsules.

However, the preparations with various hardening times of 6 and 18 hours could be observed that D_{50} value was decreased and the particle size

distribution was narrow when the process was taken long time for hardening microcapsule wall. This could be supported by Ritthidej and Tiyaboonchai (1995) that with longer hardening time, the lower glutaraldehyde content could cause more complete crosslinked and tightening of microcapsule membrane than at lower hardening time.

2.3 Percentage of drug entrapment, drug recovery and yield

Indomethacin could be encapsulated into chitosan-CMC and chitosan-pectin microcapsule. The percentage of indomethacin entrapment depended on chitosan concentration, CMC or pectin concentration, glutaraldehyde content, indomethacin content in the process and hardening time (only for chitosan-pectin). However, calcium chloride content for chitosan-pectin and hardening time for chitosan-CMC did not affect the percentage of drug entrapment. The percentage of indomethacin recovery and the microcapsule yield relied on chitosan concentration, CMC or pectin concentration, glutaraldehyde content, calcium chloride content and hardening time for chitosan-pectin, washing process with isopropanol.

The increment of chitosan concentration caused increment of percentage of drug entrapment and drug recovery in chitosan-CMC but decrement in chitosan-pectin microcapsules. The percentage of yield decreased when increasing chitosan concentration because the excess of chitosan content was filtered out in the washing process. The increment of percentage of drug entrapment and drug recovery of chitosan-CMC microcapsule was due to the strength of microcapsule wall when the microcapsule membrane contained more chitosan than CMC molecules. This result was in agreement with Ritthidej and Tiyaboonchai (1995). For the percentage of drug entrapment and drug recovery of chitosan-pectin microcapsules, it could be

observed that increment of chitosan concentration affected directly to drug recovery. This was because the remaining chitosan molecule did not interact to pectin hence the yield and percentage of drug recovery was decreased.

Considering CMC concentration, it was found that CMC 1 %w/v had optimum viscosity and negatively charged density for chitosan 0.25% and 0.5%w/v. For pectin concentration, it could be observed that higher pectin concentration caused lower percentage of drug entrapment but higher percentage of drug recovery. The reason may be less drug:pectin polymer ratio when pectin concentration increased hence the percentage of drug entrapment was decreased. In contrary to percentage of drug recovery, the microcapsule membrane with high pectin concentration was thick enough for less indomethacin loss while washing the microcapsule with isopropanol. However, the percentage of yield increased when increasing concentration of CMC or pectin solution. It was due to more anionic polymer interacted to cationic polymer.

According to glutaraldehyde content of 0.25 gm /gm polymer, the result indicated that the percentage of drug entrapment, drug recovery and yield increased due to the microcapsules had more completely crosslinked membrane than preparations with using glutaraldehyde 0.1 gm. The stronger microcapsule wall was less drug loss while washing the microcapsules with isopropanol.

Obviously, the percentage of drug entrapment increased with more indomethacin in the formulation because drug:CMC or pectin polymer ratio increased.

For the hardening time for chitosan-pectin microcapsules, it was found that the percentage of drug entrapment, drug recovery and yield were increased when the process of chitosan-pectin microencapsulation was allowed longer time for completely crosslinking and hardening with glutaraldehyde.

The content of calcium chloride influenced percentage of drug recovery and yield because it completely precipitated the chitosan-pectin microcapsule wall. Therefore, higher calcium chloride content caused less drug loss in the washing process with isoprapanol.

2.4 Drug release of indomethacin microcapsules

The drug release pattern of chitosan-CMC and chitosan-pectin indomethacin microcapsules was of the square root of time model, which was known as Higuchi's model. The kinetic drug release of indomethacin microcapsules was elucidated from the maximum values of correlation of determination (r^2) of percentage drug release against time, percentage drug release against square root of time and log percentage drug remained against time. These values shown in Table 21 in the Appendix revealed that most maximum values appeared at percent drug release against square root of time. The square root of time model of these microcapsules was conformed with other investigators who prepared microcapsules by coacervation technique (Madan, 1980 ; Deasy, 1989).

The results of the optical photomicrograph, scanning electron photomicrograph and the release profile of Higuchi's plot which were described by a linear square root of time dependence showed that microcapsules was uninuclear

or cluster of microcapsule which composed of aggregates of tiny microcapsules and release of drug from microcapsules was a membrane transport phenomenon.

The mechanism of drug release from microcapsules involved the diffusion of drug molecules from a region of high concentration in the microcapsule to a region of low concentration in the dissolution medium through the membrane.

The release of indomethacin from chitosan-CMC or chitosan-pectin microcapsules by complex coacervation could be sustained to a long period of 24 hours and the percentage of drug release from microcapsules of various preparations ranged from 1.15-96.77 at 1 hour up to 24 hours.

The released amount of indomethacin from the microcapsules increased linearly with the square root of time. It indicated that the diffusion of indomethacin from the microcapsule membrane, which was regulated by the porosity and tortuosity of microcapsule wall, may be a rate-limiting step in the release of indomethacin from microcapsule. Microcapsule swelling was therefore an important factor in controlling the release rate of indomethacin as it affected the capsule permeability, the available surface area for contact with the dissolution medium and also the intracapsular concentration as the active ingredient was dissolved inside the capsule (Polk et al.,1994). It could be observed from this research that chitosan-pectin microcapsules swelled more than chitosan-CMC microcapsules in the medium hence the release rate of chitosan-pectin microcapsules was slower than chitosan-CMC microcapsules.

The effects of the processing variables such as polymer concentration, glutaraldehyde content, hardening time, indomethacin content and calcium chloride content on the drug release profiles were discussed as followed.

a) Effect of chitosan concentration : From the release profile, it could be found that microcapsules prepared from higher chitosan concentration had slower drug release while the notable exception was preparations prepared from chitosan 0.25 % and 0.5 %w/v with pectin 5.0 % or 7.5 %w/v, calcium chloride 3 gm /gm chitosan, glutaraldehyde 0.1 gm /gm polymer, indomethacin 1 %. This was due to the reduced porosity of thicker wall (Deasy,1984) which had more chitosan molecule acted as more positive charge interacted to negatively charged polymer.

b) Effect of CMC or pectin concentration : The effect of CMC or pectin concentration on drug release could illutrate that increasing in polymer concentration decreased the percentage drug release. The occurrence of the result confirmed from optical photomicrographs and scanning electron photomicrographs was thicker wall on higher concentration of CMC or pectin. The higher polymer concentration of CMC or pectin referred to higher viscosity and higher negatively charged polymer.

c) Effect of glutaraldehyde content : The drug release of microcapsules generally decreased with the increment of glutaraldehyde content because of the reduction in polymer chain mobility, increasing its glass transition temperature and decreasing the diffusity of penetrant molecules (Deasy, 1984) until a point was reached where a sharp drop to the minimum release rate occured then the rate increased again with the increasing of glutaraldehyde content. The initial dropped in drug release with increasing of the glutaraldehyde content was because the

increasing of glutaraldehyde content helped strengthen and increased the tortuosity of the microcapsule wall in the crosslinking process. When glutaraldehyde content increased, the release rate increased because excessive hardening treatment caused excessively denaturing and cracking the microcapsule wall (Luzzi and Gerraughty, 1967 ; Nakatsuka and Andrady, 1992 ; Ritthidej and Tiyaboonchai, 1995).

From this research, increasing of glutaraldehyde contents from 0 to 0.1 and up to 0.25 gm /gm polymer obviously increased the drug release. The reason could be confirmed by scanning electron photomicrographs that microcapsule walls of preparations with glutaraldehyde 0.1 gm had more folding hence the drug took long time to release from the microcapsules.

d) Effect of hardening time : For the release profile of chitosan-CMC indomethacin microcapsules, it was found that increasing the hardening time from 2 to 3 hours of preparations prepared from chitosan 0.5 %w/v, CMC 1.0 %w/v, glutaraldehyde 0.25 gm /gm polymer exhibited no significant difference in the release profile of the Higuchi's plot slope ($p \geq 0.05$) as shown in Table 22. This may be due to the complete crosslinking of the membrane at 2-hour hardening time and the hardening time of 2 and 3 hours was not sufficient to reveal the difference.

The release profile of chitosan-pectin indomethacin microcapsules exhibited that increasing time for hardening from 6 up to 18 hours decreased the percentage of drug release ($p<0.05$ as shown in Table 23). The reason was chitosan-pectin microcapsules needed more time for complete crosslinking of the membrane hence the drug was difficult to diffuse from the more tortuous and stronger membrane (Hou et al.,1985). Except the release profiles of Prep.24c&24d with chitosan 0.25%w/v, pectin 7.5%w/v, glutaraldehyde 0.25 gm, calcium chloride

3 gm, indomethacin 3%, 6 and 18 hours hardening time, respectively, there were no significant difference ($p \geq 0.05$) because D_{50} values of Prep.24c&24d were not different.

e) Effect of indomethacin content : From the result of effect of indomethacin content on the percentage drug release, it was noticeable that the higher indomethacin content gave the more percentage drug release due to the higher density of the drug in microcapsules.

f) Effect of calcium chloride content : From the of release profiles of chitosan-pectin indomethacin microcapsules, when considering the calcium chloride content, it exhibited that the more calcium chloride content caused either higher or lower the percentage of drug release because the agglomeration of microcapsules affected on particle size of microcapsules.

2.5 Determination of infrared spectra

Infrared spectra of microcapsules prepared from chitosan-CMC and chitosan-pectin showed new peaks appearing at 1710 and 1580 cm^{-1} which were assigned to the carboxyl groups of CMC or pectin bound with chitosan and amino groups of chitosan bound with CMC or pectin, respectively (Fukuda and Kikuchi,1979). The result was similar to the infrared spectra of chitosan-sodium polyacrylate which was investigated by Takahashi et al. (1990). The infrared spectra clearly indicated the interaction of chitosan-CMC and chitosan-pectin by ionic bonding as a primary binding forces between cationic amine groups of chitosan with anionic carboxyl group of CMC or pectin. However, infrared spectra

of microcapsules containing indomethacin displayed obviously double peaks of indomethacin to hinder the peaks of complex coacervate.

When considering the crosslinked microcapsules with glutaraldehyde, peaks of C=N group appeared at 1660-1590 cm^{-1} which the peaks clearly indicated the process of a Schiff's base type of crosslink in the glutaraldehyde-treated microcapsules. The result was similar to crosslinking chitosan membrane with glutaraldehyde which was investigated by Thacharodi and Rao (1993).

2.6 Determination of differential scanning calorimetric thermogram

The differential scanning calorimetric thermograms of chitosan, CMC, pectin, chitosan-CMC without glutaraldehyde, chitosan-pectin without calcium chloride and glutaraldehyde, chitosan-pectin with calcium chloride exhibited endothermic peak. The thermogram of the complex showed broad endothermic peaks around 75°, 117°, and 115°c of chitosan-CMC without glutaraldehyde, chitosan-pectin without calcium chloride and glutaraldehyde and chitosan-pectin with calcium chloride, respectively. Although the endothermic peak around 100°c seemed to be attributable to the elimination of water, they were observed that water was absent from the complex after drying which was stated by Imai et al. (1991). Therefore, the endothermic peak around 75°c of chitosan-CMC without glutaraldehyde may be related to the melting of crystallined chitosan through complexation with CMC. Furthermore, the peak around 115° and 117°c of chitosan-pectin with and without calcium chloride may be the result of a shift to low melting peak of the formation of carboxylic group of pectin and the amino group of chitosan. The complexation endothermic peaks indicated the formation of new crytals by the complexation of chitosan with CMC or pectin.

3. Reproducibility study

Preparation 2 prepared from chitosan 0.25 %w/v, CMC 1 %w/v, glutaraldehyde 0.25 gm /gm polymer, indomethacin 1% and preparation 17 prepared from chitosan 0.25 %w/v, pectin 5 %w/v, calcium chloride 3 gm /gm chitosan, glutaraldehyde 0.25 gm /gm polymer, indomethacin 2% were chosen to determine reproducibility. The reproducibility study showed no difference in indomethacin microcapsule morphology, size and size distribution, percentage of drug entrapment and drug recovery, and the release profile of each preparation in 3 batches. The analysis of variance of Higuchi's plot slopes of preparations 2 and 17 are shown in Tables 23 and 24 in the Appendix, respectively. They exhibited no significant difference in Higuchi's plot slopes of various batches ($p \geq 0.05$). Therefore, this microencapsulation method by complex coacervation of indomethacin chitosan-CMC or chitosan-pectin had high reproducibility.

4. Conclusion

The indomethacin sustained release for 24 hours could be prepared by complex coacervation method using nozzle to spray small uniformed droplet size of carboxymethylcellulose or pectin solutions into chitosan solution to form chitosan-CMC and chitosan-pectin microcapsules.

This complex coacervation method used aqueous vehicle to avoid toxic to human and environment. The microencapsulation depended on the electrostatic interaction between cationic amino groups of chitosan, soluble in acid, and anionic carboxyl groups of CMC or pectin, soluble in water.

The processing temperature during microencapsulation was low, about less than 15 °c hence it was good for encapsulation of heat sensitivity drug, vaccine or peptide substances in solid or liquid form. The drug or core material had to be insoluble in both water and acid.

The optimum drug formulation which conformed to the USP drug release specification from this research was chitosan 0.25 %w/v, CMC 1 %w/v, glutaraldehyde 0.25 gm /gm polymer, indomethacin 1 % with 2-hour hardening time of chitosan-CMC microcapsules. That of chitosan-pectin microcapsules was chitosan 0.25 %w/v, pectin 5 %w/v, calcium chloride 3 gm /gm chitosan, glutaraldehyde 0.25 gm /gm polymer, indomethacin 2 % with 2-hour hardening time. Morphology of chitosan-CMC microcapsules showed smooth surface and less creasing than chitosan-pectin microcapsules.

Many factors affected the percentage of drug entrapment, drug recovery and drug release profile of the yielded microcapsules. These variables are summarized as follows.

- Increasing of chitosan concentration increased the percentage of drug entrapment and drug recovery but decreased the percentage of drug release in chitosan-CMC microcapsules while decreased the percentage of drug entrapment, drug recovery and drug release in chitosan-pectin microcapsules.

- Increasing of CMC or pectin concentrations decreased the percentage of drug entrapment and drug release but increased the percentage of drug recovery.

- Increasing of glutaraldehyde content and indomethacin content increased the percentage of drug entrapment, drug recovery and drug release in both chitosan-CMC and chitosan-pectin microcapsules.

- Increasing of hardening time increased the percentage of drug entrapment and drug recovery but decreased the percentage of drug release from chitosan-pectin indimethacin microcapsules.

- Increasing of calcium chloride content increased the percentage of drug recovery for chitosan-pectin indomethacin microcapsules.

- Microcapsules prepared with glutaraldehyde 0.25 gm /gm polymer gave optimum crosslinked membrane.

- Microcapsules prepared with calcium chloride 3 gm /gm chitosan exhibited maximum precipitating of chitosan-pectin droplets.

The reproducibility could be successfully achieved from chitosan-CMC and chitosan-pectin indomethacin microcapsules by complex coacervation using unelaborate manufacturing equipment. This method could be developed to industrial scale production. However, chitosan-CMC indomethacin microcapsules were preferable to chitosan-pectin because of ease of collecting the yield.