CHAPTER IV

DISCUSSION AND CONCLUSION

Effect of Spheronizer Speed, Spheronization Time, Binder Type and Binder Concentration on Appearance and Physical Properties of Lactose-Avicel PH101^{R} Placebo Pellets

The microscopic appearance of lactose-Avicel PH 101^{R} placebo pellets in this study are presented in Figures 12-19.

The results indicated that spheronizer speed, spheronization time,binder type and binder concentration had effect on the appearance of the placebo pellets. Forming the pellets during spheronization step may be explained that the extrudates with sufficiently plastic property are spheronized by the forces.The forces occur from moving of friction plate of spheronizer. When the friction plate is moving, the extrudates are initially broken down into short lengths and formed spherical pellets in the later. So, all spheronization times, binder types and binder concentrations studied, pellets obtained from high spheronizer speed were more sphericity than those from low spheronizer speed. Because the forces from higher speed were more than those from lower spheronizer speed. Increasing spheronization time will increased time to apply the forces. From the above reason, increasing shorter rod shape or increasing sphericity with smooth surface of placebo pellets were obtained from low or high spheronizer speed, respectively, when

spheronization time was increased. Increasing binder concentration, the longer rod shape or decreasing sphericity with larger size pellets were obtained from low or high spheronizer speed, respectively. Because increasing binder concentration was increased binding properties,except for placebo pellets used various concentrations of HPC-M^{R} at high spheronizer speed the appearance of these pellets were little difference. Each spheronization time and each binder concentration at high spheronizer speed, pellets using HPC-M^{R} as a binder were more sphericity than pellets using with the other binders. This was noticed that it may be due to HPC-M^{R} could be a suitable binder for pelletization process so that change in concentration and high spheronizer speed had little effect on microscopic appearance. In the case of spheronizer speed,the results obtained confirmed that high spheronizer speed was better and would be selected for further studying on physical properties of the pellets.

The physical properties of lactose-Avicel PH101^{R} placebo pellets in this study are shown in Tables 6-16 and Figures 20-66. The results indicated that spheronization time, binder type and binder concentration had effect on some physical properties of the pellets; such as the following paragraphs.

Almost spheronization time and binder concentration, which were studied, had no effect on bulk density and tapped density. Bulk density was not different from tapped density. The reason may be due to the pellets which were probably arrange in closest packing, which in agreement to Funck, et al.(1991). The authors indicated that the

pellets using 2% w/w of HPC or MC as binder were not different between bulk density and tapped density.

Almost spheronization times, binder types and binder concentrations, which were studied, had also no effect on the percent friability. And the percent friability of pellets in this study was very low value because adding binder in the formulation of pellets may help to increase binding property and decrease the percent friability. The results also corresponsed with Funck, et al. (1991).

Almost spheronization times, binder types and binder concentrations, which were studied, had no effect on the angle of repose and the values were low which indicated good flow property.In the case of flow rate of pellets in this study varied by spheronization time,binder type and binder concentration. However, the range of flow rate for all pellets in this study indicated good flow and are in agreement with angle of repose value which were below 30^{o}. Flow rate of the pellets prepared with lower binder concentration were higher than the others except for HPC-M^{R} at 2.00 % w/w was higher. Compared with various binder types,pellets using HPC-M^{R} as binder gave the highest flow rate value.

Particle size distribution, mean particle size and percent sieve fraction on 14/20 mesh cut in this study depending on spheronization times, binder types and binder concentrations. Mean particle size of pellets were increased with increasing spheronization time. When spheronization time was increased, pellets may be combined with the

fine particles that occurred in the process. But increasing spheronization time at each binder concentration had no effect on the percent sieve fraction on 14/20 mesh cut. The results may be explained that changing of mean particle size was occurred with increasing spheronization time, however, particle size was in the range of 14/20 mesh cut. Increasing binder concentration, the pellets had increasing mean particle size but decreasing percent sieve fraction on 14/20 mesh cut. Because increasing mean particle size may decreased in desirable particle size. These results did not included with the pellets using HPC-M^{R} a binder. Pellets using HPC-M^{R} as a binder were more narrow size distribution than pellets using the other binders especially at 2.33 % w/w of HPC-M^{R}. In addition, it was observed that increasing concentration of HPC-M^{R} at each spheronization time did not change in mean particle size. All spheronization time and binder concentrations were studied. The percent sieve fraction on 14/20 mesh cut of pellets using HPC-M^{R} as a binder was higher than that used the other binders because more narrow particle size distribution obtained.

From these results, HPC-M^{R} could be a suitable binder for spheronization process because the pellets had narrow particle size distribution, high desirable particle size and flow rate, low angle of repose and percent friability and not different between bulk density and tapped density. The interesting formulations and conditions for producing lactose-Avicel PH101^{R} pellets were prepared by using 1.67 % w/w or 2.00 % w/w of HPC-M^{R} as a binder, 10 and 15 min of spheronization time at 951 rpm of spheronizer speed.

It was found that the formulation that consisted of 2.00 % w/w of HPC-M^{R} as a binder, 15 min of spheronization time at 951 rpm of spheronizer speed gave the best results and was selected for studying the effect of water content on appearance and physical properties of lactose-Avicel PH 101^{R} pellets.

Effect of Amount of Water on Appearance and Physical Properties of Lactose-Avicel PH101^{R} Pellets

The microscopic appearance of lactose-Avicel PH 101^{R} pellets in this study, are presented in Figure 67. The results showed that the optimal amount of water that gave sphere shape pellets was in the range of 40 % w/w to 44 % w/w base on dry basis. When the lower amount of water was utilized, the pellets had long rod shape. It may be explained that the lower amount of water did not give enough plastic mass properties. In this case, the extrudates can be broken ,however the sphere shape pellets were not occurred. When the higher amount of water was utilized, the larger size of pellets were obtained. This because of the extrudates become over wetting and plastic mass were not broken into short rod. Then, the extrudates aggregated to produce larger size pellets. The results were similar to the reported by Remon and Schwartz (1987), they found that increasing quantity of granule solution and sieve size obtained larger granules with reduce friability. Lovgren and Lundberg(1989) also found that increasing addition suitable amount of water improved to moulding properties of the mass so that the extrudates were more easily and effectively rounded to spherical pellets. Baert and Remon (1993) suggested that round sphere shape with

smooth surface pellets were obtained by using the higher amount of water but not over wet. Therefore, the formulation that used 40 % w/w , 42 % w/w of water base on dry basis were selected for studying on various physical properties of the pellets.

The physical properties of lactose-Avicel PH101^{R} pellets in this study are shown in Table 17. The results showed that the optimal amount of water was approximately 40 % w/w to 44 % w/w of water base on dry basis. The pellets had narrow size distribution. The mean particle size and percent friability of lactose-Avicel PH101^{R} pellets prepared with 40 % w/w, 42 % w/w and 44 % w/w of water base on dry basis were not significantly different at 95% confident level. Flow rate, percent sieve fraction on 14/20 mesh cut, bulk density and tapped density of the pellets decreased with increasing amount of water. Therefore, the formulation that consisted of 2.00 % w/w of HPC-M^{R} , 15 min of spheronization time, 40 % w/w of water base on dry basis at 951 rpm of spheronizer speed was selected for modifying to prepare uncoated terbutaline sulphate pellets.

Physical Properties of Uncoated Terbutaline Sulphate Pellets

Terbutaline sulphate had some effect on appearance and physical properties of pellets. After intensive study of the uncoated terbutaline sulphate pellets formulation, were found that 1.67 % w/w of HPC-M^{R} as a binder, 15 min of spheronization time,40 % w/w of water base on dry basis at 1010 rpm of spheronizer speed were suitable conditions.

The microscopic appearance of product in each step of pellets preparation is presented in Figure 68 and 69. The products in dry mixing, wetting, extrusion and spheronization step were powder, wet mass, extrudates and pellets, respectively.

The physical properties of uncoated terbutaline sulphate pellets is shown in Table 18. The results indicated that uncoated terbutaline sulphate pellets had narrow size distribution. The mean particle size was approximately 0.962 mm and percent sieve fraction on 14/20 mesh cut was $\tilde{}$ 77.00. The pellets had high flow rate but very low in percent friability. Thus, uncoated terbutaline sulphate pellets had good physical properties.

The dissolution profiles of uncoated terbutaline sulphate pellets is presented in Figure 70. The results indicated that the release of terbutaline sulphate from uncoated terbutaline sulphate pellets was very fast.About 90 % of terbutaline sulphate was released in 15 minutes. But terbutaline sulphate was not completely released after 12 hours of dissolution test. The reason may be due to the drug remained intact with microcrystalline cellulose during dissolution test. The result is in agreement with Millili and Schwartz(1990). They found that drug release from microcrystalline cellulose pellets using water as granulating liquid remained intact during at least 12 hours of dissolution test.

Physical Properties of Film Coated Terbutaline Sulphate Pellets

The microscopic appearance and dissolution profiles of film coated terbutaline sulphate pellets are presented in Figures 71-84.

1 Appearance of Film Coated Terbutaline Sulphate Pellets

The microscopic appearance of film coated terbutaline sulphate pellets appeared to be round shape with fairly smooth surface.

2 Dissolution Profiles of Film Coated Terbutaline Sulphate Pellets

2.1 The Effect of Amount of Propylene Glycol on the Released Profiles of Film Coated Terbutaline Sulphate Pellets

The microscopic appearance and dissolution profiles of film coating solution formulation 1 and 2 at 5.4 % coating level were compared. Formulation 1 and 2 had 10 % and 20 % propylene glycol by weight of ethylcellulose, respectively. Film coated pellets before dissolution test of both formulations had round shape with fairly smooth surface. After dissolution test of both formulations;the pellets had round shape with a little collapse film and some pores on the film coating layer. In the cross-section view ; there were some channels in the film coating layer. These appearance showed that drug may be released through the channels during dissolution, however , propylene glycol may effect on pores of the film coating layer and were blocked

at high coating level. In the case of continuous film coating layer, drug may diffuse through the film, therefore drug release from film coated pellets on both formulations were similar.

2.2 The Effect of Amount of Ethylcellulose on the Released Profiles of Film Coated Terbutaline Sulphate Pellets

The results from scanning electron microscopy showed that film coated pellets had round shape with fairly smooth surface. Relatively thicker of film layer was obtained by increasing percent of film coating or increasing amount of coating solution. After the dissolution test, film coated pellets still had round shape, however, some collapse film and and some pores on the film coating were observed. In the cross-section view, there were channels in the film coating layer. These appearances indicated that drug may be released through the channels during dissolution . The release of terbutaline sulphate from film coated pellets depended on percent of film coating layer. The results from dissolution test showed that the increasing coating level decreased drug release from film coated pellets. These were suggested that the film was controlling the release process. Therefore ,the drug solution had to diffuse through a thicker membrane before dissolved in the surrounding medium. The results corresponsed with Sheen, et al. (1992); Yuen, Deshmukh and Newton (1993); Chetty and Dangor (1994).

2.3 The Effect of Ratio of HPC-M^{R} and Ethylcellulose on the Released Profiles of Film Coated Terbutaline Sulphate Pellets

The microscopic appearance and dissolution profiles of coating formulation 3, 4, 5 at 3.2 % coating level ware compared. Formulation 3, 4, 5 contained ratio of HPC-M^{R} and ethylcelulose 1:9, 2:8 and 3:7, respectively. Film coated pellets before dissolution test had round shape with fairly smooth surface. After dissolution test,the pellets still appeared to be round shape with some pores on the film coating layer and channels in the cross-section view of the film coating layer. These appearance showed that drug may be release through the channels during dissolution test. The release of terbutaline sulphate from film coated pellets depended on ratio of HPC-M^{R} and ethylcellulose in coating layer.The results from dissolution test indicated that the increasing ratio of HPC-M^{R} and ethylcellulose in coating layer were increased drug release from film coated pellets. Hydroxypropyl cellulose is a water soluble polymer, therefore, there were suggested that the formulation of pores were increased by increasing ratio of HPC-M^{R} and ethylcellulose in coating layer. In this case, drug could be dissolved and pass through these pores to the dissolution medium. The results were similar to report by some researcheres. Sheen, et al.(1992) found that the pellets coated with combination of Surelease^{R} and HPMC had faster rate of drug release than those coated with Surelease^{R} alone. Yuen, Deshmukh and Newton (1993) found that the pellets coated with ethylcellulose contained coating additives (such as acacia, NaCl, MC 15, MC 400, PEG 400 or PEG 4000) increased drug release rate but the rates depended on additives properties. Chetty and Dangor (1994) found that the release rate increased with increasing HPMC leval in ethylcelulose film.

2.4 The Effect of Loading Dose on the Mixture of Uncoated Terbutaline Sulphate Pellets and Film Coated Terbutaline Sulphate Pellets

The release of drug from 1.1 % and 1.5 % coating level of formulation 1 were lower than that from Bricanyl^{R} Durules. But increasing initially drug release and no effect on the later period of dissolution test was required.The results from dissolution test showed that combination of uncoated terbutaline sulphate pellets and film coated terbutaline sulphate pellets increased initial drug release. There were suggested that uncoated pellets can be used as loading dose for initial drug release.

2.5 Dissolution Profiles of Selected Formulation Compared with Commercial Product

The formulation selected to compare with commercial product was capsule containing mixture of 1.1 % ethylcellulose coated pellets (Formulation 1) and uncoated pellets at ratio 7:1.This formulation gave satisfactory profile such as less standard deviation, high drug release at 12 hours (about 97.59 %) and dissolution profile close to the commercial product.

2.6 Reproducibility of Film Coated Terbutaline Sulphate Pellets

The dissolution profiles of the selected formulation found to be reproducible indicating the extruder and spheronizer used

for these studies were quite efficient to produce the spherical granules or pellets. And the fluidized bed with Wurster column used for these studies was also quite efficient in applying the coating solution to the surface of pellets to produce the satisfactory coating.

CONCLUSION

The sustained release terbutaline sulphate pellets capsule could be prepared by coating terbutaline sulphate pellets with an appropriate amount of ethylcellulose using a Wurster column process. The terbutaline sulphate pellets were prepared by the selected conditions using extrusion and spheronization process.

In this study, there were many factors which were effected on appearance and physical properties of lactose-Avicel PH101^{R} pellets. These factors were spheronizer speed, spheronization time, binder type, binder concentration and amount of water.

We can conclude that,

1. The sphericity of pellets were increased with increasing spheronizer speed.

2. Increasing in sphericity, smooth surface and mean particle size of the pellets were obtained when spheronization time was increased

3. Increasing binder concentration, the pellets were longer rod shape at low spheronizer speed or decreased in sphericity at high spheronizer speed, increased in mean particle size, decreased in desirable particle size and flow rate.

These results did not include with pellets using HPC-M^{R} as a binder.

4. Pellets using HPC-M^{R} as a binder were sphere shape (at high spheronizer speed) narrow size distribution, high desirable particle size and flow rate, when pellets using the others binder were compared. And increasing HPC-M^{R} concentration had no effect on shape and mean particle size of pellets.

5. When spheronization times, binder types and binder concentrations were studied, the pellets with low angle of repose, low percent friability and not different between bulk density and tapped density were obtained.

6. Increasing amount of water had effect on shape, flow rate, bulk and tapped density of the pellets.

The selected formulation for preparing lactose-Avicel PH101^{R} placebo pellets consisted of 2.00 % w/w of HPC-M^{R}, 40 % w/w of water base on dry basis, 15 min of spheronization time at 951 rpm of spheronizer speed. However, the formulation of uncoated terbutaline sulphate pellets were modified from the selected formulation of lactose-Avicel PH101^{R} placebo pellets because binding property of drug.

In this study, the composition and the amount of film coating solution had effect on drug release. The drug release from film coated terbutaline sulphate pellets were decreased with increasing amount of

ethylcellulose coating solution. When amount of HPC-M^{R} in coating solution was increased, the drug release from film coated terbutaline sulphate pellet was also increased. Both extrusion and spheronization process and coating with a Wurster column process could be reproducible.