CHAPTER IV
DISCUSSION AND CONCLUSIONS

In this study, propranolol HCl, a highly water soluble drug, was produced in two preparations: capsule filling wax matrix pellets prepared by pelletization process using an extruder-spheronizer machine, and matrix tablets prepared by compression of the pellets. Amounts and types of excipient including waxes and diluents, drug content, and dosage forms of these two preparations could affect the physicochemical properties and drug release.

Avicel PH 101® was used as a filler because it has spheronization enhanced property. Because of its high internal porosity and large surface area provide highly absorbent and moisture retaining properties which are essential to the extrusion process. The retained moisture acts as a lubricant during extrusion and helps to manipulate the pellet shape during spheronization (Ramaro and Bhagwan, 1998). Other studies have been reported using microcrystalline cellulose with functional application as pelletization aid in pellets containing glyceryl palmitostearate and Gelucire 50/02® (Edimo A. et al., 1993), pellets containing glyceryl monostearate (Blanque D. et al.,1995). But from the experiment, the pellets could be still formed although Avicel PH 101® in the formulation is lower than 20 %. Because the wax compensated the lack of plasticity and cohesiveness of the mass wetted with the water. If the wax in the formulation increased, the lactose was totally replaced. And then Avicel PH101® will be the next diluent to be replaced. Avicel PH101® was depleted from the formulation when the wax is increased up to 50 %.

Carbon tetrachloride has two major roles in the melting process of the wax (Tables 5, 6). Firstly, it is required to increase the volume of the wax solution enough for forming matrix by distribute throughout the powder bed. Secondly, it is used to slow down the congealing step between the mixing process of the wax solution and powder bed. Carbon tetrachloride was then evaporated during the drying process

in the hot air oven of the pellets. Lactose in the formulation was the filler and was replaced when the wax in the formulation increased.

After homogenous mixing, the bed became agglomerate and harder than the powder characteristic. These agglomerate were passed through the extruder to produce powder bed again because the moisture content of the wet mass is an important variable, especially in the extrusion and spheronization process (Bains D. et al., 1991; Baret L. and Remon J.P., 1993; Fielden K.E. et al., 1993; Otsuka M. et al., 1994). The wet mass must meet the requirement for the extrusion process that is the ability of the powder material to form a cohesive plastic mass upon wetting, that remains homogenous throughout the extrusion process. For spheronization, a balance between plasticity and brittleness of the wet mass is needed to successfully obtain the product. Water in the formulation has two major roles in the granulation process. It is required to bind powder mix during granulation. Its plasticizing and lubricating properties also aid the spheronization-extrusion process. (Lucy S.C.W. et al., 1993)

In the spheronizer, pellet formation in the presence of sufficient moisture is driven by three external forces: 1) centrifugal forces 2) gravitational forces 3) frictional forces. The centrifugal forces is generated by rotating of the friction plate, and it force the particles toward the wall of the chamber. The particle cascade down towards the bottom of the plate by gravitational forces. And then, the particles rotate around the friction plate by the frictional force. This sequence is then repeated until completion of the process.

The study showed that suitable mass load should not be less than 250 grams for completely mixed and suitable moistened mass (Table 4). Too small batch made difficult thoroughly mix because the paddle of planetary mixer was rather higher than the powder bed and the yield from extrusion step was too low for the next step. Too big batch overloaded the machine. There was no remarkable difference in size, shape, morphology, when different spheronization speed was used. Thus, the lower

speed was chosen for saving the energy and preventing overload of the machine. The shortest spheronization time which smooth surfaced, sphere and rigid pellets were made was 10 minutes. In the contrary, the longer spheronization time than the standard time showed no significant difference in physical properties.

Recently, wax was widely proved to be a suitable material for controlled release preparations. (Thomsen L.J. et al., 1994; Evrard B. and Delattre L., 1996; Vasuhiko M. et al., 1996) Thus, it might delay the release characteristics of both pellets in capsule and tablet preparations in this study. Almost all pellets dosage form showed uncontrollable release rates that were not good enough to be formulated into sustained release preparations. Compression of these pellets was an alternative way to prolong the release rate and achieve the preferred release characteristic especially for uncoated pellets. The size and shape, as well as, surface properties of microspherical particles , the type and amount of retarding agent, selection of the external additive, and the rate and magnitude of the pressure applied were found to be the most critical factors to be considered in order to obtain and maintain the desired drug release properties of microsphere (Celik M. and Maganti L., 1994). But McGinity, Cameron and Cuff (1983) reported their interesting result that compaction force as well as hardness should play minimal role on release rate within the ordinary range of 7.0-15.0 kg hardness. From that data, it could be concluded that as the compaction force was increased up to a certain limit, the microparticle would elastically deform so that the tablet porosity fell to minimum value and remained constant thereafter. So the hardness in this experiment was set to the range of 18 – 24 kp or about 8 – 11 kg.

Tablets produced from pellets compressed by hydraulic press faced some problems during tabletting process. Because the die could not be locked with the base of lower punch. So, when increasing the pressure to the pellets containing rather soft mass wax such as beeswax, Gelucire®, glyceryl monostearate, some parts of the tablets were squeezed through the lower part of the die and resulted the sheet of the wax matrices around the edge of the matrices. The weight of these tablets was

decreased. This situation could be corrected by applying the force to fix the die close with lower punch base and adding more pellets to the die cavity to compensate the weight of wax matrice sheets that was detached from the edge of the matrices during testing. This situation was not found with the other waxes or when using single punch tabletting machine to compress the matrices.

This study concerned with concentrations, types of wax and concentrations of active ingredient that were suitable for pelletization process, tabletting process and release profile.

Physicochemical Properties of Preparations.

Wax matrix pellets preparations.

Morphology of pellets from different formulations was studied by SEM using different magnifications (Figures 13 – 17). The shape and surface topography of wax matrix pellets were found to be affected by the type of wax material. When the carnauba wax was used, the roughness of the pellets were clearly seen. These results may be due to physical properties of the wax. Carnauba wax had hard and weak texture. Carnauba wax were still small rough particles and could not produce the plasticity and cohesiveness in the powder mass when subjected to the extrusion process only one time. Even though some water was added to the powder mass. So, extrudate containing carnauba wax had non-continuous and rough texture. It showed short and weak extrudate rod. Some was still found in the powdered form. Not only this reason, but also the high melting point temperature of the wax. Carnauba wax would become rigid from the molten state rapidly before homogenous mixing. Thus, it cannot distribute, disperse thoroughly and remained in small particle form. The pellets obtained from carnauba wax mainly showed small size fraction, rough texture.

When using Gelucire®, almost all pellets were found in long dumbbell shape. Gelucire® posses too soft mass and had a trend to adhere with the chamber of spheronizer. This effect may be due to low melting temperature of Gelucire®. So, spheronization time must decreased before agglomeration of the extrudate containing Gelucire® occurred.

The higher spheronization speed obtained smaller, rounder and smoother pellets (Lucy S.C. et al., 1993). These effects could be clearly seen when the difference of spheronization speed was more than 500 RPM. The over dried surface of the pellets was disadvantageous when using higher speed. Spheronization time also did not have significant effects on this study (Figure 17). This may be due to too low variation in spheronization speed in this experiment. A combination of speeds ranging from 1000 to 2000 RPM and residence time between 5 and 15 minutes might be used to produce spheroid with a modal fraction in size range of 0.7 – 1.0 mm. It was summarized that these two factors controlled the pellet shape and density (Hileman G.A. et al., 1993).

Particle size distribution of the pellets also does affect the performance of the final product. The particle size distribution should be as narrow as possible. (Harris M.R. and Ghebre S.I., 1989). Because A narrow particle size distribution from the same formulation should give the same release rate and release profile. In addition, this could eliminate surface area variation of the particle in dissolution studies.

Only type of wax material used significantly affected the size distributions (Figures 18 – 25), while different amount of wax and propranolol HCl in pellet formulation showed no effect on pellet size. Carnauba wax produced wider size distribution pellets than those the other waxes (Figure 18). An increase in the yield of the smaller fraction was seen, probably due to a greater degree of fragmentation of weak extrudate rod during the initial state of the spheronization process. As the reason

mentioned above, carnauba wax could not create enough plasticity and cohesiveness for the wet mass during the extrusion process.

Pellets containing Gelucire® exhibited the larger size than those used other waxes used (Figures 21, 25). Almost all pellets had dumbbell shape and were in the range of 14-18 size. Gelucire® possessed too soft mass for spheronization and had tendency to agglomerate with the other particle during the process. So, spheronization process had to stop before agglomeration took place. The particles were in dumbbell shape and only a little were in spheroid at that time.

Beeswax had harder mass than Gelucire® but softer than the other waxes. The highest percent of beeswax in the formulation could not give the size of the pellets in the preferred range and exhibited wide size distribution. High percentage of beeswax also showed a tendency to agglomerate (Figures 18, 22).

The results demonstrated the feasibility of using pelletization technique adopted in this work to produce pellets of relatively narrow particle size from the other waxes excluding carnauba wax, Gelucire® and beeswax.

In general, products containing greater amounts of fine particles often have higher bulk densities because those smaller particles could easily fill the void between the large particle. The slight difference of tapped and bulk density was formed when the size distribution of the product was narrow and the shape of every particles in the product were closely to spheroid and hence low percent compressibility. But in the formulations such as 50 % propranolol HCl with 40 % carnauba wax and 40 % propranolol HCl with 50 % beeswax had some problem in the shape and size. The size of the former was mainly retained on sieve size of 14-mesh range but these large particles were adhered by the fine particles. These fine particles could fill the void between large particle resulting in higher bulk density. The shape of

the latter showed as long as ellipsoid shape. The pellet bed of this formula contained high void volume resulting in low bulk density (Table 7).

If the tapping force could make the repacking of the particle and reduce void volume in the pellet bed. The percent compressibility would be increased especially the long shape of particle like pellets containing Gelucire® or high content of beeswax.

The term of "angle of repose" which lower values indicated better flow characteristics (Aiache J. and Beyssac E., 1995). All wax matrix pellets had good flow characteristic (Table 7). As a result of the low value of bulk and tapped density and high value of compressibility index. Angle of repose of wax matrix pellets from this study generally ranged from 21.20 – 30.40^0 from funnel method that was in the acceptable range (25 – 45 ^{0}). Wax matrix pellets showed rather low angle of repose and high flow rate. This may be due to physical characteristic of the pellets. These pellets contained single large and spherical particles so higher flowability was obtained. Pellets containing beeswax and Gelucire® showed sticky and frictional effect to the other particle or contacted surface. Moreover, pellets obtaining these two waxes were not complete spheroids. These results would lead to high angle of repose and a reduction in free flowability of Gelucire® or beeswax pellets.

The amount of water is very critical to achieving pellets of desired quality, sphericity and yield in the extrusion/spheronization process (Elbers J.A.C. et al., 1992). Optimum moisture content and distribution are desirable in order to produce a dense extrudate and to lubricate the wet mass during extrusion. Poorly wetted masses create excessive pressure and friction in the extruder, ultimately resulting in pellets that crumble and, consequently, too many fines are produced. Masses that are over wet, on the other hand, promotes coalescence, spheroid growth and produce larger pellets. The same result was obtained by Ramaro C. and Bhagwan D.R., 1998. There was a relationship between the amount of water and the "stickiness"

of the mass. When using Gelucire® or high percent of beeswax in the formulation (Table 8), The amount of water was decreased until the mass did not adhere to the plate and the wall of the chamber of spheronizer. The addition of water to the Gelucire® system could result in large hydration and soften the wet mass (Blanque D. et al., 1995). On the contrary, beeswax possessed the stickiness by itself. So, amount of water had to decrease to prevent the adhesion of wet mass with the plate and the wall of chamber. The presence of varying quantities of other waxes in the formulation did not change the amount of water significantly.

Formulation modification that included the type of waxes could affect the percent yield of pellets. Extrusion and spheronization of some waxes include beeswax, carnauba wax, and Gelucire® allowed low yield of the products (Table 8). The percent yield of pellets containing these waxes were lower than other kinds of waxes about 5-10 %. These formulations which incorporated beeswax and Gelucire® were proved to be sticky (Blanque D. et al., 1995). The behavior of these masses was not very satisfactory, as they tended to adhere to inside wall of the extruder, the plate of spheronizer and resulted in the lower percent yield. As previously mentioned, carnauba wax characteristic was not appropriate for producing pellets. The optimum water amount used in the formulation containing carnauba wax was very narrow. So if the amount of water in the formulation was higher than optimum point, the large pellet size would occur. Fine particle would obtain from the opposite way. So, the mass must repassed through the extruder and adjusted the water again until the pellets could be obtain from spheronization process.

Generally, if the coating of the pellets is necessary to be applied as part of the manufacturing process. The spherical shape provides ideal conditions for a uniform application of the film, improving the flowability and controlled release product (Podezeck F. and Newton J.M., 1994). It could be concluded that type of the wax had more significant effect to the sphericity than amount of wax in the formulations (Table 9). Some of possible reasons were previously described.

Moreover, the wet powder mass containing beeswax and Gelucire® tended to adhere the plate of spheronizer. Therefore, its grooves were blocked and the material was transported from pellets to pellets via the plate. Thus the whole principle of the spheronization, i.e., the rolling movement of particles along the grooves of the plate, became ineffective. The result reflected in pellets that failed to produce spherical pellets, as they gave product of varying degrees of roundness (Blanque D. et al., 1995). Hellen L. and Yliruusi J. (1993) claimed that the elongation or aspect ratio (d_{max}/d_{min}) provided the best differentiation of the shape of a set of pellets. Chapman et al., 1988 have clearly shown that circularity, i.e. four times the squared perimeter (P) divided by the projected area (A) ($4P^2/A$) which is the factor of form factor, will not provide a clear differentiation between pellets of different shape. According to the results, form factor indicated the sphericity closer to unity and there is no clearly difference between the formulation. Loading dose did not show any effect to the sphericity of the pellets.

Pellets that showed friability less than 1 % were mechanically acceptable for the next process. The friability is an indicator of pellet strength or hardness that is the lesser the friability, the greater the hardness (Vervaet C. et al., 1995; Erikainen S., 1991). The wax matrix pellets prepared from the above mentioned process showed low and narrow range percent friability in all formulations (Table 10). This could be due to the wax in these formulations would induce the hardness of the pellets by forming the matrix in the pellets. These matrix pellets should stronger than those pellets without waxy materials or hydrophilic polymer as additive.

The percent drug content of matrix pellets was not affected by the method of preparation (Table 11). The good percent drug content was obtained. This result indicated that the mixing of wax solution and other powder in planetary mixer could produce the homogenity of propranolol HCl, wax and other filler. This can be seen from percent drug content was in the range of ± 5% of theoretical drug content.

IR spectra was used to confirmed the interaction of drug and fillers in wax matrix products (Figures 28 – 31). The resulted peak of wax matrix pellets depicted the combination of the characteristic peaks of the original drug with the characteristic peak of wax. But the intensities of these peaks of wax matrix pellets were reduced as compared to those of single material. Some peaks of lactose and Avicel PH 101® disappeared because there was a small quantities in the formulation. All of the waxes showed the same characteristic of IR spectra because they possessed the same structure backbone. The disappeared peak at 1736 cm^{-1} of formulation containing 40 % propranolol HCl with 50 % beeswax. This might be due to the difference in batch number was used in those two formulation. The difference in batch may come from natural source different, which contained some different components (Figure 30). Some of the positions of these peaks were shift from single material not over 5 cm^{-1}. It could be concluded that interaction between drug and wax was not found and types of waxes had no effect on the IR spectra.

The crystallinity of the wax matrix pellets was investigated by x-ray diffraction analysis (Figures 32 and 33). The peaks in x-ray diffraction pattern of wax matrix pellets were less intense than those of the original crystal. Because of high intensities of peaks of beeswax and carnauba wax and broad peak of Gelucire® near 21^0 2θ in diffractogram. Thus, the changes in the pattern of diffractogram from wax matrix pellets were observed by the absence of peak at 21.00^0 2θ of propranolol HCl. There was no lactose in the formulation and Avicel PH 101® was used in low amount. So the peak of these two filler disappeared. The small change of some characteristic peaks position were detected because wax matrix pellets could not be packed into quartz slide as smooth surface. There was some deviation of the whole diffractogram when the x-ray beam exposed to the rough surface. But this would not affect the pattern of diffractogram. The x-ray diffractograms of the wax matrix pellets still exhibited the crystalline form of both propranolol HCl and wax.

The major use of the thermal analysis in evaluation wax matrix pellets was to identify the change in the physical state of propranolol HCl and wax (Figures 34 – 38). The DSC thermograms verified the identity of each of the components by their thermal properties. The thermogram results showed that the major peaks of the components remained visible. Therefore, there was no indication of interaction, since the position of the major peaks remained relatively unchanged. The melting peaks of beeswax from different batch number were the same characteristic. They were broad peak and had the melting point at 64.50 ^{0}C and 65.13 ^{0}C that so close to each other between first batch and second batch of beeswax. These DSC result will support the reason of IR data of beeswax.

Wax Matrix Tablet Preparation.

Morphologies of matrix tablets containing matrix pellets were investigated morphology by scanning electron photomicrograph both before and after dissolution (Figures 39 – 45). Some waxes, which has high melting points such as Lubritab®, Compritol® still showed faint pellets border in the compressed tablet. It could be clearly visible when using carnauba wax. For carnauba wax (Figure 41, II), this may be due to the tabletting process could not provide enough energy for fusing the rim of the pellets to each other because of high melting point of carnuaba wax. So, particle characteristic was still shown. The wax material in the matrix pellets acted as a dry binder to bind the pellets and forming hard tablets.

The surface of matrix tablet was smooth and had no pore in every side of tablet before dissolution. After finishing the dissolution test, the tablet surface covered with numerous pores and showed small crack around the side surface of the tablet. The crack was found when there was swellable material like Avicel PH 101® in the formulation. Avicel PH 101® will swell when contacted with water. It was appeared that the dissolution medium entered the pore that was produced by the soluble material at the surface. Then, the dissolution medium progressively dissolved

accessible soluble drug and fillers which then moved out of the tablet by diffusion through the surface of the tablet, the resultant enlarge pores, and the crack. These pores and the crack disappeared when using higher percent of wax material. The same result was seen from the controlled release of diclofenac sodium from wax matrix granule produced by Miyagawa Y. et al. (1996).

In addition, matrix tablets containing carnauba wax showed erosion during the dissolution test (Figure 41, II). As mentioned from the former result, there was pellets like structure in the tablet. This characteristic indicated a tendency for erosion.

The tablets containing Gelucire® were swell after one hour of the dissolution studies. But drug release occurred predominantly via diffusion. Gelucire 50/02® consisted mainly of hydrophobic glycerides (80%) with only 20 % of hydrophilic PEG esters (Sutananta W et al., 1995). The inclusion of PEG esters in Gelucire 50/02®, therefore, resulted in swelling and water uptake which was not observed in Gelucire® containing only glycerides.

Thus, it was concluded that the release mechanism of wax matrix tablet was assumed as swelling and crack followed by diffusion in low percent of wax, whereas it showed only diffusion when higher percent of wax was used. Not only those release mechanisms, but also erosion was included when using both low and high percent of carnauba wax.

One of the simple ways to produce the matrix tablets is to use hydraulic press as compression mean (Wadke et al., 1989). Every wax matrix pellets could form hard compacts without exhibiting any tendency to cap or chip. The tablet produced from beeswax or Gelucire® had high thickness and low hardness. Because their soften masses, the mass flow through the clearance between the die and upper or lower punch if maximum pressure was used. So, the highest thickness of the tablet was produced

from pellets containing 50 % Gelucire®. All formulations of tablets were in intact form after two hours of disintegration test (Table 16). This could be proved that all formulation could be the candidate of controlled release system.

Dissolution Characteristics.

The release of drug from sustained release dosage form for oral route as tablets or capsules should be constant over a wide range of pH values during passing the upper gastrointestinal tract. The medium used in in vitro dissolution test should cover this pH.

The drug release profiles of pellets and tablets containing propranolol HCl and microcrystalline cellulose were similar. The drug release was rapid and essentially completed within 0.25 and 1.5 hour., respectively (Figure 46), though the pellets remained intact at the end of the dissolution period. It is apparent that the retarding effect of the matrix formed with microcrystalline cellulose alone could not produce prolonged drug release. This is consistent with the findings of O'Conner R.E. and Schwartz J.B. (1985) where poor sustained release effect was observed when microcrystalline cellulose was used alone as the matrix material, even at a high microcrystalline cellulose to theophylline ratio of 9:1.

The mechanism of drug release for the spherical membrane reservoir systems prepared in the study of Rekhi G.S. et al. (1995) appears to be diffusion controlled accompanied by osmotic effects. Inderal® possesses the same controlled release system and used the same release mechanism as mentioned above. Inderal® is the only one controlled release propranolol HCl in the market. So, it was chosen to be the reference in this experiment.

From the result, wax matrix pellets formulation containing waxy material were not capable to reduce the rate of drug release in all formulations and could not exhibit satisfactory controlled release profile. This may be considered from

1. The release characterization.

The drug release mechanism will probably due to a combination of pore, erosion, and matrix diffusion. When propranolol HCl or lactose located at the surface dissolved, thereby allowing producing pore at the surface of the pellets. These pores also allowed better penetration of the dissolution solvent (Montousse C. et al., 1999). The superior effect of Avicel PH 101® may be due to their marked contribution to create pores in the matrix and due to their higher affinity to water which increased the wettability and rapid solvent penetration inside the pellets to dissolve the drug more rapidly and to get it diffused out. This indicated that the pellets had high erosion. They were in intact form but the surface of the pellets after dissolution studies were covered with many pores and no controlled release patterns were obtained at this level. The same experimental scheme was done by Shanawanz S.E. (1993) and the nearly same results was produced when Aerosil® or Avicel® was used at level of 20 % w/w.

The combination of diffusion of drug through tortuous pores (causing increase in pore volume), with the erosion of the matrix (causing a shortening of diffusional path lengths) would support the explanation of such release pattern of wax matrix pellets (Bain J.C. et al., 1991).

2. Pellets characteristics.

Pellets is one of the microparticulate systems, which has more surface area than single unit system. In addition, one pellet possesses much shorter diffusional path length than single unit system like tablet. This characteristic is one possible why wax matrix pellets could not produce satisfactory controlled release profile.

3. Solubility of the drug

Sustained release effect of the system was also depended on the solubility of model drug. High water solubility drug as propranolol HCl will act like one of the channeling agent. Thus, high water penetration to the system when using this drug in the wax matrix pellet formulation. On the other hand, if the system contained with moderate or low solubility drug like theophylline, nifedipine and NSAIDs, more sustained release could be exhibited.

The Effect of pH of Dissolution Medium on the Release Rates.

One of the limiting factors in the choice of prolonging mechanism for the oral route is chemical condition throughout the length of the gastrointestinal tract. This is constraint on the dosage form design.

In blank propranolol HCl study, the release rate was affected by the solubility of propranolol HCl in two-pH medium. All formulation of wax matrix pellets gave the release rate of propranolol HCl in 0.1 N HCl was slightly faster than in phosphate buffer pH 6.8. Rekhi G.S. et al., 1989 studied release property propranolol HCl coated bead by aqueous polymeric dispersion and found that the release rate of propranolol HCl was slightly faster in 0.1 N HCl compared to phosphate buffer in pH 6.8. Their results were the same as the present study. The difference was only coating system and matrix system. This could be caused by the different solubilities of the drug in the two mediums and not depending on the used system. The mean equilibrium solubilities of propranolol HCl at 37 ^{0}C ± 0.5 ^{0}C are reported by Rekhi G.S. et al. (1989). Propranolol HCl, a basic drug with a pKa of 9.45, should be more soluble in acidic solutions (in which the ionized form of the drug is dominant) than in alkaline solutions (in which it is predominantly unionized). Therefore, more drugs were released in 0.1 N HCl when compared to pH 6.8 buffer.

Influences of Wax Content on Drug Release Profiles.

It was found in the present study that incorporation of wax into the formulation could markedly improve the sustained release behavior and produced a matrix that has greater retarding effect than when microcrystalline cellulose was used alone. Thus, decreasing in release rate and percentage of drug release was obtained if the amount of wax in the formulation increased.

Lipophilic excipients have been shown to be able to retard the drug dissolution of a dosage form (Levy G. and Gumton R.H., 1963). Thus, the ability of wax to retard the rate of drug release from pellets or tablets may be attributed to its lipophilic property. Wax or lipid structure consisted of glyceryl backbone and long chain hydrocarbon. Thus, incorporation of wax caused and increased in the lipophilicity of the matrices, leading to a decrease in the effective interfacial area between the drug and dissolution medium, resulting in a reduction of wettability (Banakar U.V., 1991). Consequently, there is a slower rate of water penetration and dissolution of the drug within the system and hence a slower rate of drug release.

Influence of Loading Dose on Drug Release Rate.

It was the propose of this study to evaluate loading dose effect on drug release rate. The matrix has physical erosion caused by the high hydrophilic additives. When lactose was used as channeling agent, the matrix was gradually eroded. Then lactose dissolved and was released from the matrix, as the result channels were formed and the porosity was increased. The drug released by a matrix leaching mechanism, in which drug and lactose particles at the surface of matrix dissolved first, forming pores through which drug particles farther from surface could escape in turn. These channels would increase release rate.

Consideration in the effect of drug loading on the drug release. The dissolution medium apparently penetrated the wax matrix at the same rate when the pellets or tablet were surrounded with plenty of medium like the digestive tract. The more amount of drug had greater opportunity to contact with the dissolution medium. Consequently, if increasing the amount of propranolol HCl in the formulation of wax matrix tablet, slightly increasing in amount of drug released in milligrams. But when the percent of drugs released was plotted versus time, the release rate and the percent release decreased with increasing loading dose because the amount of drug released was divided by the more amount of total drug in the formulation.

Sustained Release Power of Various Wax Materials.

Ranking of sustained release power from the result in pH 1.2 and 6.8 are closely to each other. This may be due to the effect of the length of fatty acid chain and number of fatty acid that formed ester bond in glycerol on release rate. The fatty acid chain length increases from Gelucire® which is specific mixture of mono, di, triglyceride to Compritol 888ATO® which is glyceryltribehenate. There is a little difference in sustained release power between Gelucire®, carnauba wax, glyceryl monostearate. It could not clearly indicate the relationship between fatty acid chain length with sustained release power of those three waxes. Because carnauba wax is the complex mixture from natural source whereas Gelucire® is the specific mixture of mono, di, triglyceride. As expected, application of wax with long chain triacyl glycerol demonstrated the most extensive prolonging of drug release. The effect of fatty acid chain length on release from compressed physical mixtures were studied by Shaikh N.H. et al., (1991) who found that increasing fatty acid chain length decrease the release rate.

Previous work of Schwartz J.B. et al. (1994) to characterize the compaction parameters of beads containing microcrystalline cellulose concluded that microcrystalline cellulose beads are relatively non compressible, but will form soft intact tablets. To improve the compressibility of the beads, a waxy material was added to the bead formulation, which formed harder tablets, without any external additives or additional lubrication. Because pellets or beads had good flow properties and wax material act as self-lubricant. Compritol® has been used primarily as a lubricant at a level of 1.5 – 3 % alone, or 1 % in association with 0.2 – 0.3 % of magnesium stearate (Lapeyre F. et al., 1988). In addition, Compritol® can use up to 70 % of the formulation (Lloanusi, N.O., and Schwartz, J.B. 1998). Consequently, wax matrix system showed a tendency to scale up and used in the pharmaceutical industry. Despite the wax matrix pellets in this study could not show satisfactory controlled release, but wax matrix tablets gave rather good release profile characteristic. Both those tablets made by tabletting machine and by hydraulic press gave the same release pattern from the same formulation. But speed of the tabletting machine should be decreased from the normal tablet to avoid heat and sticking in the production. Moreover, wax matrix tablet can compare with Inderal® in pH change method and both gave the release profile within USP XXIII for 12 hours period. But when medium was change to basic, slightly decreasing in release rate was found. This conformed to the reason as mentioned above in the influence of pH medium on release rate.

Since both first order and square root of time plots are acceptable linear, the two models were clearly differentiated by plots of rates as functions of Q and of 1/Q. The latter proved to be more linear than Q, indicating that the process definite follows a higuchi release pattern in these system. The rather low value of correlation coefficient was obtained when using carnauba wax in the formulation. This may be due to the erosion and cracking of the matrices.

Figures 102-105 and Tables 20-21 clearly shows that the drug release rates were influenced by the wax content and loading dose in the matrix. As the

proportion of wax increases, there is a progressive decline in the release rate. This can also be shown by plotting the release rates ($\%F.hr^{-0.5}$) for propranolol HCl against the percentage of wax or loading dose in the formulation. This curve could be used to allow predictions of the release rate to be made for wax content and loading dose not experimentally, provided that no drug/wax interactions are encountered which will complicate the calculations. However, this equation can be used with every kind of waxes in this study except carnauba wax. Because of the erosion and cracking of the matrices especially when containing low amount of carnauba wax or loading dose. Fluctuate release rate was obtained and no linear relationship between release rate with amount of wax or loading dose.

The trend of the release exponent n was decreased when the wax or loading dose was increased. These indicated that at low concentration of wax presented a much more complicated system was presented. Since the release mechanism was not only Fickian diffusion but have combined mechanism. Those were diffusion partially through a swollen matrix and partially through water-filled pores or leaching from the water channel. Erosion and cracking may be occurred at low amount of wax in the formulation. These effects was produced from water-soluble additive such as lactose and water swellable additive such as Avicel PH 101® in the formulation. These pores will gradually decrease until almost disappeared when the formulations contained highest percent of wax. Because water soluble or water swellable additive was replaced by the wax which is more hydrophobic than lactose, or Avicel PH 101®, the tablet was in the intact form throughout the dissolution test. Thus, the main release mechanism of this situation was only diffusion from the wax matrix. The value of n approached to 0.45 for the cylindrical sample as tablet, phenomenologically one might conclude that the release was approaching Fickian diffusion.

Conclusions.

In the present study, propranolol HCl wax matrix pellets was successfully prepared by extrusion and spheronization process. It was demonstrated in this work that with proper control of the process conditions and suitable wax would show good pellet characteristic. Several kinds of waxes were used as matrix forming agent in the study. Glyceryl monostearate, Lubritab®, Compritol®, and Precirol® were proved to be the most suitable waxes for producing wax matrix pellets by extrusion and spheronization technique. Those determined from ease of manufacturing, wide range of amounts of water to be used in the formulation, the percent yield and pellet characteristic. Almost all waxes were not good enough to control the drug release from wax matrix pellets except high level of Compritol®.

After compression of these matrix pellets into tablet, the effective controlled release was obtained from all waxes except low percent of carnauba wax. Beeswax and Gelucire® were proven not suitable for producing tablet because of its soften mass. The pH of dissolution medium affected drug release rate of all formulations in this study due to difference in solubility of propranolol HCl in different pH medium. The release of drug from the system investigated could be varied within wide limit by adjusting the wax content and loading dose. Compritol®, Precirol®, and Lubritab® appeared to be the most suitable substances for wax matrix system production. It was observed that presence of these waxes enabled this tabletting process to proceed in a controlled, regular and harmonic way. In addition, they could create the desired drug release profile. The mechanism of drug release from wax matrix table is anomalous transport and the model of drug release from the wax matrix tablet would possibly be Higuchi model.