Chapter IV

Discussion and Conclusions

I. Film Coating Formulations.

Water-soluble Film Formers.

The physical appearance of the obtained film coating formulations depended mainly on the nature of the raw materials, particularly their color and water solubility. CS is yellowish while the cellulose derivatives are almost white powder, resulting in color of the coating formulations. Difference in substituted groups and/or degree of substitution on the polymer chain may affect water solubility of the materials, resulting in clarity of the coating formulations. The clear coating formulations of CS and HPMC could be obtained because they are well soluble in citric acid solution and water, respectively. The turbid coating formulations of MC and HPC might be due to the alteration in solubility characteristics of the polymers, resulted from substituted methyl and hydroxypropyl groups, respectively. These properties could further affect the appearance of the coated tablets and cast films obtained.

At low concentration, the rheograms of the film coating formulations behaved as almost straight line passing through the origin, implying that they were Newtonian-like systems (Martin, 1993). With increasing in concentration of the film formers, the film coating formulations exhibited as pseudoplastic systems. In addition to the concentration effect, pseudoplasticity also increases with increasing

molecular weight of the polymers. Since all of the film coating formulations were in the same concentration range, variation in the rheograms obtained might be attributed to difference in molecular weight of the film formers.

Because viscosity coefficients were calculated from the rheograms. Therefore, any factor that could affect the rheograms, could also affect the viscosity coefficient, further resulting in pattern of the viscosity coefficient concentration relationship. Again, the factors might include concentration and molecular weight of the film formers.

Following these aspects, the concentrations of the film formers in the coating formulations which had the same viscosity coefficient, were unequal to each other, consequently resulting in the different concentration of those used in this investigation.

Water-insoluble Film Formers.

The appearance of CT pseudolatex product obtained, especially its color, was again resulted from the nature of the raw material. The CT pseudolatex, prepared by solvent change and self-dispersible technique, had the solids content much lower than that of the EC pseudolatex which was prepared by phase inversion technique. Chang, Iturrioz and Luo (1990) also used the same technique as in the present study to prepare shellac pseudolatex. They obtained the product with only 3% w/w solids content. On the other hand, the commercial available products, Eudragit® RS 30 D and RL 30 D, which were also prepared by this technique, had much higher solids content of 30% w/w. Therefore, the low solids content of the CT pseudolatex obtained was probably due to the polymer itself, not to the technique.

In addition to larger particle size of the CT product, its short sedimentation time could be also related to the absence of any emulsifying/dispersing agent in the system. The pseudolatex was stabilized by the positive charge on the polymeric spheres arising from acetamido groups on the polymeric chains, probably resulting in "flocculated-like" particles of the product. This property might further support the easily redispersible characteristic of the CT pseudolatex only by gently shaking.

Concerning that the large size and "flocculated-like" particles of the CT coating formulations would require much free volume of the dispersion medium to disperse, increasing concentration of the pseudolatex to attain a high solids content product was very difficult. To obtain a product with smaller particle size, the viscous liquid of polymer in the water-miscible organic solvent should be passed through a homogenizer or submicron disperser prior the pseudolatex dispersion to be formed with addition of water (Chang and Robinson, 1990).

In the investigation of the compatability between water - soluble and water-insoluble film coating formulations, the CT pseudolatex was found to be compatible with both CS and HPMC film coating formulations. Since CS, considered as a weak base, is brought to be soluble in form of $R\text{-}NH_3^+$ by a certain amount of acid (Skaugrud, 1989, 1991); whereas, HPMC has no ionic charge and is subsequently considered to be nonpolyelectrolytes (Dow Chemical Co., n.d.). Therefore, both polymers could be compatible with the CT pseudolatex which was believed to be stabilized by the positive charge presented on the polymeric particles. In addition, the EC pseudolatex was also compatible with HPMC film coating formulations. This was

probably attributed to the nearly absence of any ionic charge on the polymeric molecules of both polymers. Because of its high pH stability, HPMC can be useful in a wide pH range of 3.0-11.0 (Dow Chemical Co., n.d.). Therefore, it could be mixed with the commercial available EC pseudolatex which was stabilized by ammoniated water, resulting in high pH of approximately 9.

On the other hand, the EC pseudolatex was incompatible with CS film coating formulations which had lower pH value of about 4, resulting in instant precipitation once they were mixed together. This problem might be overcome by using the other commercial available EC pseudolatex product, Aquacoat®, which has lower pH value of 4.0-7.0, instead (Harris and Ghebre-Sellassie, 1989). But this was not studied in the present investigation.

II. Tablet Evaluations.

Tablets Coated with Film Coating Formulations Containing One Film Former.

During coating process, the tackiness problem was found with CS film coating formulations. The problem was attributed to the stickness in nature of the CS film itself, which was also confirmed during detaching the CS cast films. In the case of HPC coating formulations, the tackiness problem seems to be common which was stated in texts (Porter, 1981 a; Seitz, Mehta and Yeager, 1986).

Since the main compositions of the core tablets, i.e. the active ingredient, lactose, and PVP K 30, are water-soluble and dispersion medium of the CT pseudolatex was water; therefore, some

portions, particularly at the surface, of the core tablets could be slightly dissolved or eroded out. The tablet weight was initially decreased and gradually increased as the coating deposited on the tablet surface. This event also further affected the drug amount remained in the core of the CT coated tablets. As a result, the CT tablets reached the maximum amount of drug released lower than 100%.

From the results, all of the film coated tablets had higher hardness than the core tablets, implying that the coating deposited on the tablet surface could result in increasing the tablet hardness. In some cases, it could be clearly observed that the tablet hardness increased with increasing the coating level.

Bianchini, Resciniti and Vecchio (1991) suggested that the tablet hardness could define the mechanical resistance of the film deposited on the tablet surface. Therefore, the tablet hardness would also depended on properties of the film formers and other additives in the coating formulations, in addition to the coating level applied.

At the same coating level, the CS coated tablets appeared to have the least tablet hardness. Among the cellulose themselves, the HPC coated tablets had the tablet hardness lower than the HPMC and MC coated tablets, the tablet hardness of which were comparable. These could be informed that the CS films were probably softer and more flexible than the HPC films, and the HPMC/MC films, respectively. Banker et al (1981) also reported that the HPC coated tablets were softer than the HPMC coated tablets, reflecting the more flexible HPC film.

In cases of the film coated tablets applied from the CT and EC aqueous dispersions, the degree of density and continuity of the

films, which could be evidently noticed from the scanning electron photomicrographs, resulted from the properties of the coating formulations. These characteristics of the films deposited on the tablet surface could probably affect the tablet hardness as well.

During determination of the disintegration time, the gradual erosion of the core tablets could be observed. This was probably because there was no disintegrant incorporated in the core tablet formulation. Therefore, the disintegration time of the core tablets would depend primarily on the tablet hardness.

For the film coated tablets, the film deposited on the tablet surface had to be first dissolved and/or peeled off. The core part which was remained, was then gradually eroded as occurred with the core tablets. Since the disintegration time of the core tablets were all in the same range, the difference in disintegration time of various film coated tablets was probably affected by the film properties. Consequently, either the film solubility in the disintegration medium or the film cohesive/adhesive to the tablet substrate would be the predominant factor in determining disintegration time of the coated tablets.

The CS coated tablets exhibited the disintegraion time less than the cellulose coated tablets at the same coating level. This was probably because the citric acid remained in the CS film would promote the film solubility in the disintegration fluid. Variation in disintegration time among the cellulose coated tablets might be attributed to difference in the film solubility.

After coating, the disintegration time of the CT coated tablets at the coating level of 5% increased weight was slightly

decreased from that of the corresponded core tablets. This was probably due to the erosion of the core tablets during dip coating. Since the coating applied from the CT and EC coating dispersions was water-insoluble, the disintegration time of these coated tablets would be resulted mainly from the film cohesive/adhesive. The EC coated tablets had much longer disintegration time than the CT coated tablets at the same coating level. This might be additionally contributed to difference in the degree of density and continuity of the film deposited on the tablet surface.

The disintegration time was increased with increasing the coating level. Because the thicker film would require more time in order to be dissolved or peeled off. In addition, the disintegration time seemed to be well correlated with the tablet hardness.

During the drug release test, the core tablets were gradually dissolved in the acid stage dissolution medium. With the similar reason as previously mentioned, there was no disintegrant in the core tablet formulations accompanying with the water solubility of the compositions. Again, the rate of drug release from the core tablets would depend on the tablet hardness.

For the tablets coated with water-soluble film formers, the film deposited on the tablet surface was first dissolved and the core remained was then gradually dissolved in the dissolution medium. Concerning that the drug release from the core tablets was not different to each other, the drug release from the film coated tablets was primarily dependent on the film solubility in the dissolution fluid.

Since CS is readily dissolved in an acidic solution as the acid stage dissolution medium, accompanying with promotion of the film

solubility by the citric acid provided in the film. The drug release from the CS coated tablets was very fast even increasing the coating level.

The cellulose film dissolved in the dissolution medium more slowly than the CS film. Therefore, the coating level influenced the drug release from these tablets to a greater extent than that from the CS coated tablets. As the coating level was increased, the thicker film was obtained; consequently, more time must be taken to dissolve it.

The drug release of the MC coated tablets was not consistent with the coating level, implying that the film adhesive to the tablet substrate seemed to be another important factor in determining the rate of drug release, since the drug release was fast if the core was splitted from the film shell during the test and this problem was found to be independent on the coating level.

The scanning electron photomicrographs of the tablets coated with the water-soluble film formers also showed the difference in degree of smoothness. The difference was probably contributed to the difference in drying of the film coating formulations during coating process. The slow drying was believed to yield the high degree of smoothness (Seitz, Mehta and Yeager, 1986). At high magnification of 900x, the tablet surface of the CS coated tablets at all coating levels could not be examined. This was possibly because the heat generated by the electron beam during scanning could cause the sample damage, indicating the sensitivity of the CS film.

Considering the coating deposited on the tablet surface of the CT and EC coated tablets, the scanning electron photomicrographs obviously presented the porous structure which was formed during the

coating process. The drug release was possibly generated by the first diffusion of the dissolution medium through the porous structure to dissolve the drug in the core part and followed by the drug diffusion through the porous structure.

As the tablet coating weight increased, the release rate of the active ingredient from the coated tablets decreased. With a constant tablet surface area, it was conceivable that increased coating weight yielded thicker coating with fewer open pores and increased tortuosity. These factors probably contributed to the observed decreased drug release. This was in general agreement with Li and Peck (1989 b) who incorporated the silicone elastomer latex with polyethylene glycol and colloidal silica to produce controlled release film coating on potassium chloride tablets.

The drug release from the EC coated tablets was much slower than that from the CT coated tablets. This was possibly resulted from the much difference in the degree of density and continuity of both coatings. The scanning electron photomicrographs of the EC coating showed the higher degree of density and continuity than those of the CT coating, attributed to the more complete coalescence of the EC coating. Since the EC pseudolatex was plasticized by dibutyl sebacate during the manufacturing process, facilitating the coalescence process, while the self-prepared CT pseudolatex had no plasticizer. In addition, larger particle size of the CT pseudolatex possibly made the coalescence process occurred more difficult.

Since the coating of the CT and EC coated tablets were water insoluble, the integrity was well preserved throughout the drug release test; even when the drug was completely depleted from the

tablets, in the case of CT coated tablets. The surface topography of both tablets after the drug release test was also examined. The CT coating had the lower degree of density with the macroporous structure, while the EC coating seemed to be nearly unchanged and was characterized with the microporous structure when compared to those before being subjected to the drug release test. This might be attributed to the following situations, described by Iyer et al (1990). They 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 through which drug molecules diffused. Since the CT powder was found to have much more water wettability than the EC powder, this could result in more chain relaxation and subsequently the macroporous structure of the CT coating.

Tablets Coated with Film Coating Formulations Containing Combined Film Formers.

The hardness and the disintegration time of the coated tablets was increased when compared with those of the corresponded core tablets. The increment was probably attributed to the variation of the polymer ratio between EC and HPMC in the coating formulations as well as the coating deposited on the tablet surface. Since the coating level was fixed at 5% increased weight, the variation in the hardness and the disintegration time of the coated tablets was thus probably resulted from the difference of the polymer ratio in the coating formulations.

The polymer ratio in the coating formulations was found to affect the tablet hardness. Because the effect did not show the consistent trend, unlike the effect of the coating level. Thus, it could not be predicted. One of the reasons might be that some obtained values of the tablet hardness had exceeded the maximum limit of the apparatus.

The effect of the polymer ratio in the film coating formulations on the disintegration time of the coated tablets was obviously exhibited. Increasing the EC proportion in the coating formulations resulted in increasing the disintegration time. This was possibly due to the water-insoluble properties of EC. The higher proportion of EC in the formulations, the hydration of the film shell was more difficult to occur. As a result, the longer disintegration time was gained.

All formulations of the coated tablets had slower drug release characteristics when compared with the corresponded core tablets, but in different manners. The formulations EH 4060, EH 5050, and EH 6040 could not maintain the drug release throughout time course of the test. The films, deposited on the tablet surface, of these formulations were found to be easily ruptured during the drug release test. This was likely because these formulations contained the higher proportion of HPMC which is water-soluble.

The formulations EH 8020, EH 8218, EH 8515, EH 8713, and EH 9010 which contained the higher proportion of EC, could effectively maintain the drug release throughout time course of the test. The release profiles of these formulations were characterized by the three-phase curves.

The lag time phase was initiated by the coat imperfections that were created during the coating process and/or the hydration of the polymeric coating in the dissolution medium, followed by the chain relaxation and/or the leaching out of the water-soluble additives, and subsequently the formation of channels or pores through which the drug molecules diffused (Arwidsson et al, 1991; Iyer et al, 1990). This supposition was in consistent with the examination of the scanning electron photomicrographs of these formulations either before or after the drug release test. Some porous structures could be observed before the test and presented more after the test. This phase further proceeded by the access of the dissolution medium to the tablet core until the activity of the drug inside was constant.

The lag time were shorter when higher concentrations of a water-soluble additive like HPMC were added to the coating formulations. This was in general agreement with Ghebre-Sellassie et al (1988) who characterized Surelease®, a water-based coating, for modified-release preparations. HPMC was believed to enhance the hydration of the coating and the formation of channels or pores and subsequently the access of the dissolution medium to the tablet core.

The consistent drug release phase was achieved as the activity of the drug inside the reservoir was maintained constant (Longer and Robinson, 1990). As illustrated in Figure 36, it lasted from about 10% to about 80% of the drug amount released. Increasing the EC proportion in the coating formulations possibly caused not only decreasing the porous structure but also increasing the tortuosity. This resulted in the slower drug release characteristics.

When the activity of the drug inside the tablet core could not remain constant, the rate of drug release was decreased with time and the plateau phase was attained. This phase was apparently affected by the lag time phase and the consistent drug release phase. If the first phase was long and the second phase was slow, the plateau phase was slowly reached. With this reason, the third phase of the formulation EH 9010, containing very high EC proportion, was not observed within time course of the test.

During the drug release test, the swelling and subsequently the shape alteration of the coated tablets were observed. This was possibly due to the development of an appreciable osmotic pressure inside the coated tablets (Li and Peck, 1992), when the drug and/or the core material is of low molecular weight and water soluble (Ozturk et al, 1990), like propranolol HCl and lactose. Therefore, the drug release appeared to be concomitantly a combination of the drug diffusion through the porous structure and osmotically driven release. In addition, the osmotic pressure might also indirectly enhance the drug release from the coated tablets, since the osmotic pressure induced expansion of the coated tablets might possibly result in further pore formation and/or pore enlargement in the hydrated film coatings (Li and Peck, 1989 c).

An important prerequisite for the *in vivo* use of the delivery system is the good mechanical stability and good resistance of the film coat to rupturing during passage through the gastro-intestinal tract. None of the formulations containing high EC proportion ruptured during the drug release test as observed visually and as indicated by the absence of a burst in drug release. The empty

polymeric shells could retain the intregity and floated on the dissolution medium after close completion of the drug release. The exhausted devices could be deformed without rupturing. Thus, *in vivo* use of these formulations could be possible. This forecast was also supported by Bodmeier and Paeratakul (1990, 1991 a).

The release profile of the tablets coated with the formulations EH 8218, which passed the drug release test of the USP standard, was compared with that of the commercial available product. Although the profile of the commercial preparation exhibited the smooth convex curve, the experimental formulations yielded the complete drug release profile at 24 hours.

III. Cast Film Evaluations.

Physical Characteristics.

As aforementioned, the physical characteristics of the cast films related to the nature properties of the materials themselves, particularly their color and water solubility. The clarity of the cast films was possibly resulted from the water solubility of the film formers. In addition, CSD could reduce the stickiness in nature of the CS films to some extents, because of its antiadherent property.

Tensile Properties.

Plasticization of the CS films with PEG 400 led to a reduction in tensile strength at break and increase in percent elongation at failure. Therefore, the addition of plasticizer increased

ductility of the film, resulting in a soft, ductile film (Aulton, 1982). The results were in agreement with the plasticization effect on the tensile properties of the HPMC films (Aulton, Abdul-Razzak and Hogan, 1981; Okhamafe and York, 1983).

Aulton, Abdul-Razzak and Hogan (1981) also applied the gel theory to explained the observations. In this theory, it is assumed that polymer molecules in solution are attracted to each other by the intermolecular interactions originating from "active centres" along the polymer chain. In solution, these bonds are in a dynamic equilibrium, constantly making and breaking. As they break, water molecules are attracted to and are in competition for the sites. Thus, at any given time a certain fraction of these "active centres" will be solvated with water molecules. Plasticizer, when present in the initial solution, will also be in competition for the same sites. The rigidity of an unplasticized polymer is thought to be due to a three-dimensional gel structure formed on drying by contacts between polymer molecules at these centres. The presence of plasticizer will thus reduce the number of active centres available and consequently the number of polymer-polymer contacts, thereby decreasing the rigidity of the three-dimensional structure formed on drying. This will allow generous deformation of the film before rupture. Plasticizer can be said to work by opposing the aggregation of polymer molecules during gel formation as the solvent is evaporated.

Modification of the CS films with CSD alone or both CSD and PEG 400 resulted in increasing both the ultimate tensile strength and percent elongation at break. The ultimate tensile strength of the CS films modified with CSD alone or both CSD and PEG 400 were

comparable, whereas percent elongation at break of the CSD and PEG 400 containing CS films seemed to be a synergistic effect of CSD and PEG 400. These results indicated that the hard, ductile and subsequently the tough films were obtained.

Since CS molecules contain hydroxy groups and amino groups along the polymeric chains. Based on the gel theory, the CS molecules seem to have two types of the "active centres", which individually and specifically interacted with CSD and PEG 400. When CSD interacted with the first type centres, the ultimate tensile strength and percent elongation at break of the CS films was increased, whereas the interaction between PEG 400 and the other centres resulted in decreasing the ultimate tensile strength and increasing percent elongation at break. If both CSD and PEG 400 were incorporated into the CS films, the effect of the interaction between CSD and the first type centres on the ultimate tensile strength seemed to be suppress the same effect of the interaction between PEG 400 and the other centres. Concurrently, both the interactions seemed to synergistically result in increasing percent elongation at break of the films.

Both low ultimate tensile strength and percent elongation at break of the HPC films indicated the soft and brittle films, while the high ultimate tensile strength and low percent elongation at break of the HPMC and the MC films presented the hard and brittle films. Inclusion of EC aqueous dispersions into the HPMC films as in the formulations EH 5050 resulted in the softer and more brittle films with both lower ultimate tensile strength and percent elongation at break. This was possibly because EC and HPMC formed films by different mechanisms. As a result, low interaction between them was obtained.

Okhamafe and York (1983) proposed that an ideal tablet film coat should be hard, tough and extendible, implying that a film with these features would have a high tensile strength as well as a satisfactory elongation. Based on this consideration, the CS films modified with CSD alone or with both CSD and PEG 400 seemed to be the most appropriate candidates. The amount of the additives incorporated in the coating formulations could be adjusted to achieve the desired effect.

Moisture Sorption.

Plasticization of the CS films with PEG 400 slightly increased the moisture sorption ability of the films, while inclusion of CSD into the films virtually decreased the ability. However, incorporation of both CSD and PEG 400 into the CS films, in turn, dramatically increased the moisture sorption ability of the films.

Okhamafe and York (1983) described that the effects of the additives on the moisture permeability, which could relate to the moisture sorption property, of the films were a consequence of structural interaction. The interaction of plasticizer with the film former generally involved several bonds between adjacent segments of the film former in which the plasticizer then became sandwiched. The result was a loose structure, hence increasing the moisture permeability of the films. In the case of CSD, the interaction with the film former should be possibly resulted in the more compact film structure through which the moisture could diffuse with difficulty. When both CSD and PEG 400 were included into the CS films, very much loose film structure was obtained. This was probably attributed to some unknown interactions between the three components.

In comparison, the cellulose films seemed to have the lower moisture permeability. Inclusion of EC pseudolatex, which was hydrophobic in nature, in the HPMC coating formulations was, thus, unsurprisingly resulted in the films with lower moisture permeability.

Attempts to produce free films of the pseudolatex by casting technique did not succeed as phase separation occurred. The slow process of evaporation during free film preparation led to a breakdown of the dispersion so that the dispersed particles became flocculated and hence separated from the aqueous phase. Hutchings, Clarson and Sakr (1994) also supported this observation. A "flash casting" method was found to be superior for preparation of free film from aqueous latex or pseudolatex (Chainey and Wilkinson, 1985).

Conclusions

Chitin and chitosan could be applied as film formers in entirely aqueous tablet coating process using pan-spray method. To develop the sustained-release film coated tablets of propranolol HCl from these materials in the present conditions of the study seemed to be unsatisfactory, compared with those derived from the cellulose derivatives.

The physical properties and the drug release characteristics of the tablets coated with the coating formulations containing one film former were affected by the coating level. The coated tablets with the higher tablet hardness, the longer disintegration time, and the slower drug release characteristics would be obtained, as the coating level was increased. The extent of slow drug release

characteristics was found to be mainly dependent upon the water solubility of the film formers. The drug release was relatively fast if the water-soluble film formers were applied. On the other hand, the relatively slow drug release was obtained when the water-insoluble film formers were applied. It was also noted that the coating level seemed to unaffect the drug release characteristics of the CS coated tablets.

Variation of the polymer ratio in the film coating formulations containing the combination of water-soluble and water-insoluble film formers was found to affect all the physical properties and the drug release characteristics of the coated tablets. Increasing the proportion of the water-insoluble film formers resulted in the tablets with longer disintegration time and slower drug release. However, the effect of the polymer ratio on the tablet hardness was unpredictable. In addition, the drug release mechanism appeared to be concomitantly a combination of the drug diffusion through the porous structure and osmotically driven release.

In comparison with the commercial available preparation, the selected experimental formulation presented the superior drug release profile with complete drug release within 24 hours.

From the results of the tensile properties, the CS films owned the soft and ductile properties, while the cellulose films owned the hard and brittle properties. Modification of the CS films with an antiadherent (CSD) alone or both the antiadherent and the plasticizer (PEG 400) yielded the harder and more ductile films, the properties of which were generally required. The moisture sorption ability of the films is another important factor which should be optimized together

with the tensile properties in order to obtain the nearly ideal film coating.

Suggestion for Further Study.

The basic properties involved in the film forming process of chitin and chitosan should be examined, especially the glass transition temperature or the film forming temperature. The film formers and/or other additives should be formulated together, based on these properties in order to achieve the most effective film coating.