CHAPTER IV

DISCUSSION AND CONCLUSIONS

Preliminary Investigation on Suitable Coating Conditions

The sucrose crystal in the size range of 20/40 mesh were classified to be used as core substrate. The preliminary investigation on suitable coating condition was performed by coating sugar crystal with ethylcellulose dissolved in ethanol containing erythrosine dye.

The pink color of erythrosine dye was visually observed for coating properties and the loss of sweetened taste of sucrose was used as an indication of the completed polymer coverage on the sugar crystal.

Because of sucrose crystal can be dissolved in water ; therefore, the non-aqueous solvent such as ethanol, chloroform, methanol, ether and methylene chloride were chosen. It was found that ethanol and the mixture of methanol and methylene cholride gave clear solution and safety to coat. But the mixture of methanol and methylene chloride gave faster evaporation than ethanol. So, the spray drying of coating solution might occur. Finally, ethanol was used as coating solvent.

The coating conditions was studied by trial and error and gradually adjusted for the uniformity of coating, such coating condition process was shown in Table 4 .

The inlet air temperature was higher than the outlet air temperature about 10 C. In general , the difference of inlet and outlet temperature was in the range 10-20 C.

The spraying air pressure should be adjusted in corresponding with the feed rate of coating solution, otherwise, it might cause overwetting of coating solution and formation of sucrose crystal agglomerates.

After that, erythrosine dye was substituted by propranolol hydrochloride in coating solution as a model drug which gave coating properties as required .

The Physical Properties of The Coated Beads

Morphology of The Coated Beads

The shape and surface topography of coated beads were found to be affected by the component of coating solution. Sucrose crystal had smooth surface. Following coating by coating solution formulations which contained plasticizer, the surface of coating film was more rough when increasing plasticizer content. Result from the higher content of plasticizer could make coating solution having more solid content which gave more coating mass to bind on film resulting in rough film surface. It was found that coating solution which composed of PEG 4000 gave thicker film coating surface than glycerylmonostearate and castor oil, respectively (Figure 12-21).

For outercoating process, the formulation 11 gave more rough surface beads than formulation 12 because it contained no glycerylmonostearate plasticizer. But addition of HPMC and PG in outercoating solution (Formulation 13), it gave satisfactor smooth surface but fast release of the drug than formulation 12

was observed because of the soluble property of HPMC in water and hydrophilic property of HPMC gave porous coated film when in contact with water. Thus, water could penetrated and dissolve the drug resulting in the faster drug release of the coated beads.

The increase of EC content in outercoating (Formulation 14, 15, 12 and 16, respectively) gave more thickness of the film as previously discussed. Particularly, when drug and EC content were increased (Formulation 17), it gave more rough surface .

The double outercoating (Formulations 18-20) was not successful because friability of the beads gave more rough, porous and thick film. So that, the double outercoating was not suitable process because it did not give further reduction in release rate.

When plasticizer was changed from glycerylmonostearate to 5% castor oil (Formulations 21 and 22), more rough and spongy coated film was observed. Formulation 22 gave slightly oily coated surface of the beads because of castor oil in large content but they were not adhered together and showed low flowability of the beads.

The combination ratio of coated beads of formulation (Formulation 23-36) was attempted in order to improve drug release. But the drug release properties as required were not achieved.

The outercoating solution which composed of castor oil using formulations 37-44 gave the same surface properties because an addition of castor oil could resist friability and the thickness was increased when the volume of outercoating solution was increased.

For coated pellets, it can be explained in the same way of the sucrose crystal but the coated pellets had more spherical beads than sucrose crystals.

Particle Size Distribution

The mean size of the coated beads which composed of several plasticizers was not apparently different among formulations in both sucrose and pellet as the cores. But outercoating and increasing volume of the outercoating solution increased the mean size of the beads.

Bulk, Tapped Density and Carr's Compressibility Index

Bulk density of formulations 1-10 were not apparently different. After outercoating, bulk density appeared to decrease especially in double outercoated beads. It might be due to the formation of porous EC film which occured during outercoating process.

Compressibility index of formulations 1-10 were not apparently different. After outercoating, compressibility had a trend to decrease, and in double outercoating, it was further decreased. When the sucrose crystals were subjected to more coating layers, more spherical coated beads were attained, hence higher flowability.

When the plasticizer was changed from glycerylmonostearate to 5% castor oil as described in Formulation 21 , the compressibility index was increased. But outercoating as described in Formulation 22 decreased compressibility index.

For the pellet coating, the bulk density was not apparently different among each formulation of pellets and between pellet and sucrose beads of the same coating composition. But the compressibility index was lower than of sucrose beads, indicating higher flowability. And the compressibility indices werenot apparently different among each formulations of coated pellets.

Friability of the Coated Beads

Coated sucrose (Formulation 1-10) containing PEG 4000 as plasticizer showed a trend to increase friability resulting from the thickest coated film.

In outercoating, friability was increased due to the longer coating process causing more impaction among the beads and between the beads and the chamber wall. Particularly, in double outercoating, an increase of EC gave the highest friability of the coated beads (Formulation 20).

When using 5% castor oil as plasticizer (Formulation 21), it was found that friability of coated beads decrease. The volume of outercoating did not cause apparently different on friability.

The coated pellets showed no apparently different in friability among each formulation. Formulation 57 showed the highest friability because of outercoating process and high content of ethylcellulose.

Dissolution Studies of Coated Sucrose Beads

a. Influence of plasticizer type on the dissolution profiles of coated sucrose beads

The release profiles in 0.1 N HCl medium of formulation 1 (without plasticizer) gave the highest drug release rate because the coating film without plasticizer might be brittle and porous. In comparison among glycerylmonostearate, castor oil and PEG 4000 at the same concentration, it was found that coating solution composed of PEG 4000 gave the fastest release rate of drugs because PEG 4000 is water soluble materials resulting in porous and brittle film. But formulation which were composed of glycerylmonostearate and castor oil showed the same release rate because both of them were not dissolved in water.

The influence of dissolution medium type on release characteristics was studied and the resultant release characteristics may be classified in 2 groups according to the composition of coating solution.

The first, the coated sucrose containing glycerylmonostearate, castor oil and no plasticizer showed release rate of the drug in pH change medium lower than the release in phosphate buffer pH 6.8 and 0.1 N HCl medium, respectively.

When PEG 4000 was used as plasticizer in coating solution, the release rate of the drugs in pH change medium was found to be higher than in 0.1 N HCl and phosphate buffer.

b. Influence of plasticizer content on the dissolution profiles of coated sucrose beads

The content of three plasticizer was investigated in 3 levels at 1%, 2% and 3%. The increase of plasticizer content in coated sucrose which contained glycerylmonostearate and castor oil, showed tendency of decrease in drug release. On the other hand, at the same concentration of glycerylmonostearate and castor oil, PEG 4000 gave higher drug release because it could be dissolved in water so increasing leaching of the drug from the coated film. The result could be found in all release medium and at all sampling time.

It could be explained that glycerylmonostearate plasticizer is practically insoluble in water. Moreover, it made the film flexible and decrease the water penetration into the film and dissolved the drug. So the increase of content of glycerylmonostearate could retard drug release.

In the same manner, it could be explained on the same basis in the case of castor oil as plasticizer but PEG 4000 which could be dissolved in water made porous and brittle film. Thus, the penetration of water was faster and easier.

In pH change method, it has reflective point like plateau phase at the time between 1.5-2 hr. because the medium was changed from acid to alkali condition. The release data were almost constant.

From the release rates of formulation 1 to 10, the coated sucrose beads which contained 3% glycerylmonostearate (Formulation 4) gave the lowest release profile. So, it was chosen

to be the starting formulation in further study in order to formulated the suitable formulation of drug release.

c. Effects of non-plasticizer outercoating film on the dissolution profiles of coated beads.

The coated sucrose beads from formulation 1 and 4 were outercoated with 10% EC outercoating solution as presented in formulation 11 and 12, respectively. It was shown that coated sucrose beads of formulation 11 exhibited higher drug release than formulation 12 at 1.5, 4, 8 and 12 hrs because the coating film of formulation 1 was more brittle than of formulation 4 as previously described. And during outercoating, particles-particles and particles-wall chamber impact occured. So, the plasticizer was the important component in coating solution.

d. Effects of hydrophillic film former outercoating on the dissolution profiles.

It was found that the coated sucrose beads of formulation 13 (outercoated with the combination of 10 % EC , 5 % HPMC and 1% PG) gave percentage of drug release at 1.5, 4, 8, 14 and 24 hrs which were higher than of formulation 12 (outercoated with only 10% EC), because hydrophilic property of HPMC and PG component in coating solution might enhance water penetration to dissolve the drug.

The beads of formulation 12 and 13 gave percentage of drug release in compliance with USP XXII requirement except the release in region 0 -1.5 hr was out of limit of USP XXII standard.

e. Effect of film former contents on the dissolution profiles

From the dissolution profiles, formulation 4 gave slow drug release and release rate at 12 hr was similar to Inderal LA 80 but the initial region still showed very fast release and almost constant at 1.5 hr.

Formulation 4 was further outercoated by 5% and 7% EC coating solution as described in formulation 14 (outercoated with 5% EC) and 15 (outercoated with 7% EC). The two formulations showed faster release rate than formulation 4 without outercoating because of the friability caused by the collision of the beads at these EC levels.

On the other hand, it was found that formulation 12 (formulation 4 outercoated with 10% EC) and 16 (formulation 4 outercoated with 15% EC) were better than formulation 4 because the content of EC was high enough to be the film barrier to retard drug release. It was found that the release rate of drug during 1.5-4 hr was still out of limit as specified by USP XXII standard.

f. Effects of drugs and film former content on the dissolution profiles

The release rate of formulation 17 coated beads was higher than of formulation 12, as on the same weight basis of the coated beads. The drug content was higher, so fast evaporation of solvent , resulting in higher amount of drug release. It could be explained that the drug content in the film had an effect on dissolution rate.

g. Effect of increase of coating layer on the dissolution profiles.

From the release rate, it was found that formulation 18, 19 and 20 showed fast drug release and out of limit of USP standard and almost constant at 12 hr because of increased friability which was created by additional coating process. So that, it could not further retard drug release rate to comply with the limit of USP XXII requirement.

h. Effect of change of content and type of plasticizer on the dissolution profiles.

Formulation 21 gave slow drugs release because using castor oil as plasticizer up to 5% (changed from glyceryl-monostearate) so it could retard drug release. But formulation 22 (outercoated with 5% EC and 1% castor oil) gave faster release of the drugs. It might be the result from the fracture of the coating film due to collision.

i. The release characteristic of combined coated beads

a) Combination of formulation 12 and 21

It was found that the increase of formulation 21 gave slower drug release which was similar to the release of Inderal LA 80 at 10 hr, but the region of time 0-4 hr and 14-24 hr. were out of limit of USP standard.

Increasing proportion of formulation 12 did not have an effect on release rate as shown in formulation 23 to 31. So that, the coated sucrose beads of formulation 21 had more

influence on drug release than of formulation 12.

b) Combination of formulation 17 and 21

It was seen that increasing amount of formulation 21 in combination with formulation 17 exhibited slower release rate than the coated sucrose beads of formulation 17 alone. But the release profiles was out of limit of USP standard. Thus, combination ratio between fastest and slowest release formulation were not successful in this experiment.

j. Effects of varied volume of outercoating solution on the dissolution profiles.

Formulation 4 was outercoated with 5% EC and 3% castor oil outercoating solution in the volume of 500, 1000, 1500 and 2000 ml as shown in formulations 37, 38, 39 and 40, respectively. It was found that as the volume of outercoating solution was increased, the release rate was decreased. It could be explained that the increase of the volume of outercoating solution gave thicker film barrier to retard drugs release.

From USP standard and Inderal LA 80 release data, it was found that the beads of formulation 37 and 38 showed faster release than Inderal LA 80 and some region was out of USP limit. The coated beads of formulation 40 showed slower drug release than of Inderal LA 80.

The beads of formulation 39 gave profiles which was almost similar to Inderal LA 80 during 0-12 hr but the profiles were almost constant at 12-24 hr. So that, the volume of

outercoating solution between 1000 ml (Formulation 38) and 1500 ml (Formulation 39) was very interesting to produced the satisfactory formulation.

So that, formulations 41, 42, 43 and 44 was formulated in order to have the release profile as required. It was found that formulation 41 exhibited the suitable release pattern. But formulations 42, 43 and 44 gave slower release than of formulation 41. Moreover, the beads of formulations 42, 43 and 44 showed percentage of drug release at 24 hr was lower than USP standard.

In conclusion, formulation 41 which was composed of outercoating solution 1100 ml was the suitable formulation. The release pattern of the three different lots of formulation 41 exhibited reproducible release pattern as illustrated in Figure 59.

Dissolution Studies of Coated Pellets

a. Influence of plasticizer type on the dissolution profiles of coated pellets.

From the release rate in 0.1 N HCl medium, the beads of formulation 45 showed higher release rate than other formulation because it contained no plasticizer. So, it gave brittle and porous film resulting in ready penetration of dissolution medium and rapid dissolution of propranolol hydrochloride.

PEG 4000 gave the higher drug release when compared to glycerylmonostearate and castor oil because of water soluble

property of PEG 4000. It might cause highly porous film ; thus, the drug release was faster.

b. Influence of plasticizer content on the dissolution profiles of coated pellets.

The content of three plasticizer was investigated in 3 levels as 1%, 2% and 3%. The increase of plasticizer content in the coated pellets which containing glycerylmonostearate and castor oil gave tendency to decrease drug release. In contrary, PEG 4000 increased release rate. This was because glycerylmonostearate and castor oil are hydrophobic materials.

c. Influence of concentration of outercoating solution on the dissolution profiles

The beads of formulation 48 was outercoated with outercoating solution which composed of 5 %, 7 % and 10 % EC as shown in formulation 55, 56 and 57, it was seen that when increase of EC content in outercoating solution, the release rate was increased. Results from the high level of EC content showed that it gave faster film drying due to lower solvent content, so fast evaporation of solvent occured. Resulting in the poor coverage of the film of the beads, which established more porous. So that, the higher level of EC content exhibited fast drug release.

d. Influence of the volume of outercoating solution on the dissolution profiles

The release rate of the coated pellet of formulation 58-61 decreased when the volume of outercoating solution was increased to formed further film thickness. When compared to the USP requirement of propranolol HCl extented release capsule, the volume of outercoating solution between 1000-1500 ml was found promising. Thus, the volume of outercoating solution was investigated in interval region between 1100-1500 ml.

From release rate of the beads of formulation 62, 63, 64 and 65, it was found that beads of formulation 62 gave release profiles in the limit of USP standard. And after the tripicated reproduction of formulation 62, it was shown that the coated beads of formulation 62 gave a suitable formulation for sustained release of propranolol hydrochloride .

Donbrow and Friedman (1980) reported two mechanism for the release of a drug in such a system:

a) Transport of the drug through a network of capillaries filled with dissolution media-applicable only if the water soluble component of the film is leached out of the matrix. It would appear in the formulation using PEG 4000 as plasticizer (formulation 8-10 and 52-54).

b) Transport of the drug through a hydrated swollen film-applicable if the water-soluble component (usually high-molecular weight) is retained within the matrix. It would appear in case of HPMC (formulation 13)

Donbrow and Friedman (1986) reported that the drug release from heterogeneous film which was prepared with EC and PEG 4000 was not disturbed by pH of the dissolution fluid and the

permeability of the film was unchanged in GI tract. Addition of PEG 4000 into the EC film accelerated the permeability of the drug, so the release rate of the drug was increased. After completing dissolution of the drug and PEG 4000 , ethylcellulose film gave porous structure and fracture.

Rowe (1981) suggested that flaws and cracks in film coating are common. So, this is the case that a third mechanism must also be considered.

c) Transport of drug through flaws, cracks and imperfection within the matrix which give the fastest drug release mechanism.

The theory of flaws and cracks in film coating can be explained in terms of the presence of residual internal stresses within the film coating. These are created by the shrinkage of the film on evaporation of the solvent and by the differences in the thermal expansion of the coating and the substrate. If these stresses exceed the cohesive strength of the film, cracking will occur and film integrity will be lost. Film prepared from low molecular weight polymer with short chains are relatively weak but as the chain length and hence molecular weight is increased the mechanical properties of the films also improve untill at some critical molecular weight there is no further improvement.

After dissolution test, the coated beads showed fracture film like orange peel (see Figure 98). The surface of the coated beads film was seen in Figure 99, it gave more porous and discontinuous film.

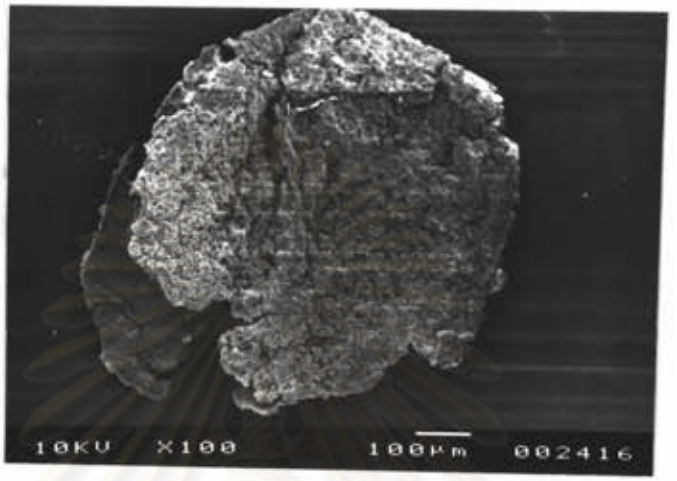
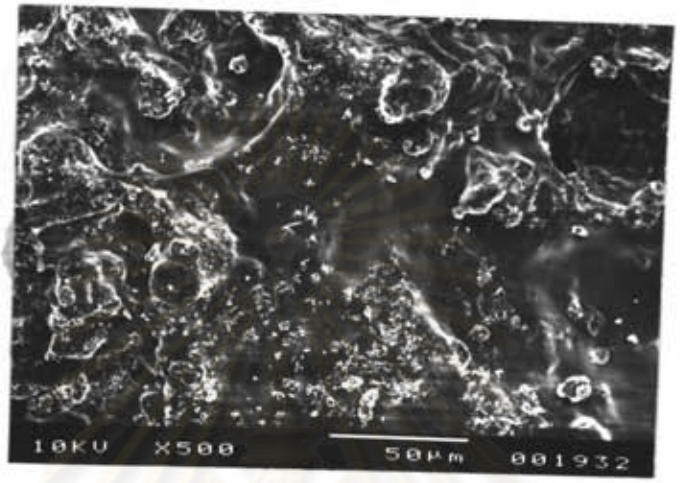


Figure 98 Photomicrographs of the representative coated sucrose beads after dissolution test (x100)



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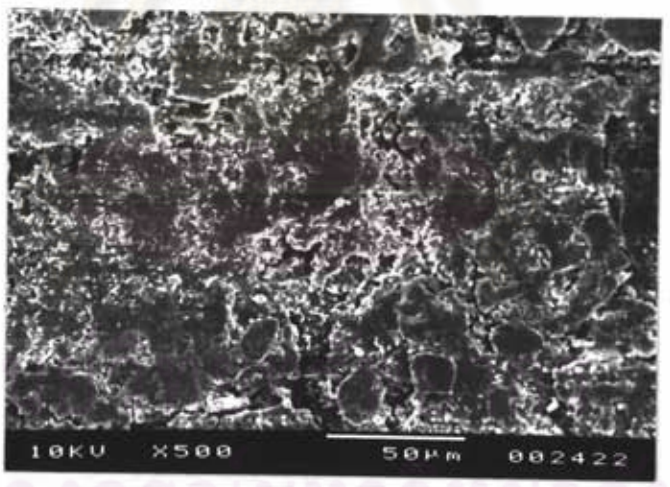

B

Figure 99 Photomicrographs of surface of the coated sucrose beads film (Before and After dissolution) (x500)

(Key: A Before dissolution test ,

B After dissolution test)

CONCLUSIONS

In fluidized-bed coating, simultaneous drying and particle enlargement are carried out by spraying the coating liquid onto a fluidized layer of dry particles. Particles growth occurs by solidification of layers of solid from the feed liquid onto the surface of the bed particles.

The samples of propranolol HCl coated beads were observed to disperse in the dissolution basket during the dissolution test and no gelled mass was formed at the base of the rotating basket. The dissolution apparatus 1 (basket) of the USP XXII standard was used because the coated beads could float on dissolution medium. So that, the dissolution apparatus 2 (paddle) was not suitable for use in this study. After dissolution test, it was found that the coated beads gave fracture film like orange peel and the sugar crystals inside the beads were entirely dissolved.

The results of the study showed that it is possible to produce coated beads with sustained release propranolol HCl film by a fluidized top spray method. The release rate of propranolol HCl depended on both the type and content of plastizicer as well as the amount coating material (Ethylcellulose).

The results from the experiments were compared between sucrose and pellets as core beads with variation of type and content of plasticizer.Three groups of plasticizer, namely polyols, organic ester and vegetables oil & glycerides were represented by PEG 4000, glycerylmonstearate and castor oil, respectively.

Generally, plasticizers are often added to polymers in order to change their physical properties and enhance their film forming characteristics. To be effective, a plasticizer must interpose itself between the polymer chains and interact with the forces holding the chain together thereby extending and softening the polymer matrix. Since polymer chain mobility is an important factor influencing the magnitude of the stress due to shrinkage. Plasticizers, by increasing chain mobility, result in film cracking and bridging.

From the representative plasticizers, PEG 4000 can be dissolved in water. The presence of drug and PEG 4000 together in ethylcellulose film gave greater pores for the drug to be leached out, leading to increase in the rate of drug release.

Glycerylmonosterate was practically insoluble in water and castor oil was insoluble in water. So, both of them were able to retard water penetration. Normally, the concentration of castor oil in delayed drug matrix usage was 5-10 %, but in this study, the concentration over 4 % gave soften and oily coated beads which had low flowability. In the case of glycerylmonostearate concentration over 4% gave the more solid part dispered in coating solution which may clogged nozzles. So, the cencentration level was chosen such as 1, 2 and 3% plasticizer. PEG 4000 was used at the same concentration, and during the dissolution test, it was found that as PEG 4000 concentration was increased, the release rate was increased.

Increase in glycerylmonostearate and castor oil could impede water penetration into the beads to dissolve drugs

resulting in decrease of drug dissolution. In contrary , water soluble property of PEG 4000 could increase penetration, established the formation of the pores and channels for water to penetrate inside and dissolved the drugs. So that, the drug release rate was increased.

In outercoating procedure, the surface of the coated film was rough and the release rate was increased because the outercoating process brought about the collision of each particle and between particles and the chamber wall which caused increase in the friability of the coated beads and fracture of the coated film.

The effect of plasticizer on dissolution profiles could be noticed from the non-plasticizer formulation(formulation 1 and 11).It showed the fast release rate because of the fracture of the film due to the collision of particles with the chamber wall.

The addition of hydrophilic film former (HPMC and PG) exhibited the faster release rate because water could easily penetrate through pores of the film to dissolve the drugs.

The volume of the outercoating solution also have an effect on the thickness of the film to retard drugs release but the large volume of the outercoating solution may be retard propranolol hydrochloride release at 24 hrs until it was lower than the USP XXII requirement. So that, the beads of formulation 41 (outercoated with 1100 ml) was the suitatable formulation for propranolol hydrochloride extended release capsules. The plasticizer used was glycerylmonostearate in coated beads, it can retard drug release. Addition of castor oil in the outercoating

process further increased the flexibility of the film. Glycerylmonostearate could retard drug release better than castor oil but in the case of flexibility of film, castor oil is better than glycerylmonostearate. For the coated pellets, when the volume of outercoating solution used was 1100 ml in formulation 62, it gave the release characteristic similar to the formulation 41 but the release pattern of the three different lots of formulation 62 was less fluctuated between several lots than formulation 41. It could be due to the fact that the spherical shape of pellet core was easily controlled during coating procedure.

This experimental study can produce propranolol hydrochloride extended release capsules in compliance with the USP XXII requirement. So, it need further in vivo studies in order to confirm its clinical performance.