Chapter IV

Dicussion and Conclusions

In this study , chitin was deacetylated to produce chitosans having different degree of deacetylation. Chitin , a starting material, used in this experiment had been pulverized and sized through 60/200 mesh before it was deacetylated. Therefore, the particle size distribution was narrow. This meant that one of the deacetylation factors was controlled. Other deacetylation factors controlled in this study were alkali reagent , temperature and atmospheric condition. Variable factor in deacetylation processes was reaction time. Chitosan products having different degree of deacetylation were obtained by varying reaction time.

Degree of deacetylation of each chitosan product was determined by colloidal titration or infrared spectrometry. The colloidal titration method was used for determining the free amino group content in chitosan. Alternatively , the acetyl content was determined by infrared spectrometry. Thus , infrared spectrometry could be used to confirm the values attained from titration method.

The comparison of molecular weight by only viscosity determination was in agreement with the results of the previous

studies (Bough , Salter , Wu , and Perkins , 1978). Solution viscosity is a basic method to measure the size or extension in space of polymer molecules. Because of the simplicity of the method and the viscosity - molecular weight relationship , the viscosity determination is often used as a valuable tool to characterize the molecular weight of the polymer (Flory , 1953).

The viscosity of the solution of chitosan was reduced when the reaction time used in deacetylation process increased. This result was in agreement with the study by Bough, Salter, Wu, and Perkins, 1978) that increasing reaction time reduced viscosity. It could be noticed that chitosan having higher degree of deacetylation (chitosan that deacetylated by using higher reaction time) exhibited lower viscosity.

In this study propranolol hydrochoride - chitosan matrices were prepared by directly compressing spray dried powder. The spray drying procedure in aqueous system was used because of three reasons:

1. An aqueous condition was used to avoid the explosion hazard because most organic based formulations contain an inflammable solvent, such as acetone or methanol. Organic solvent was one of the air pollution and also toxic for human. Futhermore, a considerable capital investment was required in the construction the flameproof fitments nescessary to prevent solvent fire and explosion. Consideration must also be given to the expense of solvent recovery or to methods for the prevention of solvent reaching the atmosphere.

There was also the continuous expense incurred in the purchase, quality control and storage of solvent.

2. More uniform distribution of polymer and drug in matrices waspossibly attained in comparison with the method of preparing the matrices by conventional wet granulation. The distribution of polymer in conventional process mostly depend upon the mixing dynamic and variation in distribution of polymer easily occured. Bot the spray drying process, the solution of polymer and drug was used so that more homogenous mixture was achieved.

3. Poor granule flowability and hence tablet uniformity could occurred if the process of direct compression was used because both propranolol hydrochloride and chitosan exhibited poor flow property. The spray drying technique had the desirable characteristics that resultant particles were spherical and free flowing.

The moisture contents of co-spray dried powder of drug-chitosan were between 1.60 to 2.34%. But the moisture contents of co-spray dried powder of drug-chitosan-HPMC were more than 2.34%. This result may be affected by HPMC that would retained more water than chitosan alone.

The thickness of the matrix indicated that the compressional force was uniform with the standard deviation never exceed ± 0.03 for all tested matrices.

The hardness value of Formulation I was 2.87 Kp that was the lowest. This result indicated that Formulation I had low binding property. It was found that the increase in HPMC caused increase in hardness value (Formulations V-VII). It was indicated that HPMC woul incresed binding property of matrices.

The tablets containing chitosan disintegrated by erosion of the tablets leading to the turbidity of the disintegrating medium (0.1N HCl). The disintegration time decreased when the reaction time used in deacetylation process increased (Formulations I-IV). The difference in disintegration time might be due to the difference in rate of gel-formation of chitosan having difference in reaction time. Formulation IV had a poor gel- forming caused decrease in disintegration time. .From these results, chitosan with low degree of deacetylation retarded the disintegration time. Therefore, It should be better disintegrants in acid medium.

The release patterns of matrix Formulations I-VII were characterized by a smooth convex curve. The release rate of these matrices were relatively fast at the initial stage, followed by a stage with decreased rate. The matrices except Formulation IV were formed gelatinous mass in pH 1.5 , swelled and gradually eroded during dissolution tested period. The matrices Formulations I-VII did not formed gelatinous mass in buffer pH 6.8 but remained intact over the dissolution tested period. The release profile of the matrices were similar in both medium. The drug release in all Formulations exceptIII

and IV was observed to greater in buffer pH 6.8, and lesser in buffer pH 1.5. In contrast, the drug release in Formulation IV was greater in buffer pH 1.5 and lesser in buffer pH 6.8. It was possible that Formulation IV were not formed gelatinous mass in buffer pH 1.5. Therefore, the matrix was rapidly diffused and eroded.

The following stages could be involved in the release process from this system :

1. Hydration/penetration of the matrix by the dissolution fluid
2. Gelation at the outer layer of the matrix
3. Dissolution of the drug in the gel
4. Diffusion of drug through the gel layer
5. Slow dissolution of the outermost gelled layer. Any or a combination of these could be a rate-limiting step in the process.

The diffusion of dissolution fluid through the gel was affected by the gel strength. The protective or barrier gel was in turn ,controlled by the viscosity and concentration of the polymer used. It could be noticed that chitosan having higher degree of deacetylation (chitosanthat deacetylated by using higher reaction time) exhibited lower viscosity(CS 2>CS 3.5>CS 7>CS 10). Therefore, formulations having lower degree of deacetylation would also increase the viscosity of the surrounding fluid which would increase the gel-strength, and thus. would slow the permeation rate of both the dissolution fluid and the drug through the gel layer. This was true for Formulation I-IV

containing CS 2, CS 3.5, CS 7 and CS 10, respectively. In buffer pH1.5 Formulations V-VIII containing CS 2 and difference concentration of HPMC, it was found that there was an inverse relationship between HPMC concentration and the rate of release. As the level of HPMC was increased, the gel formed was firmer and more cohesive. This resulted in slower drug release. In buffer pH 1.5 Formulations I-VII formed gel and gradually eroded. Therefore, the dissolution rate for these formulations was controlled by both diffusion through the gel layer and by erosion. In buffer pH 6.8 the formulations did not form gel and erose, the dissolution rate was controlled by diffusion. It was found that degree of deacetylation of chitosan and concentration of HPMC had no relationship with the rate of release.

Conclusions

The degree of deacetylation of chitosan products increased when the reaction time increased, in corresponding with an increase in viscosity. Propranolol hydrochloride matrices could be prepared by spray drying method in an aqeous condition. The pH of dissolution medium affected drug release rate of all formulations. In bufferpH 1.5 , all formulations formed a gelatinous matrix and swelled but in the buffer pH6.8, the matrices did not form a gelatinous mass and swelled. Dissolution studies revealed that using only chitosan could not achieve satisfactory controlled release system. The selection of chitosan processed by reaction time 2 hours in combination with different concentration of HPMC was found that there was an inverse

relationship between HPMC concentration and the rate of release . In addition, the hardness values increased when the formulation combined with HPMC. The 5% HPMC was a suitable concentration to acheive dissolution profiles closed to requirement for propranolol hydrochloride extended release capsule according to USP XXIII. The mechanism of drug release from matrix was anomalous transport and the model of drug release would possibly be first-order model.