# Chapter 3

## Results and Discussion

### 1. Preliminary Investigation of Core Pellets.

*Extrusion/spheronization* technology was chosen to accomplish the preparation of the drug loaded pellets. The main processing steps were dry blending of lactose, corn starch and microcrystalline cellulose (Avicel PH101), wet mixing using water as a vehicle, transferring to extruder using oscillating granulator composed of mesh #16, made into short cylindrical segments, and the last step, charging wet extrudate immediately onto rotating plate of the *spheronizer* . The wet extrudate then was broken into short segments by contacting with the friction plate, due to the collisions between particles and collision with the wall.

The four most significant continuous variables in this process were microcrystalline cellulose concentration, moisture content, *spheronizer* speed, and *spheronizer* residence time (Hasznos et al.,1992).

Microcrystalline cellulose was an essential component of pellet formulation to function as a binder. It agglomerates powders together, maintains pellet integrity, increases plasticity, reduces extrudate friability, and controls the movement of water through the wet powder mass as an extrusion aids during extrusion, modifies the rheological properties of the other ingredient in the mixture, and confers degree of plasticity which allows it to be readily extruded. Any increments of the concentration of microcrystalline cellulose enlarges an increase plasticity and reduces friability of pellets (Harrison et al., 1985).

The water was used as a blending solvent in order to form a suitable dense cohesive mass for extrusion. The water content of the wet powder mass and its

distribution were highly critical and should be controlled. In general, high moisture content in the wet mixture, typically is 20 to 30 % w/w. The aim is to produce as dense material as possible and 20-30 % w/w is a suitable characteristics for passing through the extruder since a fluffy and incompletely wet mass may fed poorly. In addition, the incompletely wet mass could cause problems by creating excessive pressure and friction within the equipment. Incompletely mass tends to produce large quantities of fines in the spheronizer. The dry extrudate was insufficiently plasticity forming, resulting in a dumb-bell shaped or ovoid pellets which never round off into spheres. On the other hand, the mixture was too wet, it produces an extrudate which adheres to the spheronizer plate and to itself. This wet product tends to uncontrollably aggregate and produces sphere of wide-size distribution.

In this study, the extrudate was prepared by extruding wet masses containing various amount of water (205, 310, 460 g/kg). The yield of granules obtained by adding 310 g/kg of water was much higher than by adding 205 or 460 g/kg of water. Increasing of water content would decrease internal porosity, friability and mechanical strength of pellets (Otsuka et al.,1994).

With spheronizer speed, low speed gave a high range of porosimetric distribution zone, between 0.1 and 10.0 μm in diameter. In general, increasing speed will decreased the porosity and the average diameter of the pores, which will deliver a greater hardness, and spheroid with a smoother surface condition (Bataille et al., 1993). A more resident time affected an outstanding decreasing of the average diameter of all pellets.

In this study, pellets were prepared by spheronizing the extrudates with various speeds (350, 500, and 650 rpm). The sizes of pellets obtained by using 350 rpm were very big and by using 650 rpm their size were too small. The suitable sizes of pellets obtained from using speed of about 500 rpm.

Mechanism of pellet formation, during wet granulation, a dry powder mixture was agglomerated with the binding liquid. This agglomerate was held together mainly by capillary forces. Depending on a degree of liquid saturation, three phases of liquid bridges remained earlier were applicable and the tensile strength of the granules varies according to absorption layers and solid bridges may also be operative. The granule were then fed into the extruder to produce high-density extrudates. These extrudates were bonded together by capillary forces and solid bridges due to the loss of moisture, mechanical interlocking, and molecular forces.

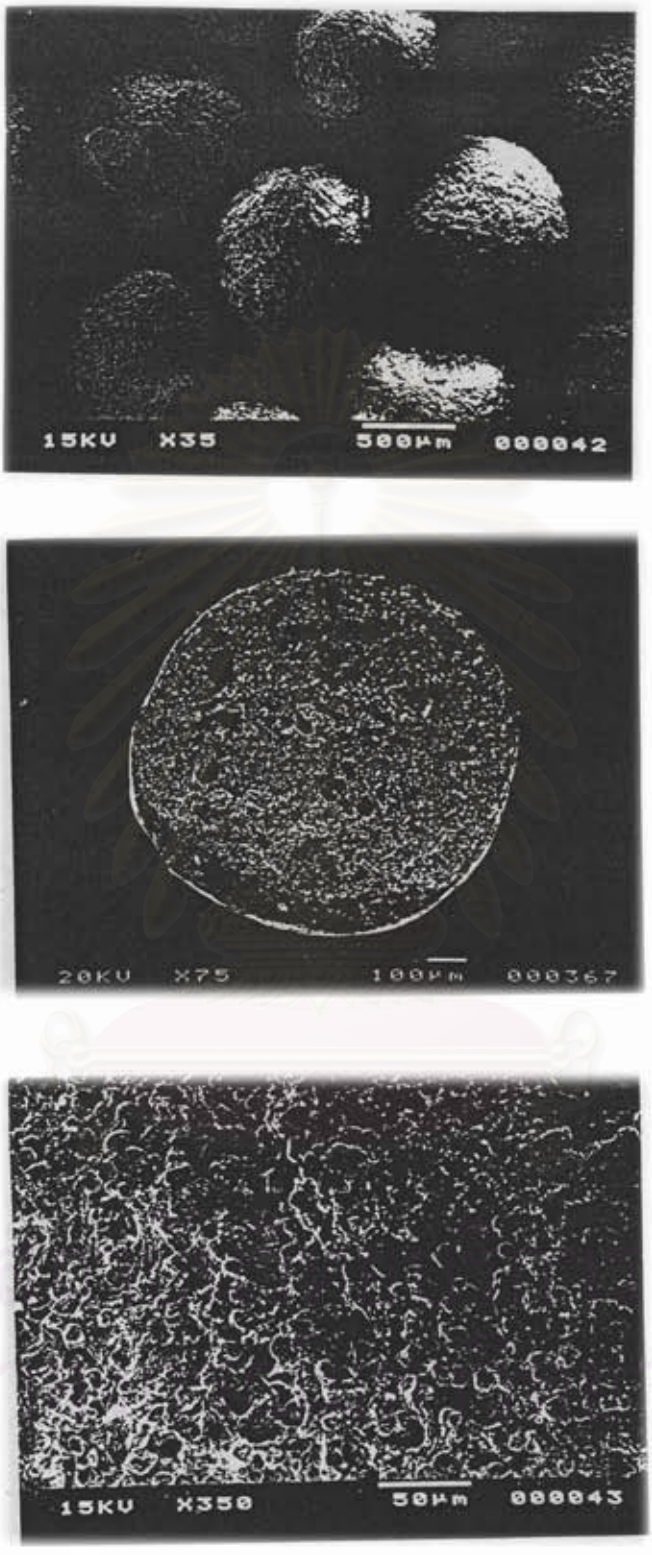
These extrudates were finally converted to pellets upon spheronization. During spheronization, moisture was forced out from the pellet interior to the exterior and imparted plasticity to the pellet surface. This surface plasticity, coupled with the concurrent tumbling of the particles in the spheronizer, allows the formation of spherical pellets.

**2. Evaluation of Core Pellets.**

2.1 Morphology

The surface morphology of core pellets were observed by using scanning electron microscope (SEM) at different magnifications (× 35, × 75, and × 350).

Figure 12 and 13 present scanning electron micrographs (SEMs) of a surface appearance of lactose pellets and propranolol hydrochloride pellets, respectively. Most of the pellets occupied the spherical shape in a range of 0.5-1 mm. On their surfaces, a random aggregation of filamentous microcrystal creates a high interval porosity. With SEM, they were not distinguishable between Figure 12 and 13 in diameter and surface characteristics.



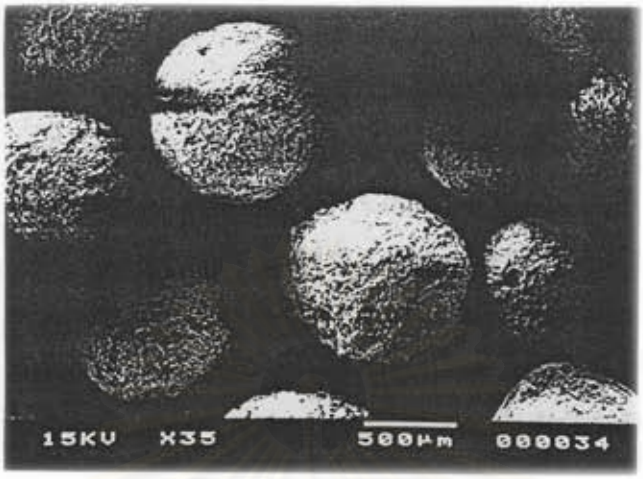

A

B

C

Figure 12 Photomicrographs of lactose pellets.

(Key: A lactose pellets × 35, B cross-section × 75, C surface × 350)

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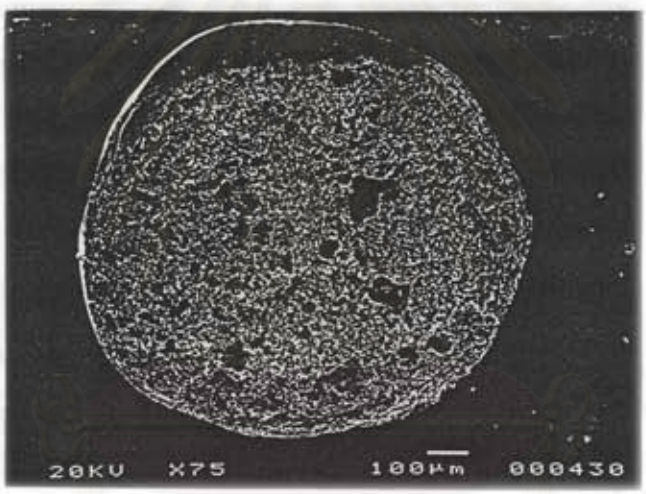


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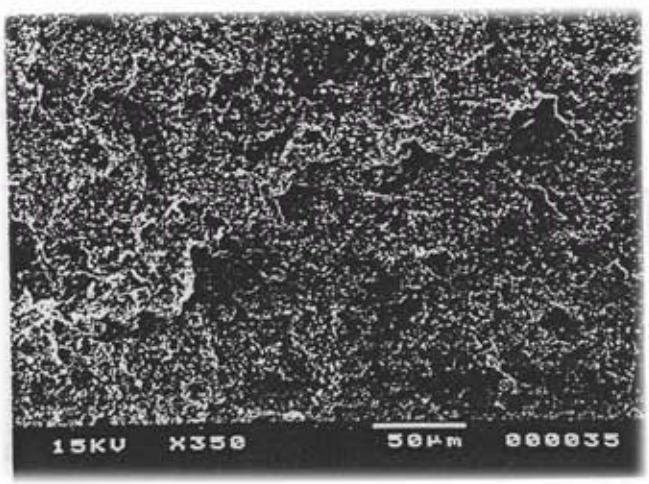



C

Figure 13 Photomicrograph of propranolol hydrochloride pellets.

(Key : A core pellets × 35, B cross-section × 75, C surface × 350)

2.2 Density

The bulk density, tapped density, and Carr's Compressibility index of propranolol hydrochloride pellets are presented in Table 11. The values were about 0.68, 0.70, and 2.86, respectively.

If a bulk volume is higher than a tapped volume, a bulk density will be less than tapped density. A high Carr's compressibility represented a large difference between bulk and tapped density. The high Carr's compressibility implied a loosen of particle. If the Carr's compressibility equal to zero, bulk density and tapped density would be equal. In this work, the Carr's compressibility value for uncoated pellets was 2.86. This number indicated packing of spherical shaped particles.

Table 11 Physical properties of uncoated pellets.

| physical properties | mean value (SD) |
|---|---|
| Bulk density (g/ml) | 0.68 (0.11) |
| Tapped density (g/ml) | 0.70 (0.87) |
| Carr's compressibility (%) | 2.86 (0.45) |
| Friability (%) | 0.27 (0.93) |
| Moisture Content (%) | 1.45 (1.08) |
| Propranolol hydrochloride content (%) | 42.88 (0.64) |
| Weight of pellets in one capsule (mg) | 373.13 (0.45) |

2.3 Friability

The friability of propranolol hydrochloride pellets is shown in Table 11. The value was 0.27 %.

The friability value of 0.27 % was very low, the pellets then was able to withstand the impact during handling and coating process. This was because during coating the

process, the pellets are subjected to appreciable particle-to-particle and particle-to-wall frictional force. Friable pellets will generate significant amount of fines that become temporarily suspended in an expansion chamber. Some of these fines returned to the product chamber (due to gravitational forces), where they run the risk of deposition of film coating deposited on the pellets. Others are trapped in the filter bags and got dislodged under their own weight or during the intermittent shaking of the filters. Once dislodged, drug particles can also become embedded in the film as the coating process progresses. As a result, during dissolution testing, the embedded particles can be leached from the coating and create pores.

The presence of such pores will not only lead to faster release rates than expected, but also, due to the randomness of the distribution of the pores, which vary release rates.

2.4 Moisture Content

The moisture content of propranolol hydrochloride pellets is presented in Table 11. The value was about 1.45 %.

The expected moisture content is 2-4 %. But in this study, the moisture content was below 2 %. In general, a very dried core pellets implied a higher friability. But in this study, friability was low (below 2 %) may be because of the pellets producing by extrusion/spheronization method.

2.5 Drug Content

The drug content of propranolol hydrochloride pellets was presented in Table 11. The average value was 42.88 %.

The triplicate values of drug content were 42.88 %, 42.95 %, and 42.71 % with 0.20 standard deviation. This standard deviation was extremely small, represented the uniform distribution of drug in core pellets.

Because main compositions of coated pellets are polymer and other additives which might absorb UV light at the same wavelength of proprannolol hydrochloride (289.0 nm). The absorbance values of pellets without drug were shown in Table 18 (Appendix B). The corresponding UV spectrum were shown in Figure 180-183 (Appendix B). No interference was indicated. Therefore, polymers and core lactose composition did not interfere with the determination of drug content.

**3. Preliminary Investigation for Suitable Coating Solution and Coating Condition.**

3.1 Coating Solution

The coating suspension was composed of various components illustrated in Table 6. The specific coating suspension mixtures of Eudragit®RL100 with ethylcellulose, and Eudragit®RS100 with ethylcellulose were implemented. In this action, 1:1 ratio of acetone : isopropyl alcohol were used as solvent mixture that can dissolve the polymers to a clear solution. The talcum and magnesium stearate were added as antitacking and antiadhesive agent. Also, dibutyl phthalate was added as a plasticizer. Finally, the milky white and translucent dispersion was formed.

The four compositions in this process were polymer, organic solvent, antitack and antiadhesive, and plasticizer. As part of polymer, Eudragit®RL100 was not soluble in digestive fluids but was very permeable, and independent of pH. The film swell within a few minutes and the drug permeates quickly out of the coating. Eudragit® RS100 was also not soluble in the digestive fluids but having retarding property over

a wide pH range. Ethylcellulose was water-insoluble polymer and possessed good film-forming properties, in addition, higher retarded release than Eudragit®RS100.

For the organic solvent, solvent mixtures between acetone and isopropyl alcohol give better dissolution properties of the polymer than in single solvent. The mechanism of the film solubility is indicated by swelling step, and then viscous layer formed around the polymer particles, rapidly disintegration and polymer chain are prolong, resulting in a high cohesive strength in transparent solution.

An important aspect is a relatively high viscosity of polymer solutions, which depends on a molecular weight and affinity of the polymer to the solvents. If the solvent has a high affinity to the polymer chains, the apparent molecular size of action of the polymer is very high, due to the spreading of chain segments, resulting in a high viscosity. If the solvent has a lower affinity to the polymer, some polymer chain aggregation and shrinkage of the polymer molecule result in lower viscosity.

The reason to implement the organic solvent system is that, the polymer are soluble in alcohols and acetones. In addition, the coating process with organic solvents can be used for much broader selections of polymers and polymer mixtures, because organic solvents have lower boiling points than those of water and have much higher evaporation numbers, which means that they evaporate much faster than water, resulting in the coating process a minimum of heating. From these excellent advantages, the hazardous pit falls such as increasing problem of air pollution from coating process and highly toxic, and cancerogenic chlorinated hydrocarbons is sometimes ignored.

For the plasticizer, dibutyl phthalate was selected to increase flexibility and reduce a brittleness by interruption of the polymer chains. With this interruption, Tg (glass transition temperature) was decreased. The high Tg leads to a hard and brittle film. A water-insoluble characteristic of dibutyl phthalate, facilitates coalescence of the coating produced from the systems, and improving the barrier properties of water-

insoluble film. With this improvement, the film layer possessed more hydrophobic property, resulting in a reduction in the release rate of the drug concerned (Rowed, 1986).

For the antitack and antiadhesive part, talcum and magnesium stearate were selected to be an antitack and antiadhesive agent, to reduce a stickiness of the coating formulations by forming lattice structures. Talcum and magnesium stearate particles are very easily embedded in polymer layers, resulting in the reduction in sticking during the film forming process. Furthermore, antitack reduces the porosity of film coating.

Nevertheless, due to water insoluble characteristics of the talcum and magnesium stearate , only 5-20 % w/w of formulation should be used. With high amount of these antitak and antiadhesive, the dissolution profiles of the drug could be shifted.

### 3.2 Coating Condition

The fluidized bed apparatus for this study was a bottom spray system. The bottom spray system contributed a smooth and continuous film. It is because the coating suspension was dried before pellets return to receive coating suspension again, resulting a completed film. In order to test a variety of coating conditions, various factors that may be considered in the process were air supply, temperature, and spray rate/ spray system.

For air supply, a fast solvent evaporation is essential for the formation of the stable film on the core surface i.e., as soon as possible after the spray droplets have reached the core and spread on the surface. A suitable amount of air supply is critical especially during the coating of small particles, there is a strong tendency toward agglomeration when the core surface is sprayed with polymer solution and the drying film layer is in a high sticky phase. High levels, even an excess of drying air is thus very important for effective coating. In fluidized-bed systems, a strong stream of air

is essential to keep the particles fluidized, so that an interparticular contact is kept to a minimum.

If the small particles are to be coated by using such equipment, it is critical to increase the air supply to a maximum level and to introduce an inlet air directly into the core bed, to optimize the drying efficiency and to stimulate more intensive movement of the cores.

The temperature of drying air can be relatively low, in the range of 20 to 40°C. For an organic coating solutions containing highly volatile solvents, such as acetone and isopropyl alcohol, may require temperature around 30 to 50°C. For this study, the suitable temperature was 45°C. The product temperature could be at room temperature or slightly above, normally not higher than 30°C. It is normally required the temperature of incoming dry air to be between 30 and 50°C. For this work, the temperature of the inlet dry the air was 40°C.

Solvent evaporation cools the surface of the cores. If a spray rate is high and the energy transported with the drying air is not high enough to compensate the heat of evaporation, the temperature at the surface of the cores may fall below room temperature. If the inlet air is taken directly from a highly humid atmosphere without a defection, the dew point may be reached, leading to water condensation. If the temperature of the inlet drying air is too high, the product temperature goes-up and film stickiness will increase. The solvent is normally very active plasticizing agent, the percentage of residual solvent retained in the polymer is therefore critical. A low level of residual solvent in the film is retained when spraying and drying are conducted continuously during the coating process and a very thin film layers are dried immediately. This will occur when the concentration of solvent in the air stream is low. As a result, it is recommended that the temperature of the inlet air should be as low as possible to keep the temperature of the core around room temperature and to increase the amount of drying air to the maximum consistent with

the capacity of the apparatus. Under such conditions, stickiness is reduced. If the cores are porous and the solvents tend to diffuse into the core, additional intermittent drying may be necessary as long as the coating is thin enough to allow diffusion of residual solvent from the core to the surface. At the end of the process, the coating normally acts as a tight barrier for traces of solvent entrapped in the core. A very long final drying time is necessary to attain low levels of residual solvents.

For the spray rate of a coating suspension, it depends on several parameters: the drying air capacity of the machinery, the mixing intensity of the cores, and the spray area. To obtain of approximately 20 μm, an atomization air pressure of about 2 to 4 bar is sufficient, and the spray rate can be regulated with spray nozzles approximately 0.8 to 1.5 mm in diameter. The coating suspension can be fed to the nozzle by a peristaltic pump. The spray rate must be reduced if the level of stickiness is too high, and more agglomerates are formed then destroyed in the normal cycle of movement of the particles in the machine. In this study, the spray rate was 20 ml/min.

Due to the dilute suspension characteristic, the above spray rate was then utilized, in order to contribute smoother and homogeneous film layers.

**4. Coating the Propranolol Hydrochloride Pellets.**

Propranolol hydrochloride pellets were coated with the coating suspension that illustrate in Table 8 and 9. The specific mixtures of Eudragit®RL100 and ethylcellulose, and Eudragit®RS100 and ethylcellulose were implemented at the above specific ratio. With the various coating levels, the morphology, density, friability, moisture content, drug content, and release profile were affected.

Eudragit®RL100, Eudragit®RS100, and ethylcellulose are GI-insoluble polymer that completely dissolved in organic solvent. Also dibutyl phthalate was a water insoluble plasticizer as described, the coating suspension is homogeneous,

continuous and rather poreless, which tend to form a complete film. Therefore, the mechanism was solution/diffusion through a continuous plasticized polymer phase. The plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving an operative movement of drug penetrant and the polymer chain segment around it. In effect, thermal fluctuations of chain segments allow sufficient local separation of adjacent chains to permit the passage of a penetrant. It is by this stepwise process that hindered molecular diffusion (Dressman et.al, 1994).

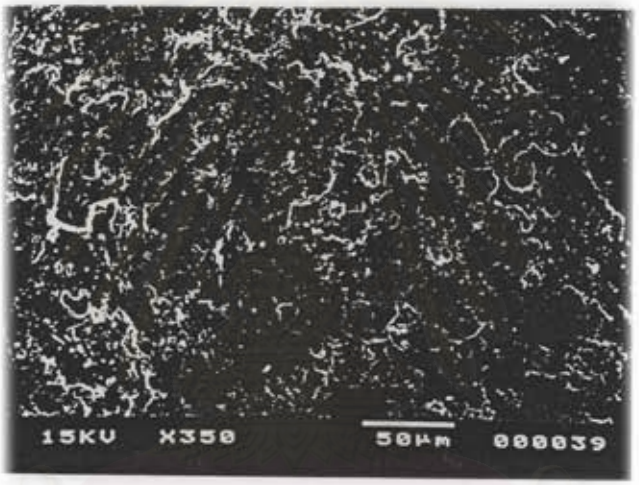
## 5. Evaluation of Coated Propranolol Hydrochloride Pellets.

### 5.1 Morphology

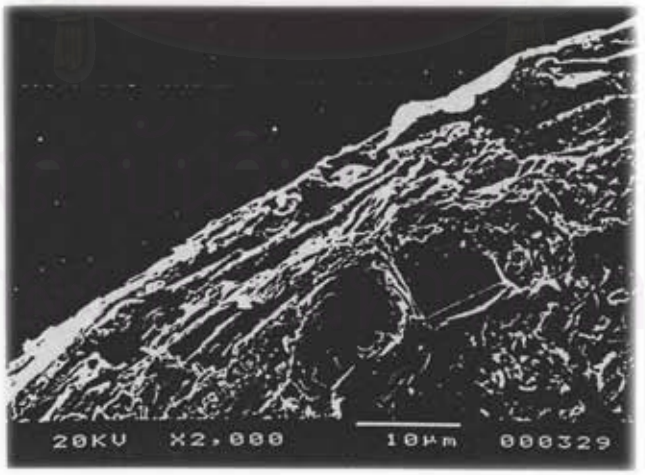
The coating with the mixture of Eudragit®RL100 and ethylcellulose are shown in Figure 14-37. Figure 14-17 illustrate pellets coated with 100 % Eudragit®RL100 at 5 %, 10 %, 15 % and 20 % coating level thickness, respectively. At × 35 and × 350 magnification, a smooth, compact, and continuous characteristic film was observed. The higher coating level causes smoother and more continuous film. At × 1500 or × 2000 magnification picture, a cross-section represent a thickness of the polymer and showed a distinctive interface between core and the coating. The coating levels were a result from the bottom spray characteristic. The spray bottom technique allowed each layer of coating dry more completely before pellets are recycled to receive the further coating. The higher percent coating contributed the thicker film than those with lower percent coating level.

Figure 18-21 illustrate pellets coated by the mixture of 80 % Eudragit®RL100 and 20 % ethylcellulose at 5 %, 10 %, 15 % and 20 % coating level, respectively. At × 35 and × 350 magnification, it could be observed that the coating solution could not entirely coat the pellets. This low level coating influenced a rough, porous, and uncontinuous characteristic for the film. Nevertheless, the higher level coating, the


A




B

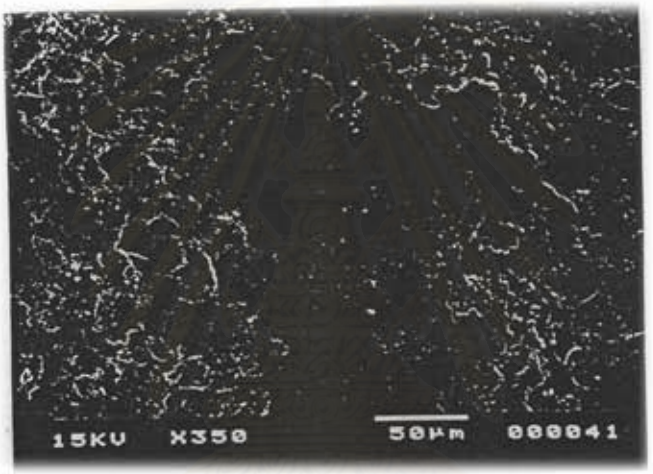



C

Figure 14 Photomicrographs of coated pellets Formulation 1 (5 % EURL100).

(Key : A coated pellets × 35, B coating surface × 350, C cross-section × 2000)


A

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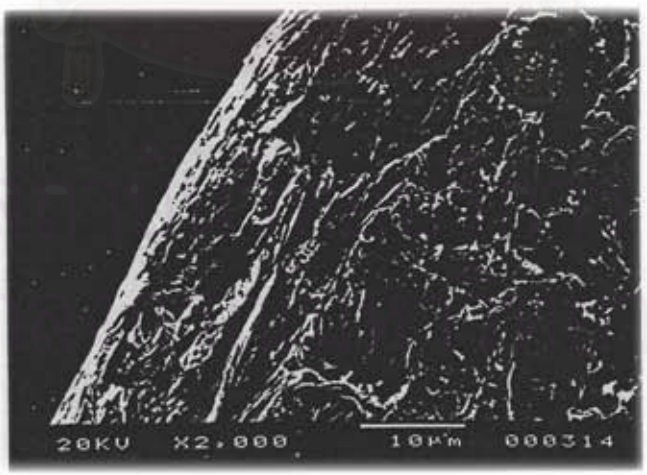
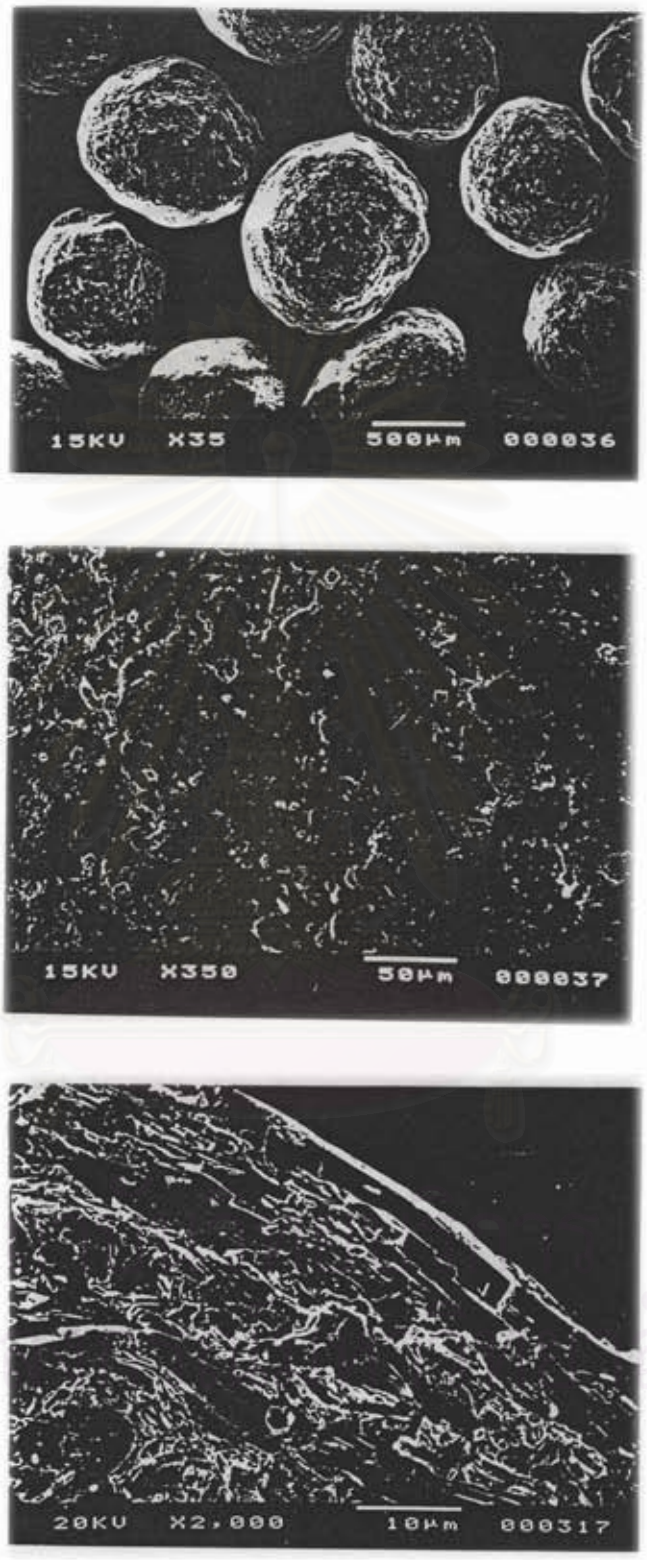



C

Figure 15 Photomicrographs of coated pellets Formulation 2 (10 % EURL100).

(Key : A coated pellets × 35, B coating surface × 350, C cross-section × 2000)



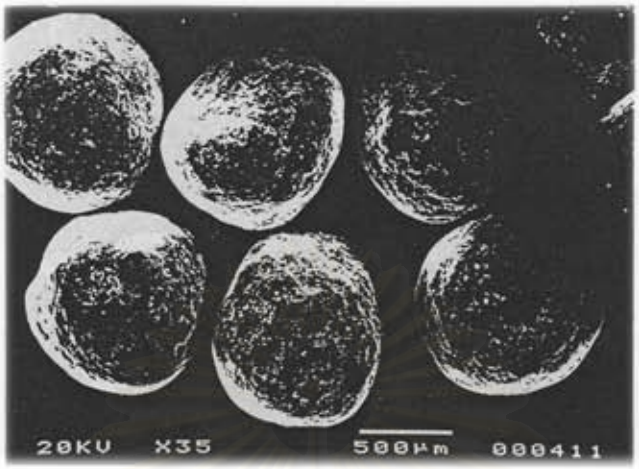

A

B

C

Figure 16 Photomicrographs of coated pellets Formulation 3 (15 % EURL100).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)

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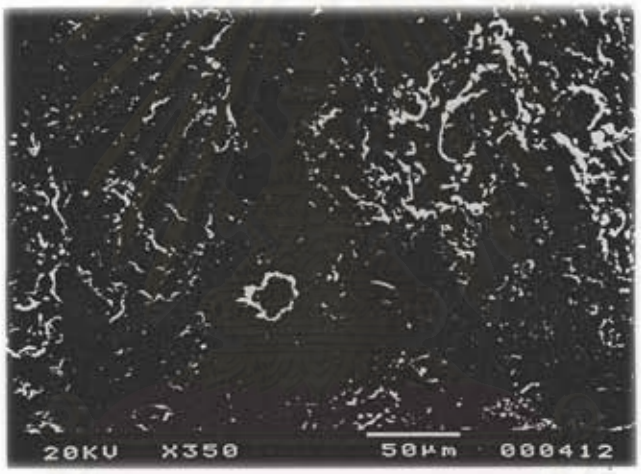
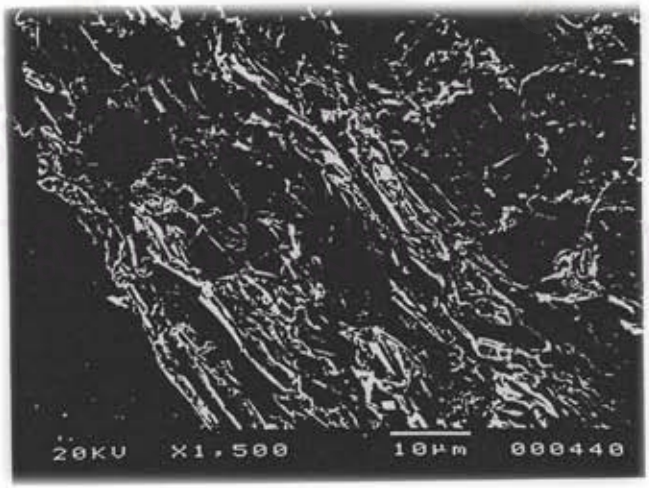


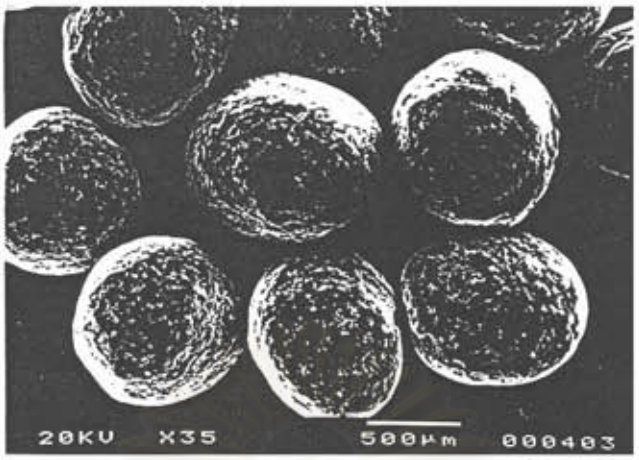

B



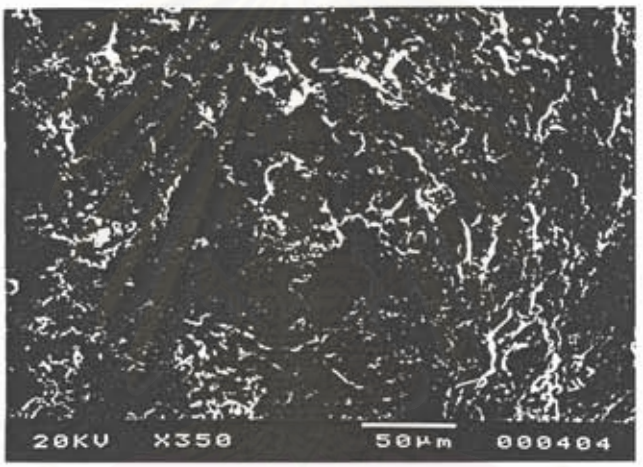

C

Figure 17 Photomicrographs of coated pellets Formulation 4 (20 % EURL100).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 1500)




A

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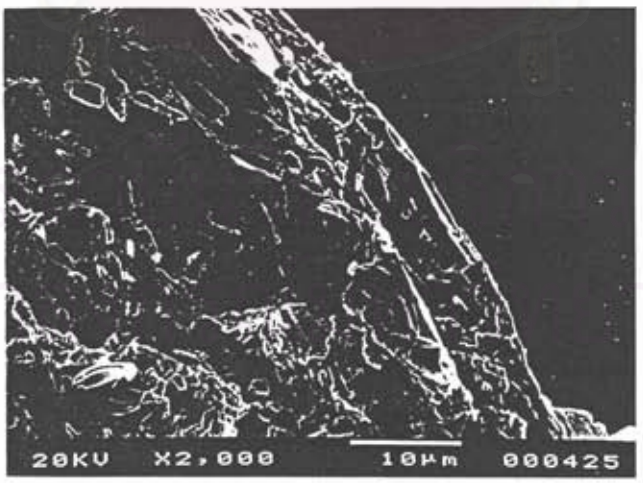
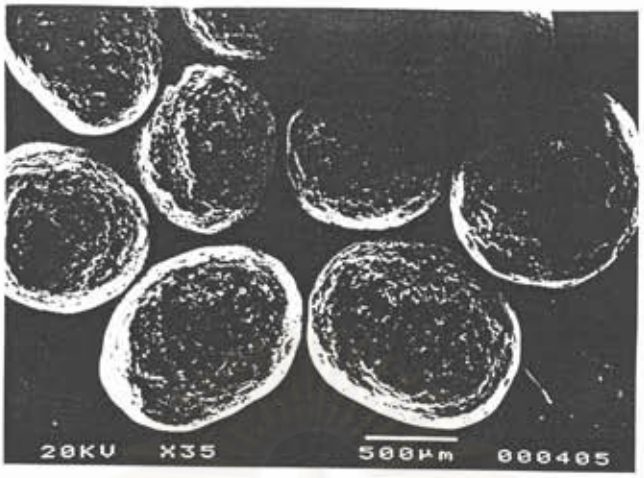



C

Figure 18 Photomicrographs of coated pellets Formulation 5 (5 % EURL80:EC20).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)

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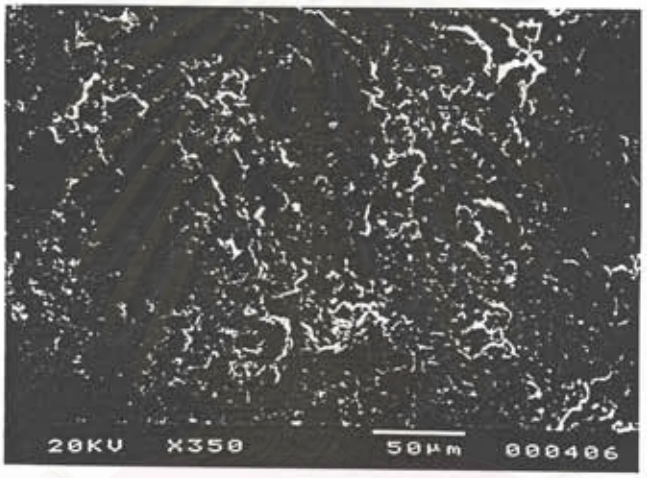
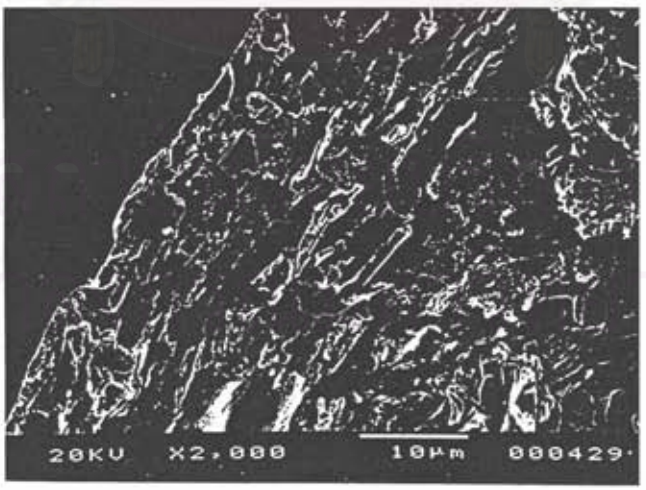


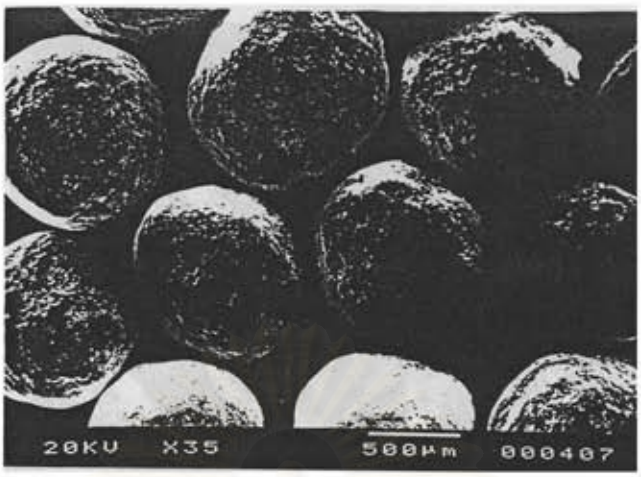

B



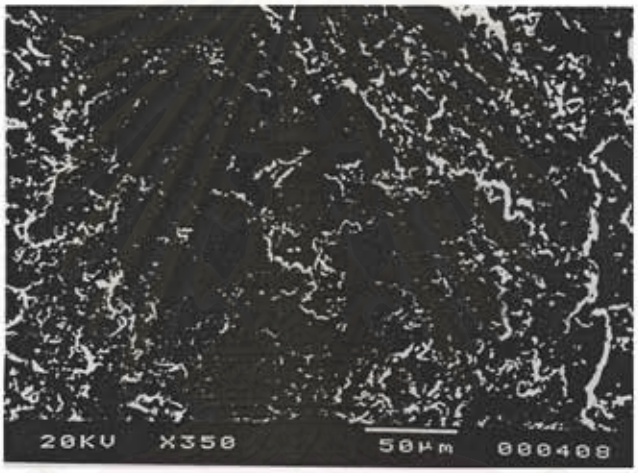

C

Figure 19 Photomicrographs of coated pellets Formulation 6 (10 %EURL80:EC20).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A

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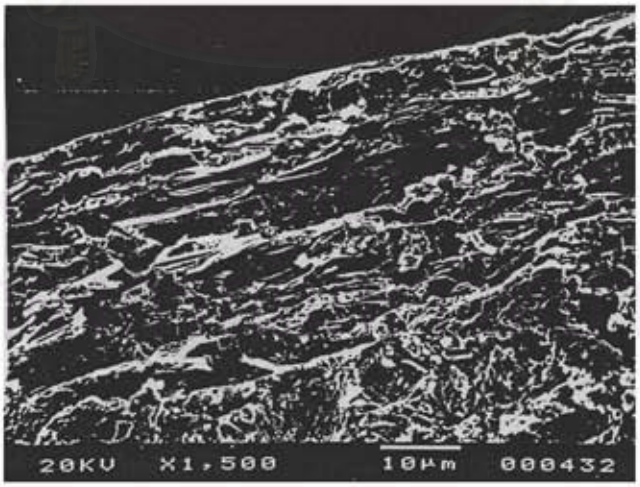
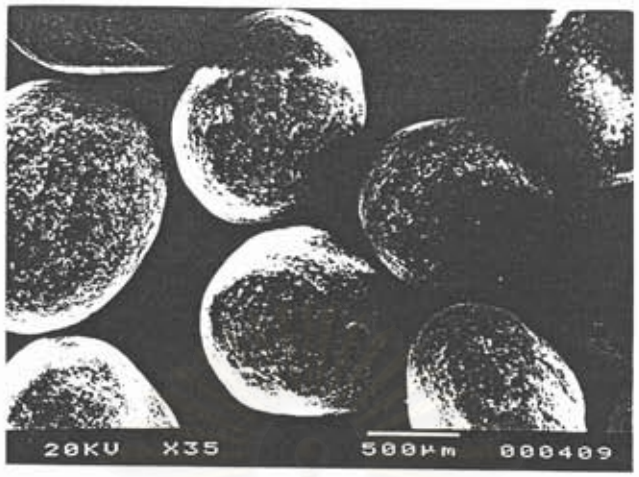


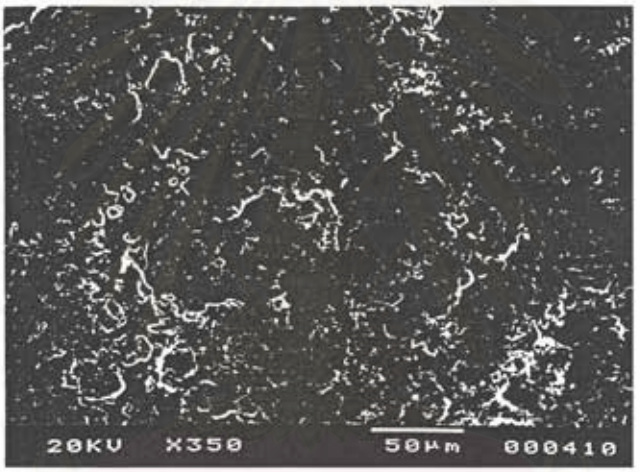

C

Figure 20 Photomicrographs of coated pellets Formulation 7 (15 %EURL80:EC20).

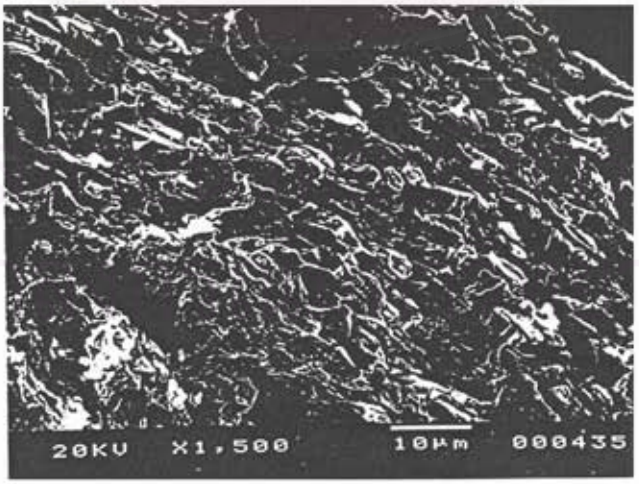
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 1500)




A




B




C

Figure 21 Photomicrographs of coated pellets Formulation 8 (20 %EURL80:EC20).

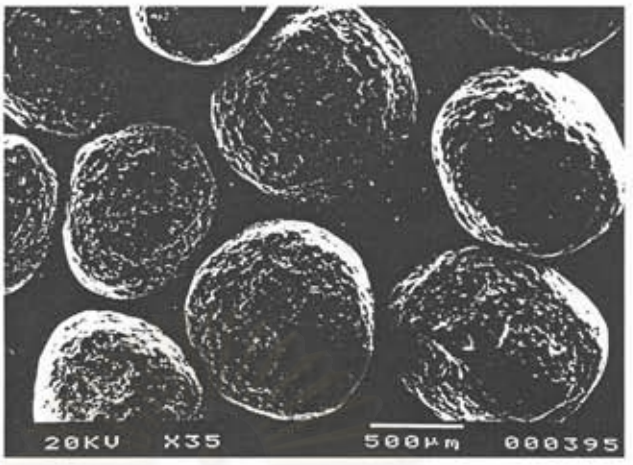
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 1500)

smoother and finer on the film. The cross-section at × 1500 or × 2000 magnification picture represent the magnificent film coating layers. The higher percent coating exhibit thicker film than those with lower percent coating level.

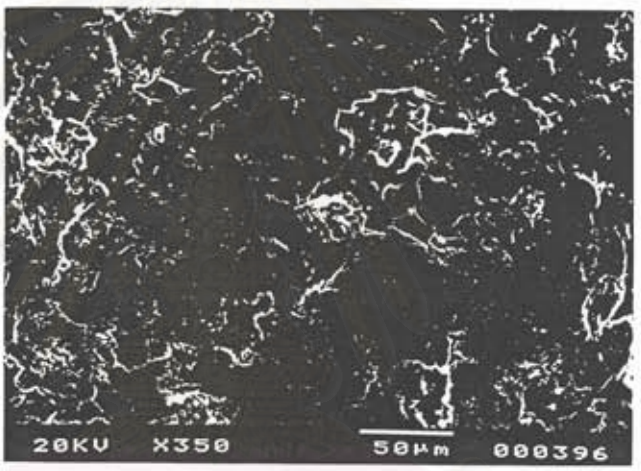
Figure 22-25 illustrate pellets coated with the mixture of 60 % Eudragit®RL100 and 40 % ethylcellulose at 5 %, 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification picture represent that the 5 % and 10 % low level coating could not entirely coat the pellet. In addition, these level coatings influenced a rough surface and numerous pores on the film. Nevertheless, the higher coating level the smoother and finer on the film. The cross-section at × 1500 or × 2000 magnification picture clearly represent the film coating layers. At higher percent coating, the thioker film was exhibited than those with lower percent coating level.

Figure 26-29 illustrate pellets coated with the mixture of 40 % Eudragit®RL100 and 60 % ethylcellulose at 5 %, 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification picture represent film which is a little bit rough and contains a few pores. At the low level, the surface was not continuous due to the high amount of ethylcellulose. At the high coating level, the film surface was still ununiform. The cross-section at × 2000 magnification picture clearly represent the layers of the film, higher percent coating exhibited thicker film than those with lower percent coating level.

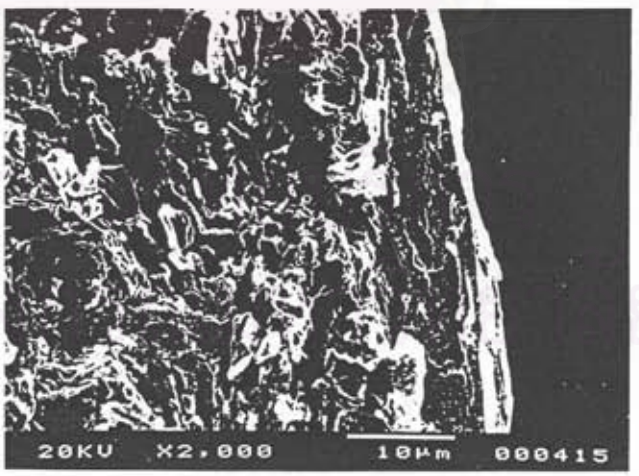
Figure 30-33 illustrate pellets coated with the mixture of 20 % Eudragit®RL100 and 80% ethylcellulose at 5 %, 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification picture represented a good entirely coating. The surface is rough, but fine. The cross-section at × 2000 magnification picture represent the film layers. The higher percent coating implied the thicker film than those with lower percent coating level.




A



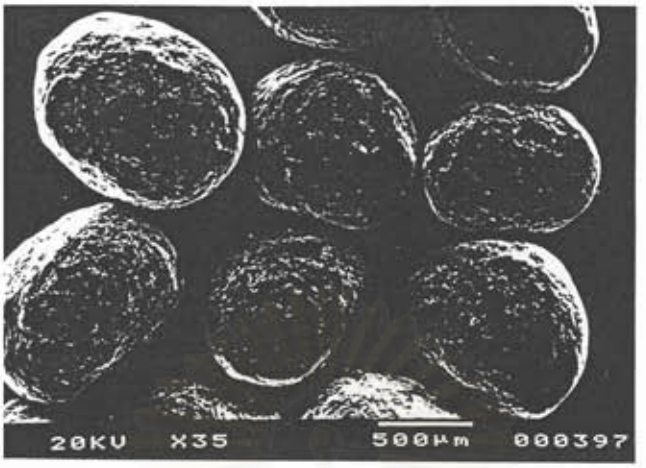

B



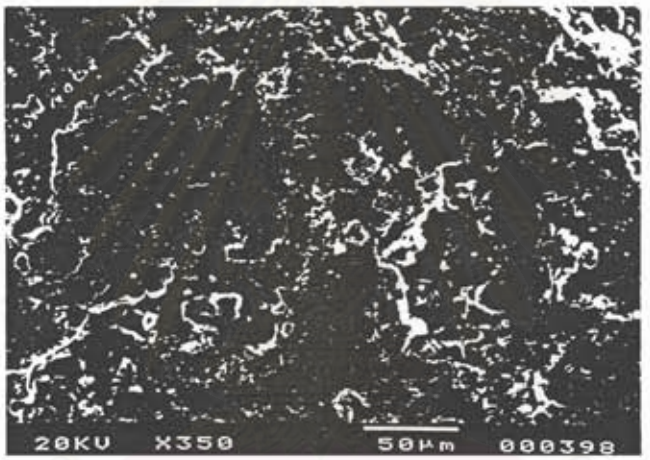

C

Figure 22 Photomicrographs of coated pellets Formulation 9 (5 % EURL60:EC40).

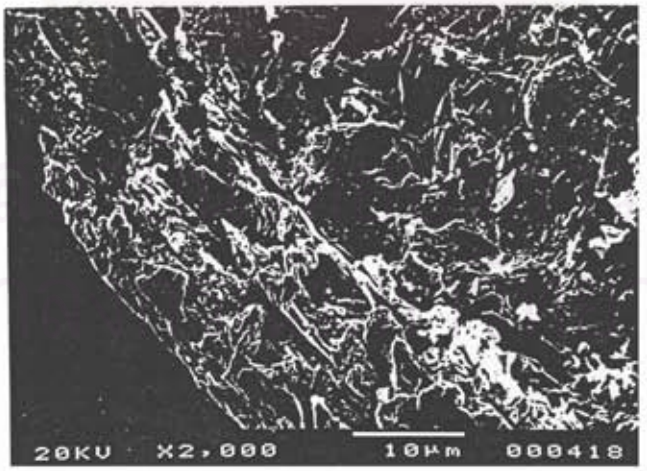
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



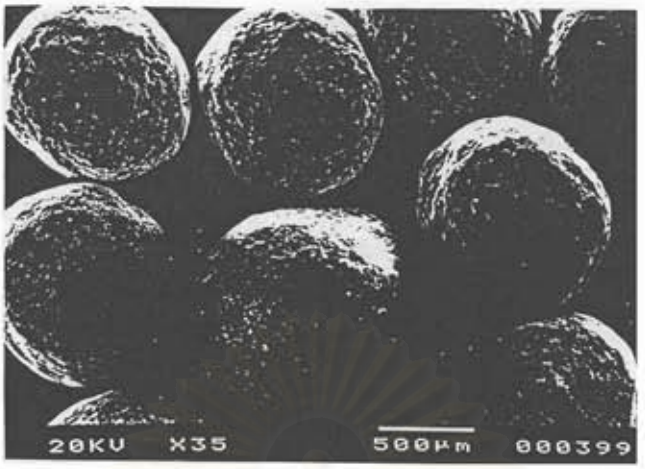

B



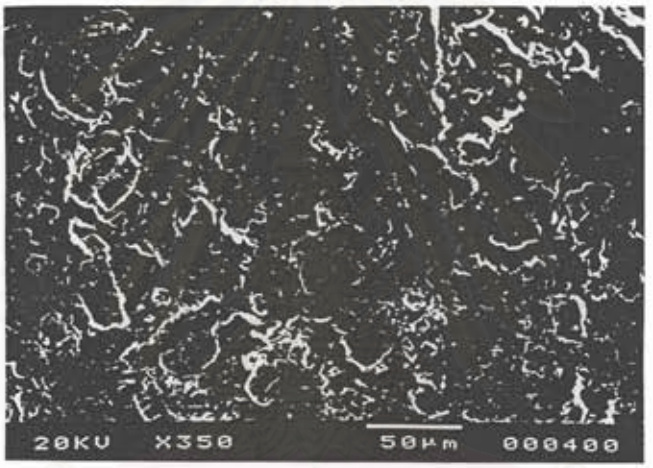

C

Figure 23 Photomicrographs of coated pellets Formulation 10 (10 %EURL80:EC20).

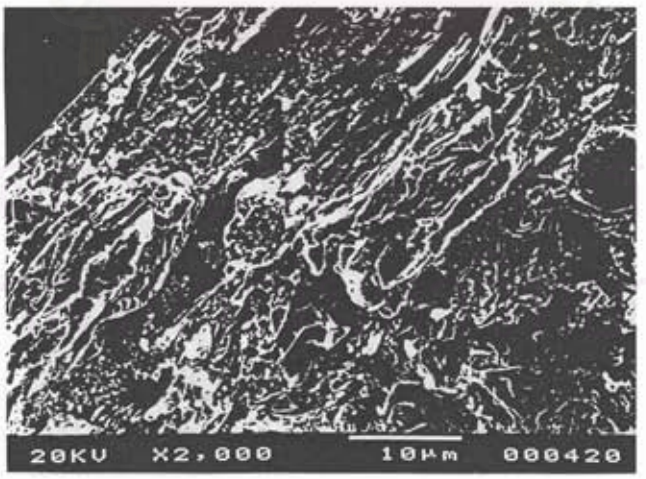
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A




B

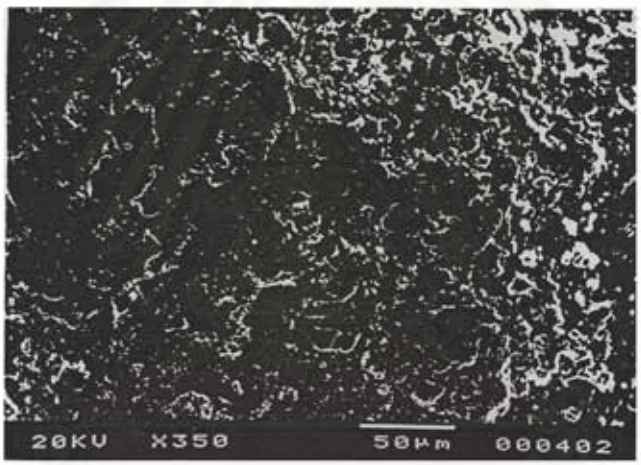



C

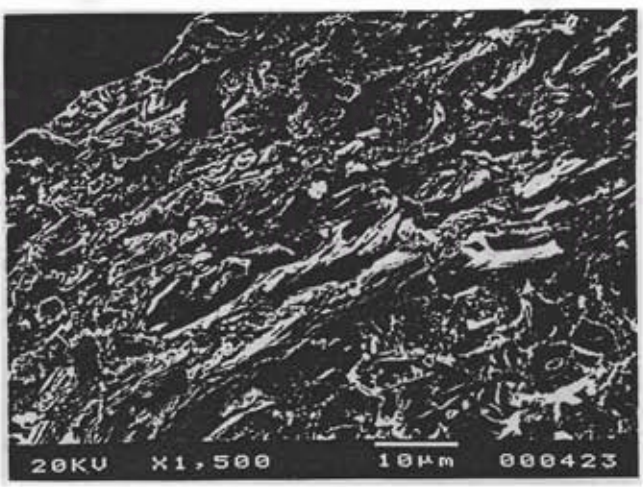
Figure 24 Photomicrographs of coated pellets Formulation 11 (15 %EURL80:EC20).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)


A



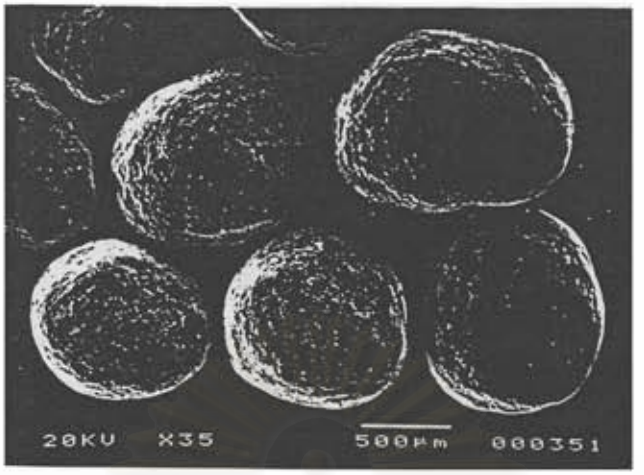

B



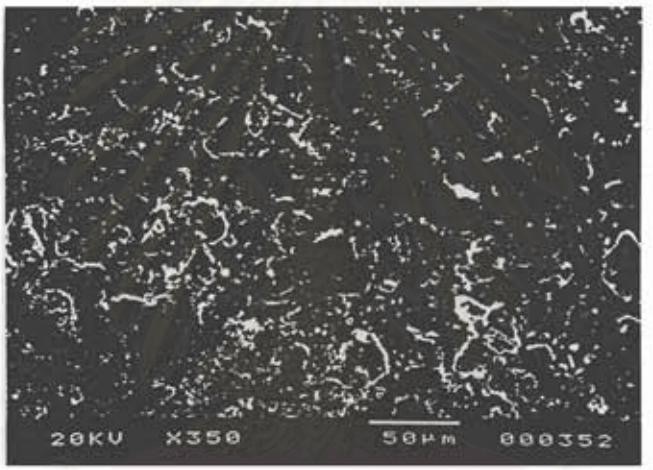

C

Figure 25 Photomicrographs of coated pellets Formulation 12 (20 %EURL80:EC20).

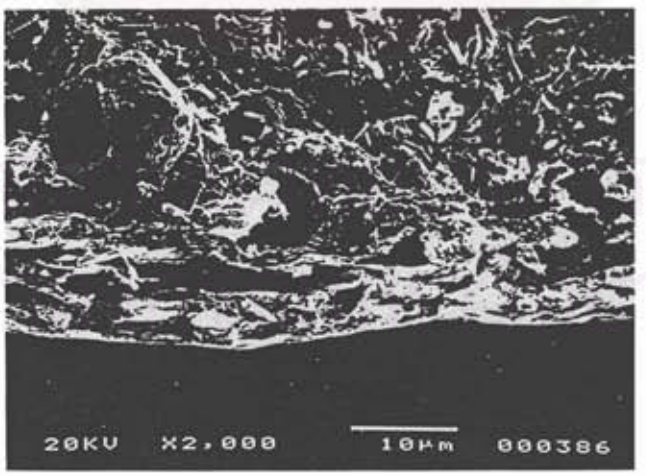
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 1500)




A



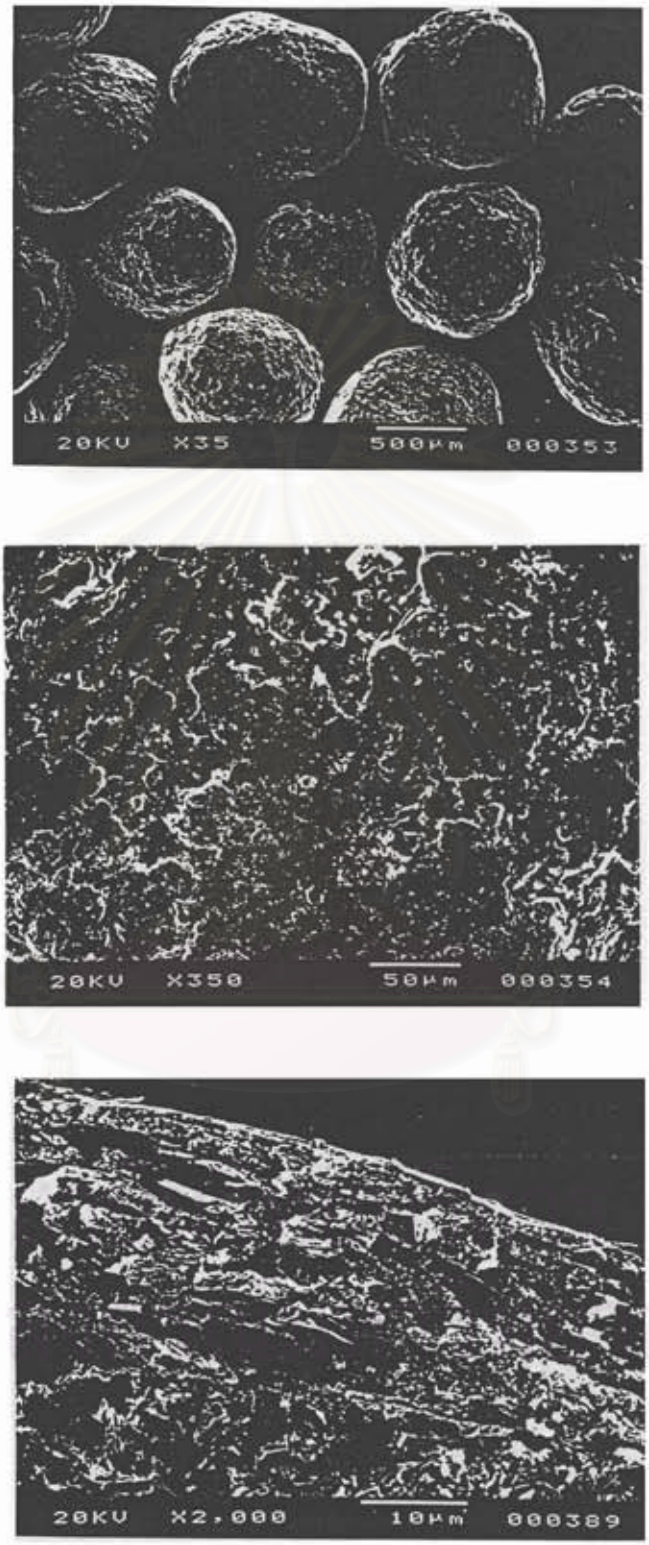

B




C

Figure 26 Photomicrographs of coated pellets Formulation 13 (5 %EURL40:EC60).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)



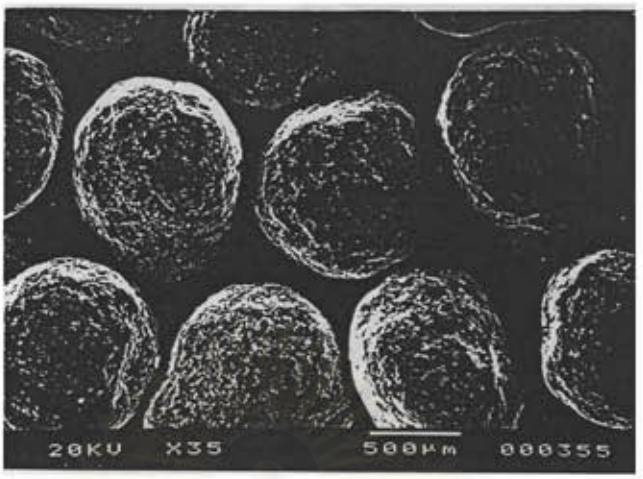

A

B

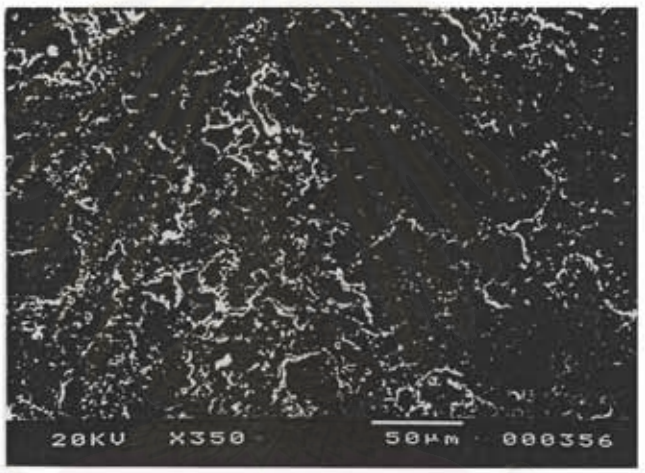
C

Figure 27 Photomicrographs of coated pellets Formulation 14 (10 %EURL40:EC60).

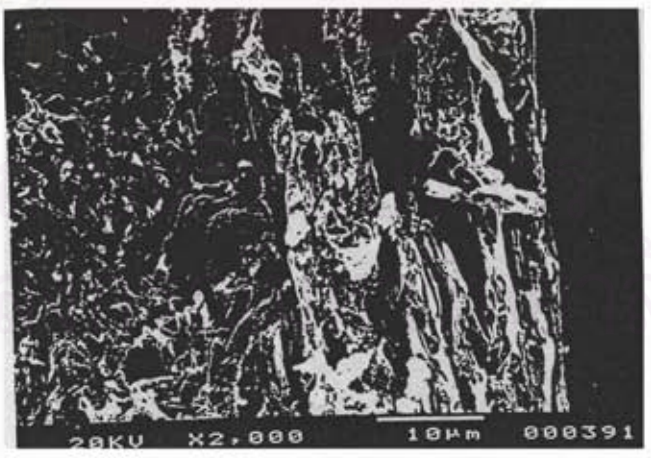
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



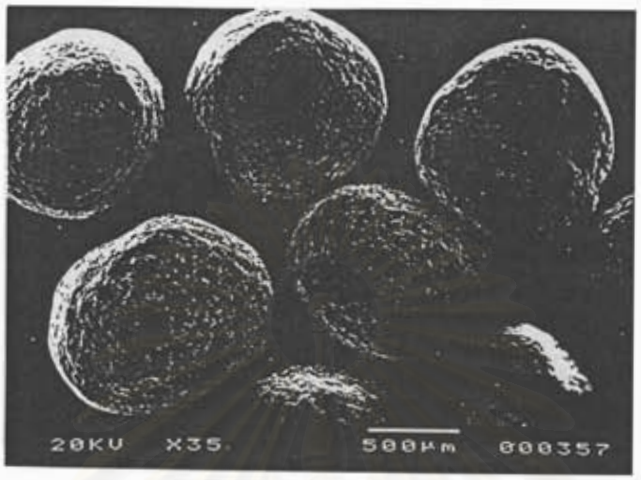

B



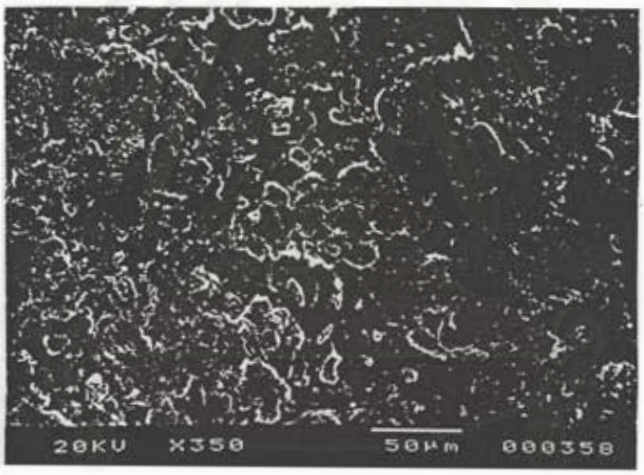

C

Figure 28 Photomicrographs of coated pellets Formulation 15 (15 %EURL40:EC60).

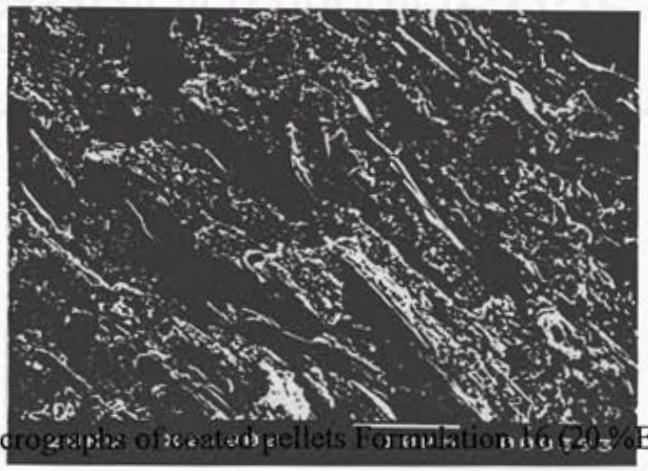
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



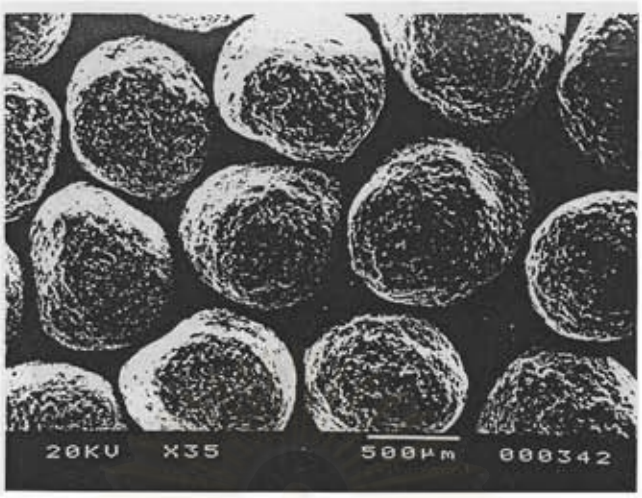

B



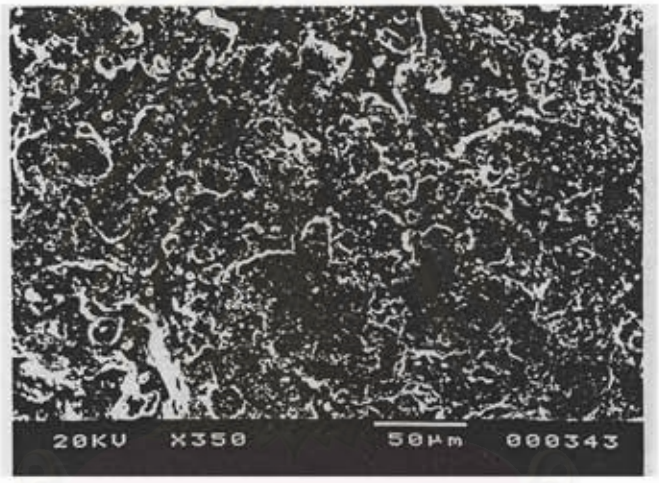
C

Figure 29 Photomicrographs of coated pellets Formulation 16 (20% EURL40:EC60).

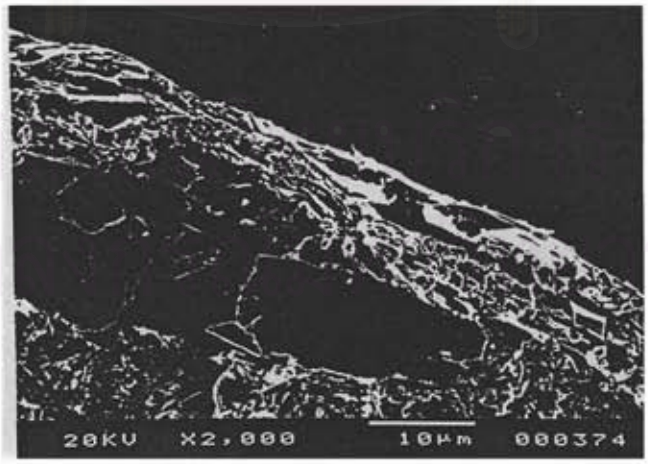
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



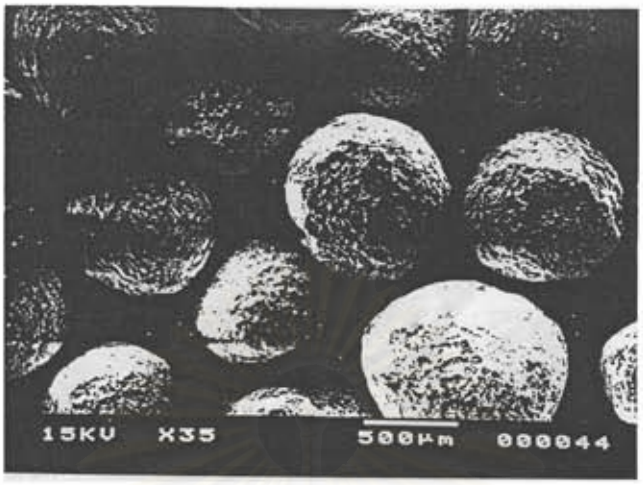

B



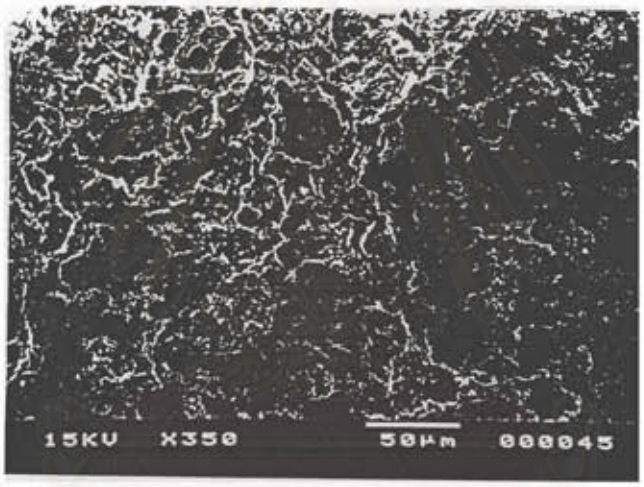

C

Figure 30 Photomicrographs of coated pellets Formulation 17 (5 %EURL20:EC80).

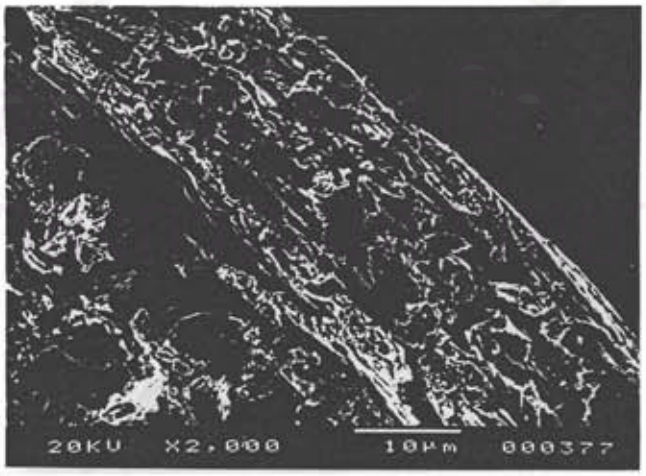
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



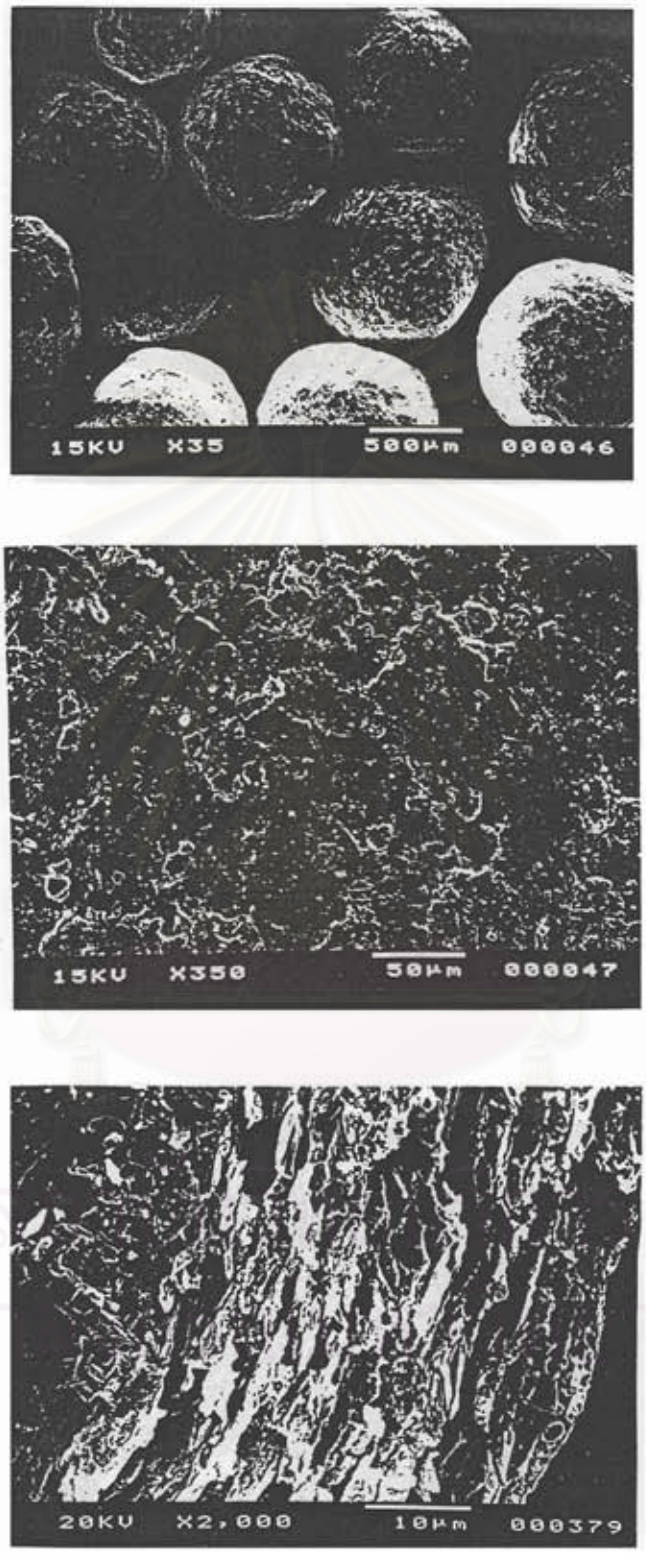

B




C

Figure 31 Photomicrographs of coated pellets Formulation 18 (10 %EURL20:EC80).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)



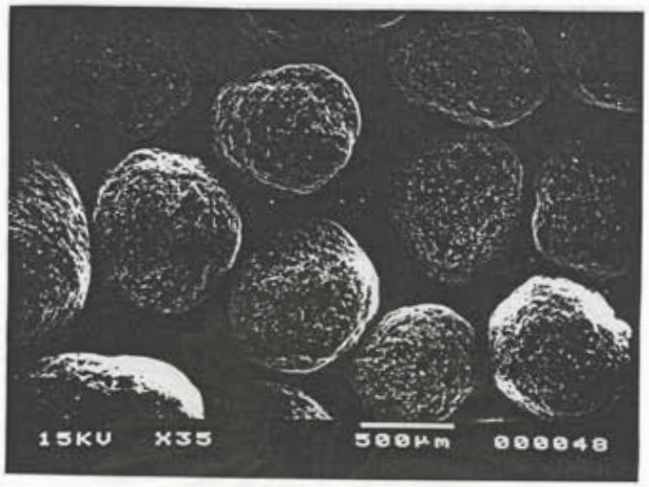

A

B

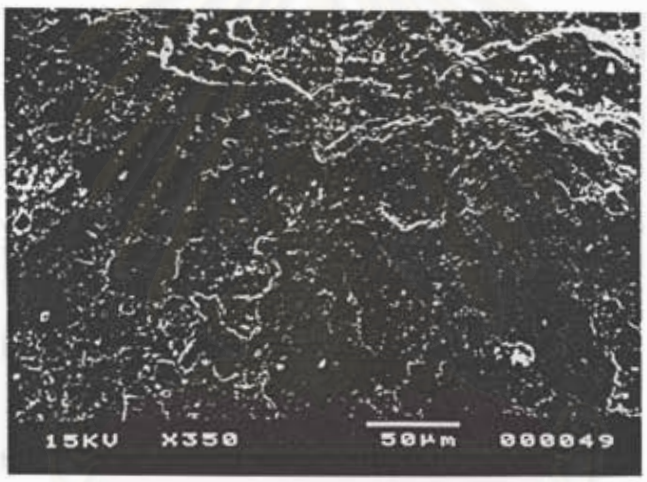
C

Figure 32 Photomicrographs of coated pellets Formulation 19 (15 %EURL20:EC80).

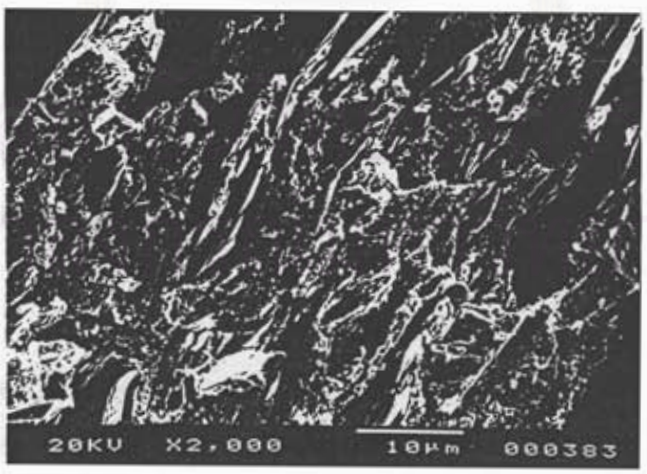
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A




B




C

Figure 33 Photomicrographs of coated pellets Formulation 20 (20 %EURL20:EC80).

(Key: A coated pellets×35, B coating surface×350, C cross-section×2000)

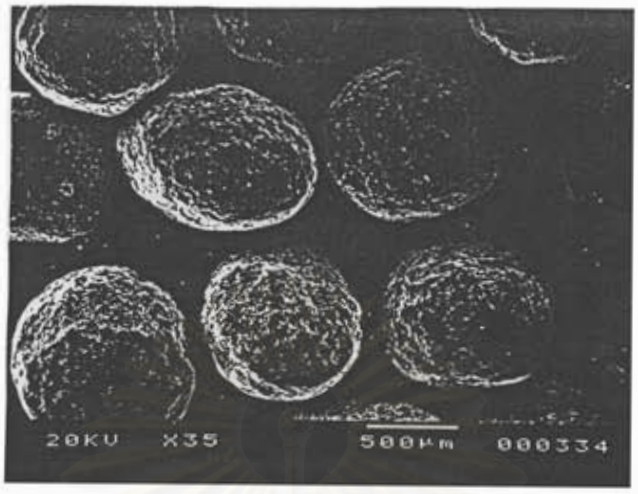
Figure 34-37 illustrate pellets coated with the 100 % ethylcellulose at 5 %, 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification picture represent a highly rough film. In addition, coated pellets was not round. The cross-section at × 2000 magnification picture represent the film layer. The higher percent coating exhibited the thicker film than those with lower percent coating level.

The coating with the mixture of Eudragit®RS100 and ethylcellulose are shown in Figure 38-52.

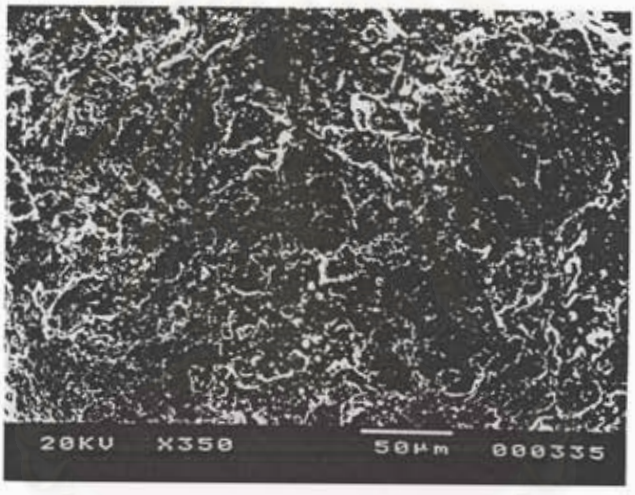
Figure 38-40 illustrate pellets coated with 100 % Eudragit®RS100 at 10 %, 15 % and 20 % coating level respectively. The × 35 and × 350 picture represented a smooth, compact, and continuous film. At a low coating level, few pores occurred. The higher coating level, the smoother and more continuous of the film. At × 2000 magnification , cross section picture represent a distinctive interface between the core and the coating. The higher percent coating exhibited the thicker film than those with lower percent coating level.

Figure 41-43 illustrate pellets coated with 80 %Eudragit®RS100 and 20 % ethylcellulose at 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification pictures show a rough film. Nevertheless, the higher coating level, the more smoother and more continuous film. At × 2000 magnification , cross-section picture represent a distinctive interface between the core and the coating. The higher percent coating exhibit the thicker film than those with lower percent coating level.

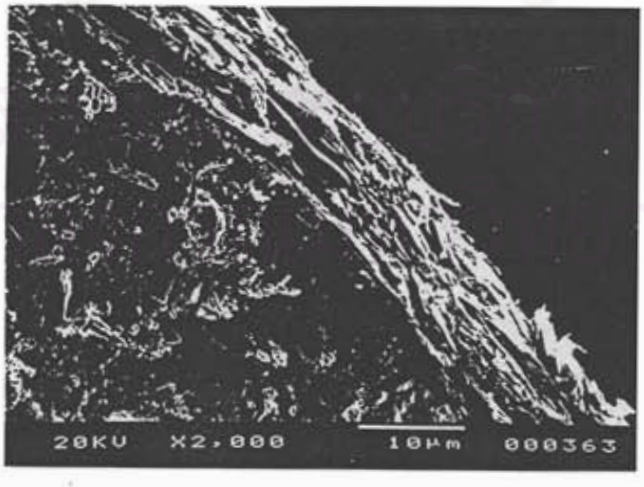
Figure 44-46 illustrate pellets coated with 60 %Eudragit®RS100 and 40 % ethylcellulose at 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification pictures show a rough film. Nevertheless, the higher coating level, the smoother and more continuous in a film. At × 2000 magnification , cross-section picture represent the distinctive interface between the core and the coating.




A




B

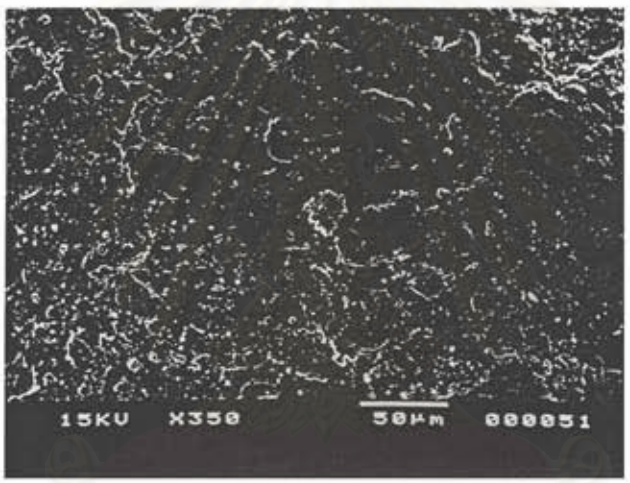



C

Figure 34 Photomicrographs of coated pellets Formulation 21 (5 % EC 100).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)


A

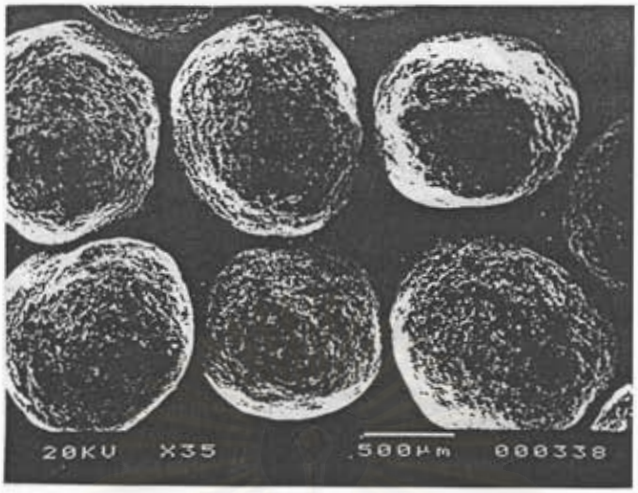



B

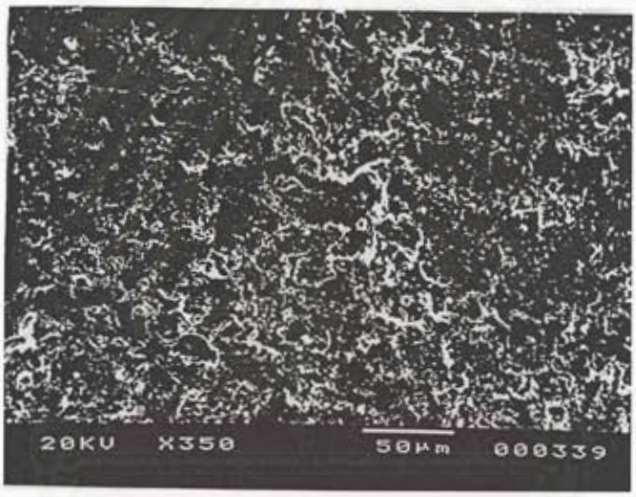

C

Figure 35 Photomicrographs of coated pellets Formulation 22 (10 % EC 100).

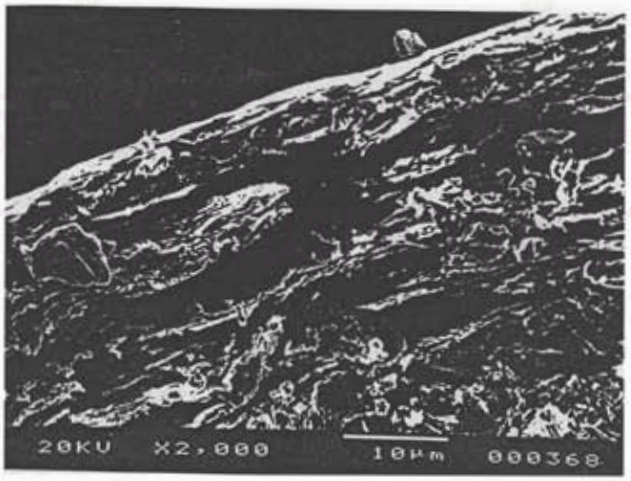
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



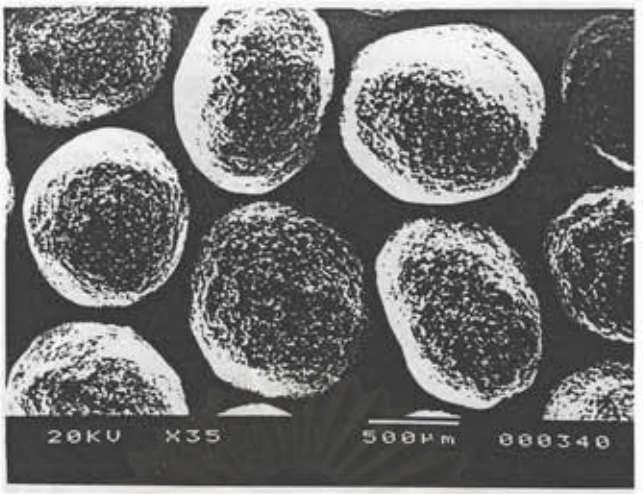

B



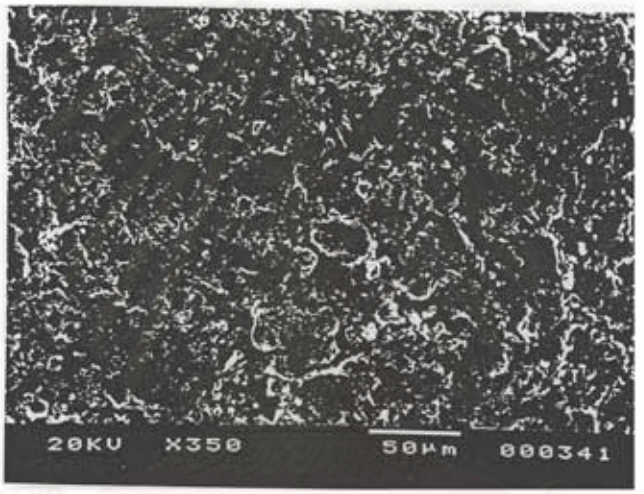

C

Figure 36 Photomicrographs of coated pellets Formulation 23 (15 % EC 100).

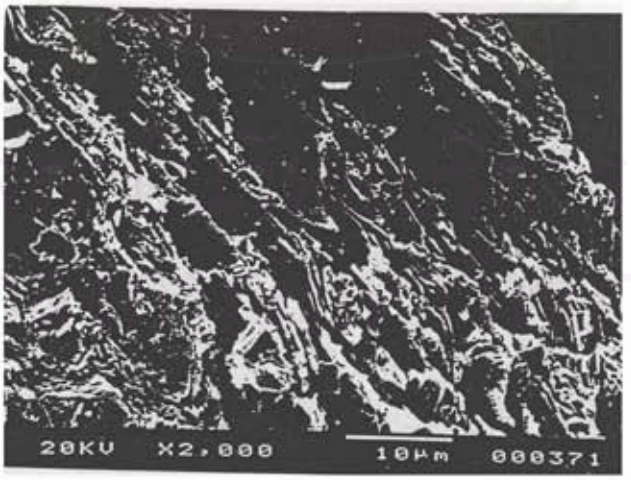
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



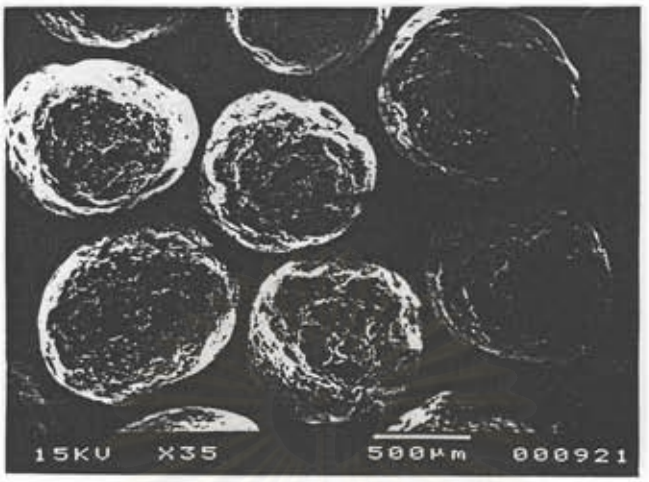

B



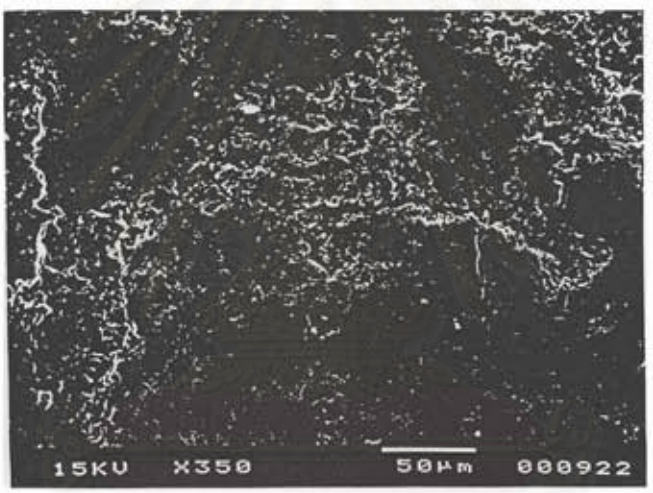

C

Figure 37 Photomicrographs of coated pellets Formulation 24 (20 % EC 100).

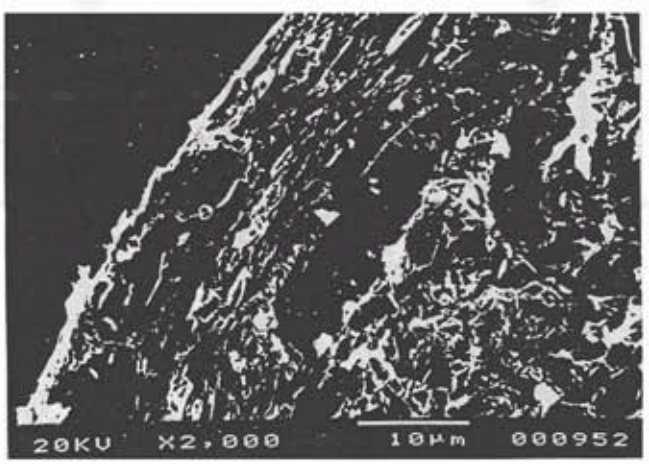
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



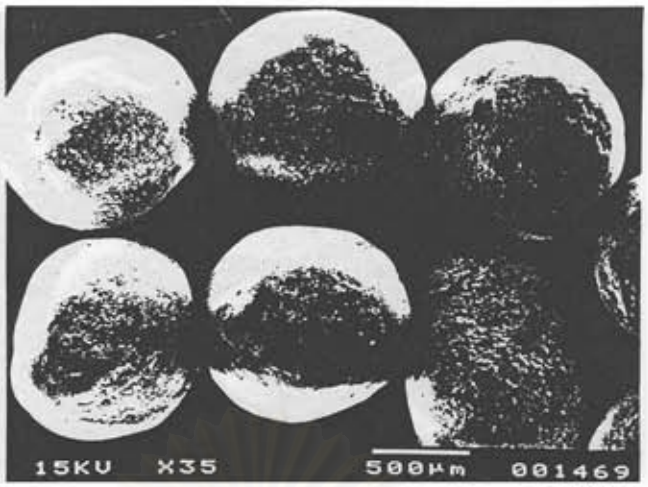

B



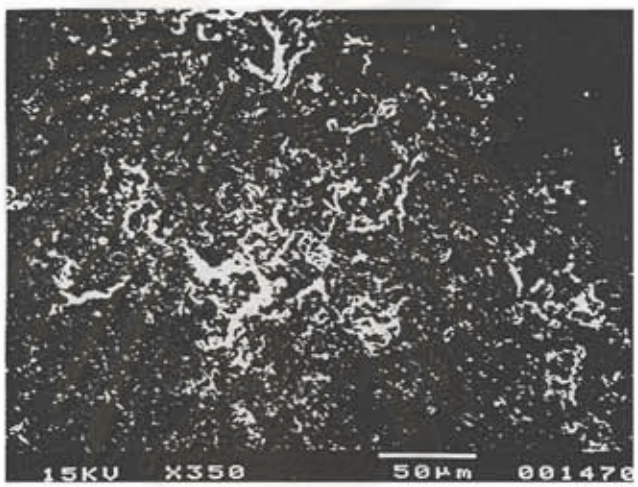

C

Figure 38 Photomicrographs of coated pellets Formulation 25 (10 % EURS100).

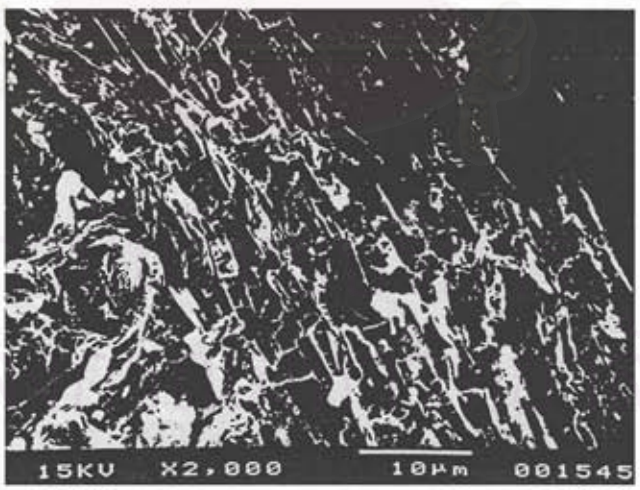
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



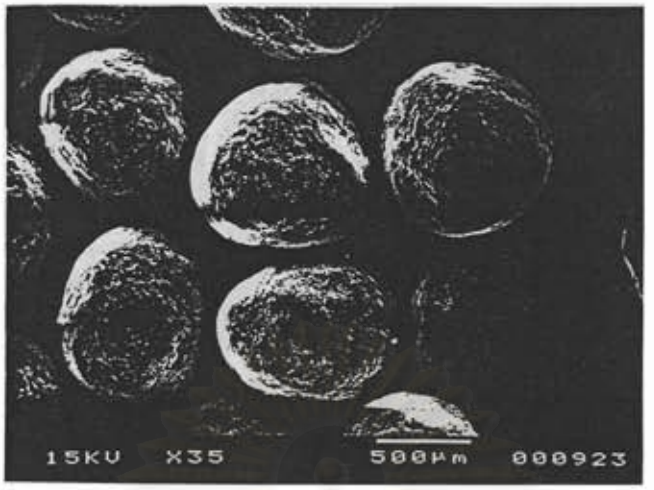

B



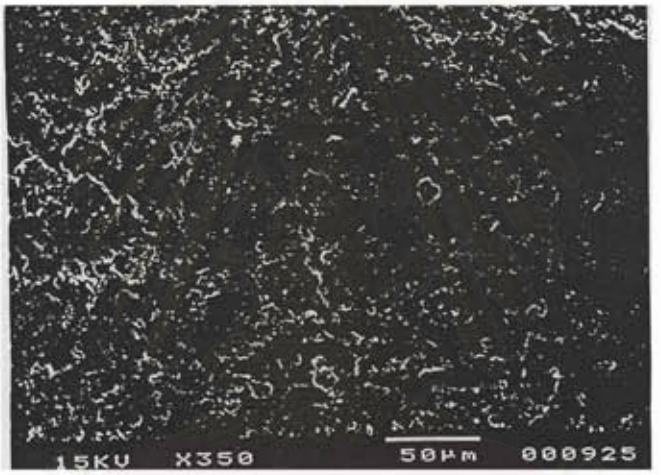

C

Figure 39 Photomicrographs of coated pellets Formulation 26(15 %EURS100).

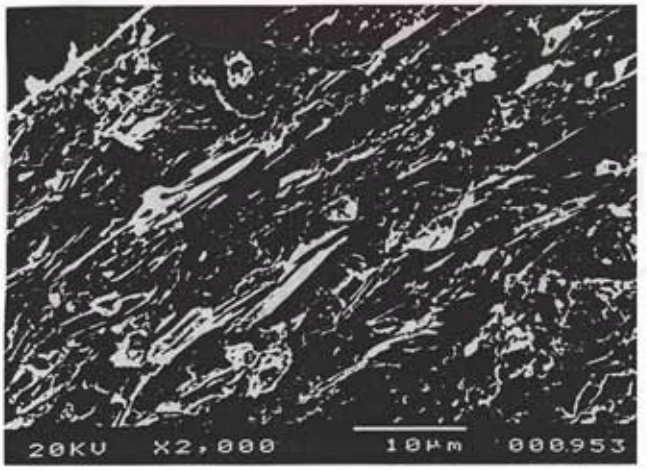
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A



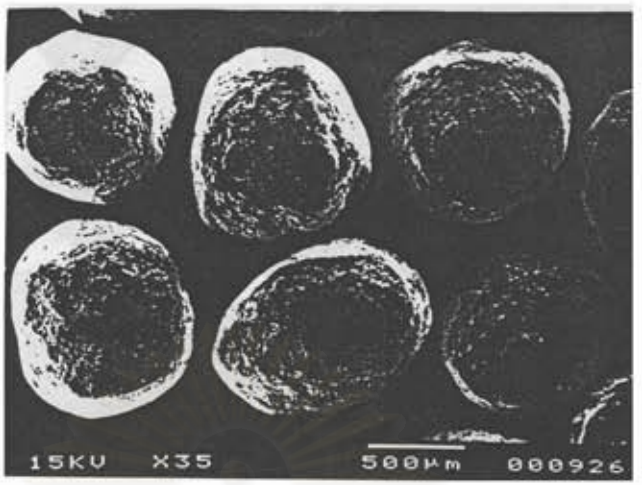

B



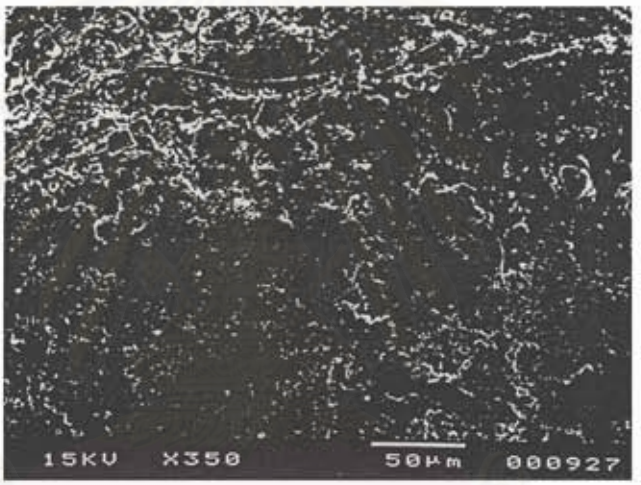

C

Figure 40 Photomicrographs of coated pellets Formulation 27(20 %EURS100).

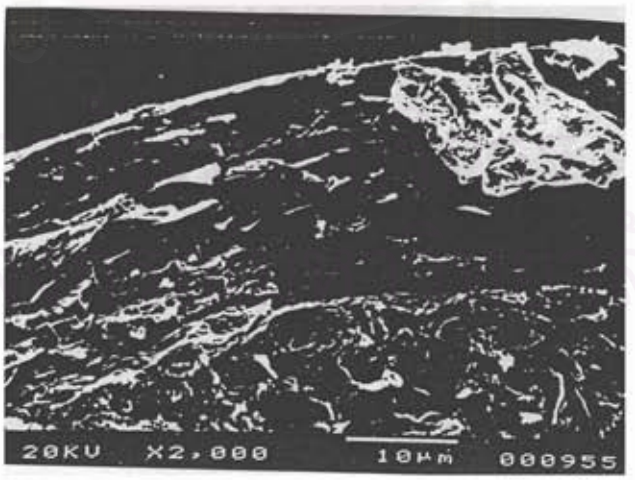
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A




B

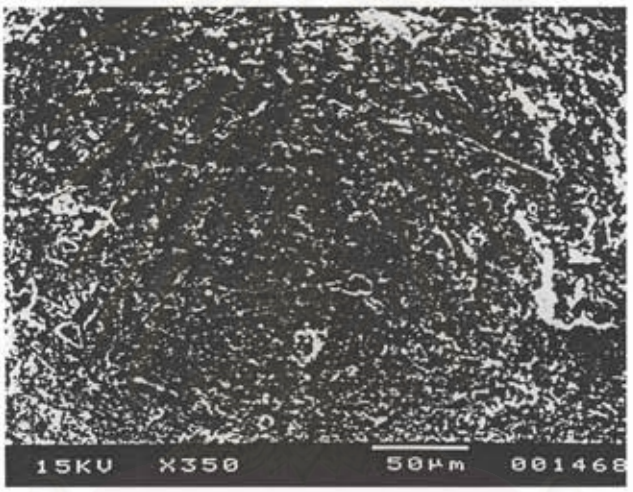



C

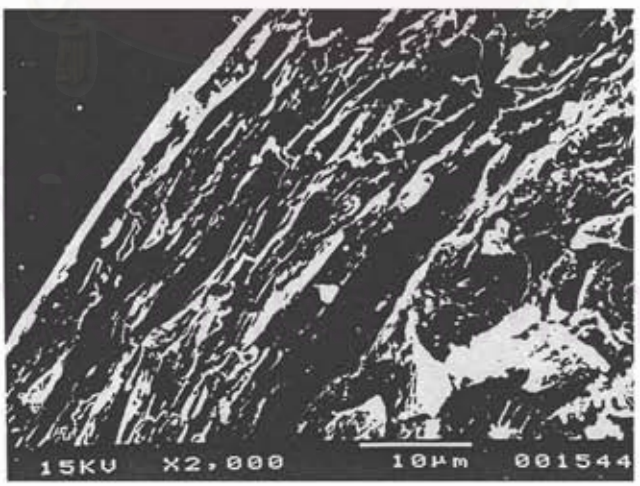
Figure 41 Photomicrographs of coated pellets Formulation 28 (10 %EURS80:EC20).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)


A



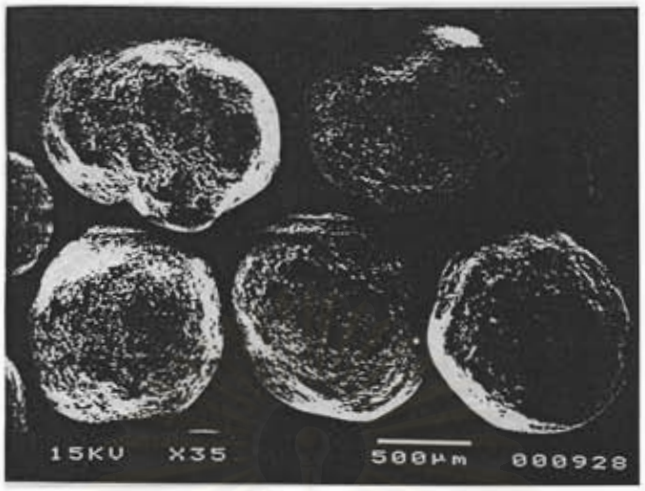

B



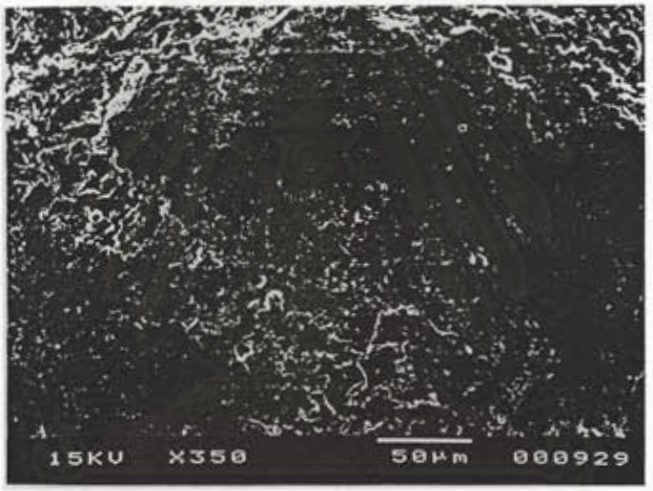

C

Figure 42 Photomicrographs of coated pellets Formulation 29 (15 %EURS80:EC20.)

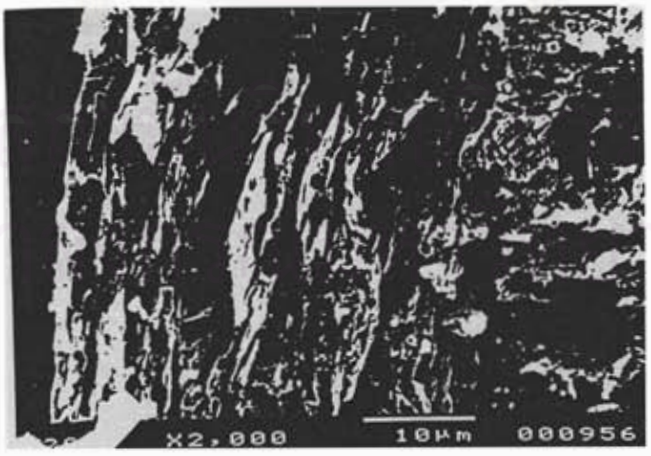
(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)




A



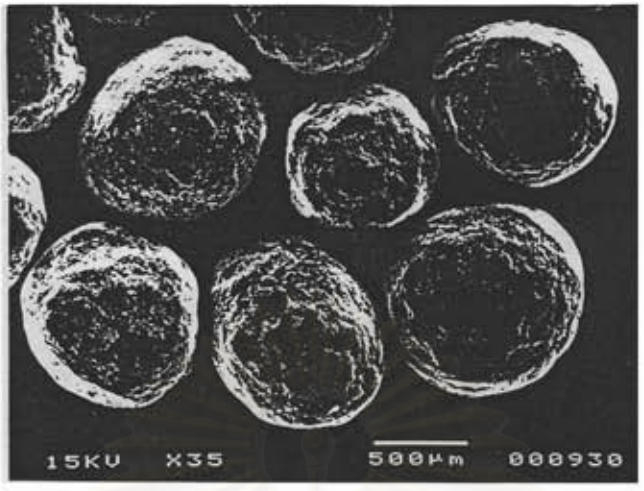

B



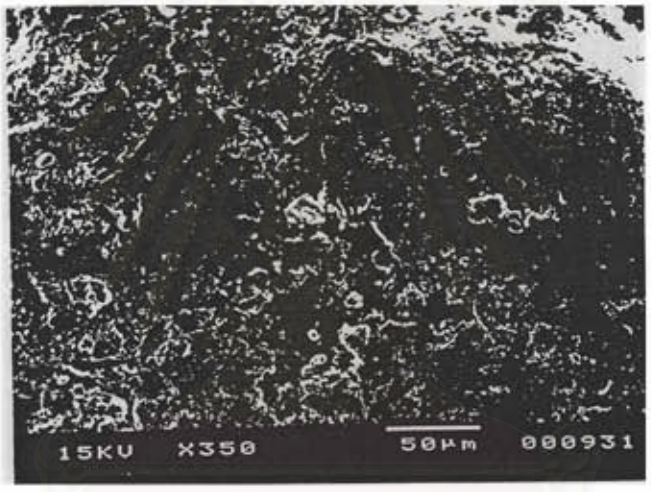

C

Figure 43 Photomicrographs of coated pellets Formulation 30 (20 %EURS80:EC20).

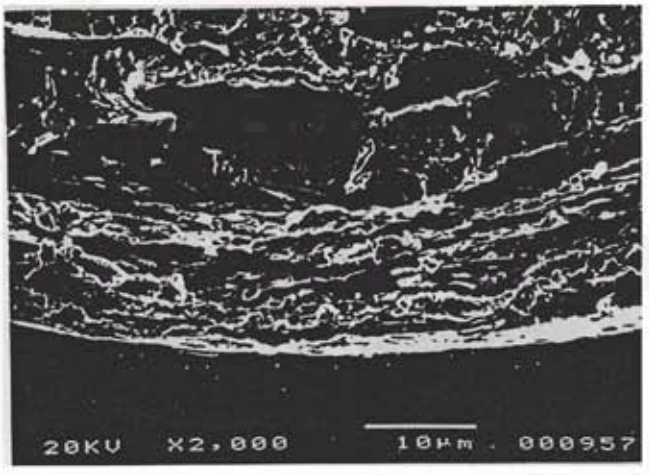
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A




B

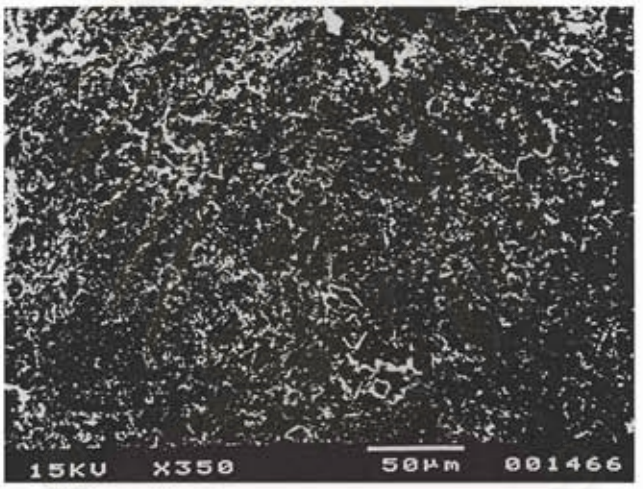



C

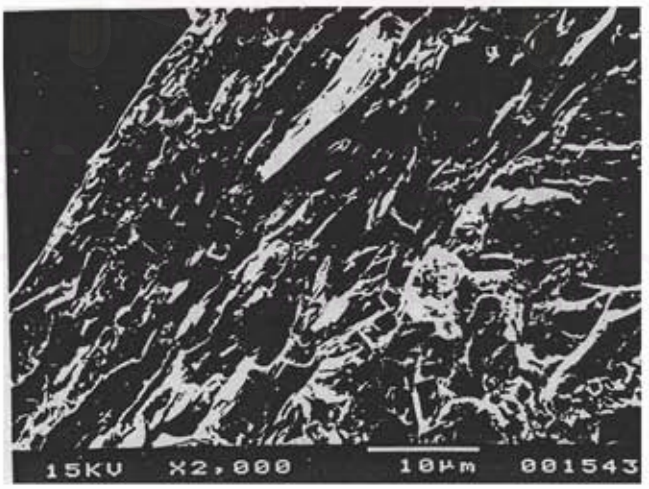
Figure 44 Photomicrographs of coated pellets Formulation 31 (10 %EURS60:EC40).

(Key: A coated pellets × 35, B coating surface × 350, C cross-section × 2000)


A



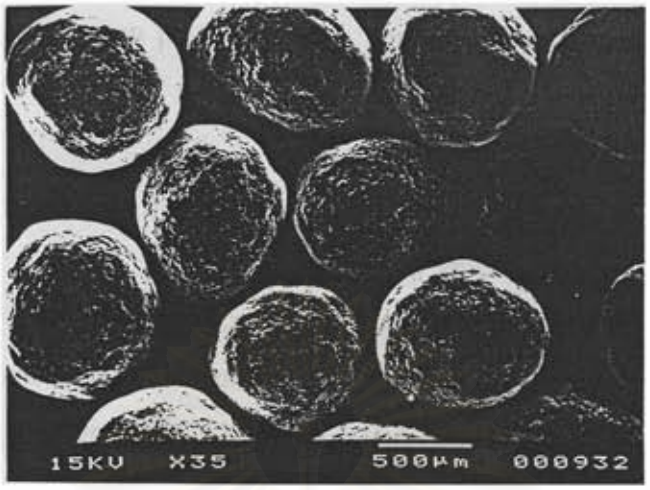

B



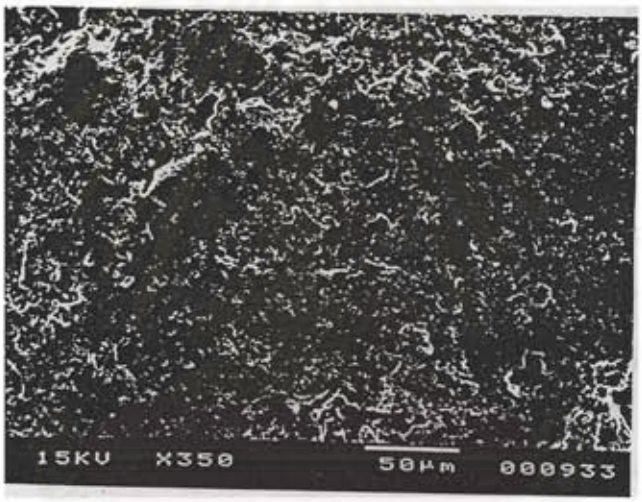

C

Figure 45 Photomicrographs of coated pellets Formulation 32(15 %EURS60:EC40).

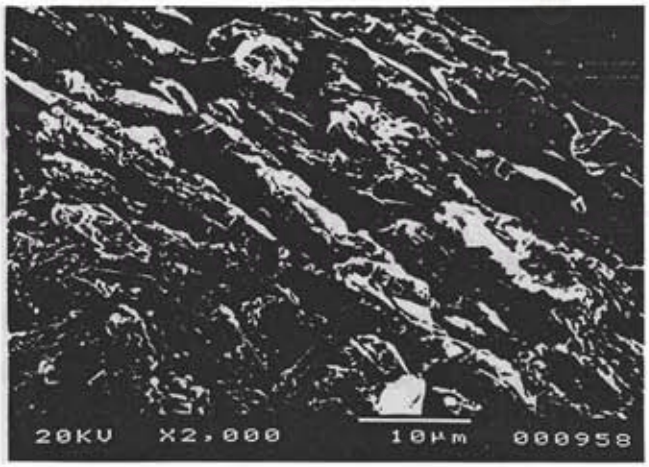
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A




B




C

Figure 46 Photomicrographs of coated pellets Formulation 33 (20 %EURS60:EC40).

(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)

The higher percent coating exhibited the thicker film than those with lower percent coating level.

Figure 47-49 illustrate pellets coated with 40%Eudragit®RS100 and 60 % ethylcellulose at 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification pictures show a rough film. Nevertheless, the higher coating level, give smoother and more continuous in a film. At × 2000 magnification , cross-section picture represent the distinctive interface between the core and the coating. The higher percent coating exhibited the thicker film than those with lower percent coating level.

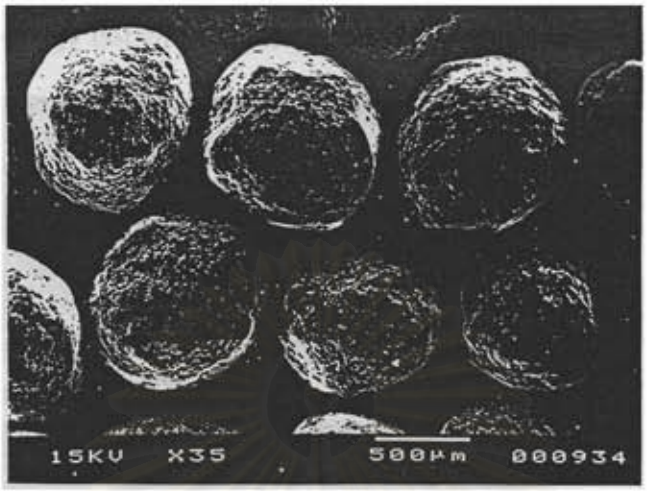
Figure 50-52 illustrate pellets coated with 20 % Eudragit®RS100 and 80 % ethylcellulose at 10 %, 15 % and 20 % coating level, respectively. The × 35 and × 350 magnification pictures show a rough film. Nevertheless, the higher coating level, the smoother and more continuous in film. At × 2000 magnification , cross-section picture represent a distinctive interface between the core and the coating. The higher percent coating exhibited the thicker film than those with lower percent coating level.

5.2 Density

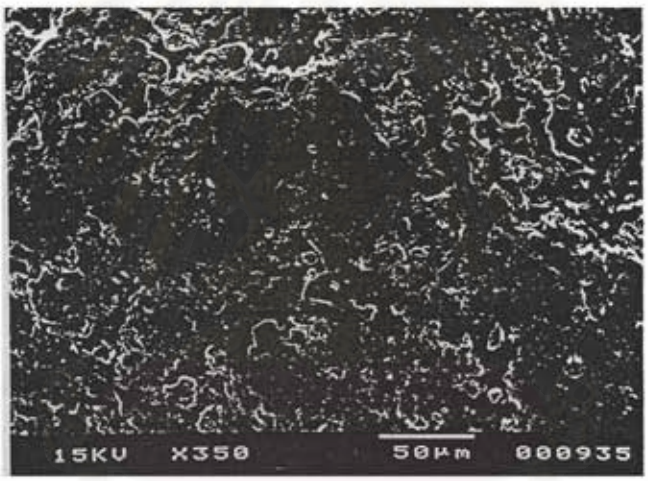
The bulk density, tapped density, and Carr's Compressibility index of coated pellets are presented in Table 12. The results were observed that there were not apparently different among uncoated pellets and coated pellets. It is because coating level had no effect on the bulk density.

5.3 Friability

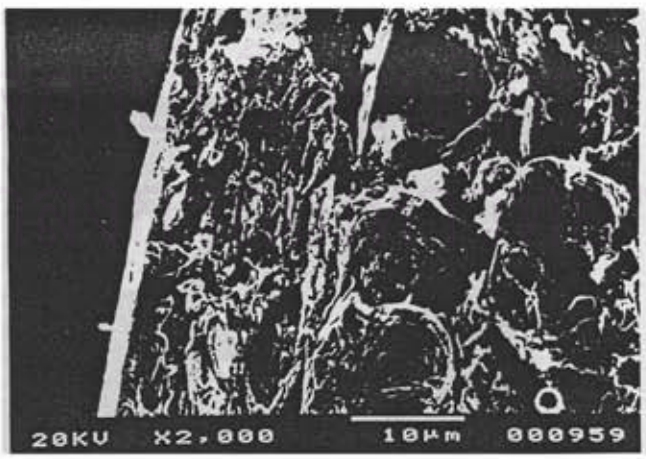
The friability of coated pellets were presented in Table 12. Because uncoated pellets have a high density and a high bonding from extrusion and spheronization




A



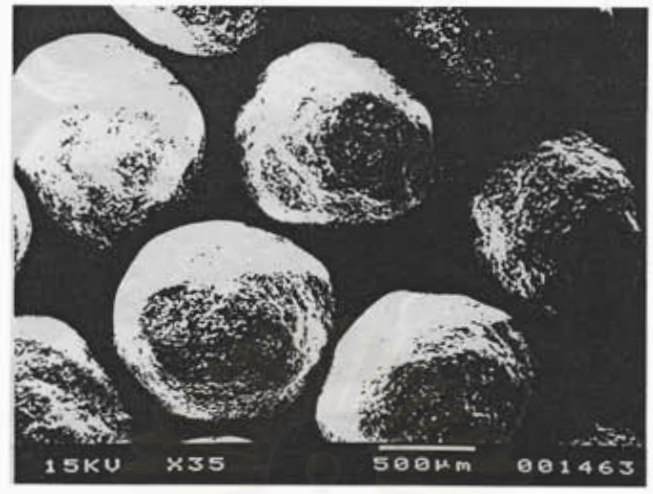

B



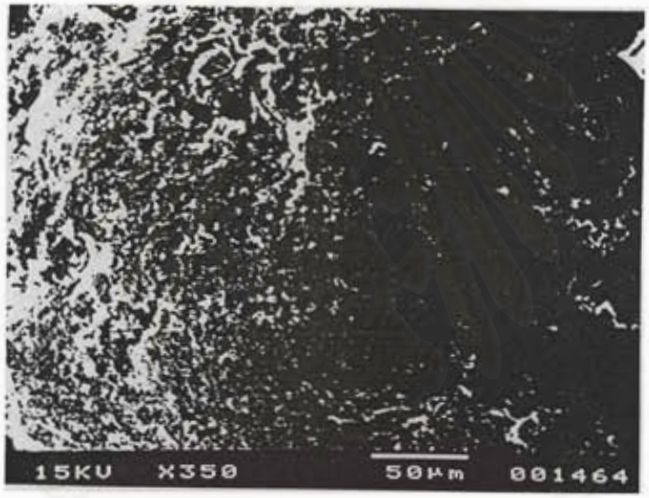

C

Figure 47 Photomicrographs of coated pellets Formulation 34 (10 %EURS40:EC60).

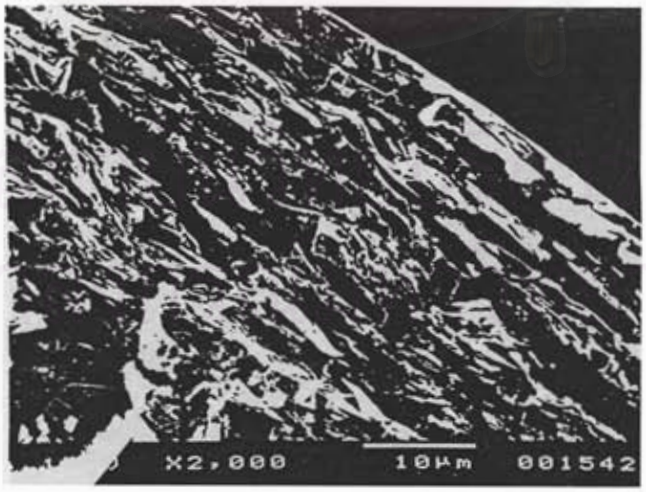
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A



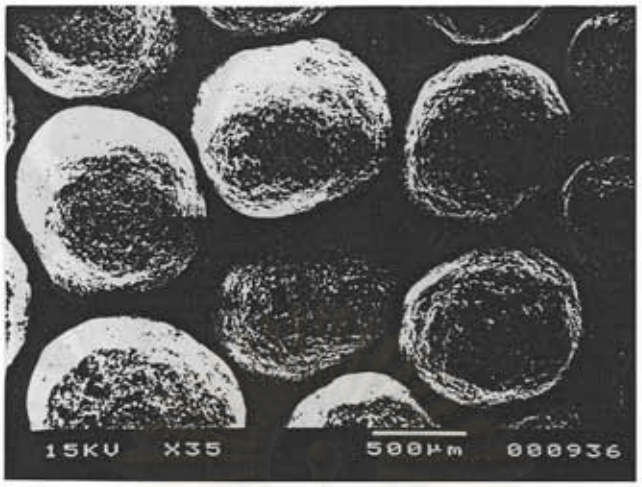

B



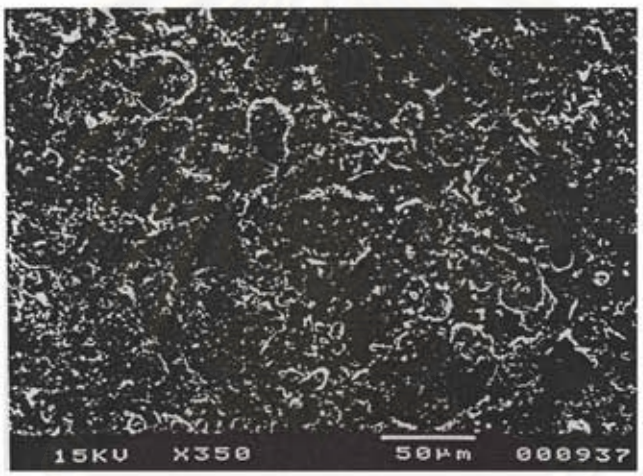

C

Figure 48 Photomicrographs of coated pellets Formulation 35 (15 %EURS40:EC60).

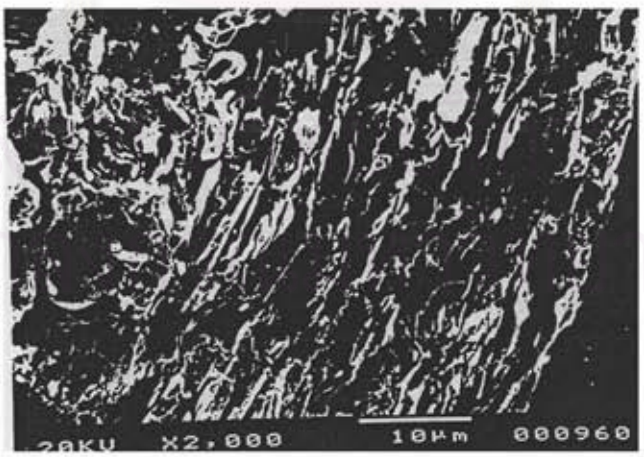
(Key: A coated pellets × 35, B coating solution × 350 , C cross-section × 2000)




A



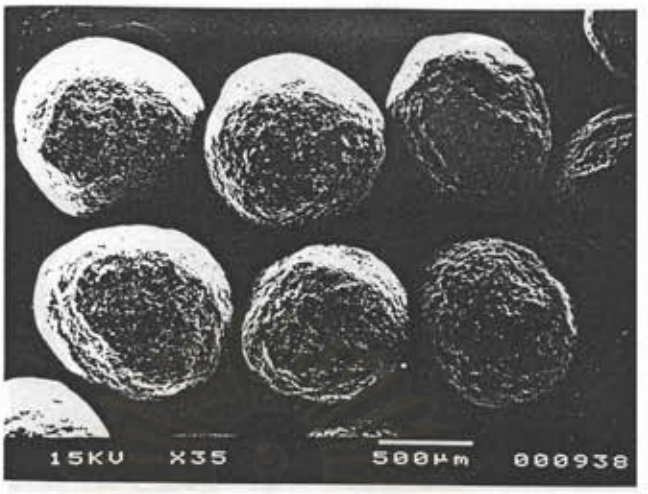

B



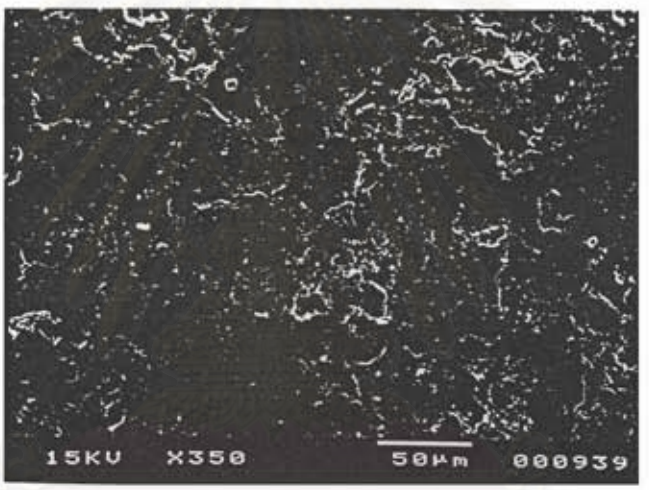

C

Figure 49 Photomicrographs of coated pellets Formulation 36 (20 %EURS40:EC60).

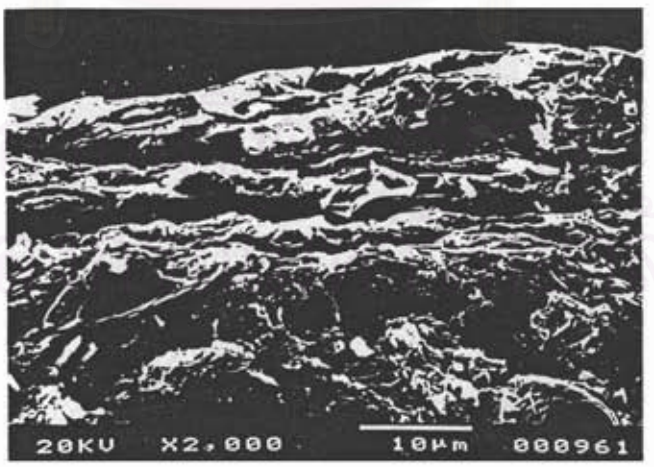
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A




B

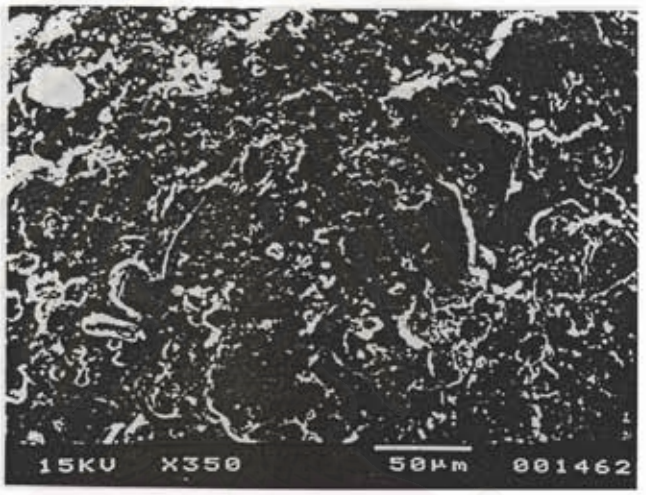



C

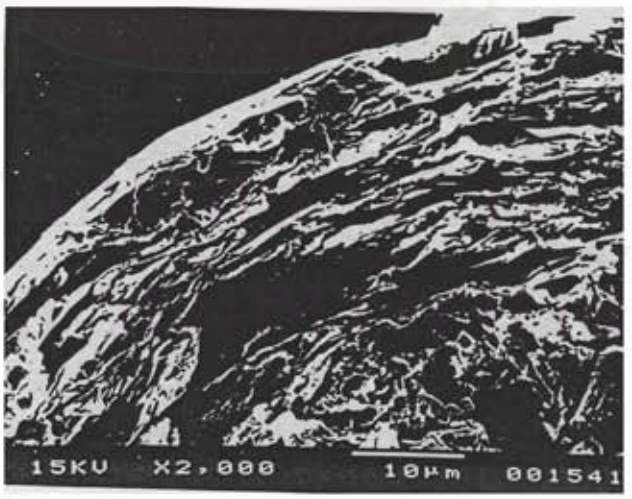
Figure 50 Photomicrographs of coated pellets Formulation 37 (10 %EURS20:EC80).

(Key: A coated pellets×35, B coating solution×350, C cross-section×2000)


A



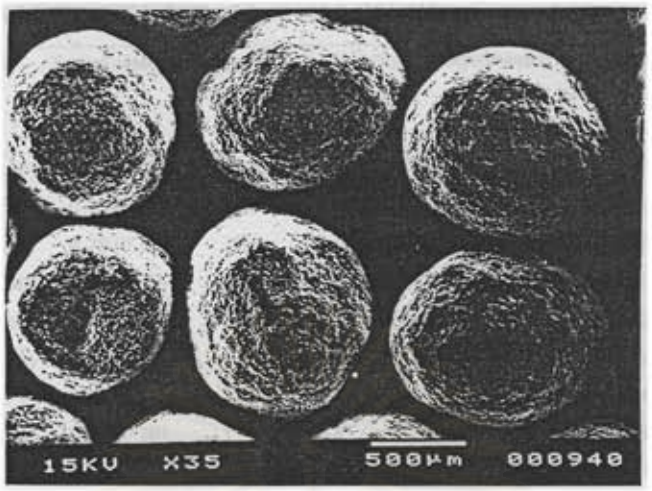

B



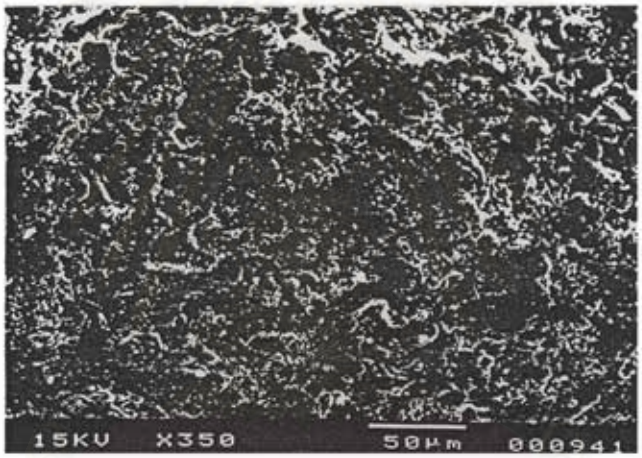

C

Figure 51 Photomicrographs of coated pellets formulation 38 (15%EURS20:EC80).

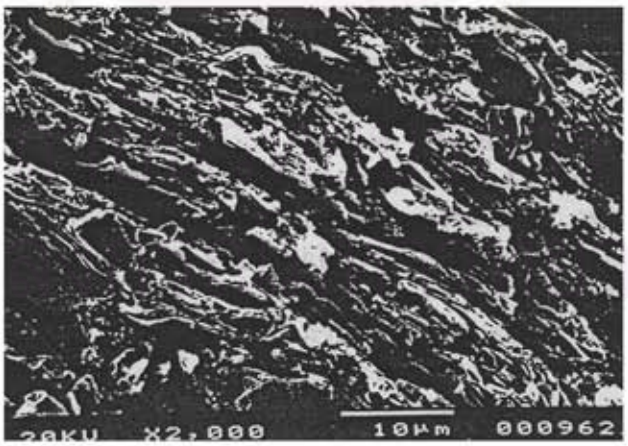
(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)




A




B




C

Figure 52 Photomicrographs of coated pellets Formulation 39 (20 %EURS20:EC80).

(Key: A coated pellets × 35, B coating solution × 350, C cross-section × 2000)

Table 12 Physical properties of coated pellets.

| Formulation | Bulk density (g/ml) | Tapped density (g/ml) | Carr's Compressibility (%) | Friability (%) | Moisture content (%) | propranolol hydrochloride content (%) | Weight of pellets in one capsule (mg) |
|---|---|---|---|---|---|---|---|
| 1 | 0.70 (0.10)* | 0.72 (0.69) | 2.78 | 0.14 (1.00) | 0.87 (0.60) | 40.84 (0.95) | 391.77 |
| 2 | 0.69 (0.08) | 0.70 (0.82) | 1.43 | 0.00 (0.08) | 0.93 (0.28) | 36.87 (1.13) | 433.96 |
| 3 | 0.68 (0.72) | 0.70 (0.39) | 2.86 | 0.05 (0. 46) | 1.03 (0.65) | 34.29 (0.97) | 466.61 |
| 4 | 0.69 (0.30) | 0.69 (0.03) | 0.00 | 0.02 (1.05) | 0.95 (0.86) | 31.66 (1.11) | 505.37 |
| 5 | 0.71 (0.43) | 0.73 (0.67) | 2.74 | 0.00 (0.09) | 0.93 (0.75) | 40.09 (0.49) | 399.10 |
| 6 | 0.70 (0.98) | 0.71 (0.47) | 1.41 | 2.00 (0.86) | 0.86 (0.69) | 36.67 (1.11) | 436.56 |
| 7 | 0.71 (0.21) | 0.72 (0.45) | 1.39 | 0.01 (0.05) | 0.70 (0.39) | 34.43 (0.68) | 464.51 |
| 8 | 0.71 (0.65) | 0.72 (0.20) | 1.39 | 0.03 (0.96) | 0.99 (0.85) | 31.50 (0.07) | 507.94 |
| 9 | 0.71 (0.46) | 0.72 (0.49) | 1.39 | 0.00 (1.03) | 1.20 (0.67) | 40.00 (0.56) | 400.00 |
| 10 | 0.71 (0.76) | 0.71 (0.50) | 0.00 | 0.04 (0.88) | 0.79 (0.86) | 38.38 (0.99) | 417.43 |
| 11 | 0.70 (0.87) | 0.72 (0.40) | 2.78 | 0.04 (0.04) | 1.31 (0.86) | 34.85 (1.13) | 459.11 |
| 12 | 0.71 (0.76) | 0.71 (0.50) | 0.00 | 0.00 (0.40) | 0.61 (0.93) | 33.70 (1.16) | 475.2 0 |
| 13 | 0.70 (0.67) | 0.71 (0.67) | 1.41 | 0.02 (0.60) | 0.10 (0.04) | 39.68 (0.58) | 406.30 |
| 14 | 0.70 (0.78) | 0.72 (0.40) | 2.78 | 0.00 (0.77) | 0.71 (0.04) | 37.33 (1.18) | 428.61 |
| 15 | 0.70 (0.98) | 0.71 (0.85) | 1.41 | 0.11 (0.95) | 0.98 (0.04) | 33.70 (0.50) | 474.78 |
| 16 | 0.69 (0.46) | 0.69 (0.59) | 0.00 | 0.00 (0.05) | 1.38 (0.87) | 31.41(1.32) | 509.39 |
| 17 | 0.71 (0.34) | 0.71 (0.40) | 0.00 | 0.02 (0.88) | 1.39 (0.87) | 38.70 (0.60) | 413.47 |
| 18 | 0.70 (0.76) | 0.71 (0.58) | 1.41 | 0.09 (0.69) | 1.42 (1.06) | 36.00 (1.19) | 444.44 |
| 19 | 0.70 (0.39) | 0.70 (0.69) | 0.00 | 0.06 (0.20) | 1.14 (2.94) | 32.89 (2.10) | 486.47 |
| 20 | 0.69 (0.38) | 0.69 (0.00) | 0.00 | 0.02 (0.86) | 1.01(0.59) | 30.59 (1.31) | 523.00 |
| 21 | 0.69 (0.78) | 0.71 (0.69) | 2.82 | 0.00 (1.09) | 1.02 (0.84) | 39.19 (0.57) | 408.27 |
| 22 | 0.68 (0.46) | 0.72 (0.59) | 5.56 | 0.01 (0.67) | 1.16 (1.04) | 36.65 (0.35) | 436.55 |
| 23 | 0.68 (0.85) | 0.71 (0.10) | 4.23 | 0.27 (1.00) | 0.96 (0.30) | 34.44 (1.19) | 464.56 |
| 24 | 0.69 (0.58) | 0.72 (0.38) | 4.17 | 0.09 (0.60) | 1.16 (1.95) | 32.39 (0.96) | 493.91 |
| 25 | 0.71 (0.95) | 0.73 (0.05) | 2.74 | 0.09 (1.04) | 1.45 (0.90) | 37.31 (0.94) | 428.84 |
| 26 | 0.70 (0.94) | 0.71 (0.92) | 1.41 | 0.12 (0.59) | 0.95 (0.38) | 34.53 (0.93) | 463.37 |
| 27 | 0.69 (0.87) | 0.70 (0.57) | 1.43 | 0.00 (0.09) | 1.28 (0.95) | 32.15 (1.90) | 497.69 |
| 28 | 0.70 (0.76) | 0.70 (0.84) | 0.00 | 0.00 (0.60) | 1.12 (0.57) | 36.98 (1.95) | 432.67 |
| 29 | 0.71 (0.57) | 0.72 (1.17) | 1.39 | 0.00 (0.60) | 1.19 (0.68) | 34.93 (1.64) | 458.03 |
| 30 | 0.69 (0.49) | 0.70 (0.90) | 1.43 | 0.05 (1.05) | 1.08 (0.86) | 32.89 (2.90) | 486.54 |
| 31 | 0.70 (0.94) | 0.72 (0.01) | 2.78 | 0.02 (0.96) | 0.83 (1.90) | 38.62 (1.98) | 444.34 |
| 32 | 0 .69 (0.56) | 0.70 (0.30) | 1.43 | 0.00 (0.85) | 1.40 (0.56) | 35.75 (2.20) | 447.55 |
| 33 | 0.68 (0.76) | 0.69 (0.66) | 1.45 | 0.00 (0.58) | 1.41 (0.68) | 33.87 (1.09) | 472.42 |
| 34 | 0.71 (0.94) | 0.71 (0.67) | 0.00 | 0.35 (0.58) | 0.99 (0.58) | 37.39 (0.68) | 427.95 |
| 35 | 0.70 (0.48) | 0.72 (0.49) | 2.78 | 0.04 (0.84) | 0.92 (0.57) | 35.75 (1.00) | 447.54 |
| 36 | 0.69 (0.49) | 0.70 (0.93) | 1.43 | 0.75 (0.60) | 1.06 (2.94) | 33.54 (0.20) | 477.04 |
| 37 | 0.69 (0.65) | 0.70 (0.89) | 1.43 | 0.03 (0.85) | 1.12 (1.86) | 37.45 (1.71) | 427.70 |
| 38 | 0.68 (0.38) | 0.72 (0.91) | 5.56 | 2.75 (0.57) | 1.16 (1.05) | 34.23 (0.50) | 457.28 |
| 39 | 0.68 (0.68) | 0.70 (0.69) | 2.86 | 0.35 (0.60) | 1.26 (0.96) | 32.28 (0.76) | 496.22 |

* (SD in parenthesis)

process, pellets were then not broken into fine powders although the coating process was 1-2 hours in the fluidized bed. The results of friability test were then not apparently different among uncoated pellets and coated pellets. The friability results also indicated that the coating film could withstand the impact during friability testing.

5.4 Moisture Content

The moisture content of coated pellets is presented in Table 12. The range was between 0.61 and 1.45. The moisture content was observed that it was not apparently difference among uncoated and coated pellets. The coated pellets in formulation 1-39 were coated using organic solvent system which can be rapidly evaporated under a low temperature. Due to a drying process, dry film was obtained, resulting in a small number difference in a moisture content.

5.5 Drug Content

Drug content of coated pellets was presented in Table 12. The data represented that the drug content of coated pellets is less than uncoated pellets. It is because the coated pellets consisted of the coating suspension. The higher coating levels implied the lower drug content. From the triple values, the drug contents were not much different. It was implied that the coating was reproducibly performed.

5.6 Determination of Drug Release from Pellets.

From the experimental data, the dissolution or the release profiles could be plotted between amount percent of drug release against time. Each point represents the average value obtained from three determinations at the given sampling time.

5.6.1 *Uncoated pellets*

The release of propranolol hydrochloride from uncoated pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown graphically in Figure 53, and the dissolution data are tabulated in Table 22 (Appendix D). The obtained result showed similar release characteristics in both mediums. The releases of the drug from the pellets were almost completed within 0.5 hour.

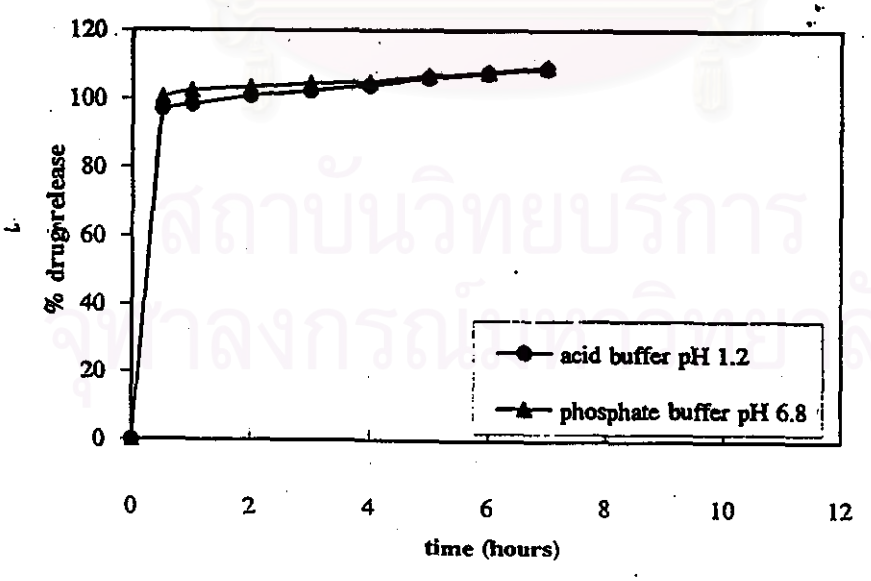



Figure 53 Release profile of uncoated pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8.

The mechanism of release from uncoated pellets could be explained in two ways, firstly, be extraction of the drug by a simple diffusional process through the homogeneous matrix and secondly, leaching of drug by the solvent phase which able to enter the drug-matrix phase through pores, crack and intragranular space. In the former case, drug presumably partitions from the crystal structure into the uniform matrix and out into the bathing dissolution medium, which acts as a perfect sink. In the latter case, however, drug dissolves slowly in the permeating fluid phase and diffuses from the system along the cracks and capillary channels filled with the extracting dissolution medium (Dyer et al., 1995).

5.6.2 *Coated pellets*

**The mixture of Eudragit®RL100 and ethylcellulose or the mixture of Eudragit® RS100 and ethylcellulose were applied to the pellets at levels ranging from 5 to 20 % by weight. The effect of polymer ratios, percent coating levels and release characteristic on different pH of acid buffer pH 1.2 or phosphate buffer pH 6.8 were investigated.**

*The Formulation 1-4 Coated Pellets*

**The dissolution data of propranolol hydrochloride from coated pellets with various coating level of Eudragit®RL100 at 5 %, 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 22-23 (Appendix D) and shown graphically in Figure 54-57.**

The obtained profiles indicated that pellets coated with low coating level about 5 % gave the similar release characteristic which was extremely fast in both acid buffer pH 1.2 and phosphate buffer pH 6.8. At the higher coating levels, acid buffer pH 1.2 gave higher release than in phosphate buffer pH 6.8 because of the acidic properties of polymer explained by Pflegel et al., 1981. They observed an increase in

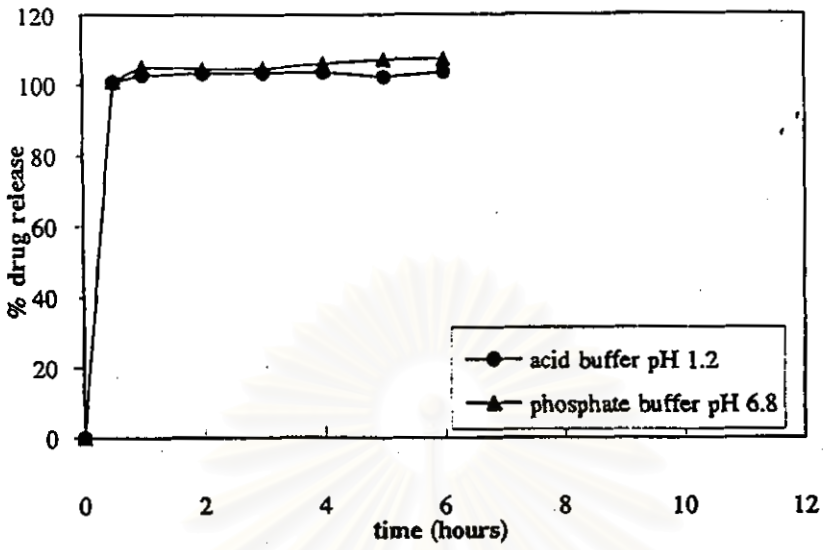



Figure 54 Release profile of coated pellets Formulation 1 (5 % EURL100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

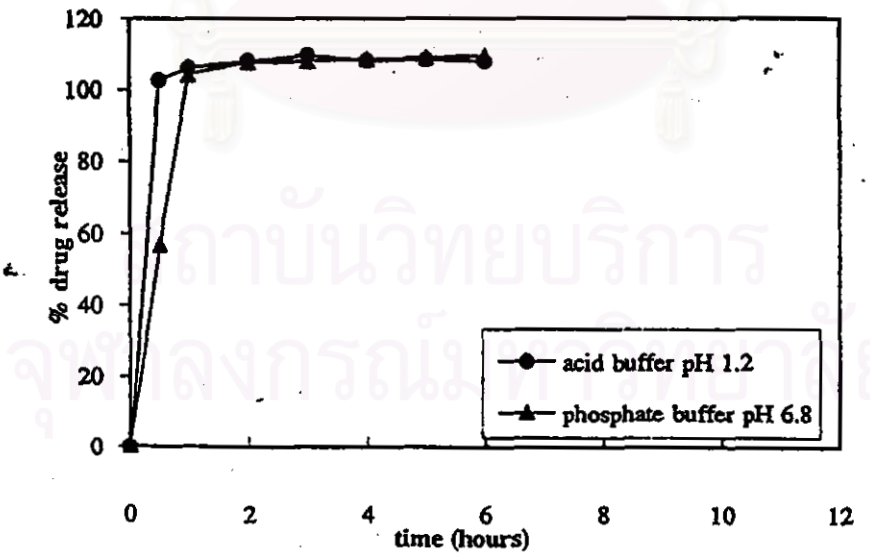



Figure 55 Release profile of coated pellets Formulation 2 (10 % EURL100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

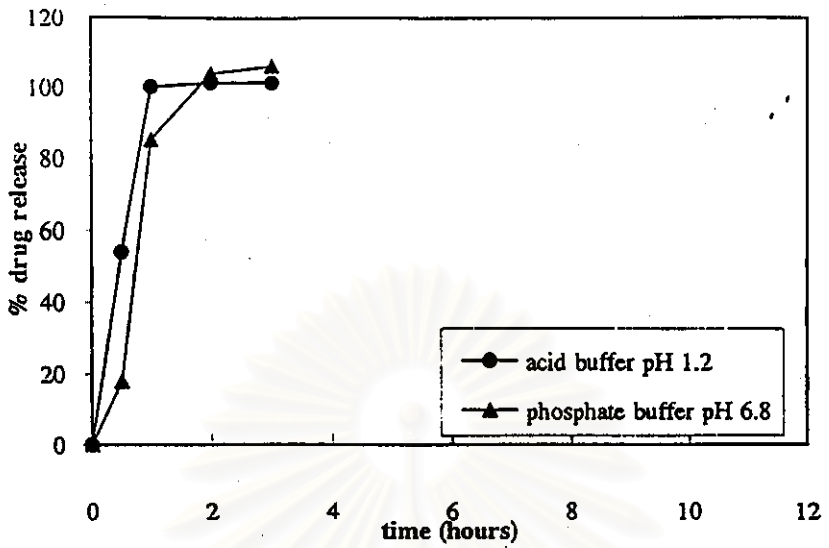



Figure 56 Release profile of coated pellets Formulation 3 (15 % EURL100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

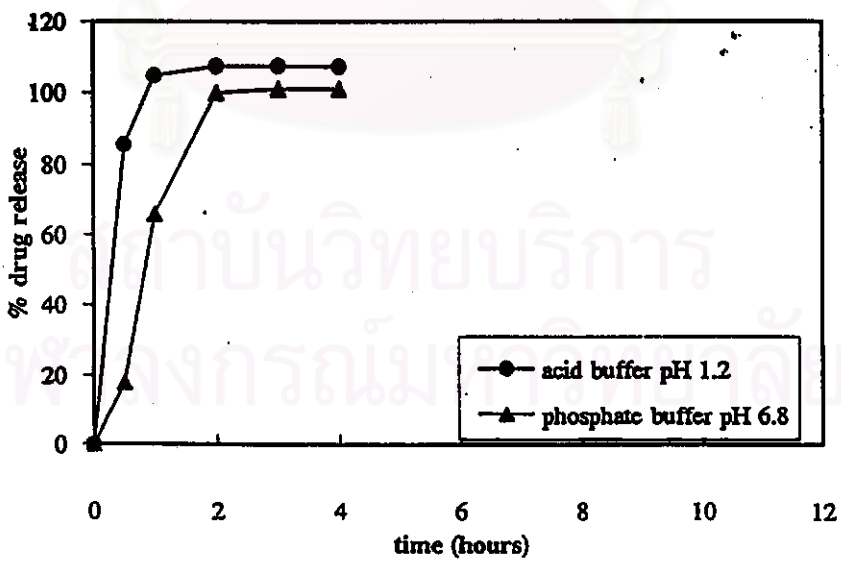



Figure 57 Release profile of coated pellets Formulation 4 (20 % EURL100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

the permeation of an acidic drug through an acrylic film when the pH was decreased, however, the permeation of a basic drug was increased when the pH was increased.

Figure 58-59 show the effect of coating levels of Eudragit®RL100 (Formulation 1-4) on the release of the drug from the pellets in acid and alkali media. Increasing the percent coating levels resulted in corresponding decrease in the drug release in alkali media. The reason for this phenomenon was attributed to the increasing amount of polymer loading which increased the thickness of the film covered around surface of the pellets, therefore amount of drug release decreases (Ozturk et al., 1990 and Zhang et al., 1991).

Eudragit®RL100 formed films which swelled rapidly and later disintegrated in the dissolution medium. Because of Eudragit®RL100 was copolymers synthesized from acrylic and methacrylic acid ester with the high proportion of about 10 % of quaternary ammonium groups attaching to the polymer backbone that made the film coating produced from Eudragit®RL100 water sensitive and gave high permeability in water, rapid hydration and drug release. Consequently, under these conditions Eudragit®RL100 film were probably unsuitable to be membranes for controlling the release as evident by the prompt release characteristic in short time period.

*The Formulation 5-8 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating level of the mixture of 80 % Eudragit®RL100 and 20 % ethylcellulose at 5 %, 10 %, 15 %, and 20 % coating level in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 23-24 (Appendix D) and shown graphically in Figure 60-63.

The obtained profiles indicated that pellets coated with low coating level about 5 % gave similar release characteristics of up to 99.78 % and 96.04 % within half an hour in both acid buffer pH 1.2 and phosphate buffer pH 6.8, respectively. But at the higher coating levels, the pellets gave slower release in phosphate buffer pH 6.8 than

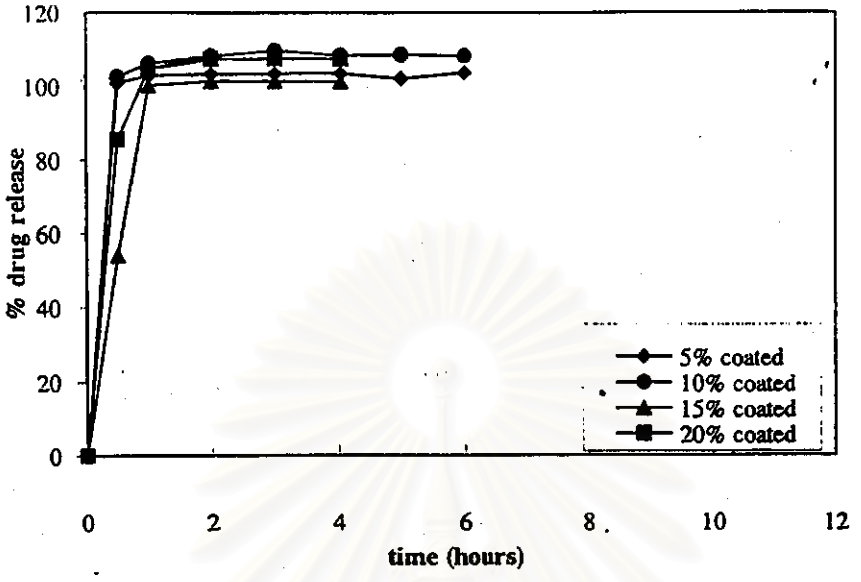



Figure 58 Release profiles of the pellets coating with different levels of EURL100 in acid buffer pH 1.2

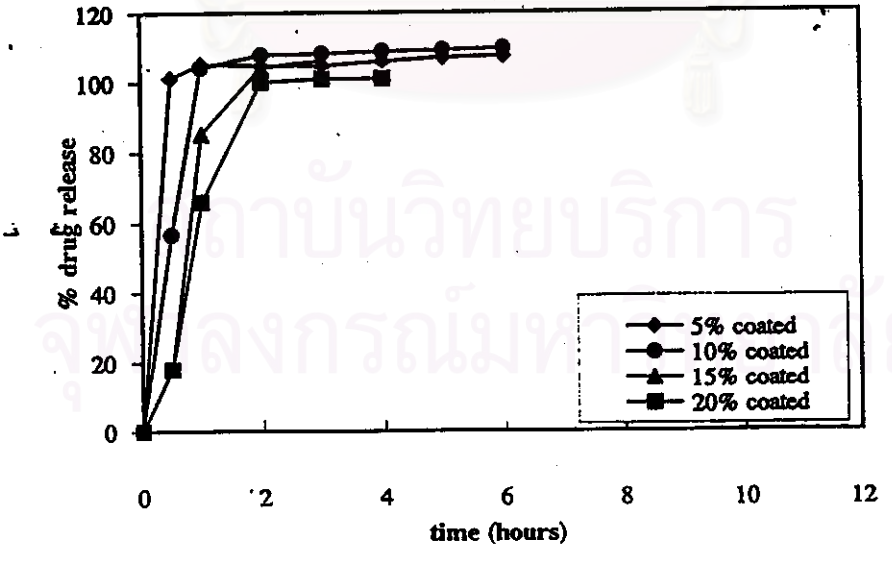



Figure 59 Release profiles of the pellets coating with different levels of EURL100 in phosphate buffer pH 6.8.

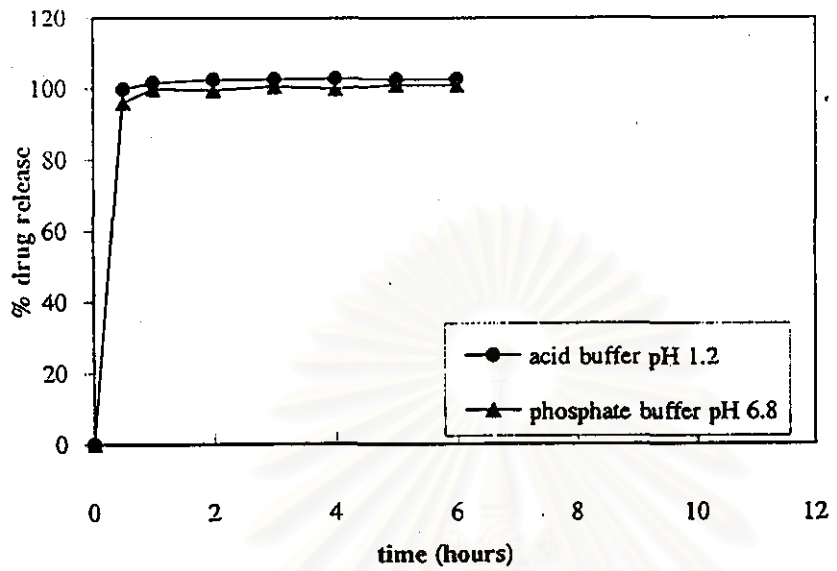



Figure 60 Release profile of coated pellets Formulation 5 (5 % EURL80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

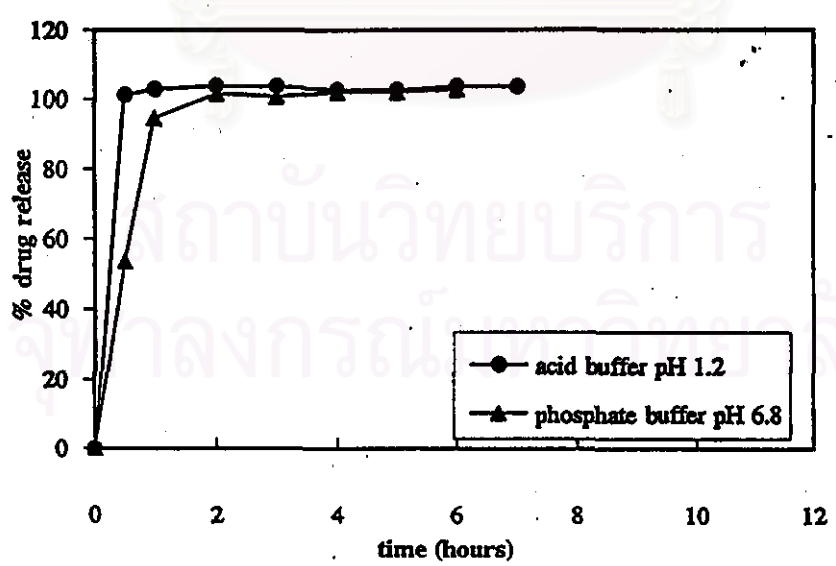



Figure 61 Release profile of coated pellets Formulation 6 (10 % EURL80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

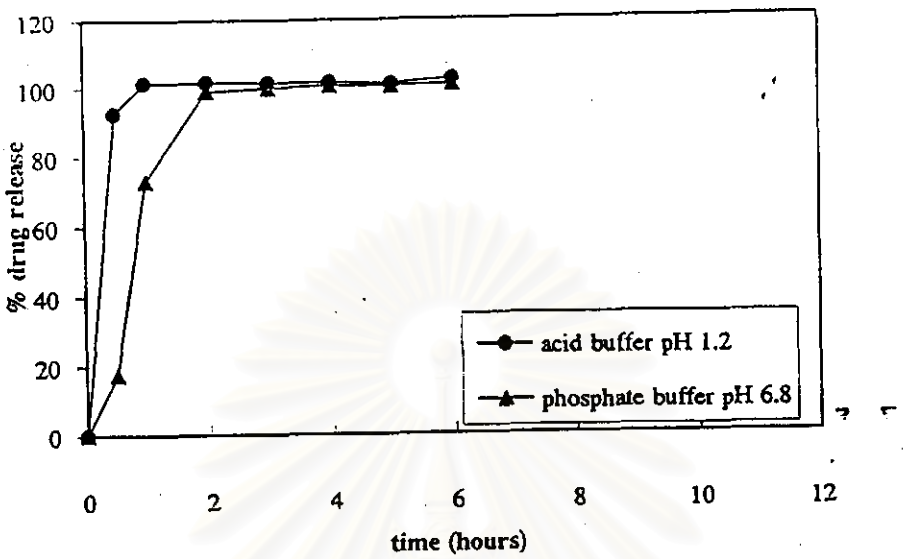



Figure 62 Release profile of coated pellets Formulation 7 (15 % EURL80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

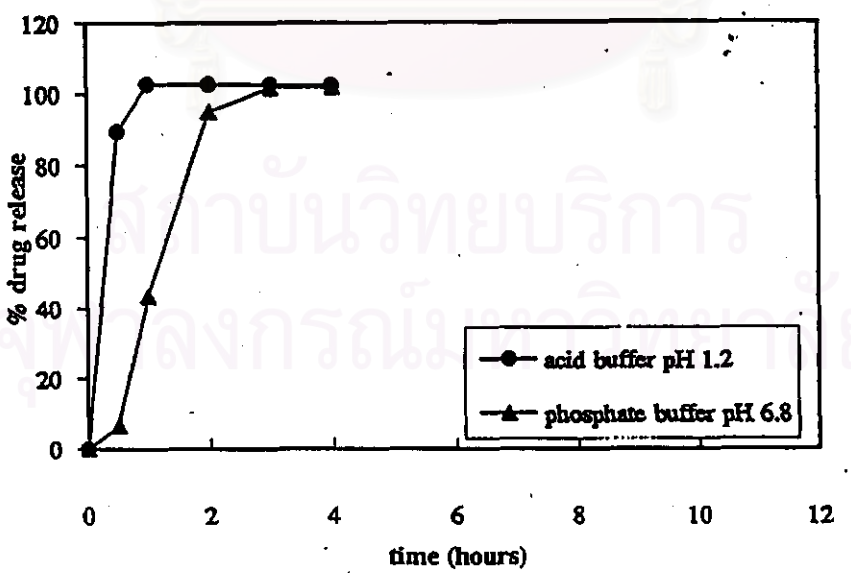



Figure 63 Release profile of coated pellets Formulation 8 (20 % EURL80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

in acid buffer pH 1.2 because the chemical properties of ethylcellulose which is resistant to alkali but sensitive to acidic materials and the physical properties of Eudragit ®RL100 which explained by Pflegel et al., 1981.

No influence of coating levels in acid medium on the release of the pellets coated with the mixture of 80 % Eudragit RL®100 and ethylcellulose were observed (Figure 64). On the other hand, increasing the percent coating levels resulted in corresponding decrease the drug release in phosphate buffer pH 6.8 (Figure 65). The reason for this phenomenon was the same as previously described.

Because of the film coating produced from Eudragit®RL100 gave water sensitive and high permeability in water, it was not suitable as membranes for controlling propranolol hydrochloride so that ethylcellulose which is the water-insoluble polymer, good film-forming properties, produces very low permeability were investigated to improve the retarding properties of Eudragit®RL100. The obtained results showed that the addition of 20 % hydrophobic ethylcellulose could not alter the film property and did not have an effect on the release of the drug when compared with the formulation using only Eudragit®RL100.

*The Formulation 9-12 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating level of the mixture of 60 % Eudragit®RL100 and 40 % ethylcellulose at 5 %, 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 24-25 (Appendix D) and shown graphically in Figure 66-69.

The obtained profiles indicated that pellets coated with low coating level about 5% gave the similar release characteristics up to 98.74 % and 88.52 % in the both of acid buffer pH 1.2 and phosphate buffer pH 6.8, respectively in 0.5 hour. But the higher coating levels, the pellets gave the slower release of the drug in phosphate buffer pH

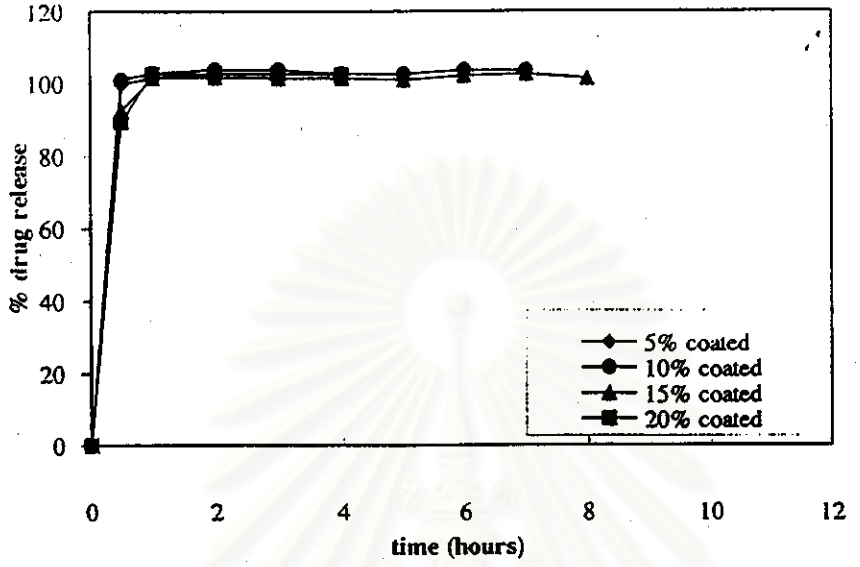



Figure 64 Release profiles of the pellets coating with different levels of EURL80:EC20 in acid buffer pH 1.2.

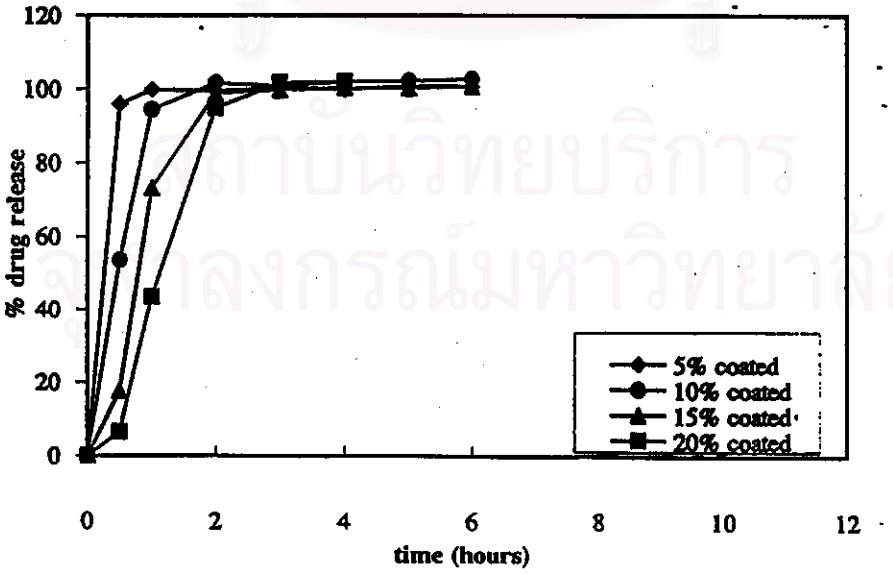



Figure 65 Release profiles of the pellets coating with different levels of EURL80:EC20 in phosphate buffer pH 6.8.

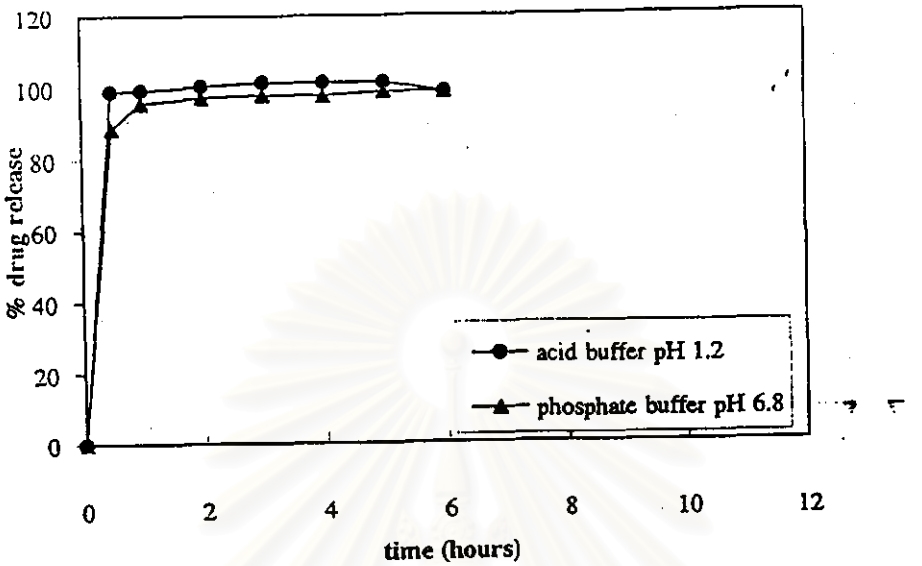



Figure 66 Release profile of coated pellets Formulation 9 (5 % EURL60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

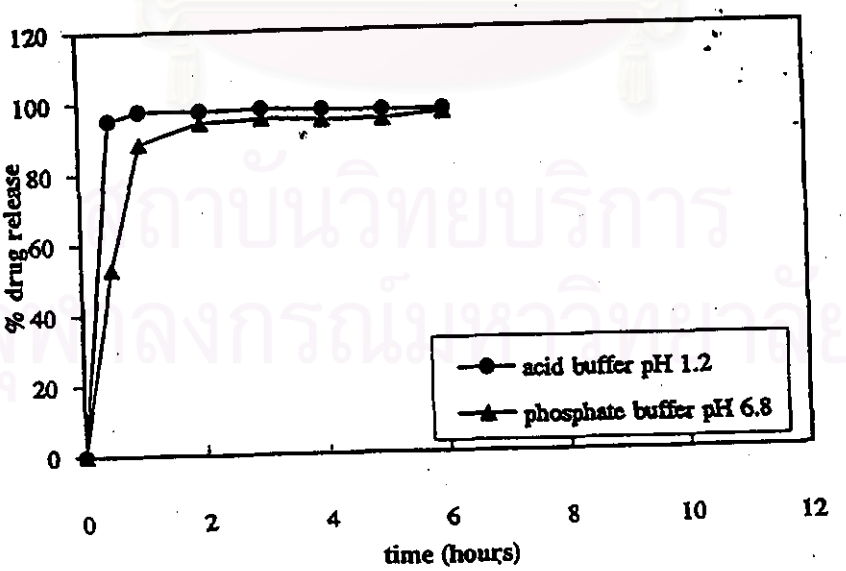



Figure 67 Release profile of coated pellets Formulation 10 (10 % EURL60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

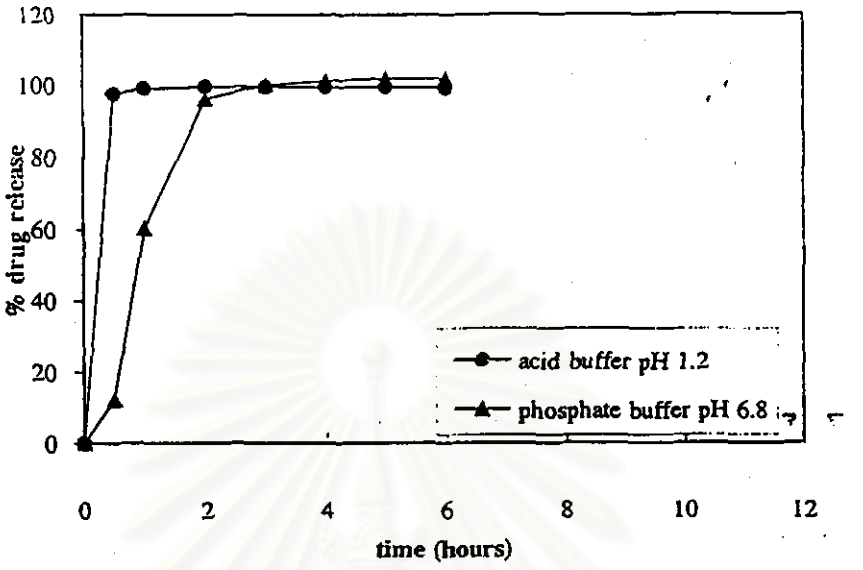



Figure 68 Release profile of coated pellets Formulation 11 (15 % EURL60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

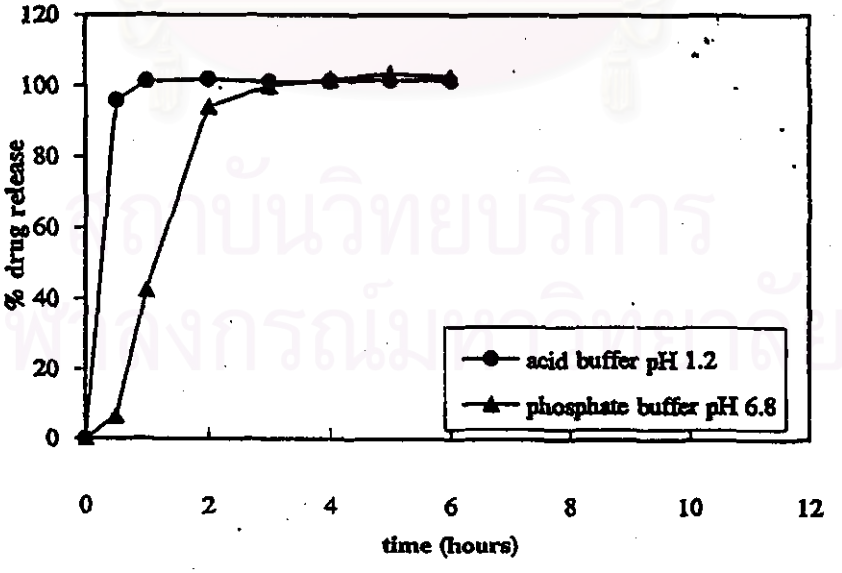



Figure 69 Release profile of coated pellets Formulation 12 (20 % EURL60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

6.8 than in acid buffer pH 1.2 by the virtue of the higher percent of hydrophobic ethylcellulose (about 40 %) which decreased the permeability of the films and the properties of Eudragit®RL100 as previously described.

Figure 70 and 71 show the effect of coating levels of the mixture of 60 % Eudragit®RL100 and 40 % ethylcellulose on the release of drug from the pellets in the acid and alkali medium. Increasing the percent coating levels resulted in corresponding decrease in the drug release in phosphate buffer pH 6.8. The reason for this phenomenon was the same as previously described.

*The Formulation 13-16 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating level of the mixture of 40 % Eudragit®RL100 and 60 % ethylcellulose at 5, 10, 15, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 25-26 (Appendix D) and shown graphically in Figure 72-75.

The obtained profiles indicated pellets coated with low coating level about 5 % gave the similar release characteristic up to 103.73 % and 97.73 % within one hour in the both of acid buffer pH 1.2 and phosphate buffer pH 6.8. But the higher coating levels, phosphate buffer pH 6.8 gave the slower release than in acid buffer pH 1.2 because the properties of both polymers which the same as previously described.

Figure 76 and 77 illustrates the difference in dissolution rates between the pellets coated with various coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8. As might be expected, the release rate decreased as the film thickness increased, suggesting that the drug solution has to diffuse through a thicker membrane before dissolution in the surrounding medium occurs. However, coating level played less effect on drug release in acid medium.

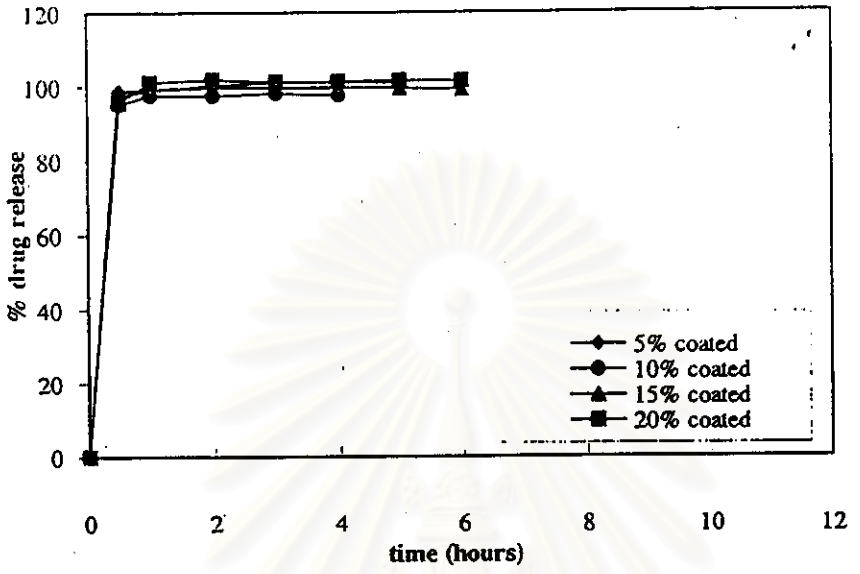



Figure 70 Release profiles of the pellets coating with different levels of EURL60:EC40 in acid buffer pH 1.2.

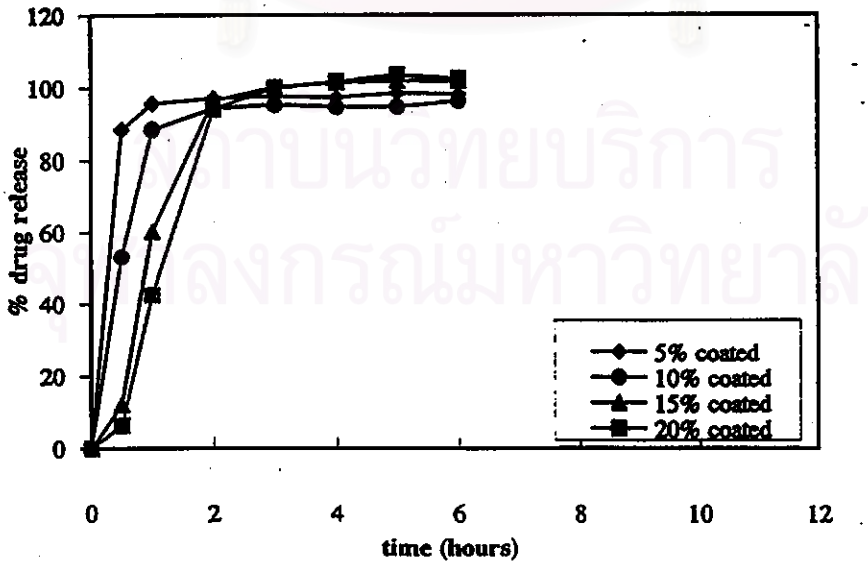



Figure 71 Release profiles of the pellets coating with different levels of EURL60:EC40 in phosphate buffer pH 6.8.

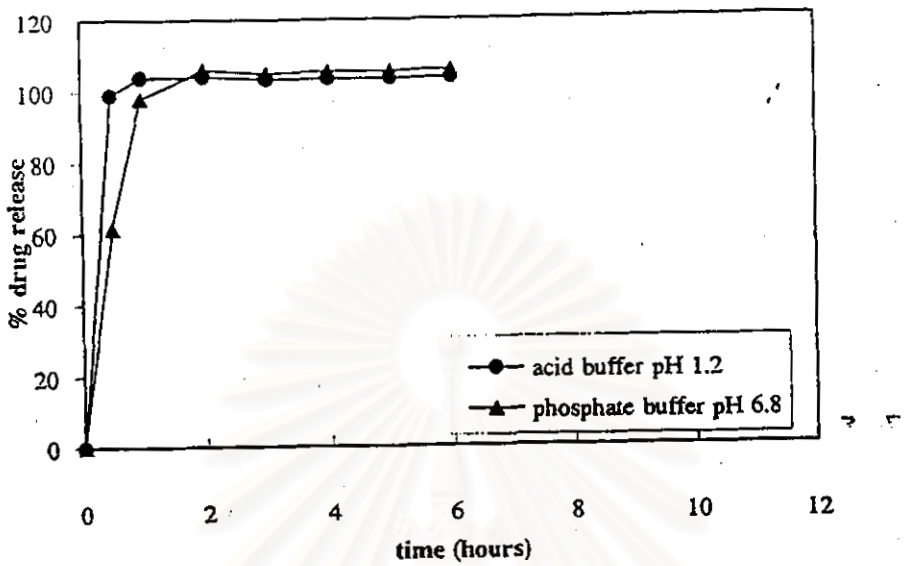



Figure 72 Release profile of coated pellets Formulation 13 (5 % EURL40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

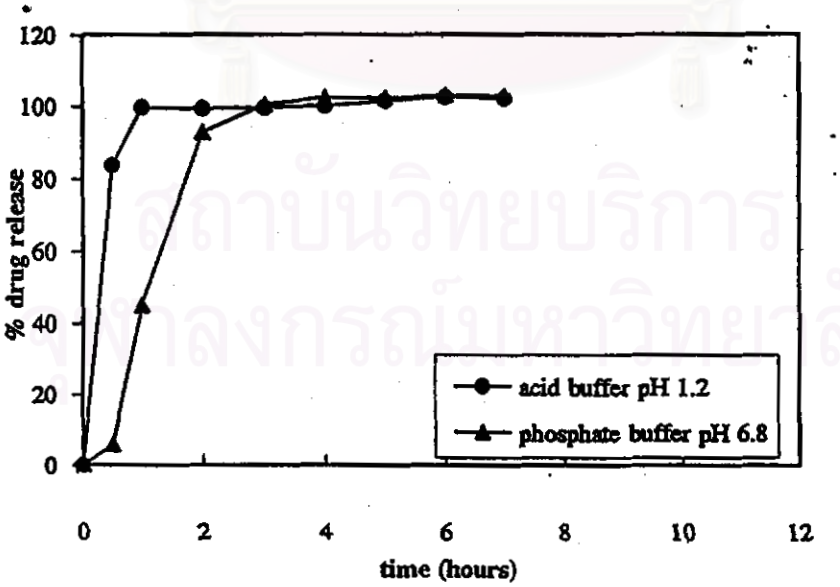



Figure 73 Release profile of coated pellets Formulation 14 (10 % EURL40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

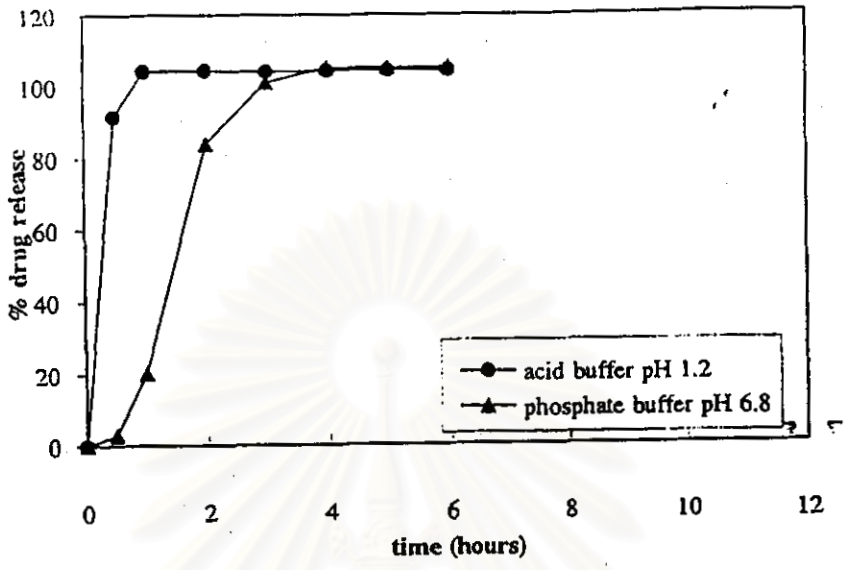



Figure 74 Release profile of coated pellets Formulation 15(15 % EURL40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

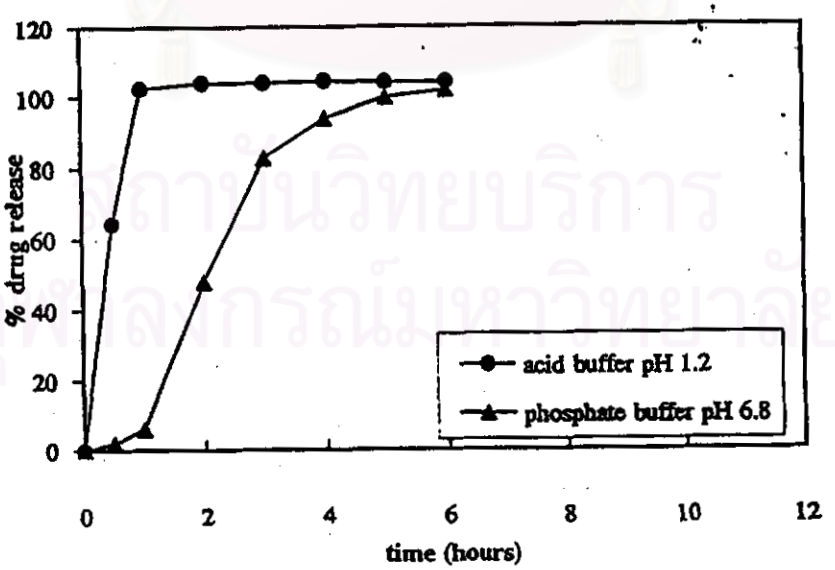



Figure 75 Release profile of coated pellets Formulation 16 (20 % EURL40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

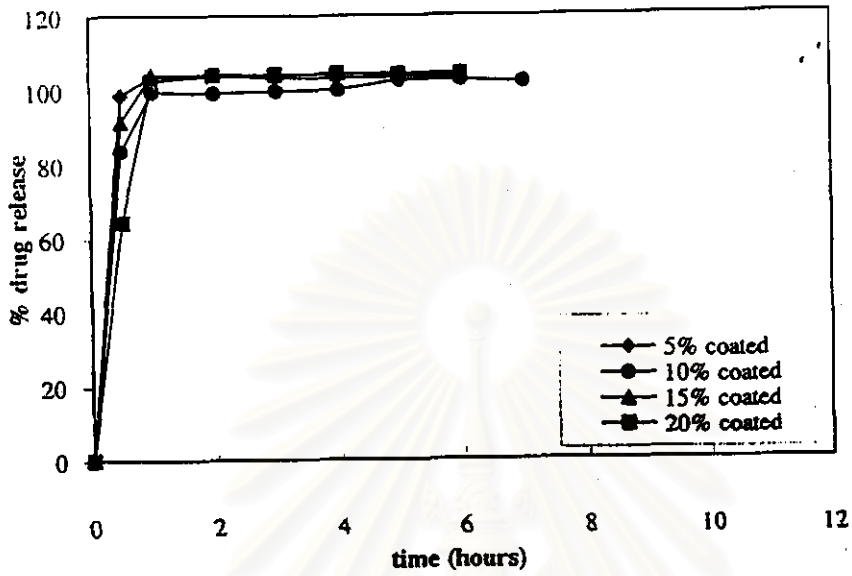



Figure 76 Release profiles of the pellets coating with different levels of EURL40:EC60 in acid buffer pH 1.2.

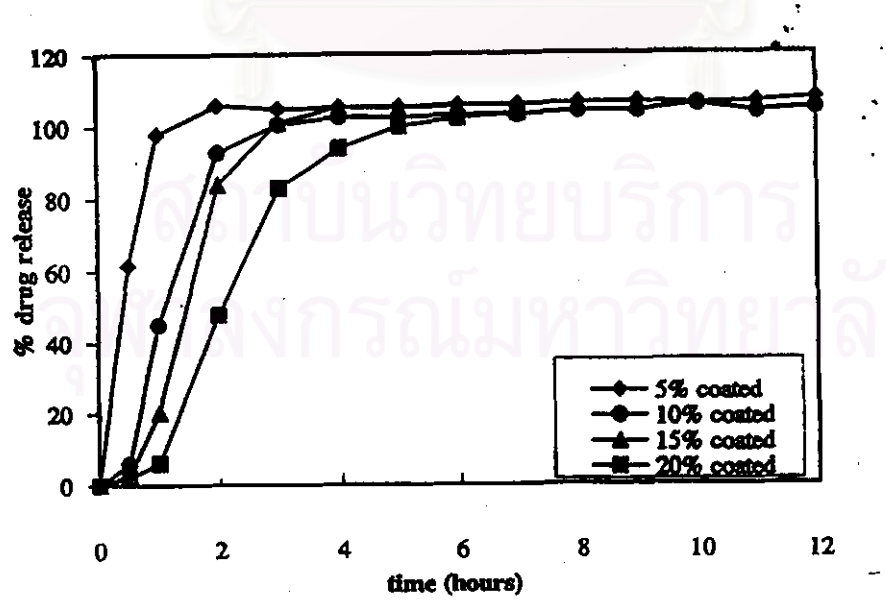



Figure 77 Release profiles of the pellets coating with different levels of EURL40:EC60 in phosphate buffer pH 6.8.

*The Formulation 17-20 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating level of the mixture of 20 % Eudragit®RL100 and 80 % ethylcellulose at 5 %, 10 %, 15 %, and 20 % coating level in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 27-28 (Appendix D) and shown graphically in Figure 78-81.

The profiles indicated the effect of dissolution medium pH on the release of propranolol hydrochloride pellets. The release of coated pellets in acid buffer pH 1.2 was higher than in phosphate buffer pH 6.8 by the virtue of both polymers which the same as previously described. It was apparent that, at the higher coating percentage of the mixture of 20 % Eudragit®RL100 and 80 % ethylcellulose, the effect of medium on drug release was more pronounced. The slow release phase of drug release profiles in phosphate buffer pH 6.8 were also observed at higher coating level (Figure 80-81).

For the influence of coating levels on the drug release profile, resultant release characteristic in acid buffer pH 1.2 and phosphate buffer pH 6.8 are depicted in Figure 82 and 83, increasing the percent coating levels resulted in corresponding decrease the drug release.

*The Formulation 21-24 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating levels of 100 % ethylcellulose at 5 %, 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 29-30 (Appendix D) and shown graphically in Figure 84-87.

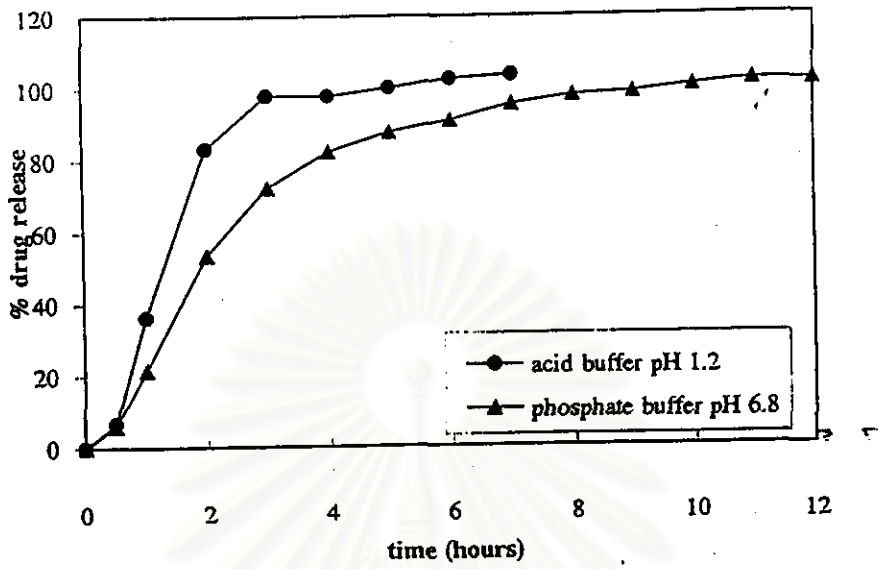



Figure 78 Release profile of coated pellets Formulation 17 (5 % EURL20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

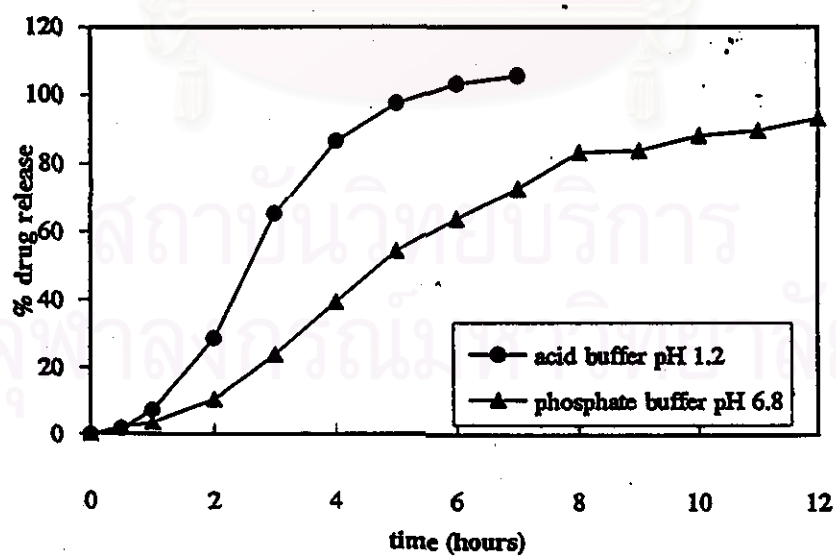



Figure 79 Release profile of coated pellets Formulation 18 (10 % EURL20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

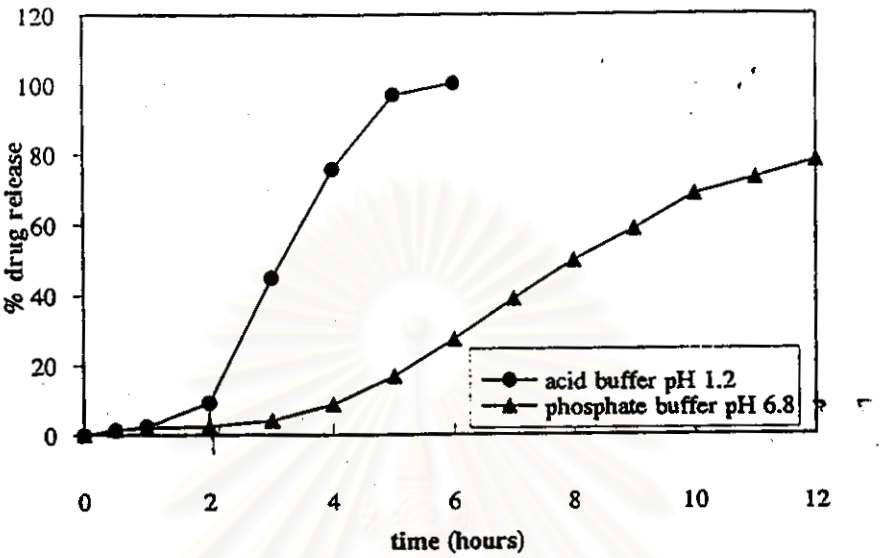



Figure 80 Release profile of coated pellets Formulation 19 (15 % EURL20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

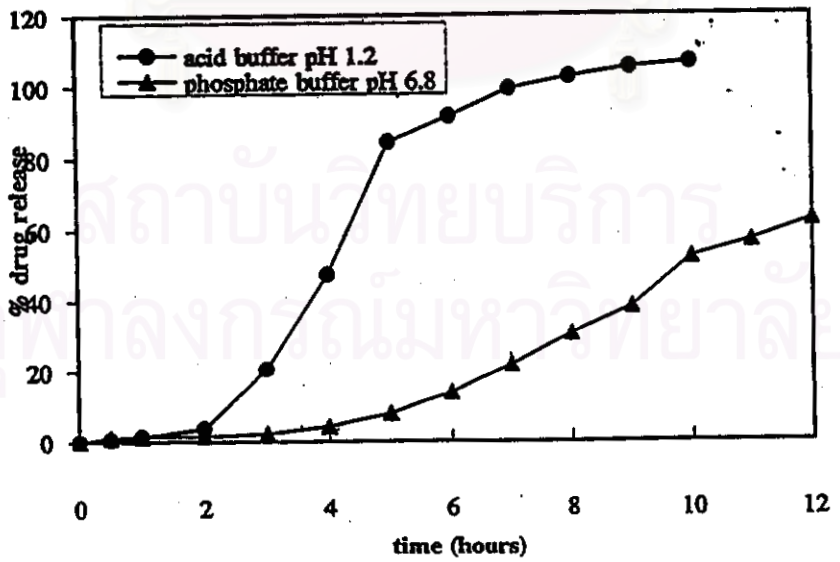



Figure 81 Release profile of coated pellets Formulation 20 (20 % EURL20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

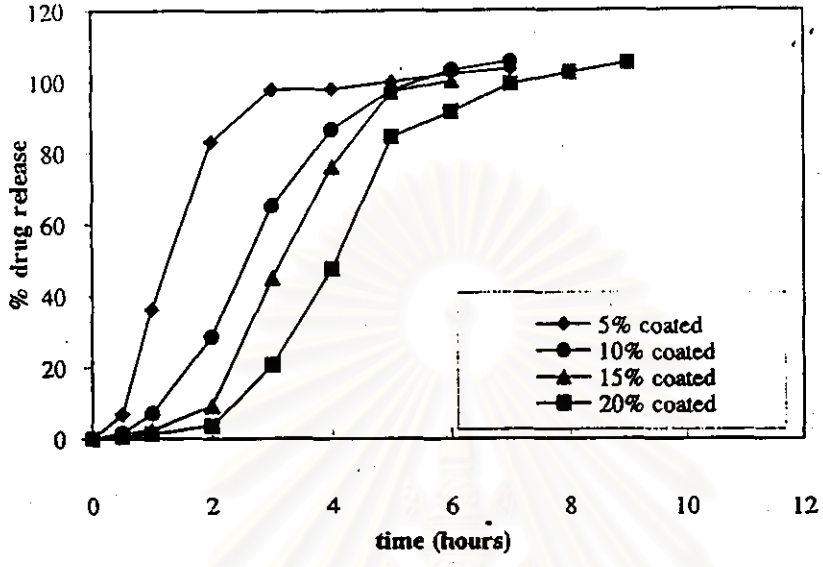



Figure 82 Release profiles of the pellets coating with different levels of EURL20:EC80 in acid buffer pH 1.2.

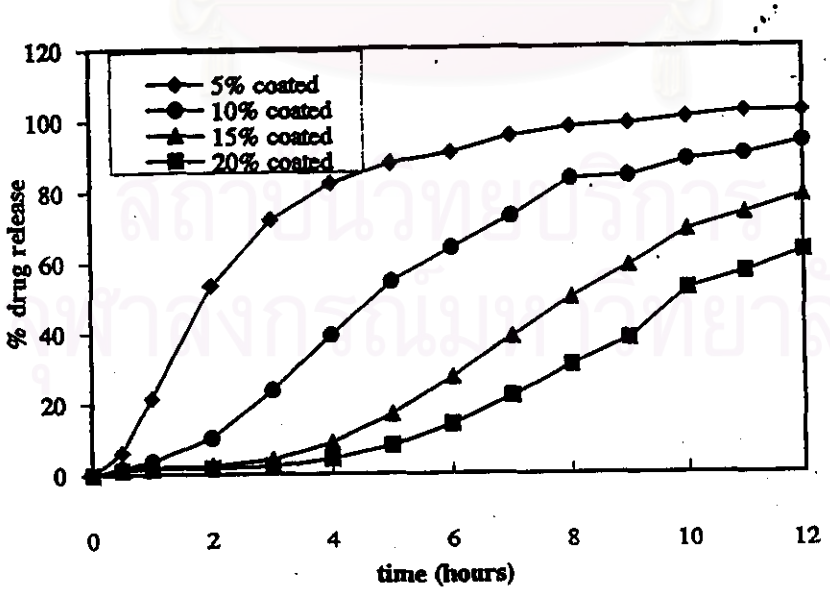



Figure 83 Release profiles of the pellets coating with different levels of EURL20:EC80 in phosphate buffer pH 6.8.

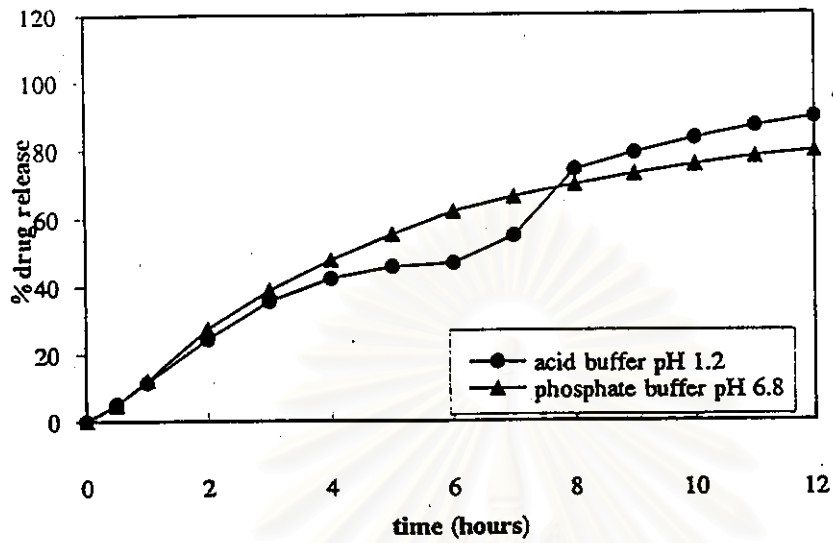



Figure 84 Release profile of coated pellets Formulation 21 (5 % EC 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

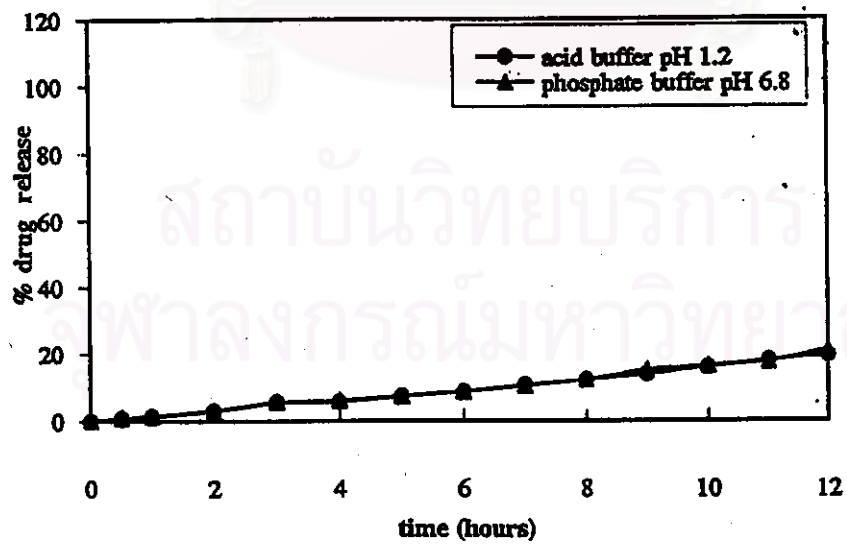



Figure 85 Release profile of coated pellets Formulation 22 (10 % EC 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

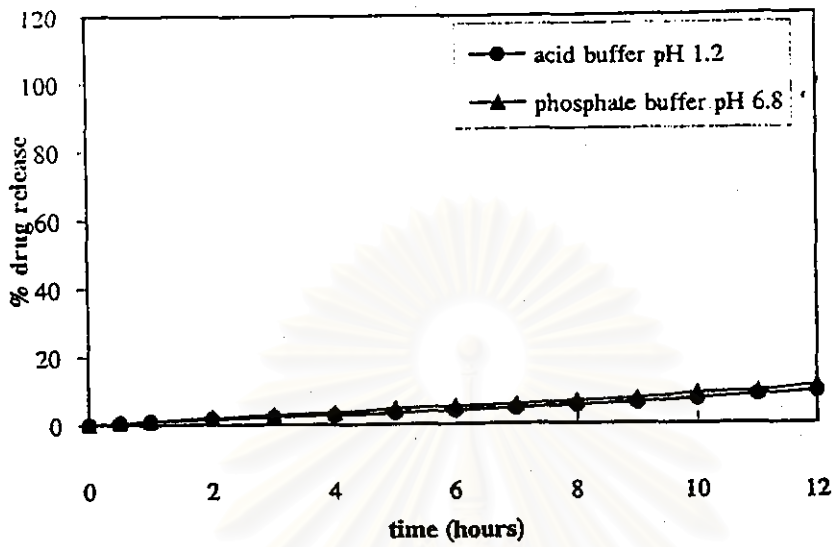



Figure 86 Release profile of coated pellets Formulation 23 (15 % EC 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

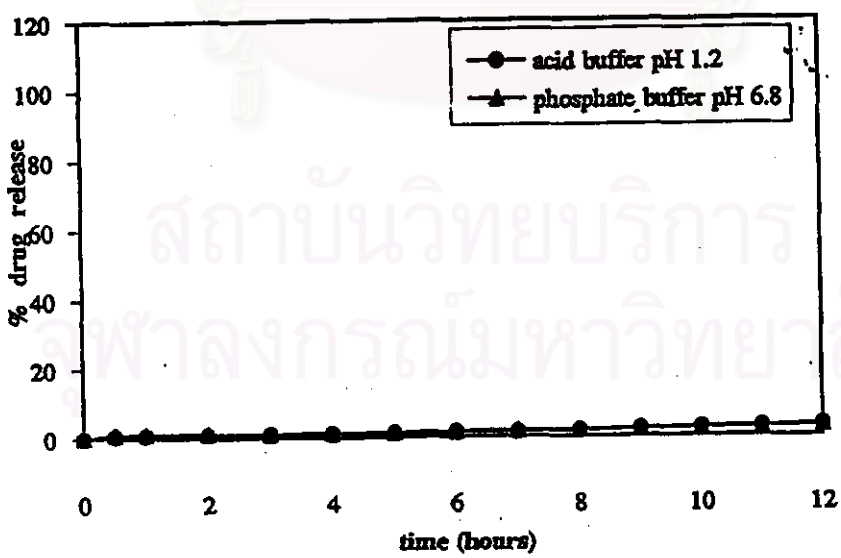



Figure 87 Release profile of coated pellets formulation 24 (20 % EC 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

The profiles indicated no effect of dissolution medium pH on release of the drug. At the coating level 10-20 %, very slow drug release was found. In particular at 20 % level, the drug dissolved from the pellets was lower than 5.

Figure 88-89 show the release of the drug from the pellets coating at different concentration of ethylcellulose. Only increasing the coating film from 5 to 10 % much decrease in drug release was exhibited.

*The Formulation 25-27 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating level of Eudragit®RS100 at 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 31-32 (Appendix D) and shown graphically in Figure 90-92.

The profiles indicated the effect of dissolution medium pH on release of propranolol hydrochloride pellets. The release of coated pellets from acid buffer pH 1.2 was faster than in phosphate buffer pH 6.8 because of the release behavior as explained in Formulation 1-4.

Similar effect of medium on release of the drug from the pellets coated with Eudragit®RL100 and RS100 was shown, the faster drug release in acid medium. However, at the same coating level, Eudragit®RS100 gave more retardant property on drug release than of Eudragit®RL100 (Figure 93).

Figure 94 and 95 illustrates the difference in dissolution rates between pellets coated within 10 %, 15 %, and 20 % of Eudragit®RS100. As might be expected, the rate of drug release from the prepared pellets was inversely proportional to the thickness of the polymer coat. The thicker the membrane, the longer is the penetration time of the dissolution medium and thus drug release is delayed.

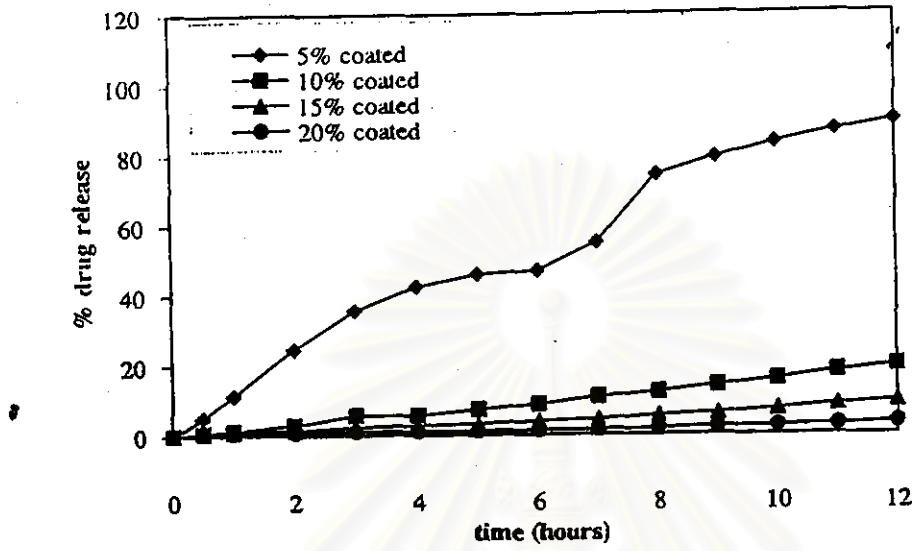



Figure 88 Release profiles of the pellets coating with different levels of EC 100 in acid buffer pH 1.2

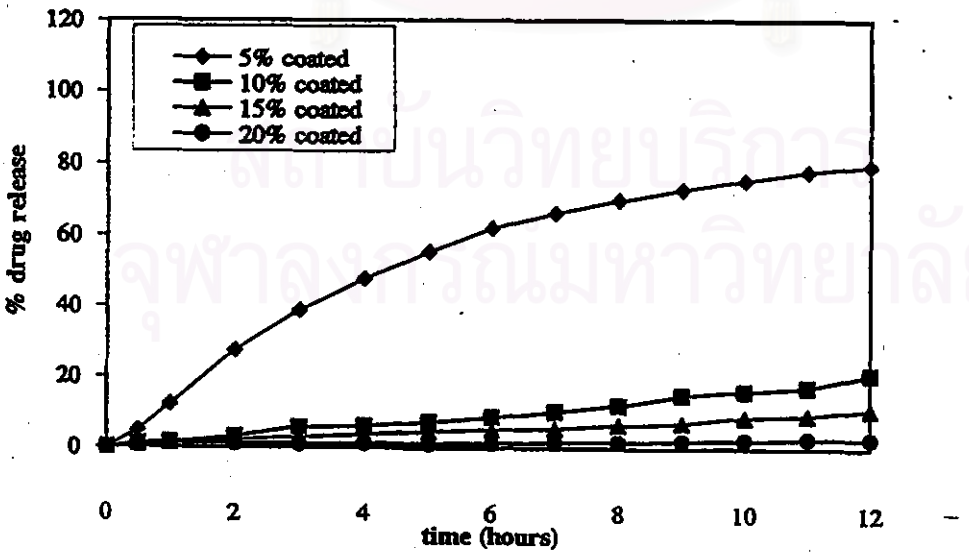



Figure 89 Release profiles of the pellets coating with different levels of EC 100 in phosphate buffer pH 6.8

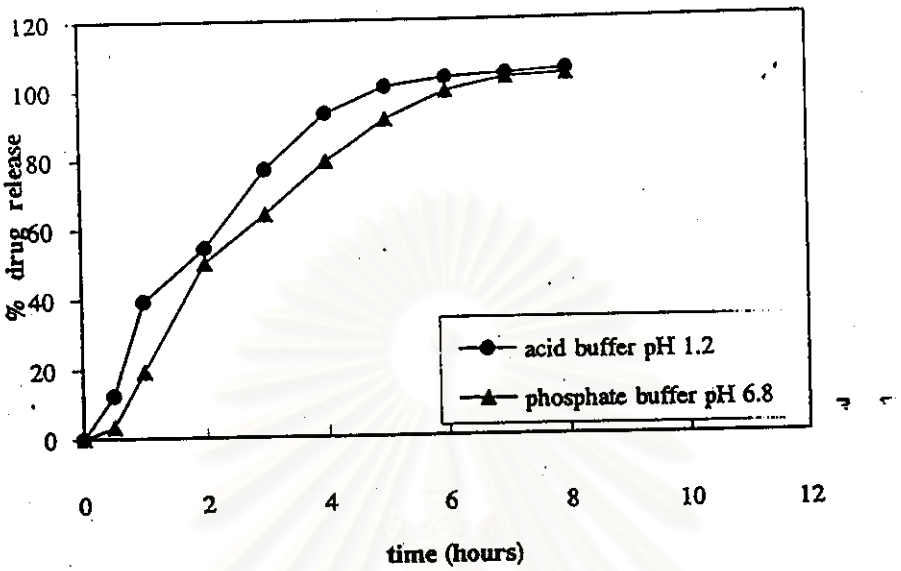



Figure 90 Release profile of coated pellets Formulation 25 (10 % EURS 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

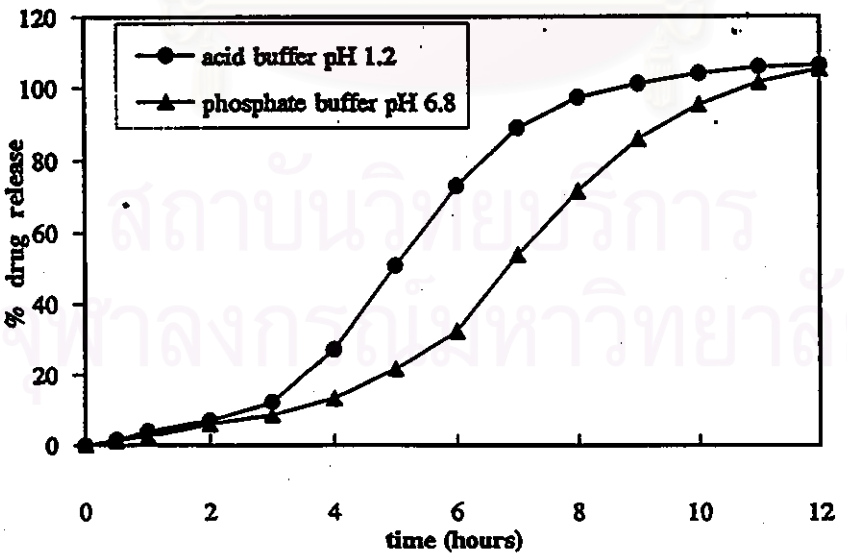



Figure 91 Release profile of coated pellets Formulation 26 (15 % EURS 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

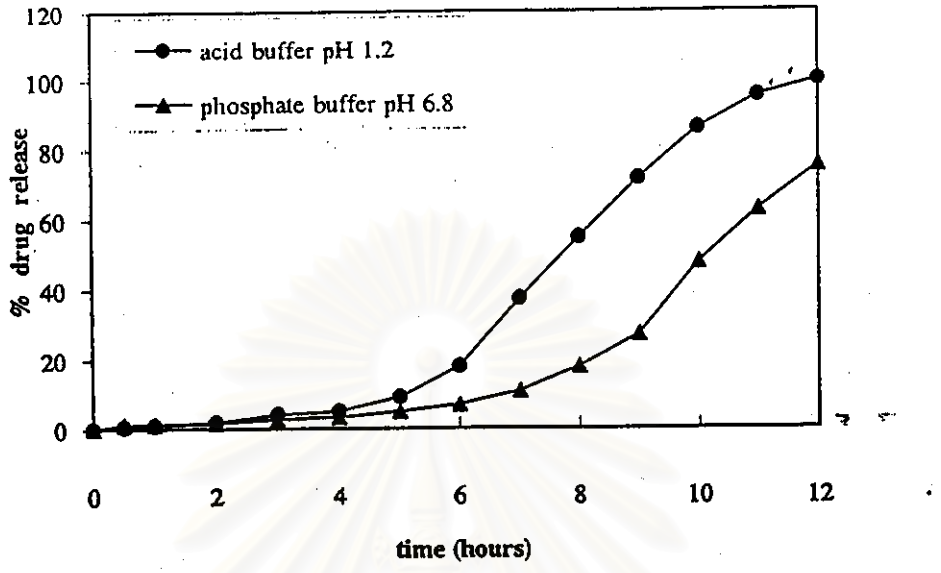



Figure 92 Release profile of coated pellets Formulation 27 (20 % EURS 100) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

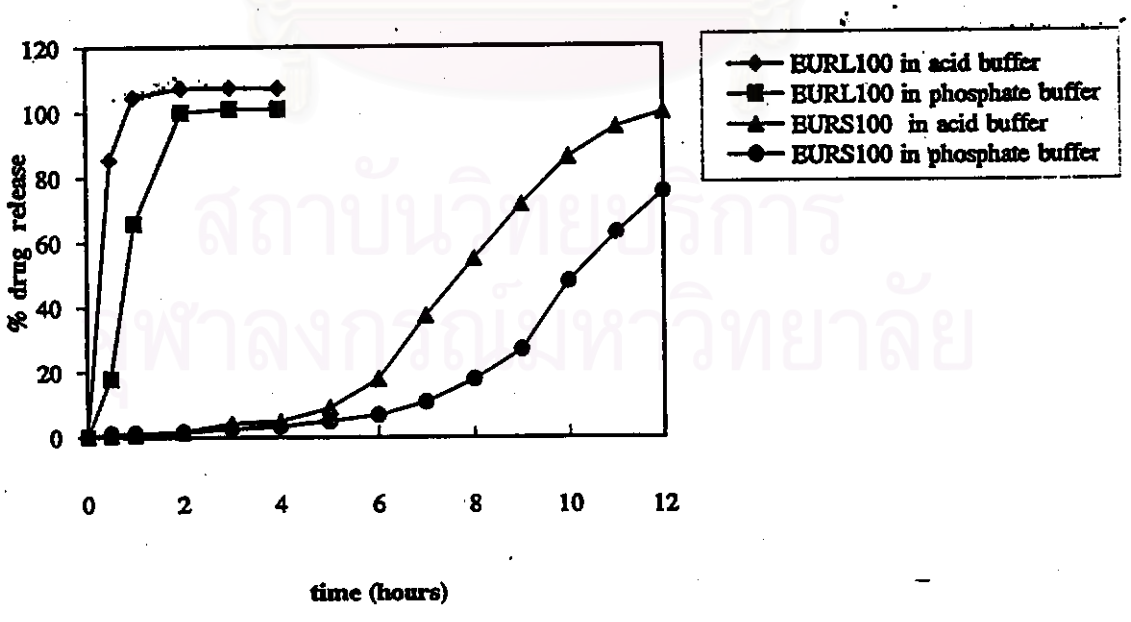



Figure 93 Comparison of retardant property on drug release of EURS 100 and EURL 100.

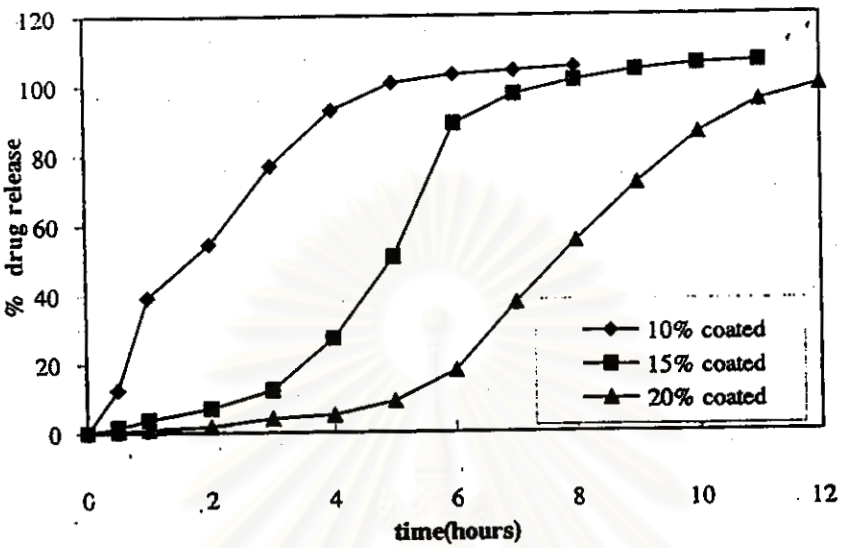



Figure 94 Release profile the pellets coating with different levels of EURS 100 in acid buffer pH 1.2.

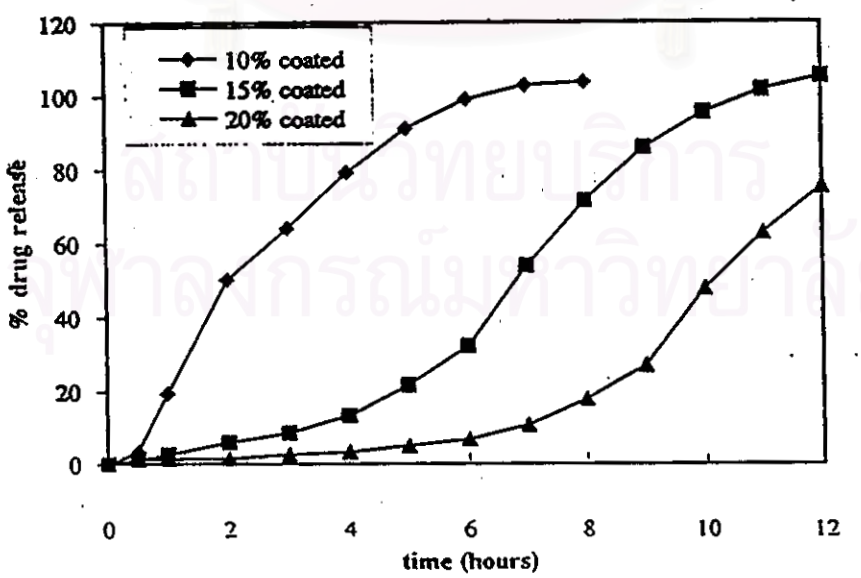



Figure 95 Release profile the pellets coating with different levels of EURS 100 in phosphate buffer pH 6.8.

Eudragit®RS100 formed films which exhibits slightly permeable to water which gave low permeability than Eudragit®RL100. Because of Eudragit®RS100 was copolymers synthesized from acrylic and methacrylic acid ester with the high proportion of about 5 % of quaternary ammonium groups which attach to the polymer backbone and make the film coating produced from Eudragit®RS100 poorly water permeable, slow hydration and drug release.

*The Formulation 28-30 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating levels of the mixture of 80 % Eudragit®RS100 and 20 % ethylcellulose at 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 32-33 (Appendix D) and shown graphically in Figure 96-98.

The profiles indicated the effect of dissolution media pH on release of propranolol hydrochloride pellets. The release of coated pellets was faster in acid buffer pH 1.2 than in phosphate buffer pH 6.8 because of the properties of the polymers.

The results of the dissolution studies for propranolol hydrochloride pellets coated with 10 %, 15 %, and 20 % of the mixture of 80 % Eudragit®RS100 and 20 % ethylcellulose solution in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Figure 99 and 100. It is clear that as the level of coating solution increase from 10 % to 20 %, the release rates decreased.

It was noted that, the initial slow release period of drug release was found at only 20 % proportion of ethylcellulose in the film mixture of Eudragit®RS100 and ethylcellulose. While in the case of film mixture between Eudragit®RS100 and ethylcellulose at the same coating level, the slow release period was seen at the proportion of ethylcellulose in the film about 80 %.

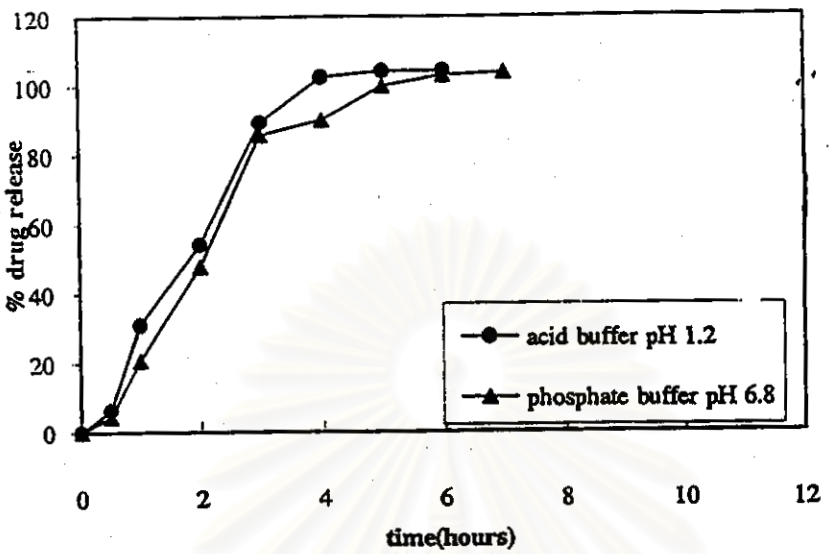



Figure 96 Release profile of coated pellets Formulation 28 (10 % EURS80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

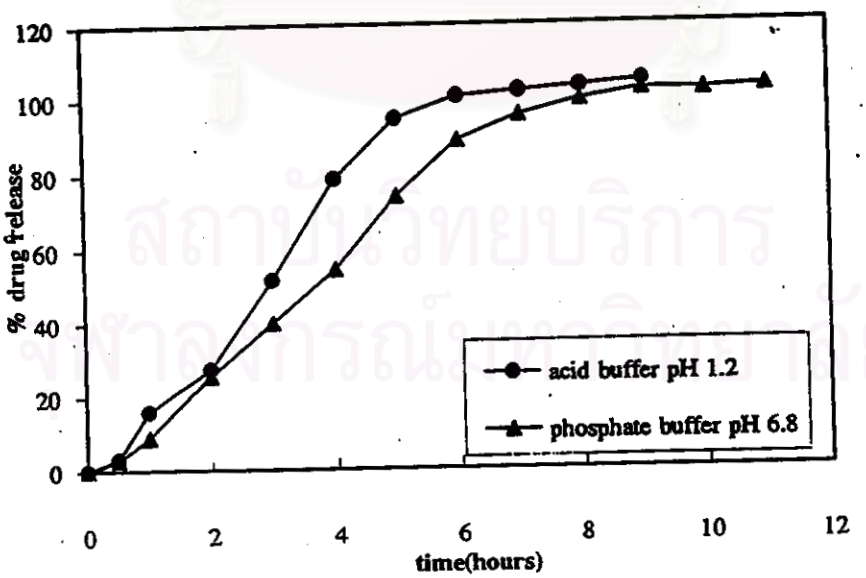



Figure 97 Release profile of coated pellets Formulation 29 (15 % EURS80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

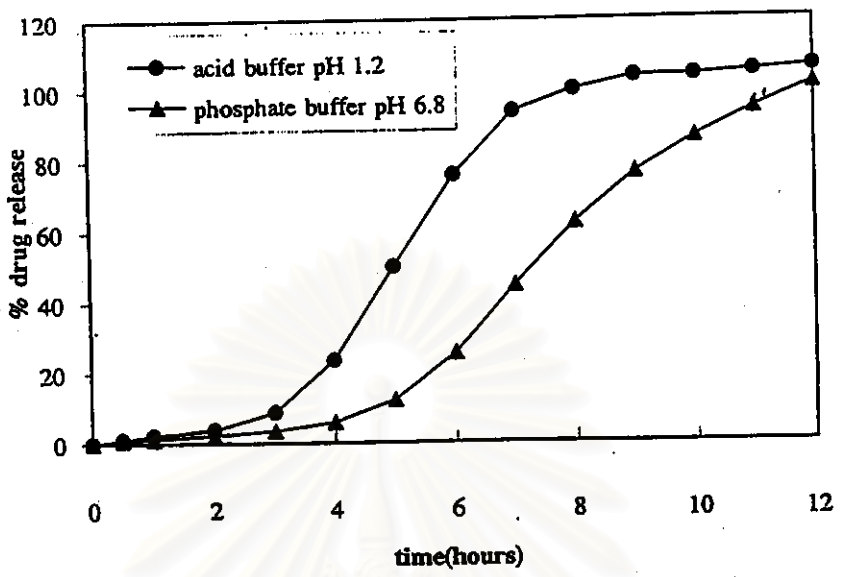



Figure 98 Release profile of coated pellets Formulation 30 (20 % EURS80:EC20) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

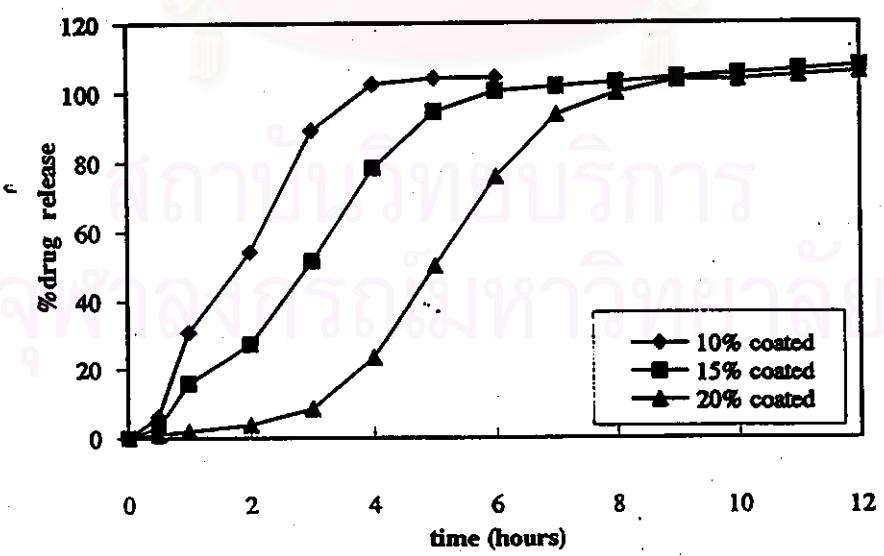



Figure 99 Release profile the pellets coating with different levels of EURS80:EC20 in acid buffer pH 1.2.

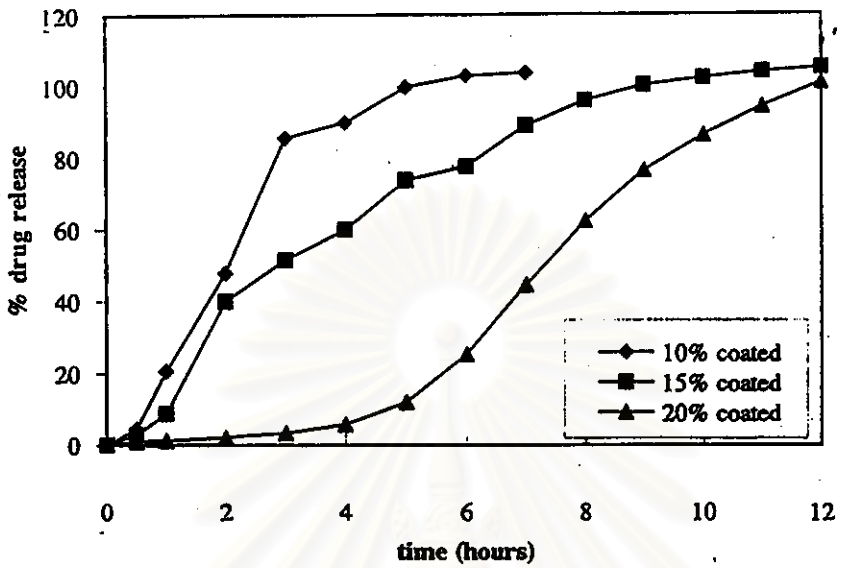



**Figure 100 Release profile the pellets coating with different levels of EURS80:EC20 in phosphate buffer pH 6.8.**

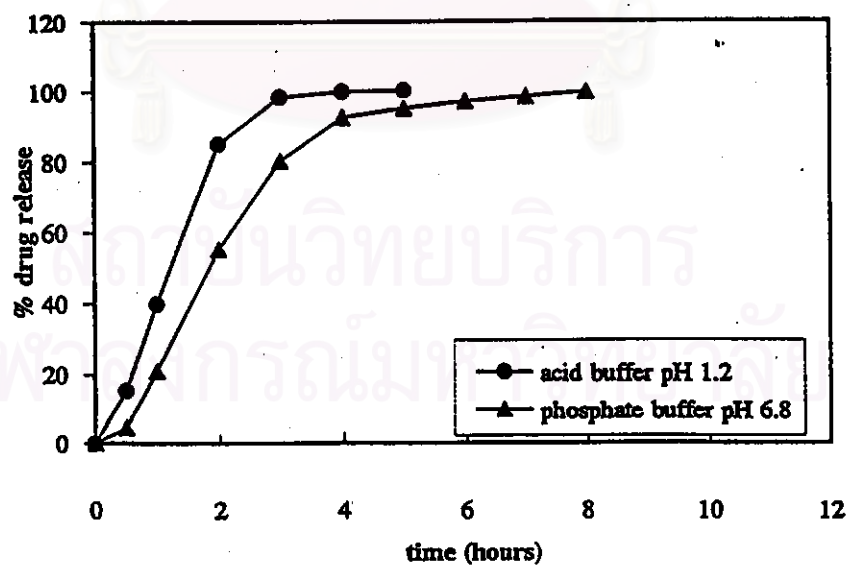



Figure 101 Release profile of coated pellets Formulation 31 (10 % EURS60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

*The Formulation 31-33 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating levels of the mixture of 60 % Eudragit®RS100 and 40 % ethylcellulose at 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 34-35 (Appendix D) and shown graphically in Figure 101-103.

The profiles indicated the effect of dissolution medium pH on release of propranolol hydrochloride pellets. The release of coated pellets was faster in acid buffer pH 1.2 than in phosphate buffer pH 6.8 because the characteristics of polymers.

As can be seen from Figure 104 and 105, the release rate of propranolol hydrochloride from coated pellets in pH 1.2 acid buffer and pH 6.8 phosphate buffer decreases as the level of the coating polymer increased.

The initial slow drug release was found at 15 % and 20 % coating level of the film mixture of 60 % Eudragit®RS100 and 40 % ethylcellulose. The observed profile showed that the initial retarding effect in both medium of this formulation exhibited the shorter period than Formulation 30.

*The Formulation 34-36 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating levels of the mixture of 40 % Eudragit®RS100 and 60 % ethylcellulose at 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 35-36 (Appendix D) and shown graphically in Figure 106-108.

The profiles indicated the effect of dissolution medium pH on release of propranolol hydrochloride pellets. The release of coated pellets was faster in acid buffer pH 1.2 than in phosphate buffer pH 6.8 because of the properties of polymers.

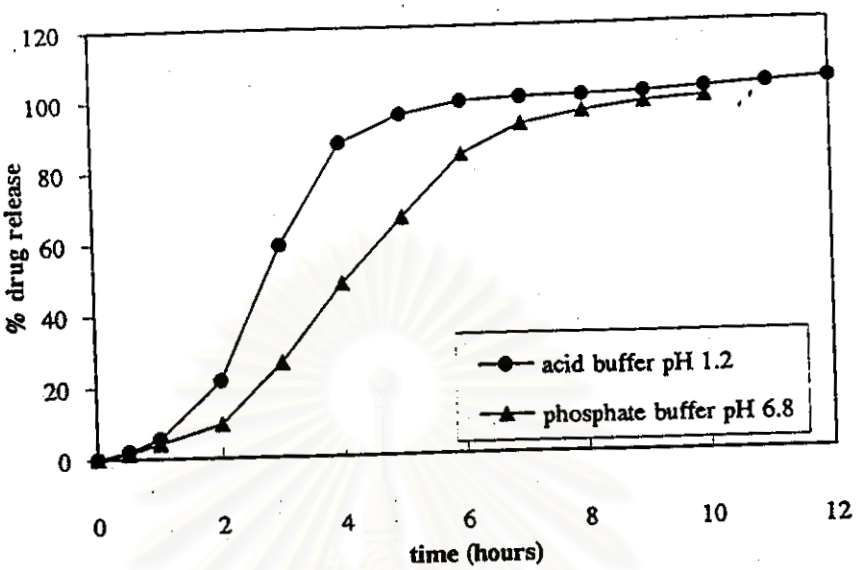



Figure 102 Release profile of coated pellets Formulation 32 (15 % EURS60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

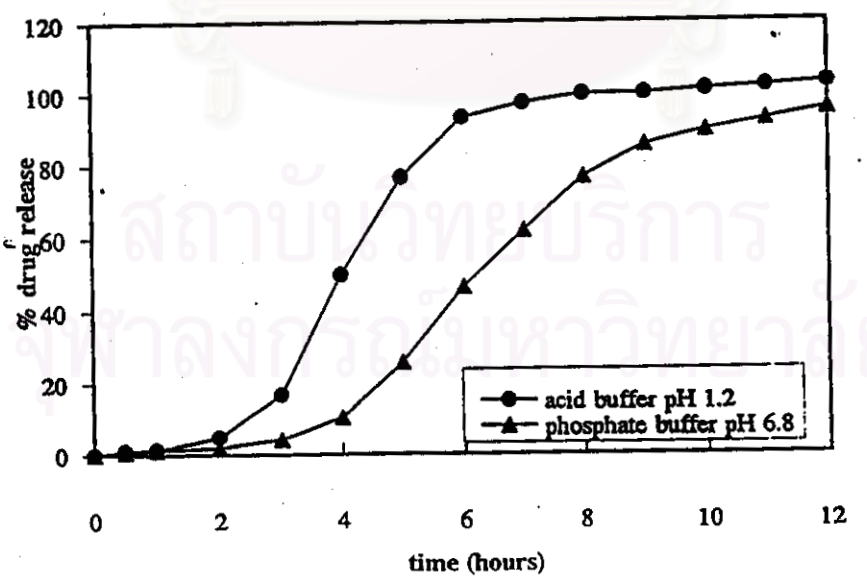



Figure 103 Release profile of coated pellets Formulation 33 (20 % EURS60:EC40) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

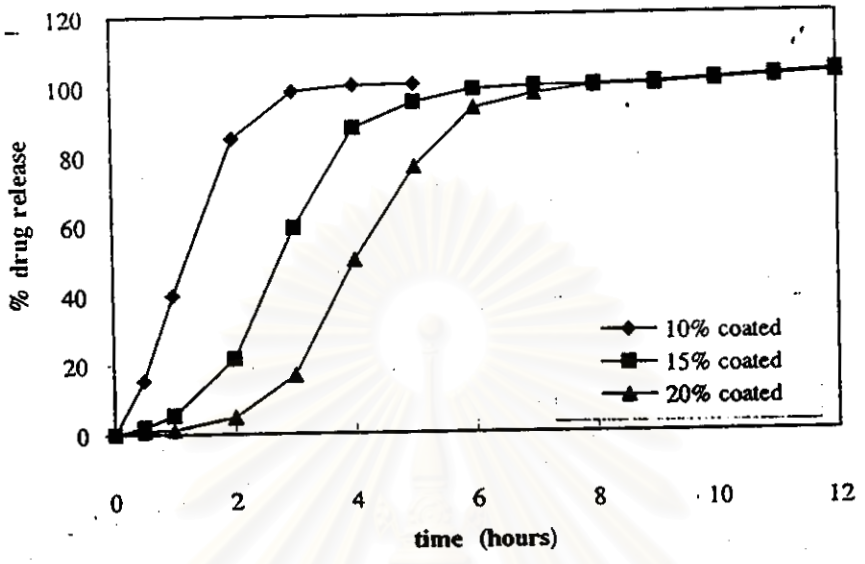



Figure 104 Release profile the pellets coating with different levels of EURS60:EC40 in acid buffer pH 1.2.

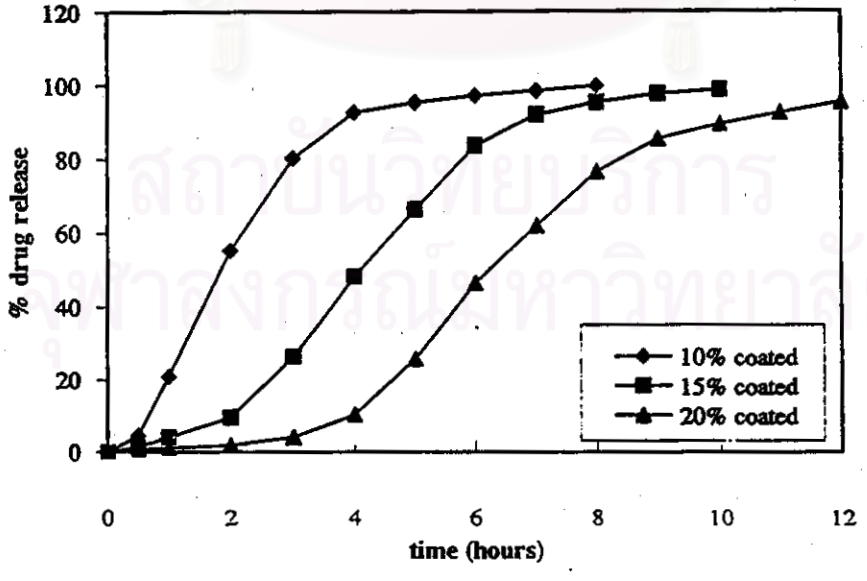



Figure 105 Release profile the pellets coating with different levels of EURS60:EC40 in phosphate buffer pH 6.8.

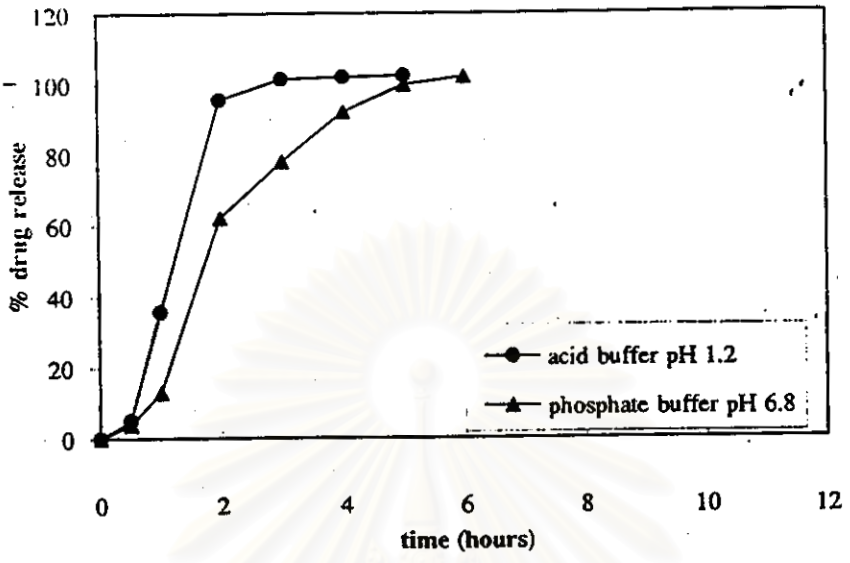



Figure 106 Release profile of coated pellets Formulation 34 (10 % EURS40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

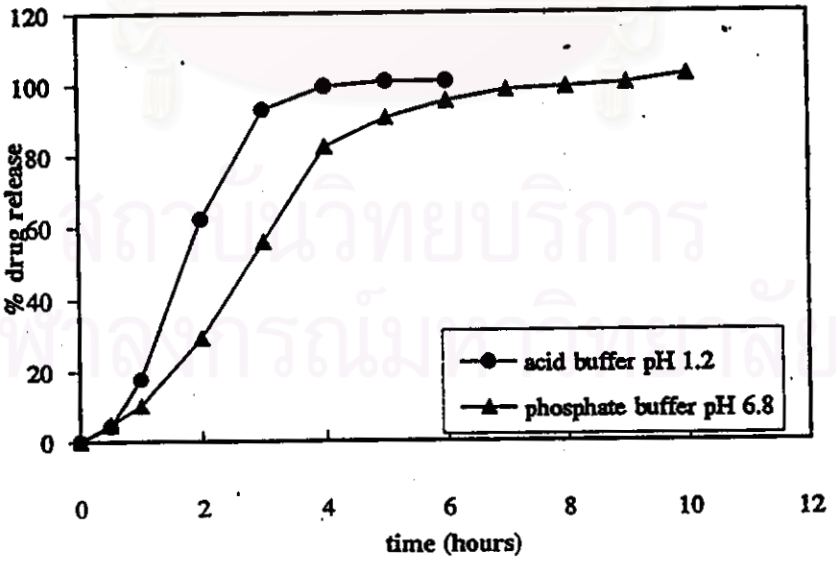



Figure 107 Release profile of coated pellets Formulation 35 (15 % EURS40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

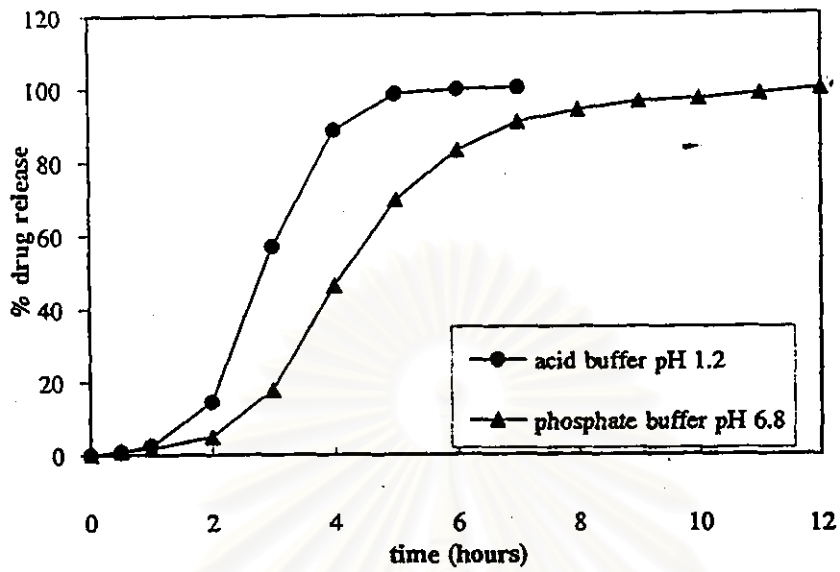



Figure 108 Release profile of coated pellets Formulation 36 (20 % EURS40:EC60) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

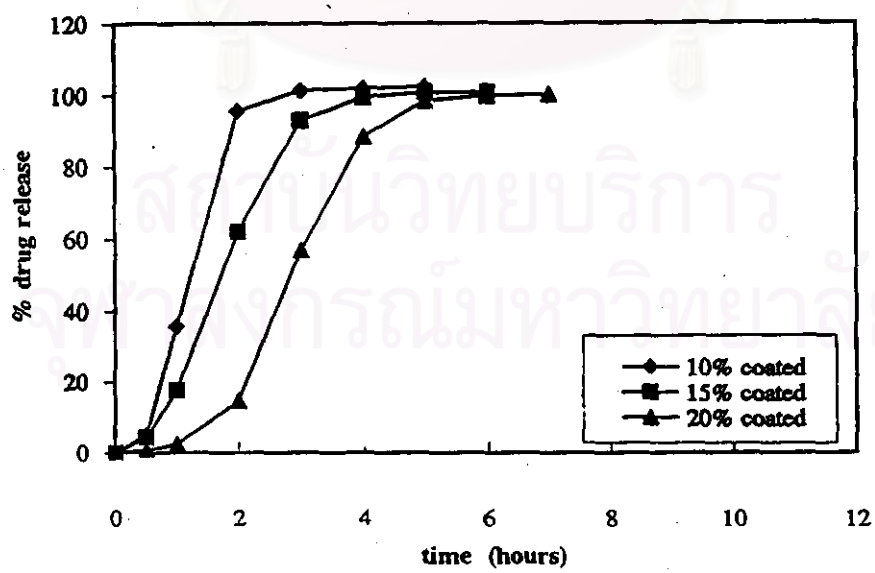



Figure 109 Release profile the pellets coating with different levels of EURS40:EC60 in acid buffer pH 1.2.

Figure 109 and 110 show the effect of various coating levels on propranolol hydrochloride release rate from coated pellets in acid and alkali buffer. It was clear that as the level of coating solution increased from 10 to 20 %, the release rates decreased.

It was observed that the initial slow drug release was found at 20 % coating level, in both acid and basic medium which gave this period of about 1 and 2 hours, respectively.

*The Formulation 37-39 coated pellets*

The dissolution data of propranolol hydrochloride from coated pellets with various coating levels of the mixture of 20 % Eudragit®RS100 and 80 % ethylcellulose at 10 %, 15 %, and 20 % coating levels in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Table 36-37 (Appendix D) and shown graphically in Figure 111-113.

The small amounts of the drug were released in these formulations due to the high proportion of ethylcellulose. The profiles indicated the effect of dissolution media pH on release of propranolol hydrochloride pellets. The release of coated pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8 were similar.

The results of the dissolution studies for propranolol hydrochloride pellets coated with 10 %, 15 %, and 20 % of the mixture of 20 % Eudragit®RS100 and 80 % ethylcellulose solution in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Figure 114 and 115. It was clear that as the level of coating solution increased from 10 to 20 %, the release rates decreased.

It was observed that the batches coated with 10 -20 % coating levels of the mixture of 20 % Eudragit®RS100 and 80 % ethylcellulose possessed released drug at a constant rate (zero-order) in 12 hour periods.

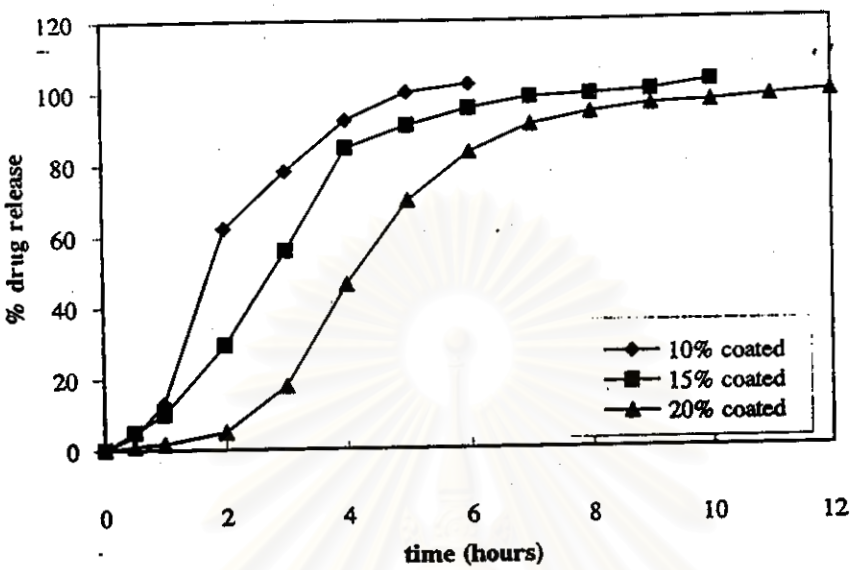



Figure 110 Release profile the pellets coating with different levels of EURS40:EC60 in phosphate buffer pH 6.8.

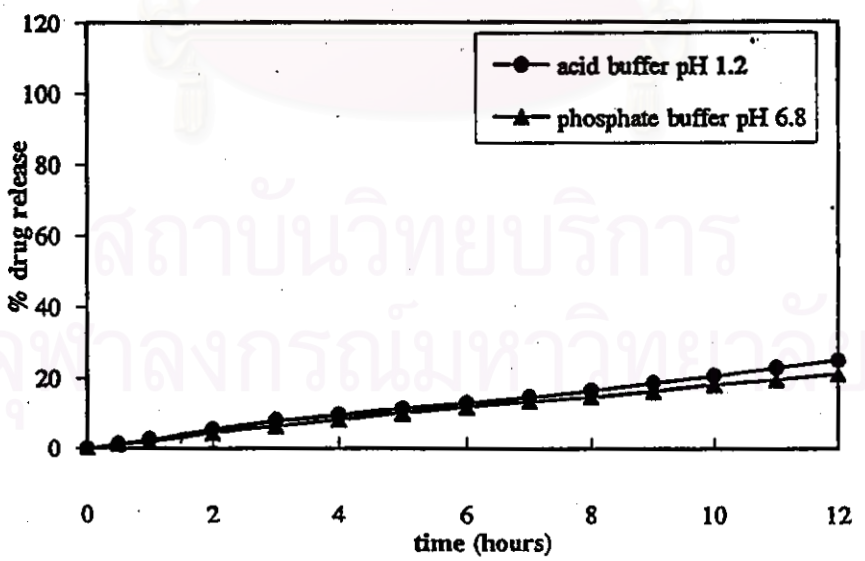



Figure 111 Release profile of coated pellets Formulation 37 (10 % EURS20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

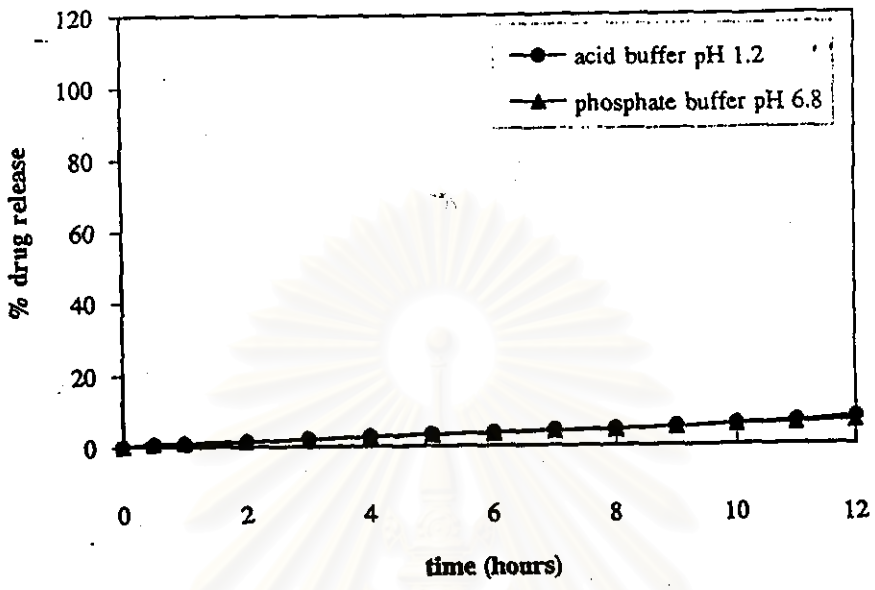



Figure 112 Release profile of coated pellets Formulation 38 (15 % EURS20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

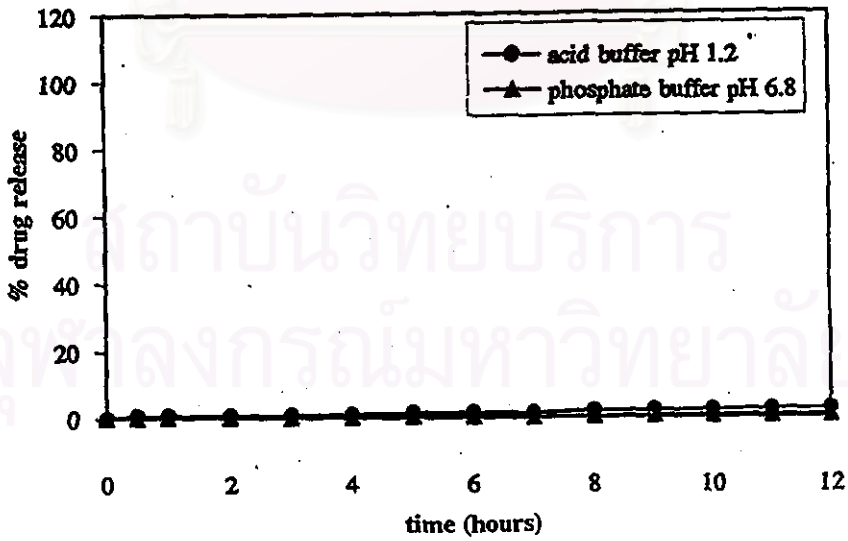



Figure113 Release profile of coated pellets Formulation 39 (20 % EURS20:EC80) in acid buffer pH 1.2 and phosphate buffer pH 6.8.

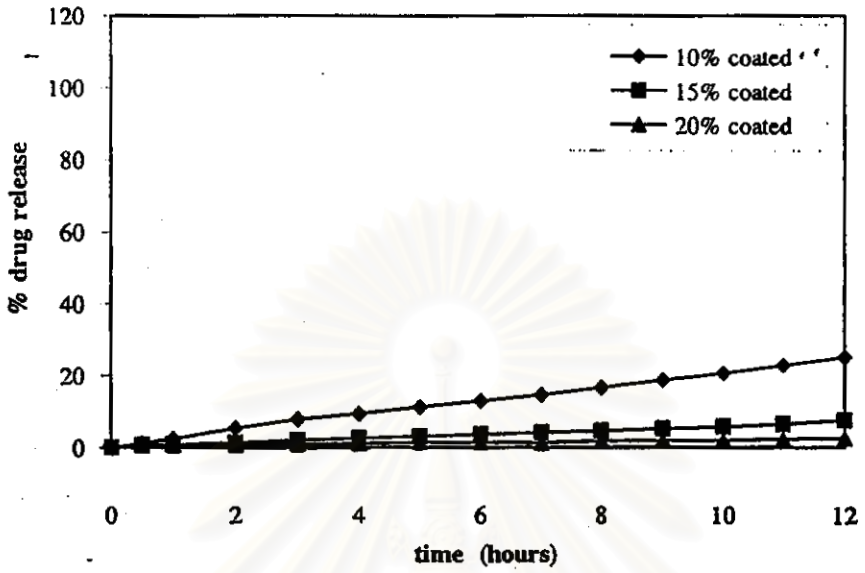



Figure 114 Release profile the pellets coating with different levels of EURS20:EC80 in acid buffer pH 1.2.

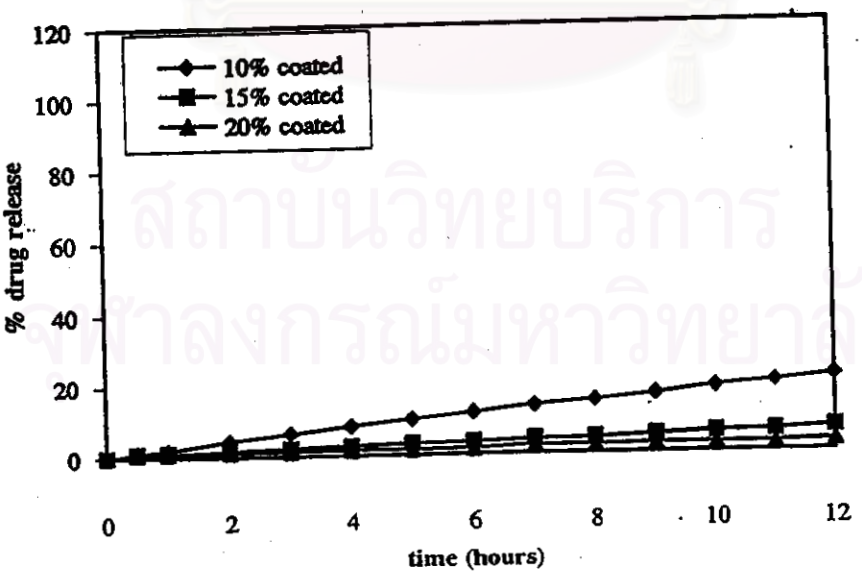



Figure 115 Release profile the pellets coating with different levels of EURS20:EC80 in phosphate buffer pH 6.8.

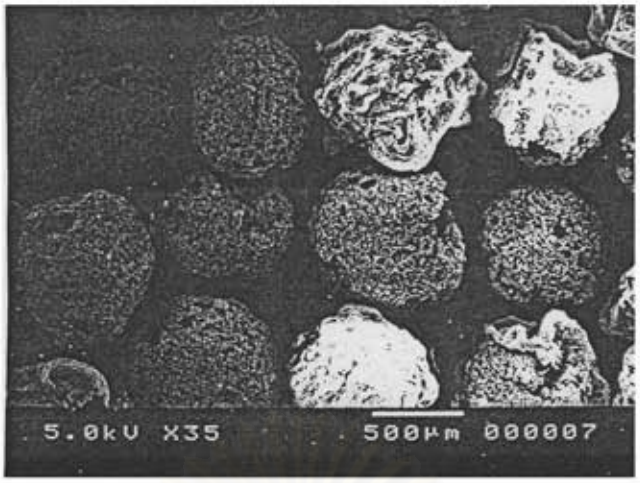
After dissolution test, the morphologies from scanning electron microscope (SEM) of coated pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8 are shown in Figure 116-121. It was seen that at the 60 % Eudragit®RS100 (Formulation 25) the film was warn out showing the core pellets surface. While the films of Formulation 27 and 29 were not disrupt.

5.7 The Evaluation of Drug Release Pattern from Different Formulations.

From the release profiles of all formulations, it could be grouped their release characteristics into three types depending on the polymer types and the mixtures proportion, pH of the medium in which the release were tested and the coating levels.

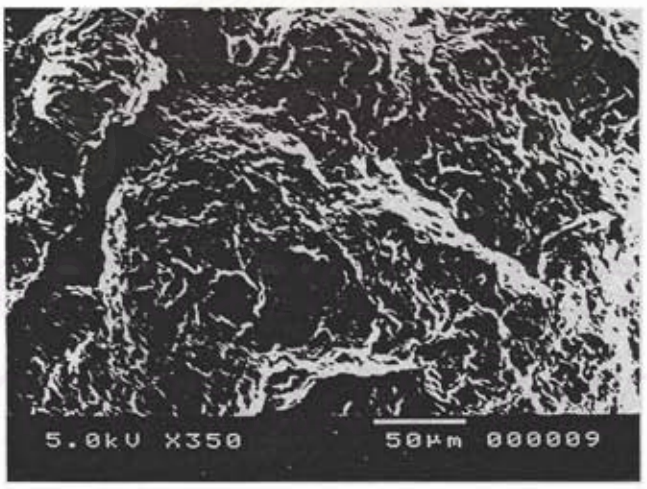
The first type is the prompt release pattern which rapidly release to the maximum point within 1-2 hours. This pattern was observed from the release of coated pellets of Formulation 1-16 as present in Table 13. Those formulations were coated with only Eudragit®RL100 and the mixture of Eudragit®RL100 and ethylcellulose in the range of 80:20 to 40:60). The time mentioned in the Table indicated the time at which most of the drug was release by direct observation from the profiles.

The second type exhibitd the biphasic pattern of drug release. They were composed of slow drug release phase which gave the constant release rate, which gave the zero-order kinetic and then gave the faster release rate in second phase (for example in Figure 80). Therefore, analysis of the release kinetic of biphasic profile might be done by selecting the formulation which gave the slow release period more than 2 hours. The second phase of the release profile was determined to fit first order or Higuchi kinetic. The analysis results of the kinetic pattern of second phase are presented in Table 14. It was seen that they were different depending on the polymer types, pH of the mediums, and coating levels. The graphically plots of zero-order kinetic (phase 1) and Higuchi or first-order plots (phase 2) are shown in Figure 122-154.




A


B

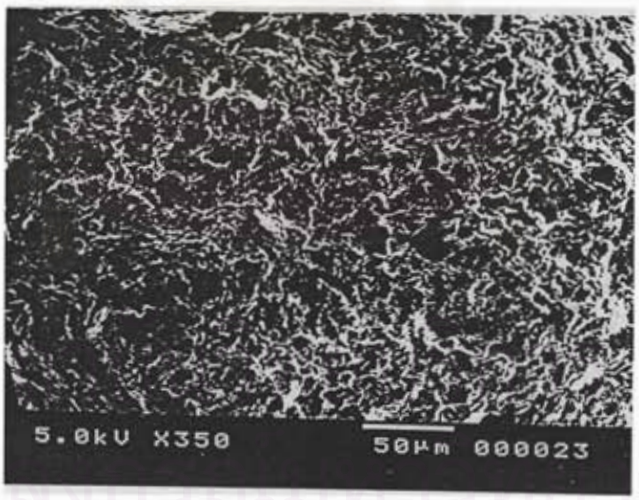



C

ıre 116 Photograph of coated pellets Formulation 25 (10 % EURS 100) after dissolution test in acid buffer pH 1.2.

(Key: A × 35 magnification, B uncoated surface × 350 magnification, C coated surface × 350 magnification )


A

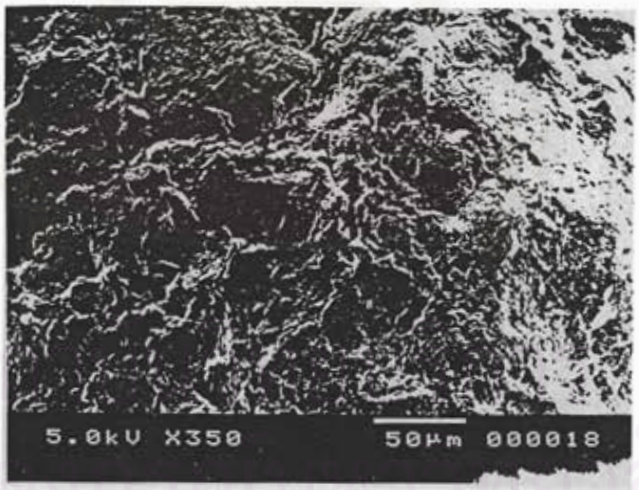



B

Figure 117 Photograph of coated pellets Formulation 25 (10 % EURS 100) after dissolution test in phosphate buffer pH 6.8.

(Key: A × 35 magnification, B × 350 magnification )

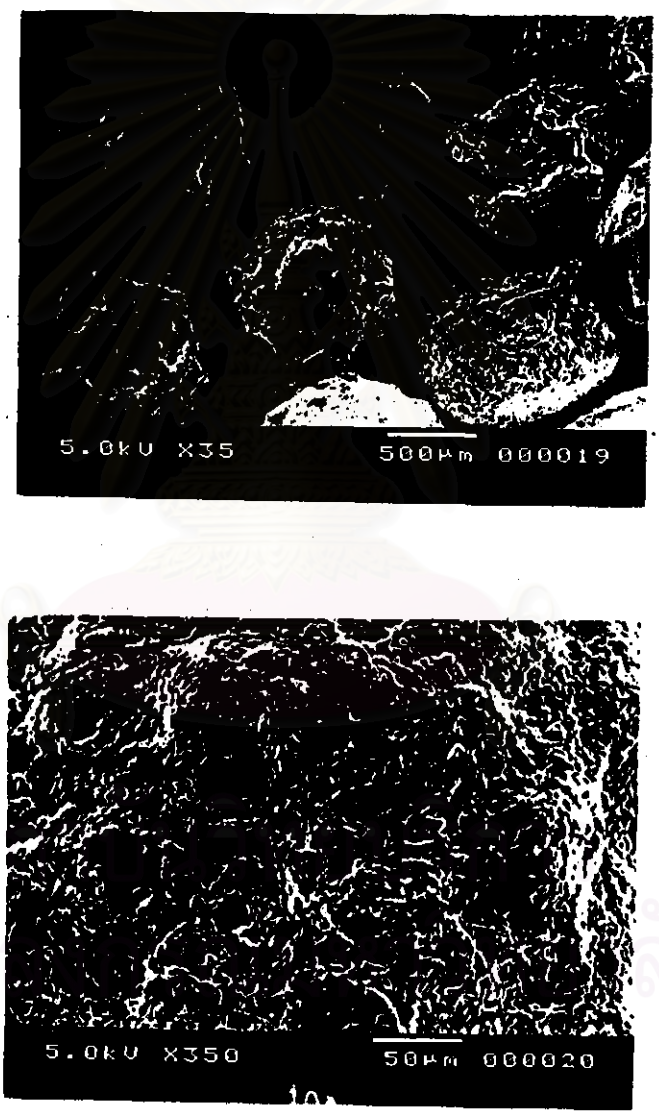

A




B

Figure 118 Photograph of coated pellets Formulation 27 (20 % EURS 100) after dissolution test in acid buffer pH 1.2.

(Key: A × 35 magnification, B × 350 magnification )




A

B

Figure 119 Photograph of coated pellets Formulation 27 (20 % EURS 100) after dissolution test in phosphate buffer pH 6.8.

(Key: A × 35 magnification, B × 350 magnification )

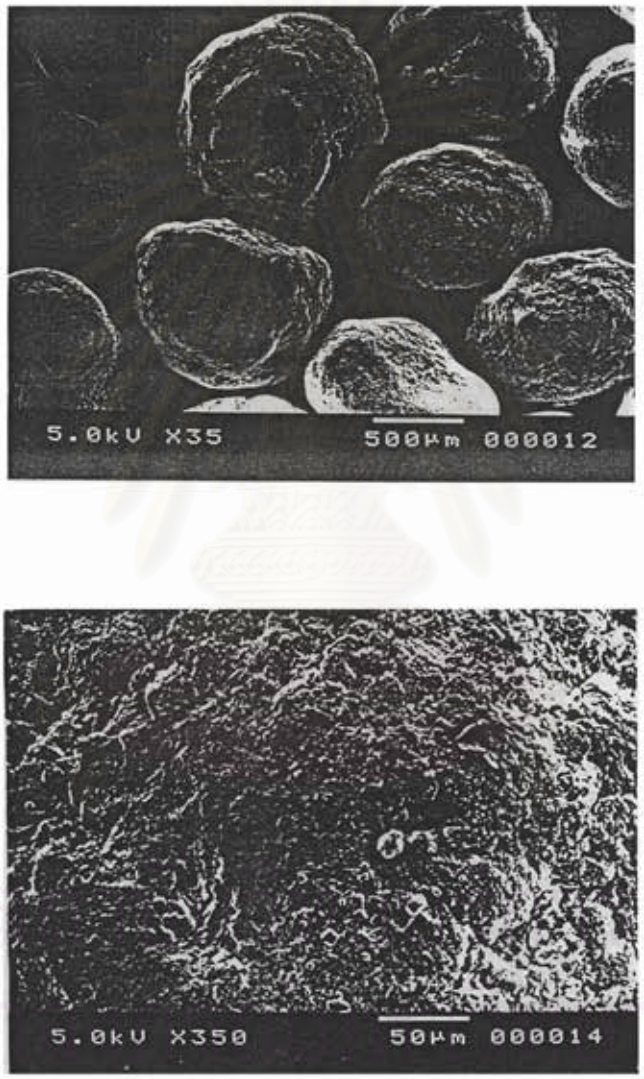
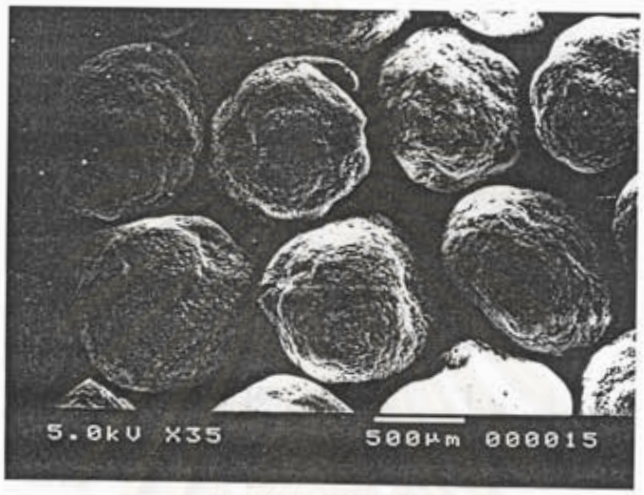
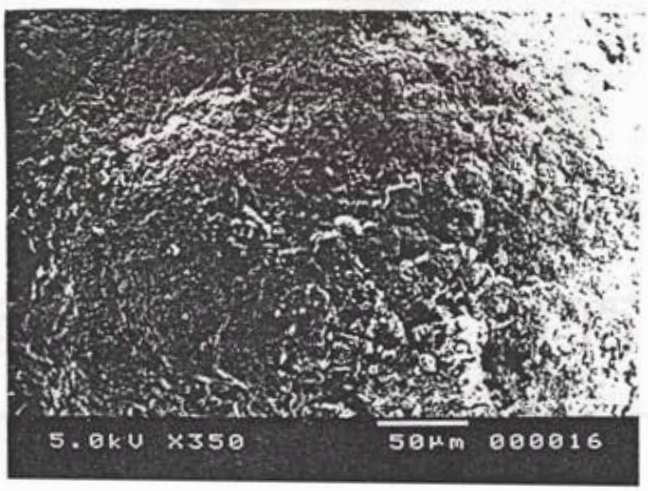



Figure 120 Photograph of coated pellets Formulation 29 (15 % EURS80:EC20) after dissolution test in acid buffer pH 1.2.

(Key: A × 35 magnification, B × 350 magnification )




A




B

Figure 121 Photograph of coated pellets Formulation 29 (15 % EURS80:EC20) after dissolution test in phosphate buffer pH 6.8.

(Key: A × 35 magnification, B × 350 magnification )

Table 13 The time at which most of the drug were release of Formulation 1-16.

| Formulation | Ratio between EURL100:EC | % Coating level | Time (hours)* Acid buffer pH 1.2 | Phosphate buffer pH 6.8 |
|---|---|---|---|---|
| 1 | 100:0 | 5 | 0.5 | 0.5 |
| 2 | 100:0 | 10 | 0.5 | 1 |
| 3 | 100:0 | 15 | 1 | 2 |
| 4 | 100:0 | 20 | 2 | 2 |
| 5 | 80:20 | 5 | 0.5 | 0.5 |
| 6 | 80:20 | 10 | 0.5 | 1 |
| 7 | 80:20 | 15 | 1 | 2 |
| 8 | 80:20 | 20 | 1 | 2 |
| 9 | 60:40 | 5 | 0.5 | 1 |
| 10 | 60:40 | 10 | 0.5 | 2 |
| 11 | 60:40 | 15 | 0.5 | 2 |
| 12 | 60:40 | 20 | 1 | >2 |
| 13 | 40:60 | 5 | 1 | >2 |
| 14 | 40:60 | 10 | 1 | >2 |
| 15 | 40:60 | 15 | 1 | >2 |
| 16 | 40:60 | 20 | 1 | >2 |

* Time at which most of the drug were release (inflection point of release profile was observed)

Table 14 Release pattern of formulations which gave biphasic release showing initial slow drug release phase (phase 1) and faster drug release phase (phase 2).

| Formulation | Acid buffer pH 1.2 | | | | Phosphate buffer pH 6.8 | | | |
|---|---|---|---|---|---|---|---|---|
| | phase 1 | $r^2$ of First order plot | $r^2$ of Higuchi plot | Best fit | phase 1 | $r^2$ of First order plot | $r^2$ of Higuchi plot | Best fit |
| 19 | * | * | * | | 2 | 0.980 | 0.935 | First order |
| 10 | * | * | * | | 4 | 0.986 | 0.978 | First order |
| 26 | 2 | 0.908 | 0.912 | ** | 3 | 0.888 | 0.977 | Higuchi |
| 27 | 2 | 0.825 | 0.937 | Higuchi | 5 | 0.898 | 0.938 | Higuchi |
| 30 | 3 | 0.978 | 0.816 | First order | 3 | 0.935 | 0.984 | Higuchi |
| 32 | * | * | * | | 2 | 0.993 | 0.913 | First order |
| 33 | 2 | 0.971 | 0.750 | First order | 3 | 0.993 | 0.947 | First order |

* no initial drug release phase
** unable to be conclude

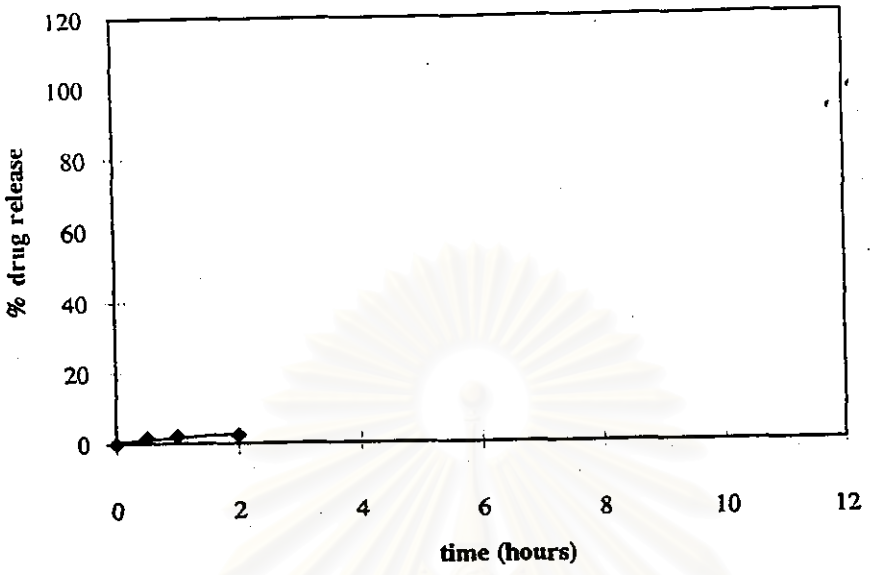



Figure 122 Slow release period of the release profile of coated pellets Formulation 19 (5 % EURL20:EC80) in phosphate buffer pH 6.8.

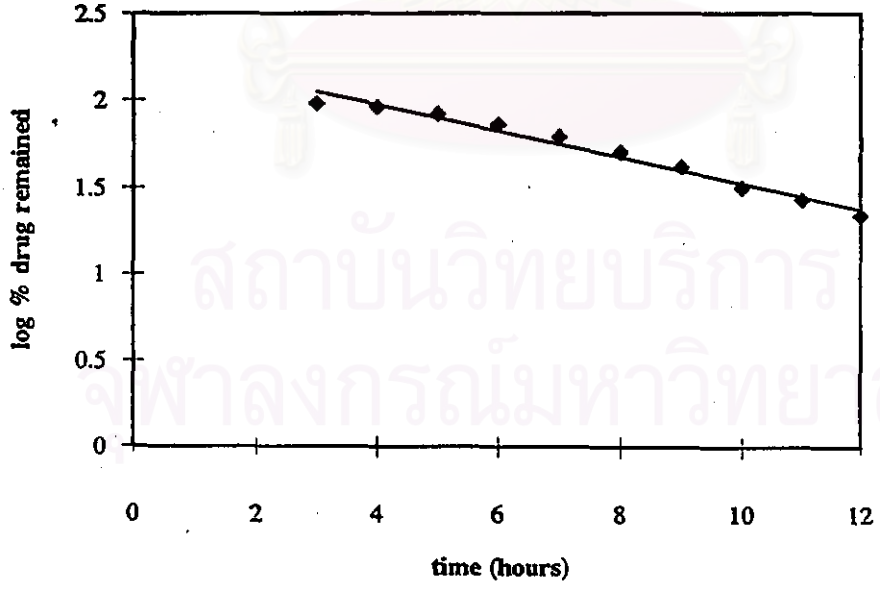



Figure 123 The first-order plot of coated pellets Formulation 19 (15 % EURL20:EC80) in phosphate buffer pH 6.8.

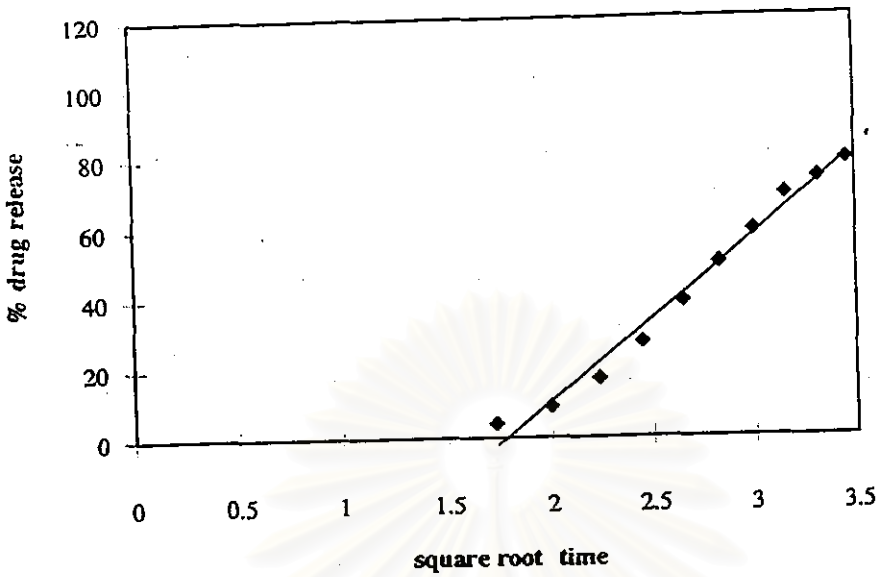



Figure 124 The Higuchi plot of coated pellets Formulation 19 (15 % EURL20:EC80) in phosphate buffer pH 6.8.

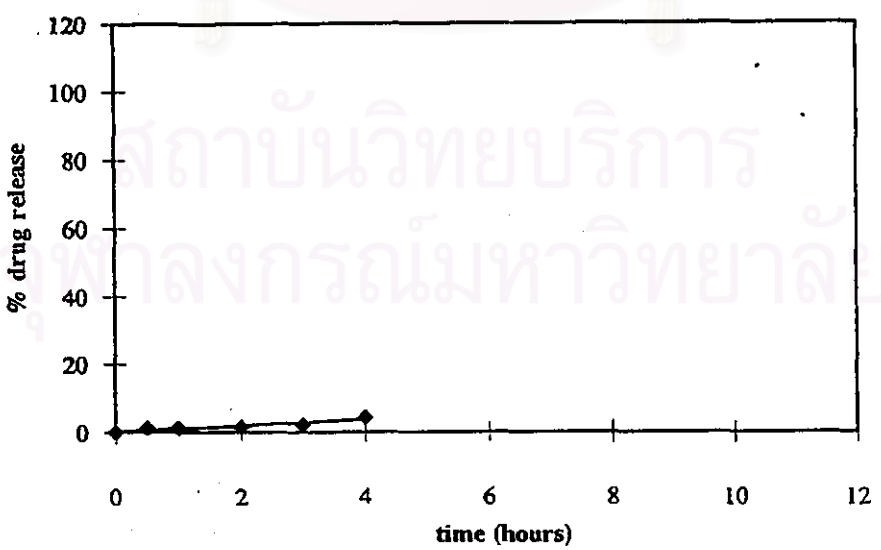



Figure 125 Slow release period of the release profile of coated pellets Formulation 20 (20 % EURL20:EC80) in phosphate buffer pH 6.8.

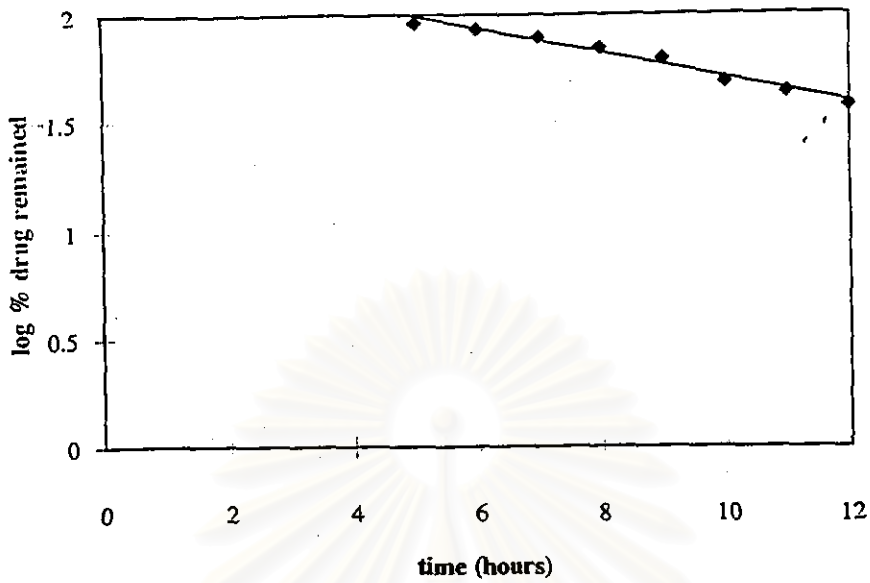



Figure 126 The first-order plot of coated pellets Formulation 20 (20 % EURL20:EC80) in phosphate buffer pH 6.8.

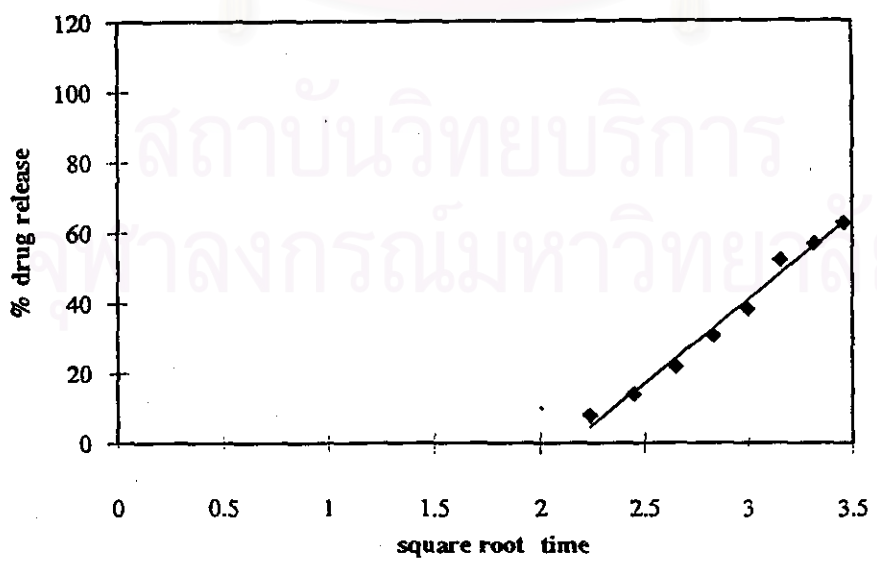



Figure 127 The Higuchi plot of coated pellets Formulation 20 (20 % EURL20:EC80) in phosphate buffer pH 6.8.

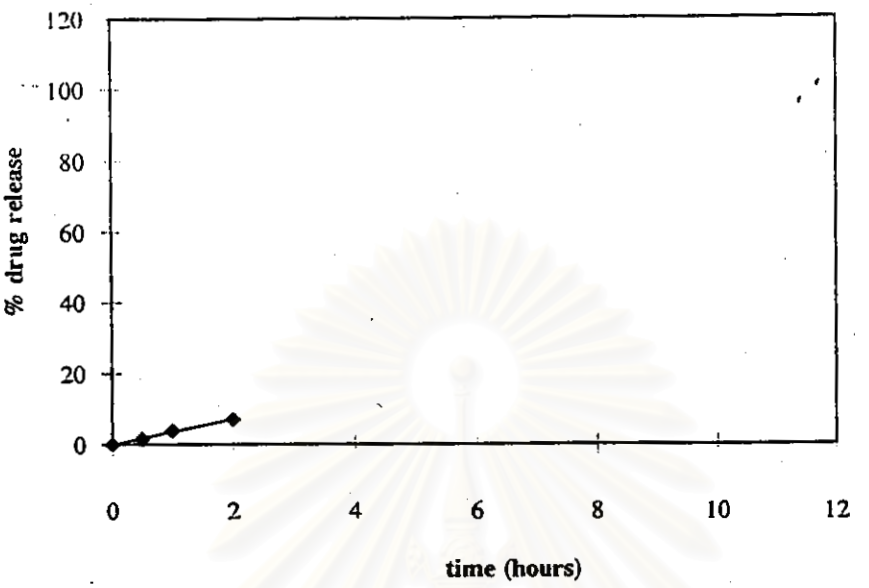



Figure 128 Slow release period of the release profile of coated pellets Formulation 26 (15 % EURS100) in acid buffer pH 1.2.

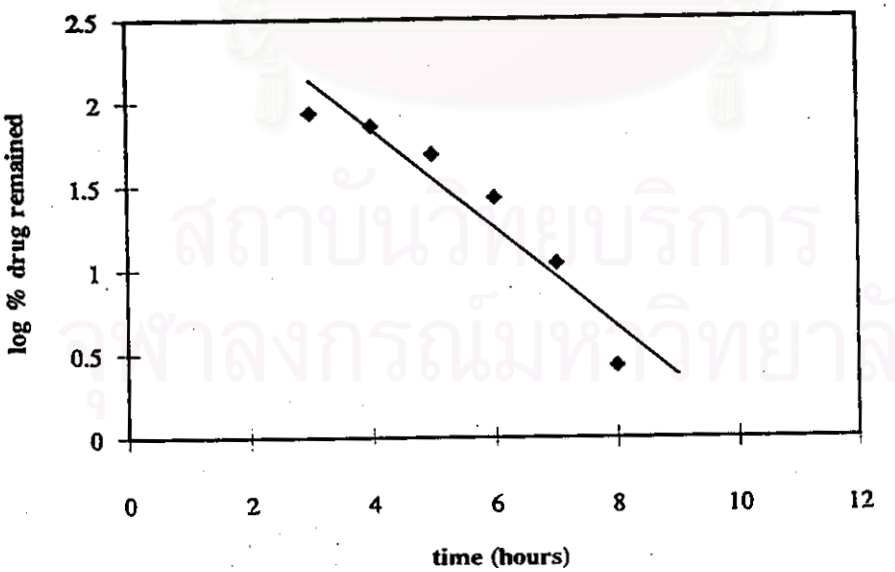



Figure 129 The first-order plot of coated pellets Formulation 26 (15 % EURS100) in acid buffer pH 1.2.

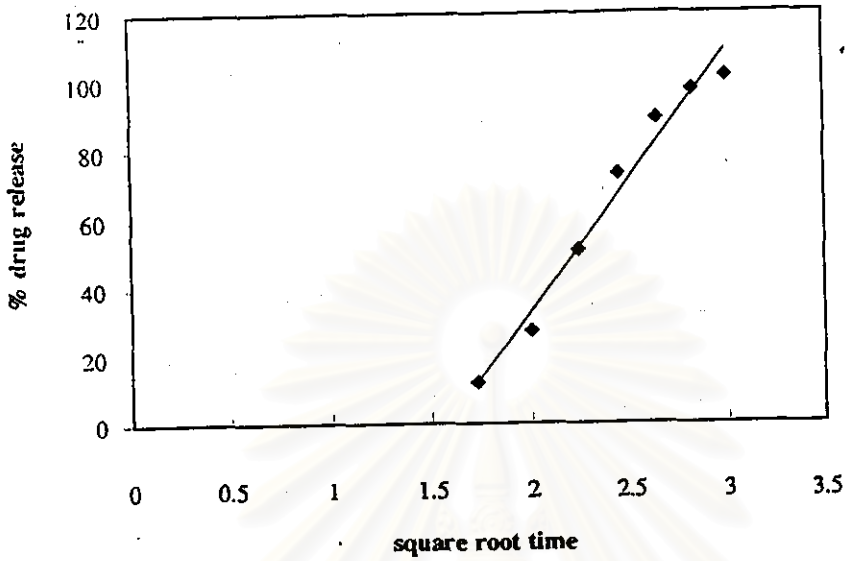



Figure 130 The Higuchi plot of coated pellets Formulation 26 (15 % EURS100) in acid buffer pH 1.2.

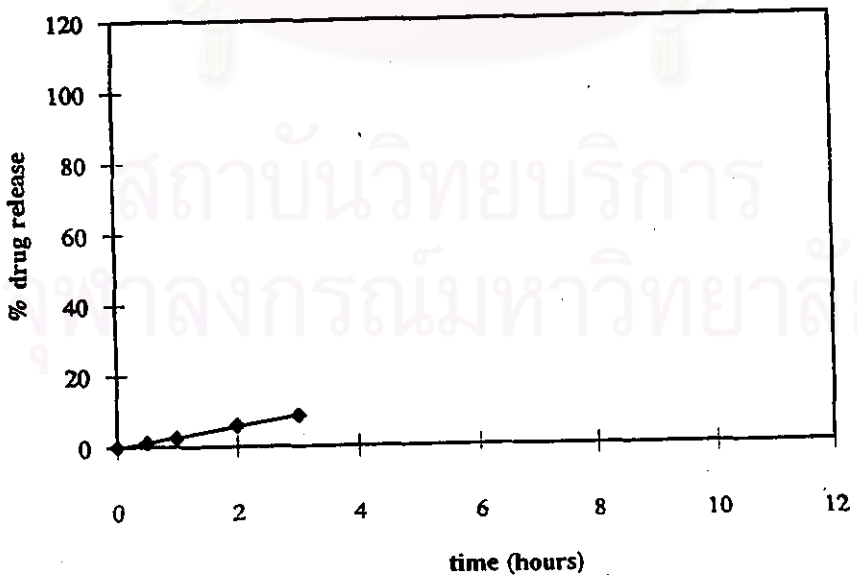



Figure 131 Slow release period of the release profile of coated pellets Formulation 26 (15 % EURS100) in phosphate buffer pH 6.8.

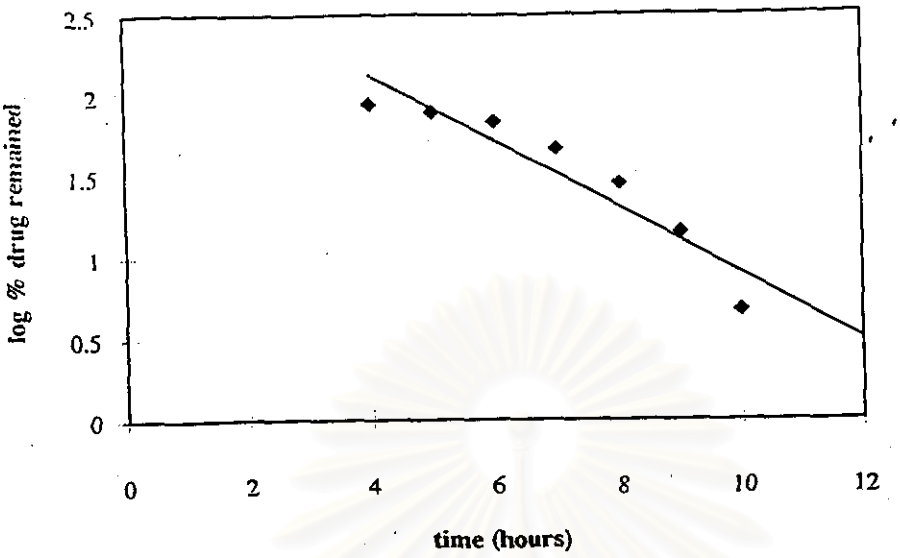



Figure 132 The first-order plot of coated pellets Formulation 26 (15 % EURS100) in phosphate buffer pH 6.8.

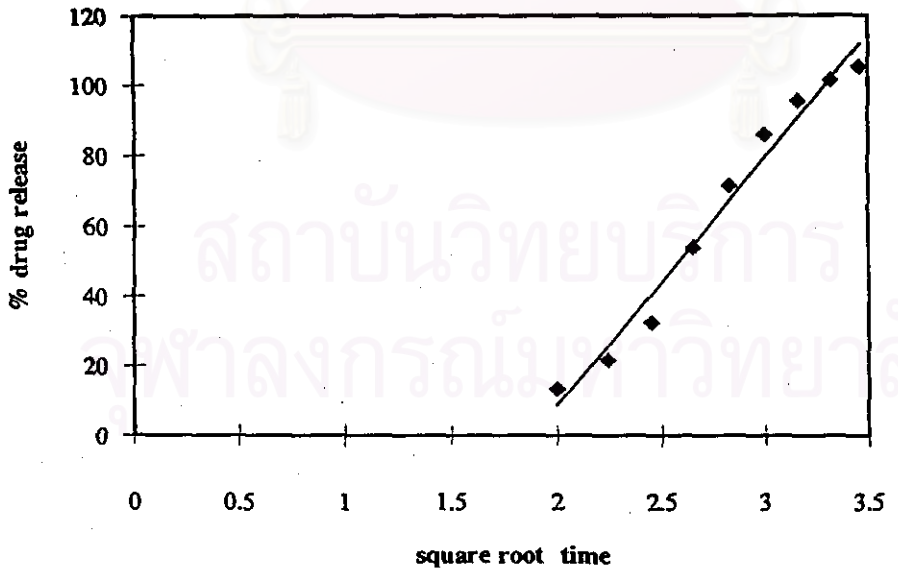



Figure 133 The Higuchi plot of coated pellets Formulation 26 (15 % EURS100) in phosphate buffer pH 6.8.

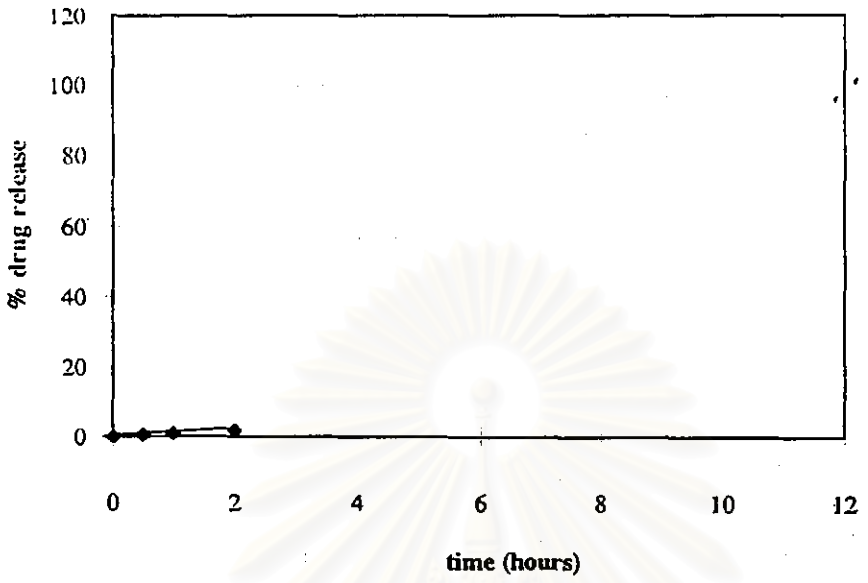



Figure 134 Slow release period of the release profile of coated pellets Formulation 27 (20 % EURS100) in acid buffer pH 1.2.

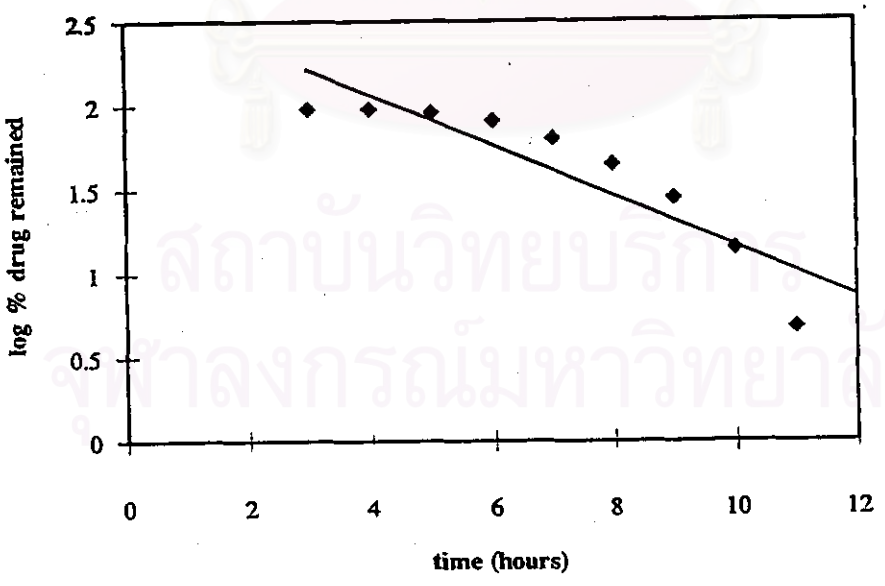



Figure 135 The first-order plot of coated pellets Formulation 27 (20 % EURS100) in acid buffer pH 1.2.

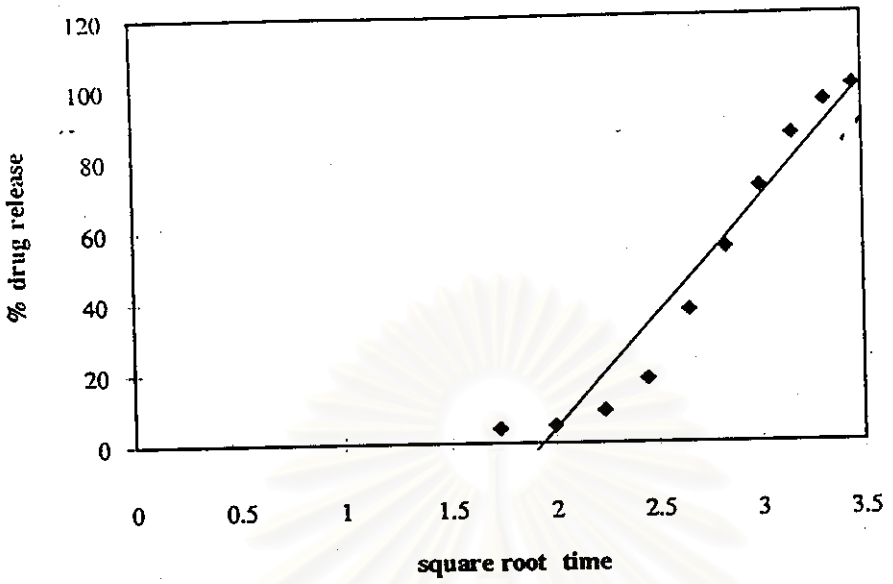



Figure 136 The Higuchi plot of coated pellets Formulation 27 (20 % EURS100) in acid buffer pH 1.2.

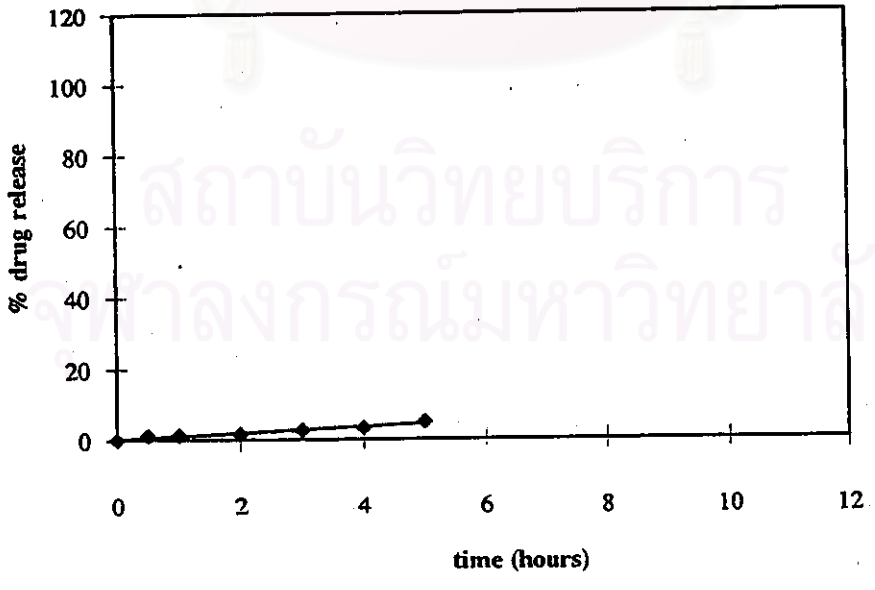



Figure 137 Slow release period of the release profile of coated pellets Formulation 27 (20 % EURS100) in phosphate buffer pH 6.8.

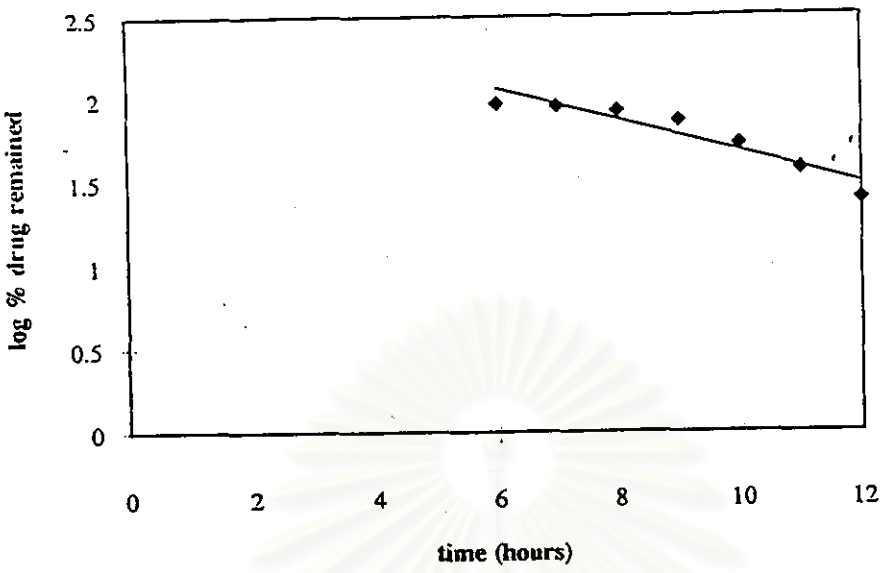



Figure 138 The first-order plot of coated pellets Formulation 27 (20 % EURS100) in phosphate buffer pH 6.8.

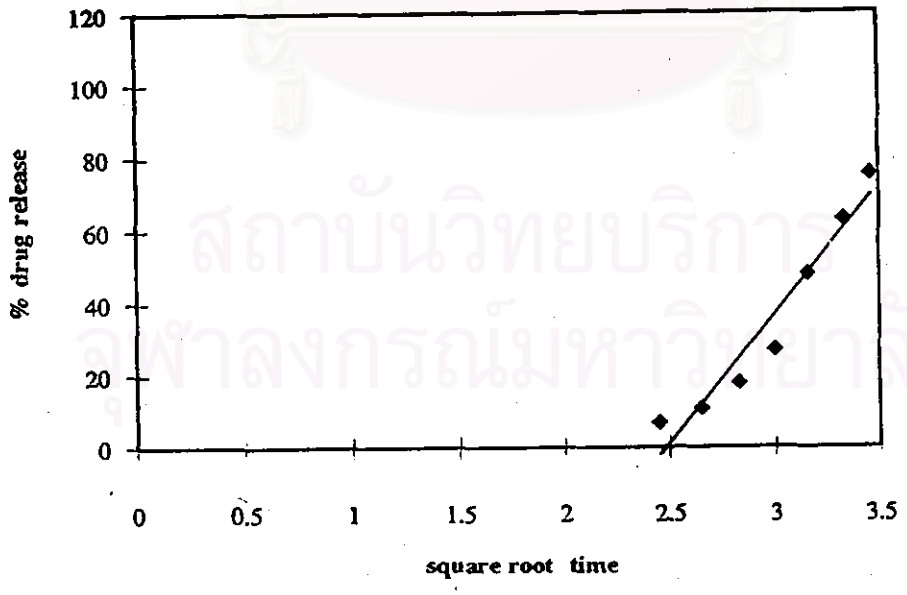



Figure 139 The Higuchi plot of coated pellets Formulation 27 (20 % EURS100) in phosphate buffer pH 6.8.

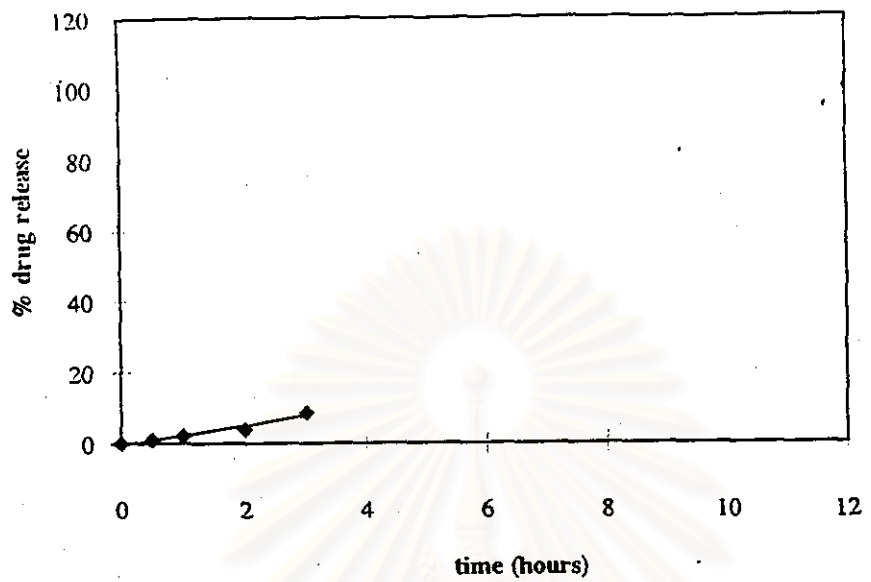



Figure 140 Slow release period of the release profile of coated pellets Formulation 30 (20 % EURS80:EC20) in acid buffer pH 1.2.

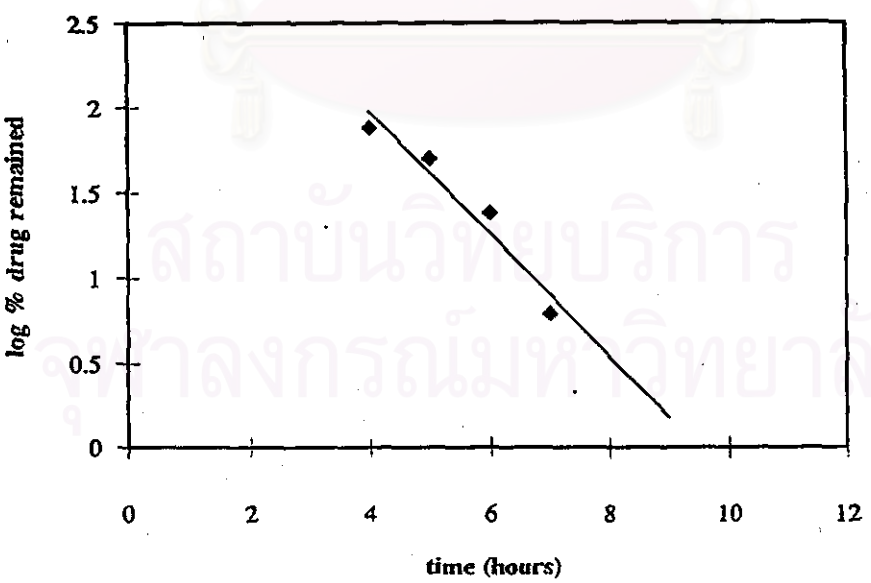



Figure 141 The first-order plot of coated pellets Formulation 30 (20 % EURS80:EC20) in acid buffer pH 1.2.

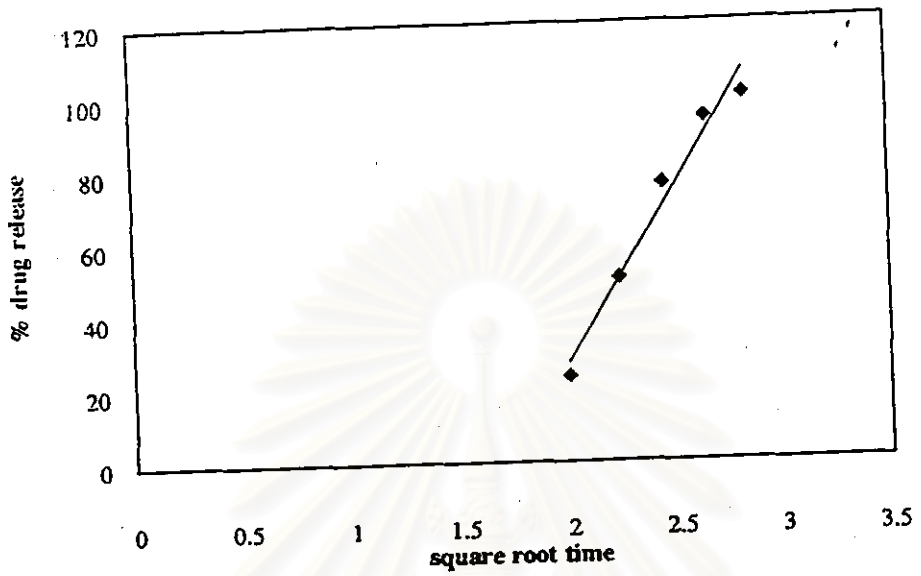



Figure 142 The Higuchi plot of coated pellets Formulation 30 (20 % EURS80:EC20) in acid buffer pH 1.2.

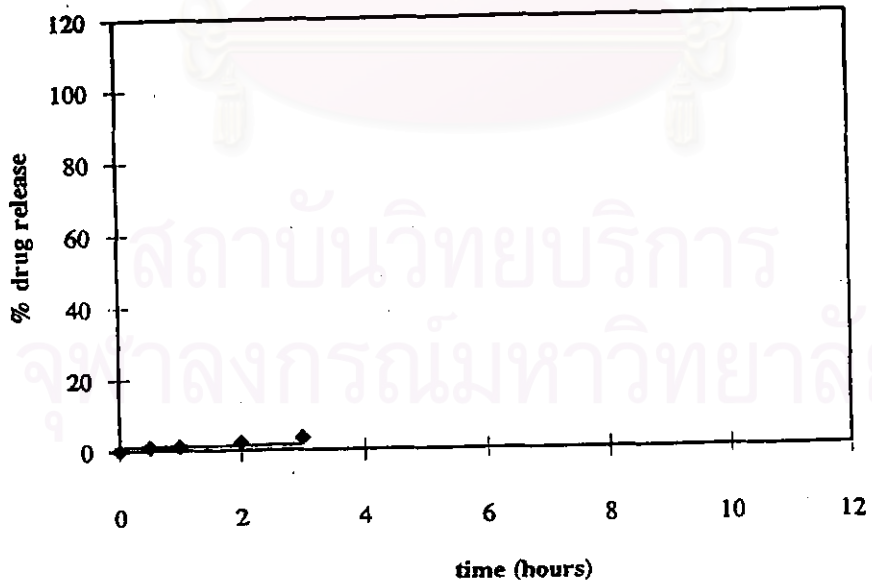



Figure 143 Slow release period of the release profile of coated pellets Formulation 30 (20 % EURS80:EC20) in phosphate buffer pH 6.8.

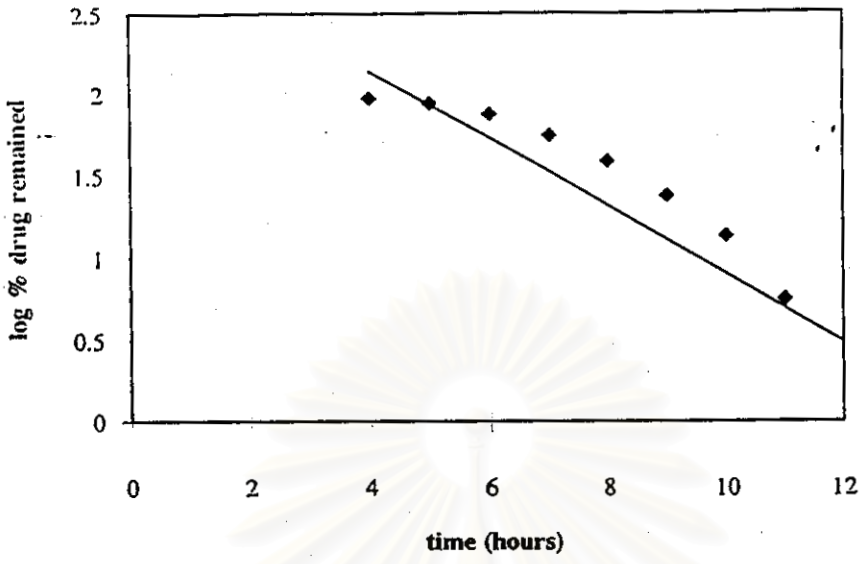



Figure 144 The first-order plot of coated pellets Formulation 30 (20 % EURS80:EC20) in phosphate buffer pH 6.8.

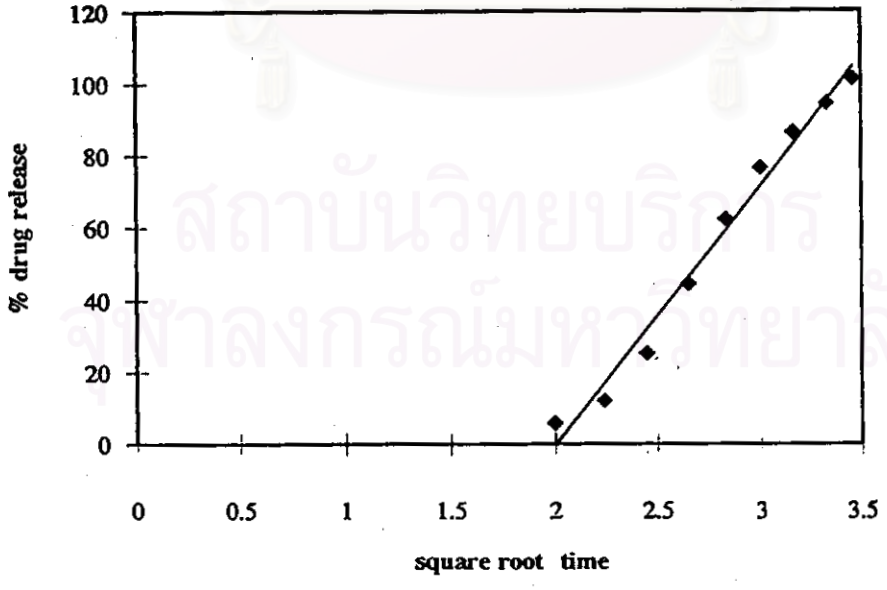



Figure 145 The Higuchi plot of coated pellets Formulation 30 (20 % EURS80:EC20) in phosphate buffer pH 6.8.

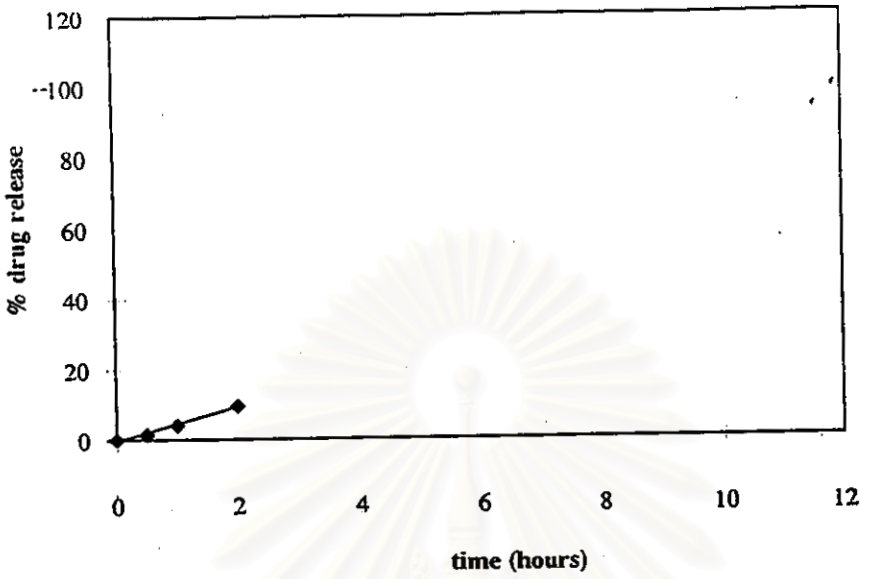



Figure 146 Slow release period of the release profile of coated pellets Formulation 32 (15 % EURS60:EC40) in phosphate buffer pH 6.8.

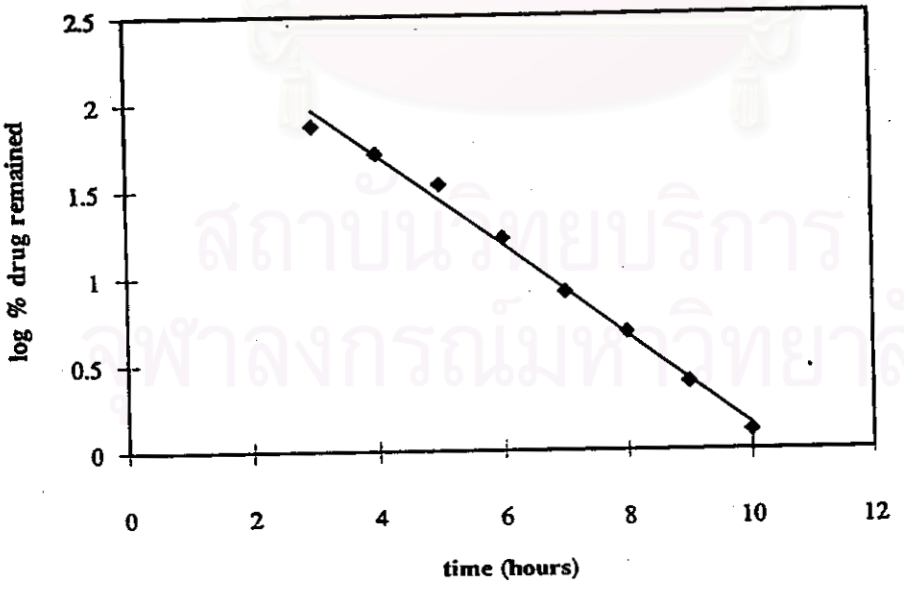



Figure 147 The first-order plot of coated pellets Formulation 32 (15 % EURS60:EC40) in phosphate buffer pH 6.8.

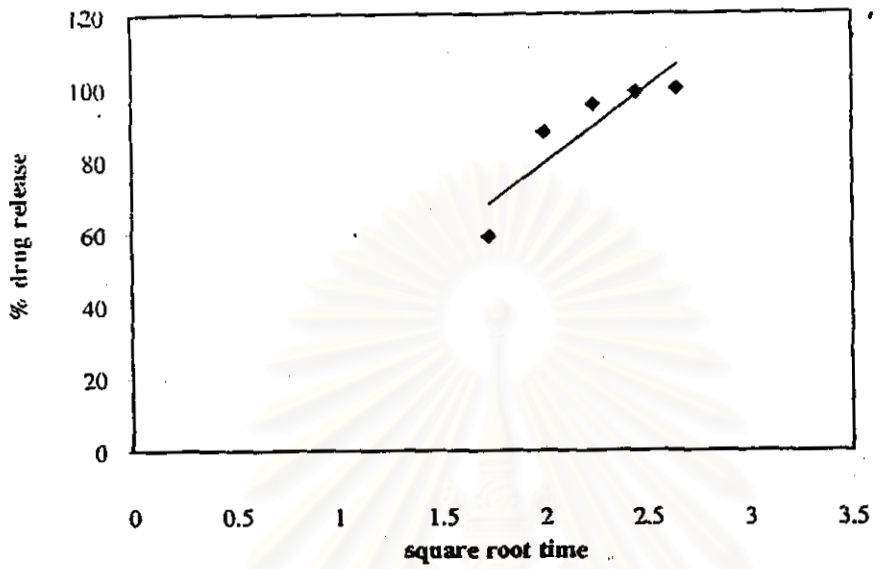



Figure 148 The Higuchi plot of coated pellets Formulation 32 (15 % EURS60:EC40) in phosphate buffer pH 6.8.

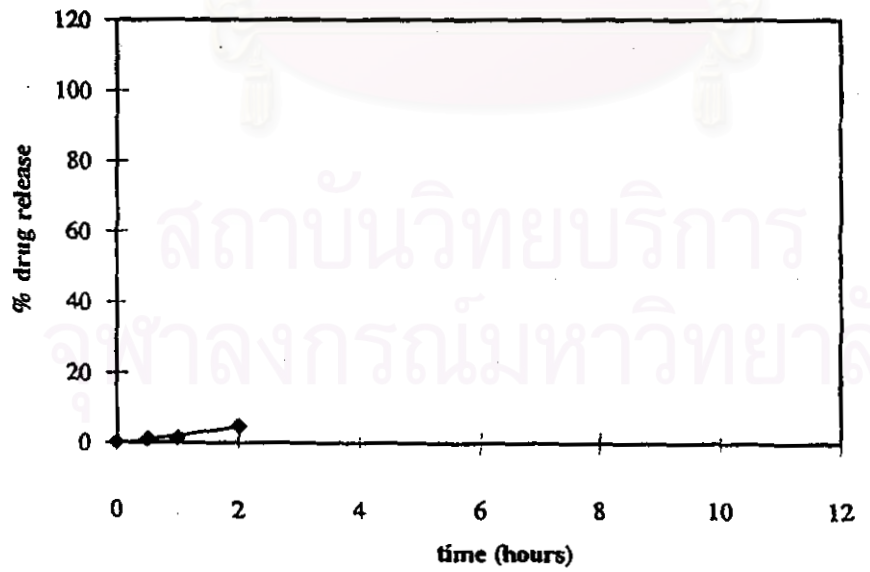



Figure 149 Slow release period of the release profile of coated pellets Formulation 33 (20 % EURS60:EC40) in acid buffer pH 1.2.

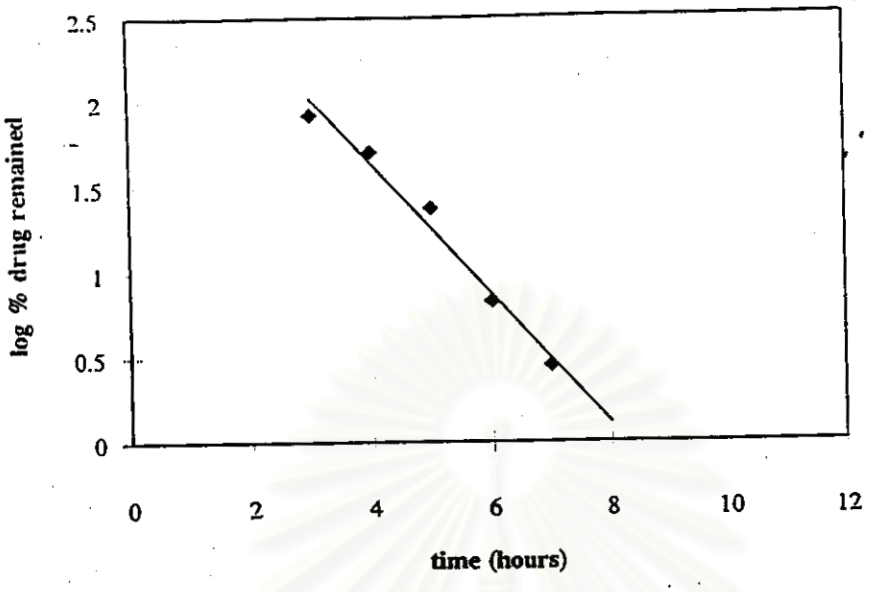



Figure 150 The first-order plot of coated pellets Formulation 33 (20 % EURS60:EC40) in acid buffer pH 1.2.

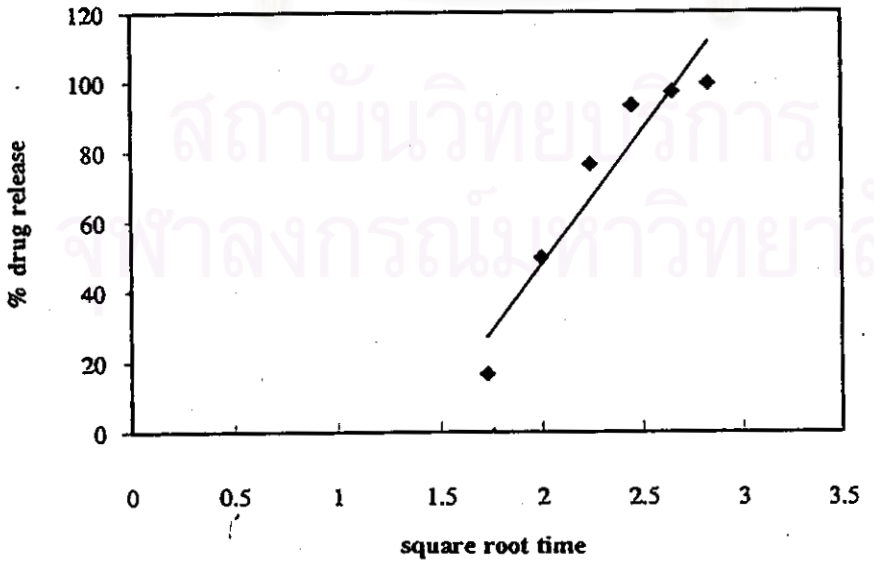



Figure 151 The Higuchi plot of coated pellets Formulation 33 (20 % EURS60:EC40) in acid buffer pH 1.2.

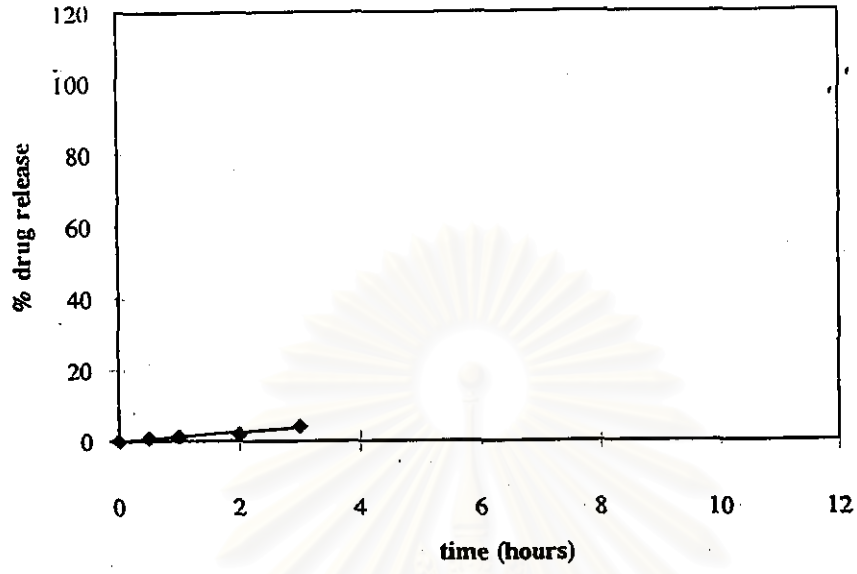



Figure 152 Slow release period of the release profile of coated pellets Formulation 33 (20 % EURS60:EC40) in phosphate buffer pH 6.8.

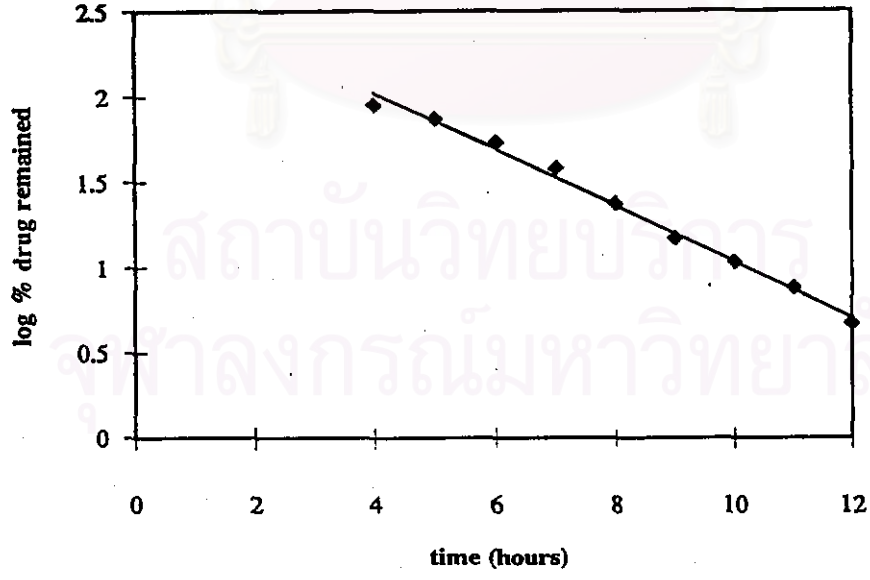



Figure 153 The first-order plot of coated pellets Formulation 33 (20 % EURS60:EC40) in phosphate buffer pH 6.8.

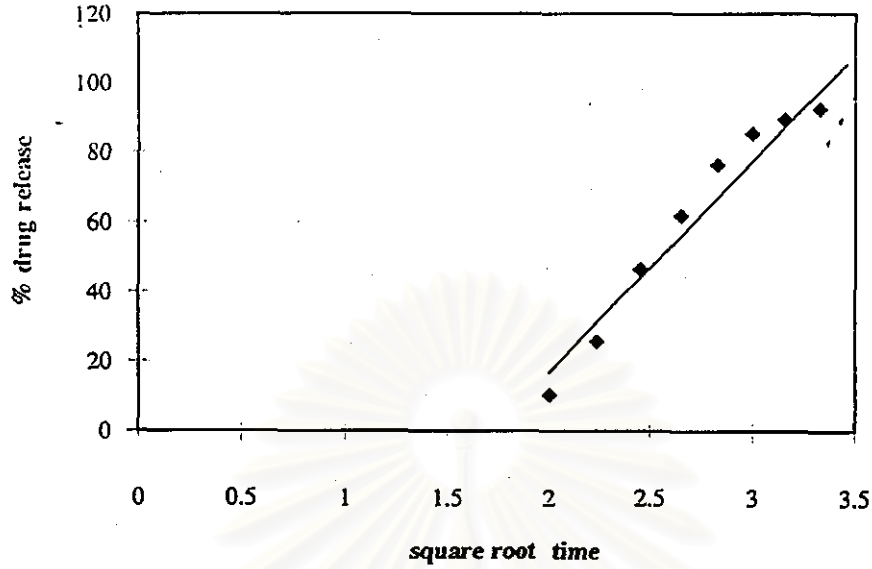



Figure 154 The Higuchi plot of coated pellets Formulation 33 (20 % EURS60:EC40) in phosphate buffer pH 6.8.

The last type of the pattern is zero-order kinetic which gave the constant rate from the beginning at 0 hour up until 12 hours. The formulation of this type were Formulation 22-24 which are 100 % ethylcellulose coating and Formulation 37-39 which composed of the high proportion of 80 % ethylcellulose plus 20 % Eudragit®RS100 at 10-20 % coating levels. Table 15 presents the release pattern of coated pellets of Formulation 22-24 and 37-39. Furthermore, graphically results are shown in Figure 155-166.

Table 15 The release pattern of coated pellets Formulation 22-24 and 33-39.

| Formulation | Ratio between EURL100:EC | % Coating level | Release pattern in Acid buffer pH 1.2 | $r^2$ | Phosphate buffer pH 6.8 | $r^2$ |
|---|---|---|---|---|---|---|
| 22 | 0:100 | 10 | zero-order | 0.995 | zero-order | 0.988 |
| 23 | 0:100 | 15 | zero-order | 0.983 | zero-order | 0.089 |
| 24 | 0:100 | 20 | zero-order | 0.941 | zero-order | 0.863 |
| 37 | 20:80 | 10 | zero-order | 0.996 | zero-order | 0.996 |
| 38 | 20:80 | 15 | zero-order | 0.993 | zero-order | 0.992 |
| 39 | 20:80 | 20 | zero-order | 0.948 | zero-order | 0.914 |

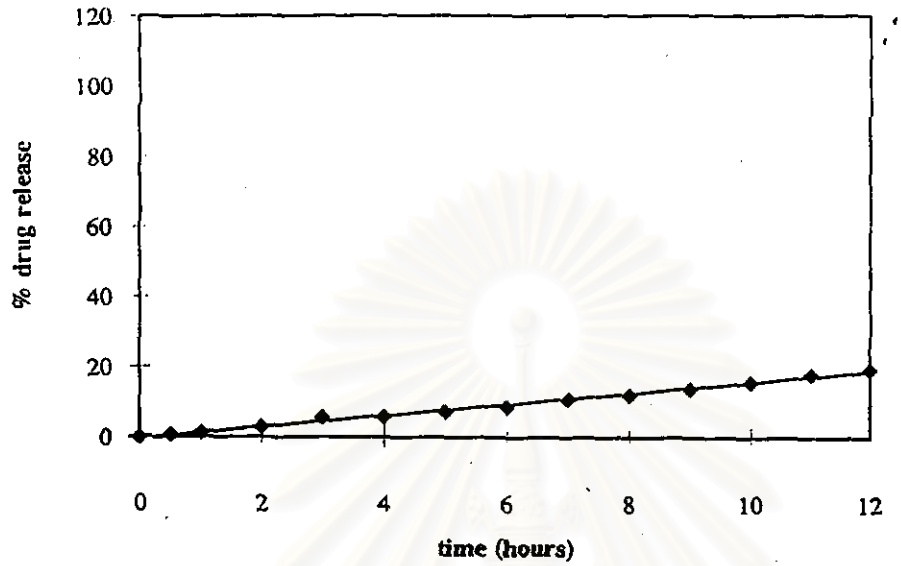



Figure 155 The zero-order plot of coated pellets Formulation 22 (10 % EC 100) in acid buffer pH 1.2.

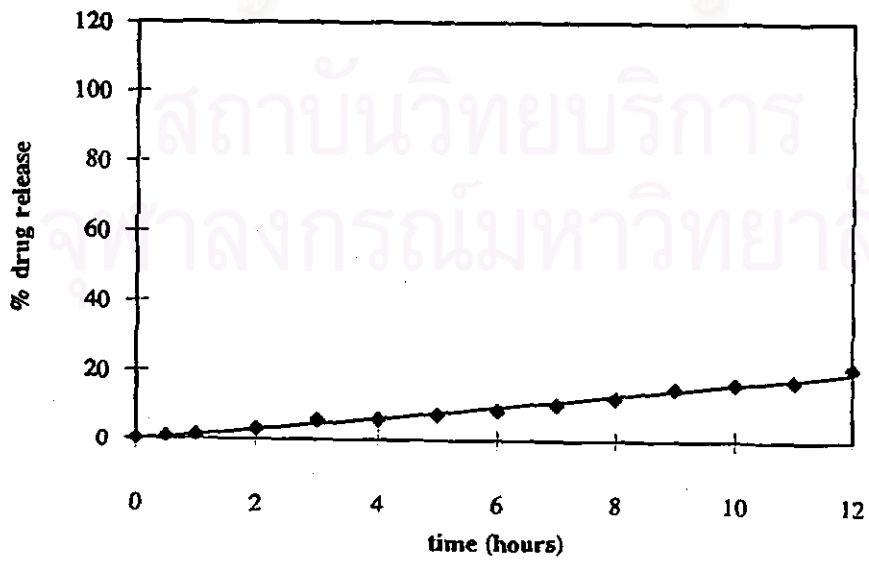



Figure 156 The zero-order plot of coated pellets Formulation 22 (10 % EC 100) in phosphate buffer pH 6.8.

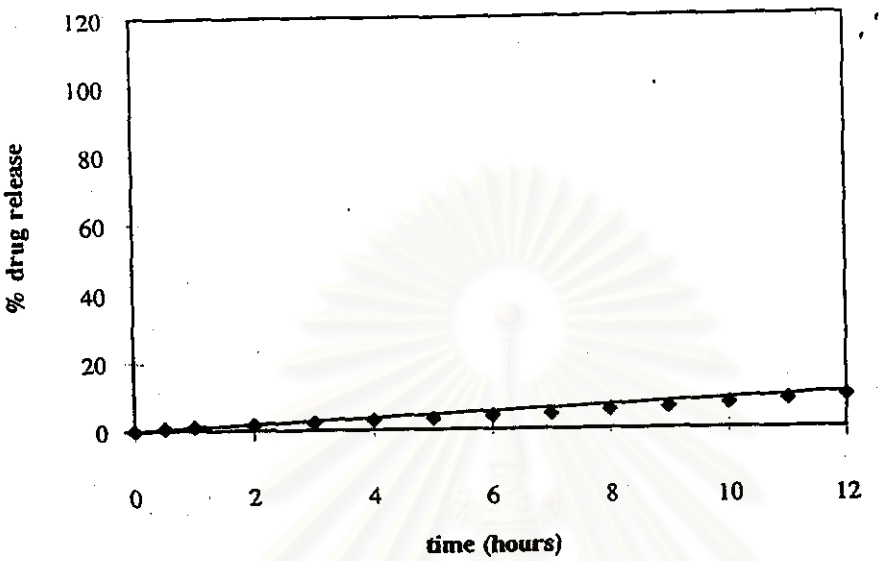



Figure 157 The zero-order plot of coated pellets Formulation 23 (15 % EC 100) in acid buffer pH 1.2.

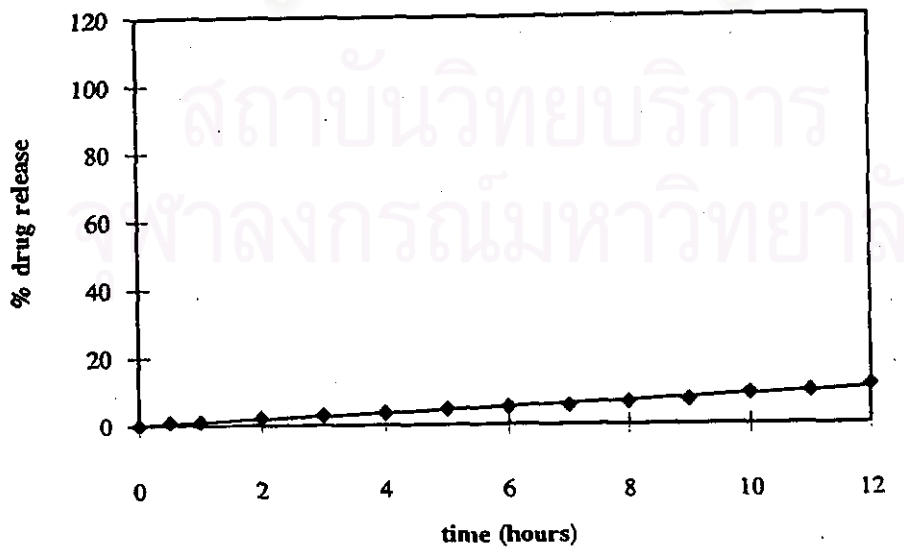



Figure 158 The zero-order plot of coated pellets Formulation 23 (15 % EC 100) in phosphate buffer pH 6.8.

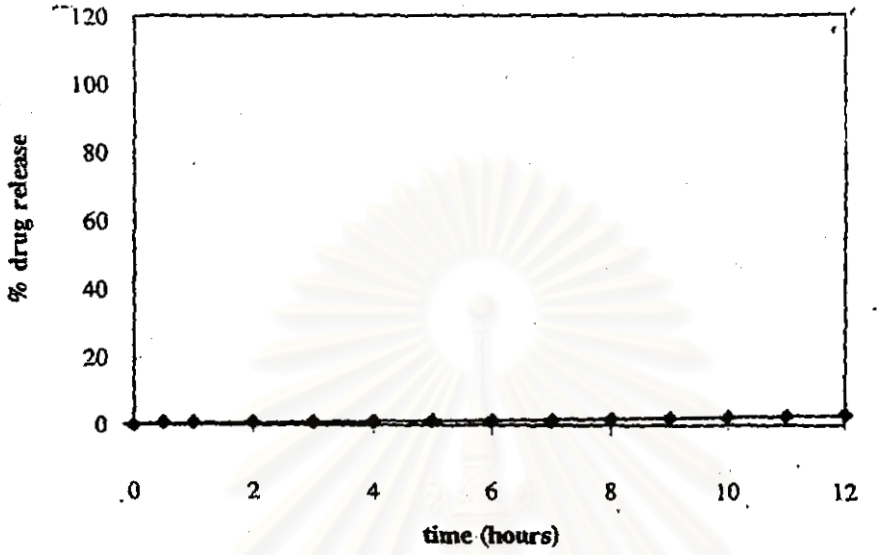



Figure 159 The zero-order plot of coated pellets Formulation 24 (20 % EC 100) in acid buffer pH 1.2.

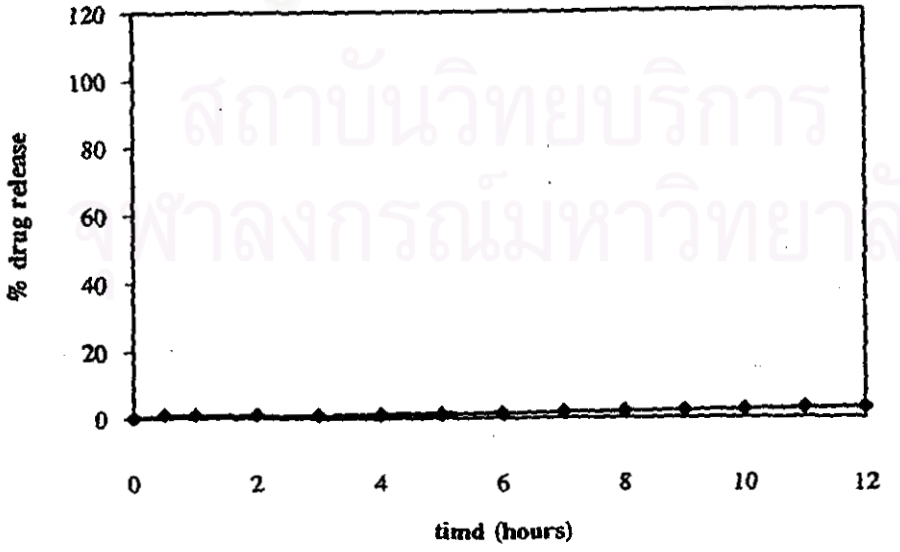



Figure 160 The zero-order plot of coated pellets Formulation 24 (20 % EC 100) in phosphate buffer pH 6.8.

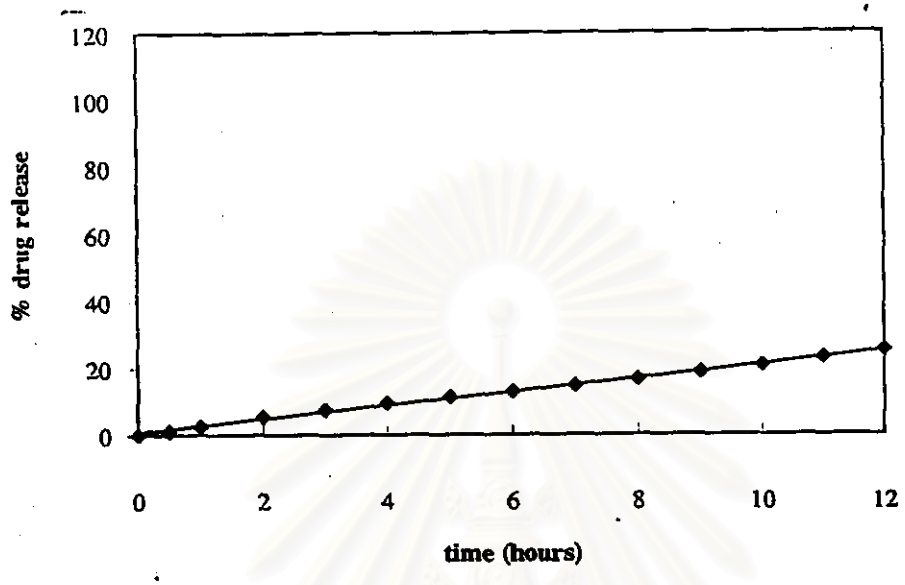



Figure 161 The zero-order plot of coated pellets Formulation 37 (10 % EURS20:EC80) in acid buffer pH 1.2.

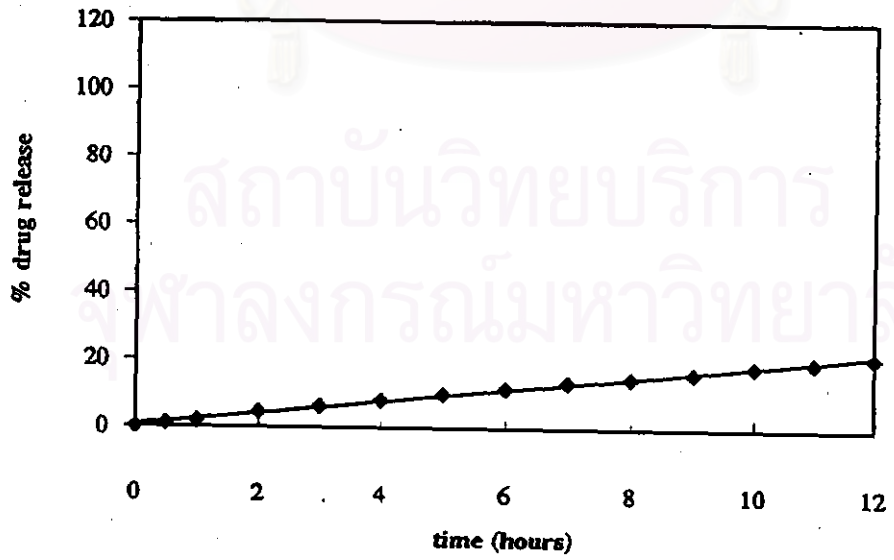



Figure 162 The zero-order plot of coated pellets Formulation 37 (10 % EURS20:EC80) in phosphate buffer pH 6.8.

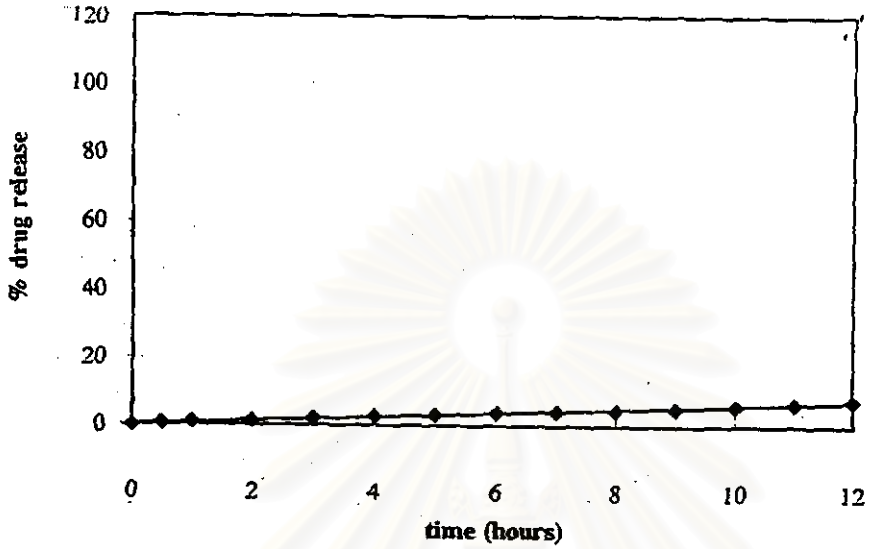



Figure 163 The zero-order plot of coated pellets Formulation 38 (15 % EURS20:EC80) in acid buffer pH 1.2.

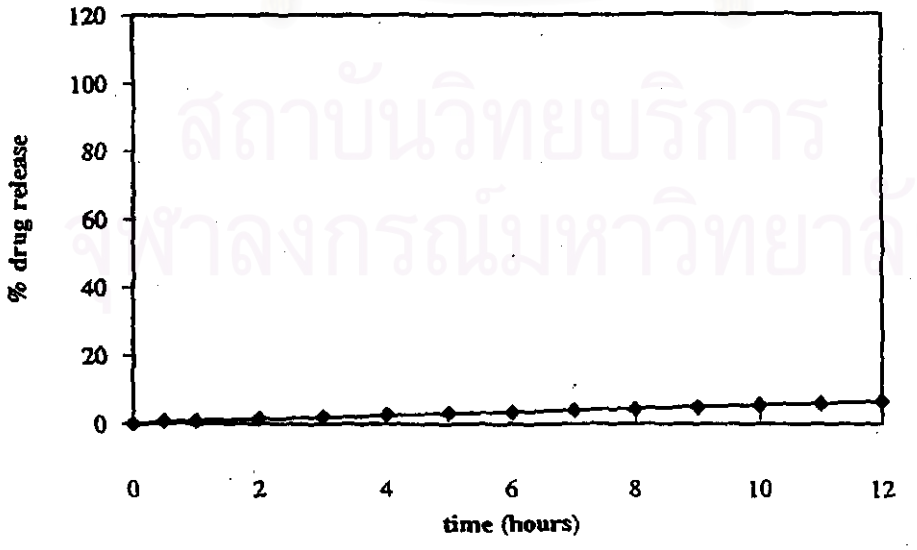



Figure 164 The zero-order plot of coated pellets Formulation 38 (15 % EURS20:EC80) in phosphate buffer pH 6.8.

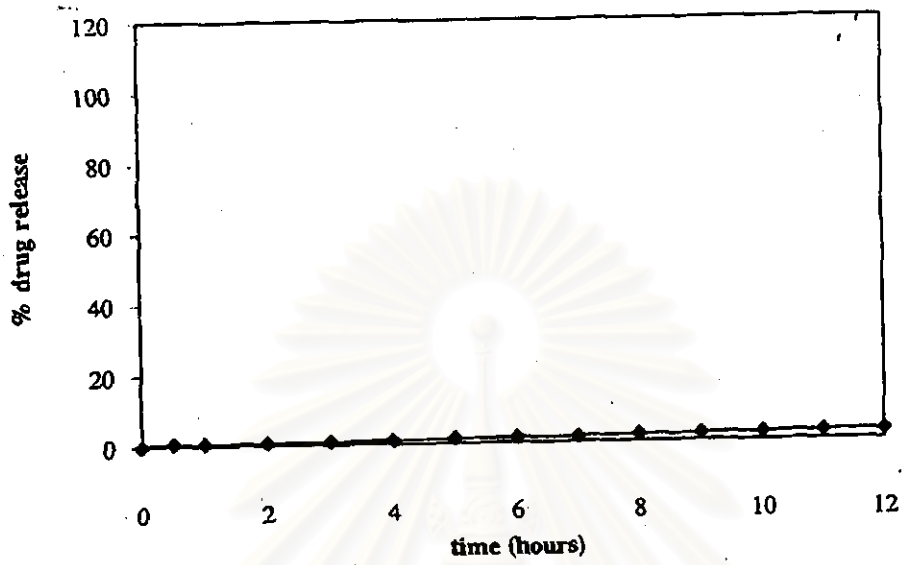



Figure 165 The zero-order plot of coated pellets Formulation 39 (20 % EURS20:EC80) in acid buffer pH 1.2.

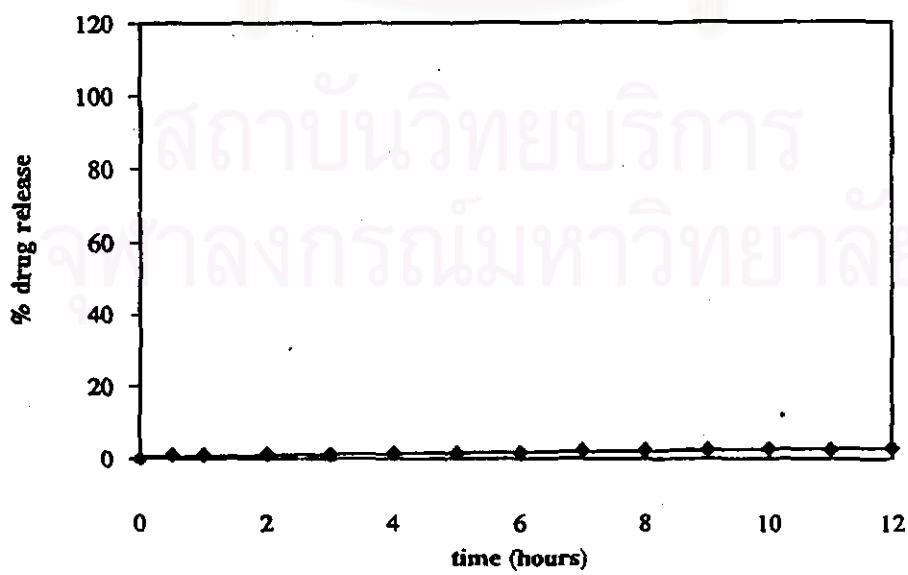



Figure 166 The zero-order plot of coated pellets Formulation 39 (20 % EURS20:EC80) in phosphate buffer pH 6.8.

5.8 Selection of Satisfactory Preparation for Study by pH change method.

In order to develop 24 hours sustained release pellets according to USP XXIII, the suitable formulations were selected to formulate 24 hours sustained release product. In this study, three formulations were used to combine and filled in the capsules. The criteria to select the formulation was as follows. The first formula must give high drug release in both acid buffer pH 1.2 and phosphate buffer pH 6.8, the second gave medium drug release in the both medium, and the last which gave long initial slow release phase in the both mediumbut exhibited higher release in later part of the release profile.

According to USP XXIII specification of drug release for extend release propranolol hydrochloride capsules, the amount of the drug dissolved at various time intervals could be calculate as following when total drug per capsule of 160 mg.

| Hours | Amount dissolve (%) | Amount dissolve(mg) | mean |
|---|---|---|---|
| 1.5 | not more than 30 % | not more than 48 mg | - |
| 4 | between 35 to 60 % | between 56 to 96 mg | 76 |
| 8 | between 55 to 80 % | between 88 to 128 mg | 108 |
| 14 | between 70 to 95 % | between 112 to 152 mg | 132 |
| 24 | between 81 to 110 % | between 129.6 to 176 mg | 152.8 |

The second step, calculated the suitable quantity (mg) from the release profile of selected formulation in both acid buffer pH 1.2 and phosphate buffer pH 6.8. The first formulation must contribute high permeability which give the rapid drug release in 1.5 hour, resulting not more than 48 mg. Thus, the first formulation selected was 10 % EURS100 coating (Formulation 25). After 1.5 hours, the medium according to USP XXIII must be change to pH 6.8, and then second formulation selected should give slow drug release in acid buffer pH 1.2 and give medium release rate in phosphate buffer pH 6.8, or should give 56-96 mg at $4^{th}$ hour and 88-128 mg at $8^{th}$ hour. Therefore, Formulation 29 (15 % EURS80:EC20) was selected. For drug release at

14th hour and after, the Formulation 27 (20 % EURS100) which had a very low permeability, slow drug release and give a long initial slow release period in both acid buffer pH 1.2 and phosphate buffer pH 6.8 was used. The finalcapsule formulation composed of the selection coated pellet formulation are presented in Table 16.

Table 16 The amount of coated pellets formulations selected to formulate sustained release propranolol hydrochloride capsules of 24-hours type.

| Formulation | Quantity (mg)/capsule |
|---|---|
| 25 | 80 |
| 27 | 200 |
| 29 | 180 |

The release of the developed formulation as shown in Table 16 was tested by pH change method. The release profile is presented in Figure 167 (Table 38, Appendix D).

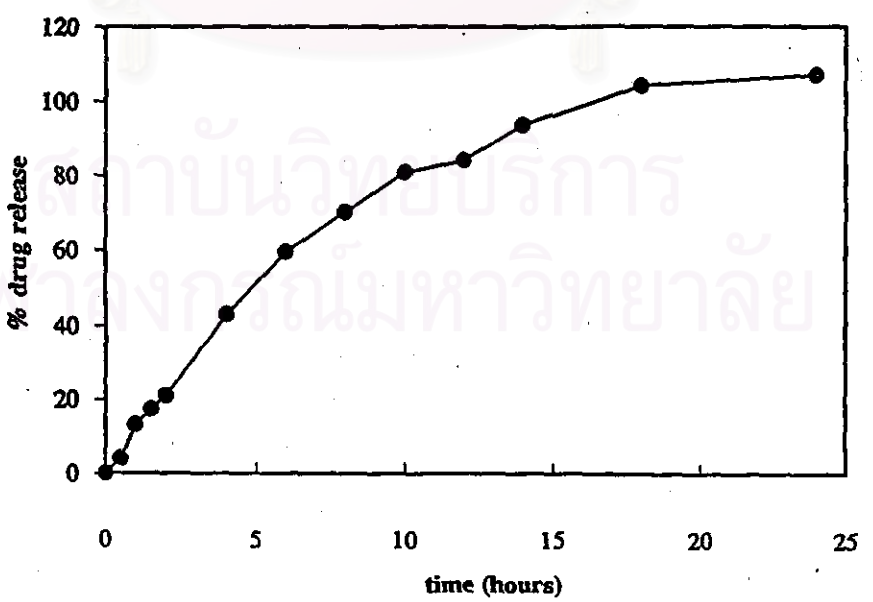



Figure 167 Release profile of developed sustained release propranolol hydrochloride capsules in pH change method.

Figure 167 show that the release profile followed USP XXIII specification. The kinetic of drug release were plotted as first order plot as presented in Figure 168 (Table 38, Appendix D) and Higuchi plot as presented in Figure 169 (Table 38, Appendix D).

The value of $r^2$ from first-order plot and Higuchi plot were 0.975 and 0.974, respectively. The release pattern of this developed product was not clearly differentiated between these two types of plot.

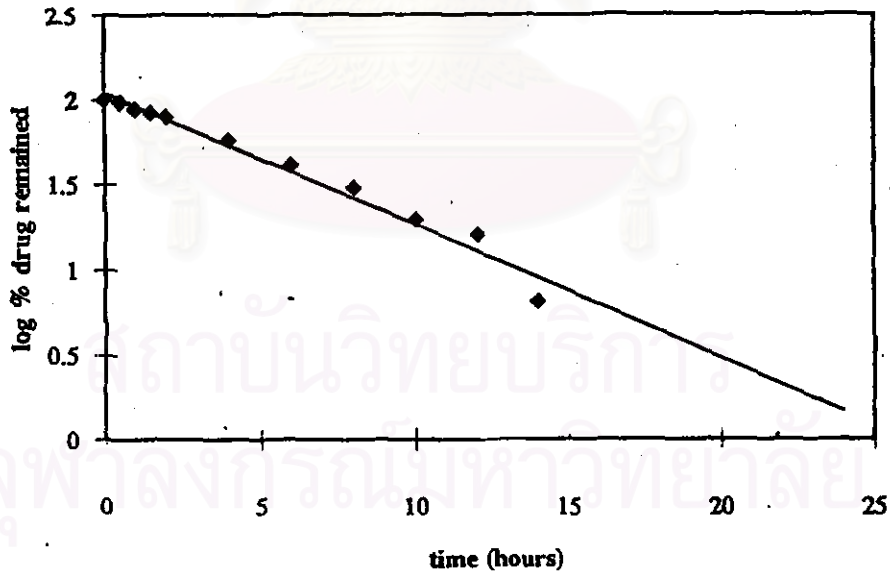



Figure 168 The first-order plot of sustained release propranolol hydrochloride capsules in pH-change method.

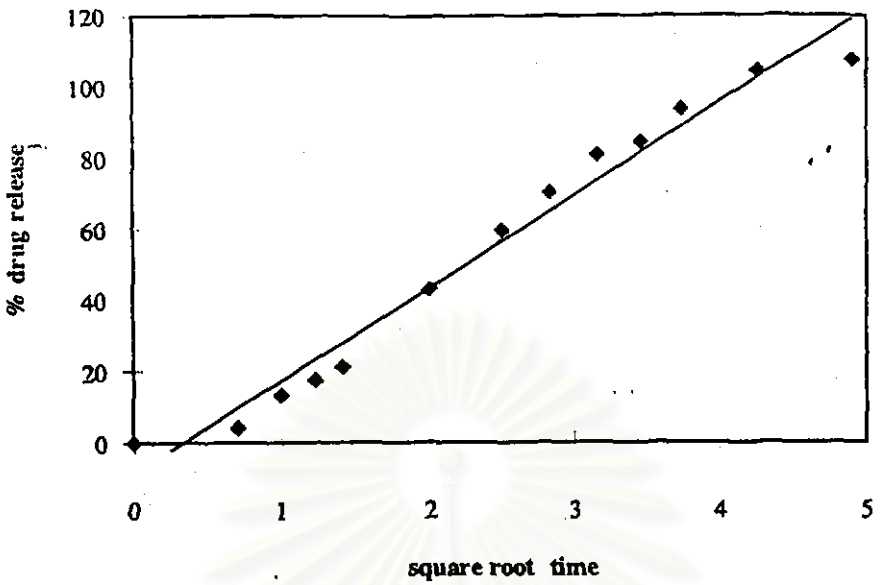



Figure 169 The Higuchi plot of sustained release propranolol hydrochloride capsules in pH-change method.

The dissolution test of the develope product in acid buffer pH 1.2 and phosphate buffer pH 6.8 were also investigated. The graph revealed that the both medium gave similar release characteristic although in acid buffer pH 1.2 gave slightly higher release of the drug because Formulation 29 composed of 20 % ethylcellulose which was not stable in acid medium. The release profile is presented in Figure 170 (Table 37, Appendix D). This indicated that the pH medium did not have much effect on release rate of the drug.

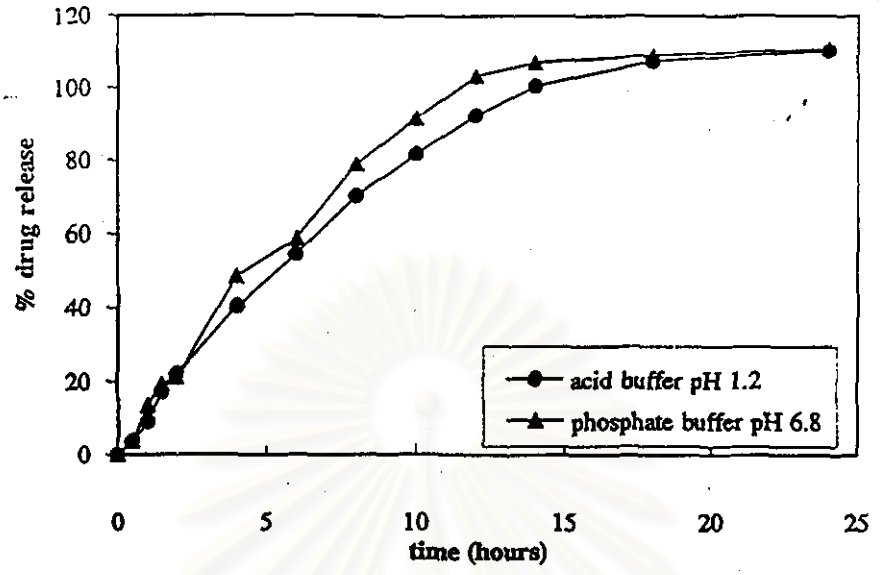
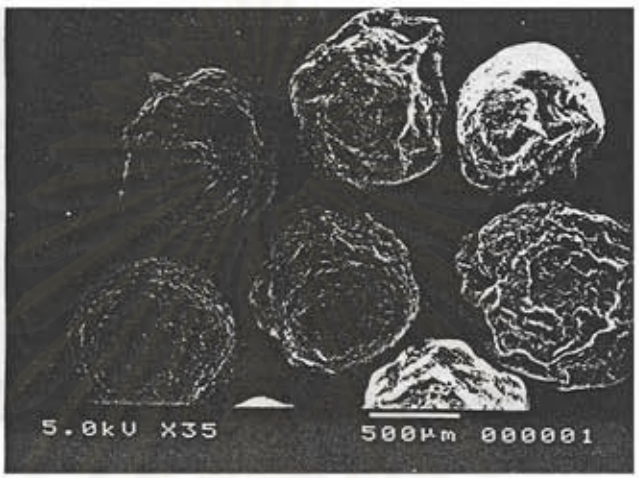
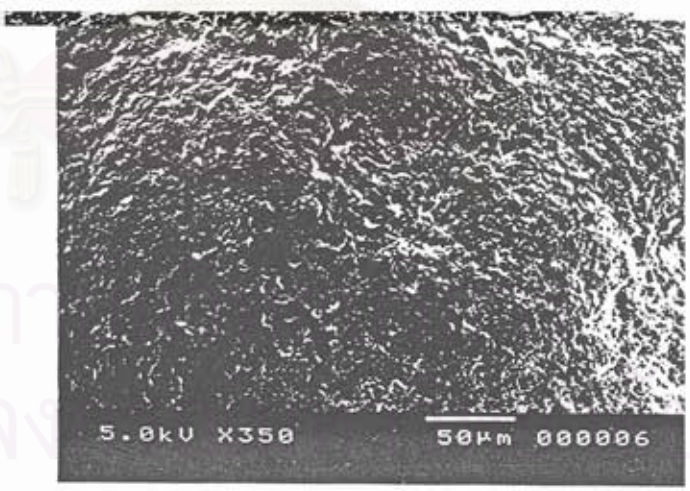



**Figure 170** Release profile of the sustained release propranolol hydrochloride capsules in acid buffer pH 1.2 and phosphate buffer pH 6.8.

The morphology of the pellets after release test in different pH, in acid buffer pH 1.2, and in phosphate buffer pH 6.8, were observed using scanning electron microscopy (Figure 171-173).

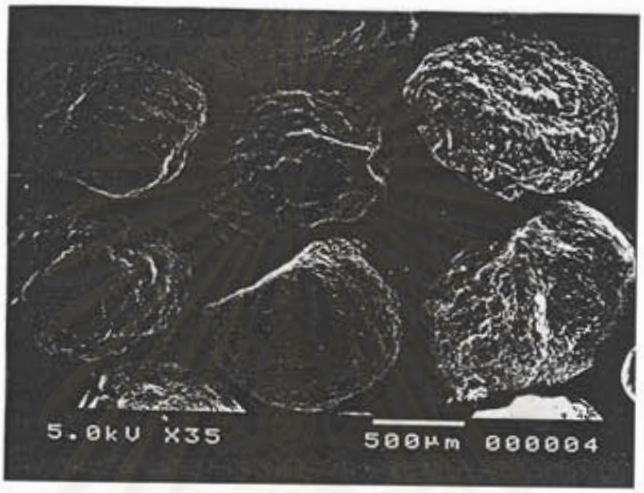



A

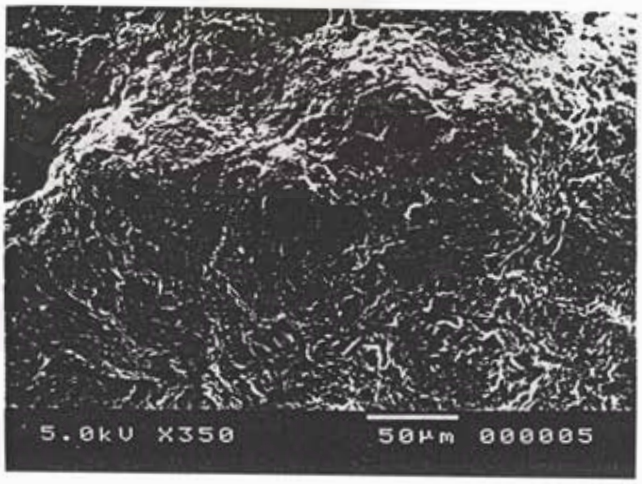



B

Figure 171 Photomicrographs of the sustained release propranolol hydrochloride capsules after dissolution test in pH change method.
(Key : A × 35 magnification , B × 350 magnification )

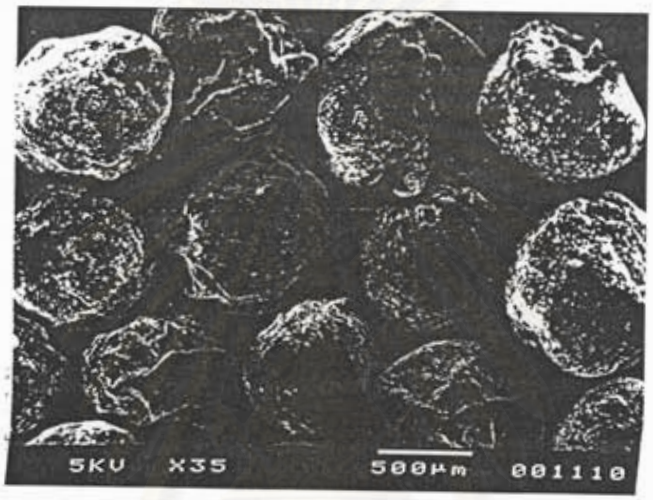



A

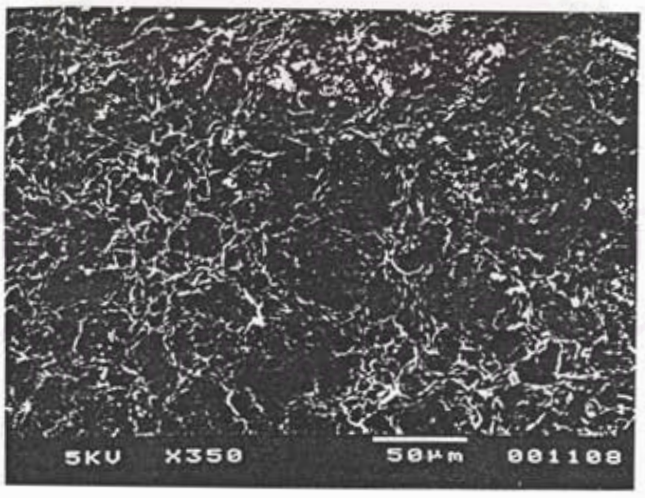



B

Figure 172 Photomicrographs of the sustained release propranolol hydrochloride capsules after dissolution test in acid buffer pH 1.2.
(Key : A × 35 magnification , B × 350 magnification )




A




B

Figure 173 Photomicrographs of the sustained release propranolol hydrochloride capsules after dissolution test in phosphate buffer pH 6.8.
(Key : A × 35 magnification , B × 350 magnification )

Commercial sustained release propranolol hydrochloride capsules, Inderal®LA160 were investigated for its release characteristics. The dissolution data is shown in Table 37 (Appendix D) and release profile is shown in Figure 174.

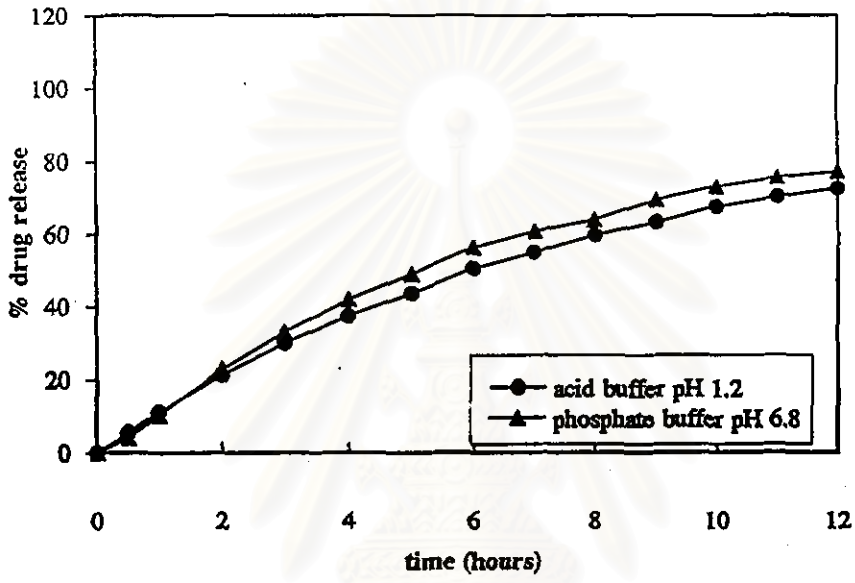



**Figure 174 Release profile of Inderal®LA160 in acid buffer pH 1.2 and phosphate buffer pH 6.8.**

The release profile of Inderal®LA160 in acid buffer pH 1.2 and phosphate buffer pH 6.8 were not much different. Slow drug release were observed at 0.5-1.5 hour, then the release was getting higher, and finally constant. It could be illustrated that core pellets were coated with the pH-independent polymer.

Figure 175 represent the release characteristic of Inderal®LA160 in pH-change method (Table 38, Appendix D).

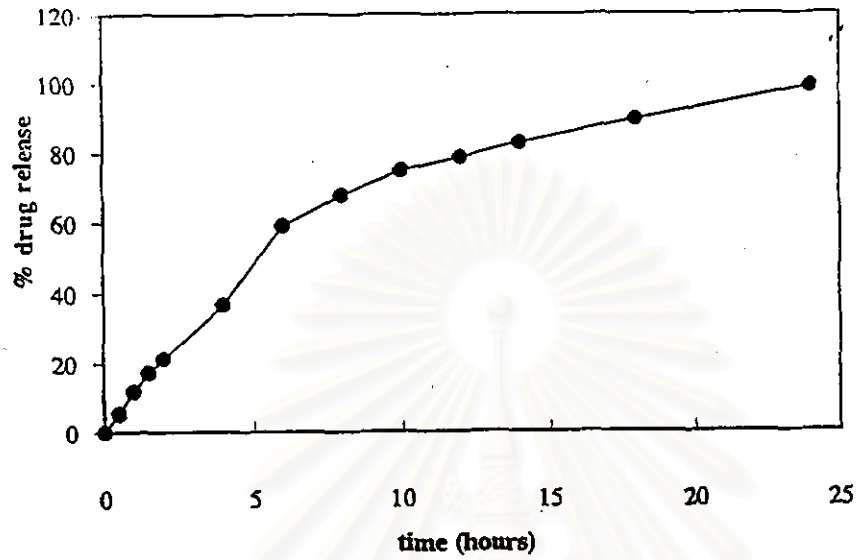



Figure 175 Release profile of Inderal®LA160 in pH change method.

Figure 175 represents that the release profile was followed the USP specification. The kinetic of drug release were plotted as first-order plot as presented in Figure 176 (Table 38, Appendix D) and Higuchi Plot as presented in Figure 177 (Table 38, Appendix D).

The value of $r^2$ from first-order plot and Higuchi plot were 0.944 and 0.969, respectively. The Higuchi plot gave higher value, thus it was likely to follow Higuchi kinetics.

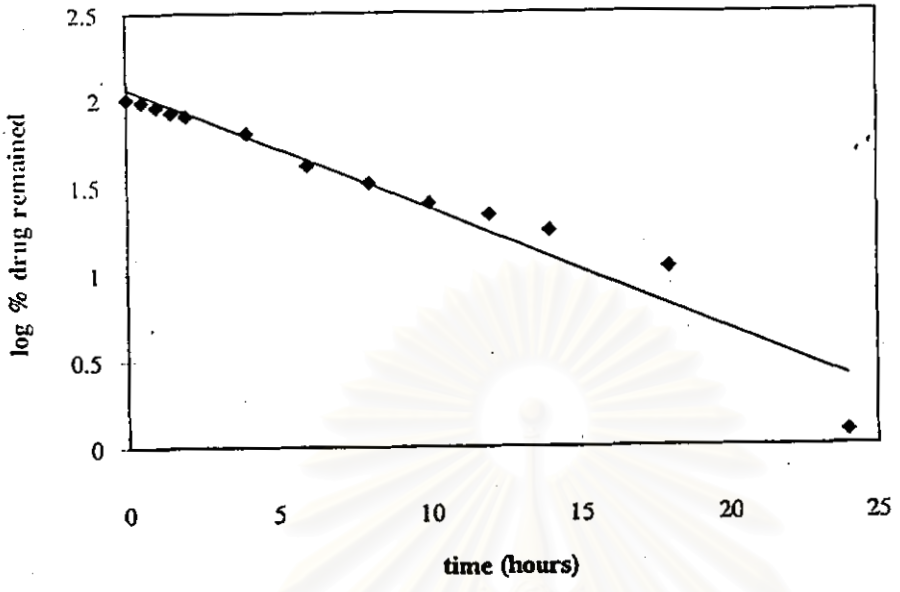



Figure 176 The first-order plot of Inderal®LA160 in pH-change method.

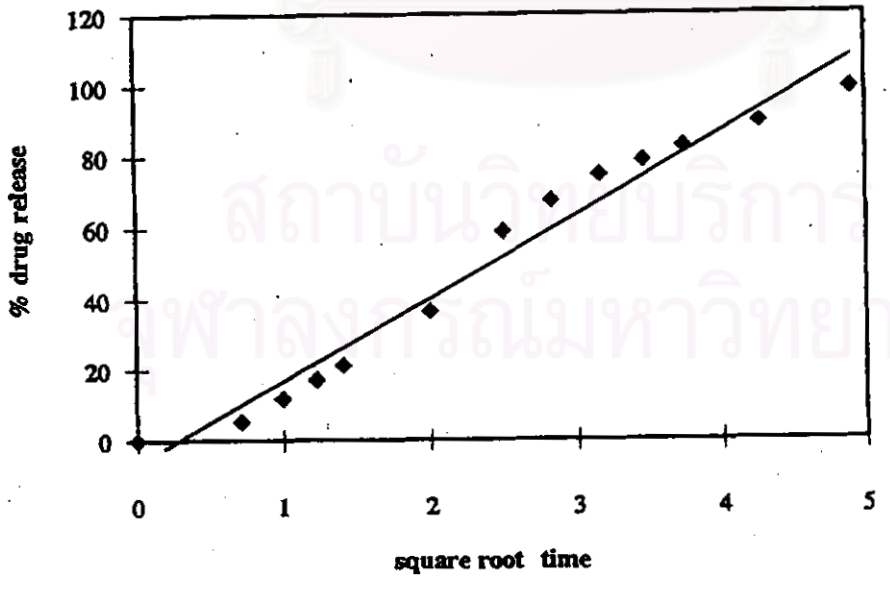



Figure 177 The Higuchi plot of Inderal®LA160 in pH-change method.

As shown in Figure 178, the developed formulation gave similar release characteristic with Inderal®LA160, and followed USP XXIII specification as presented in Table 17 and Figure 178.

Table 17 Percent release of developed capsule formulation and Inderal®LA160 in pH change method compared with USP XXIII specification.

| Time (hours) | USP specification | developed formulation | Inderal®LA160 |
|---|---|---|---|
| 1.5 | not more than 30 % | 17.45 % | 17.10 % |
| 4 | between 35 % and 60 % | 43.01 % | 36.66 % |
| 8 | between 55 % and 80 % | 70.12 % | 67.54 % |
| 14 | between 70 % and 95 % | 93.61 % | 82.63 % |
| 24 | between 81 % and 110 % | 107.13 % | 98.79 % |

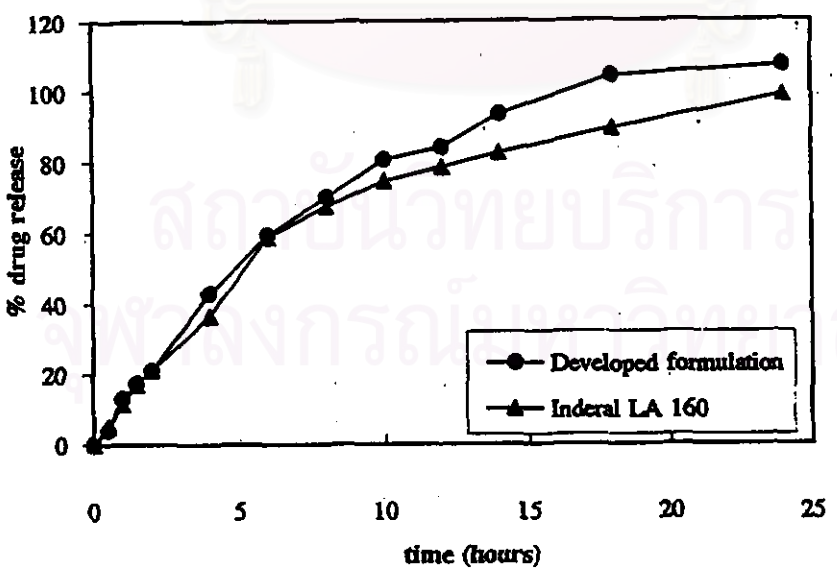
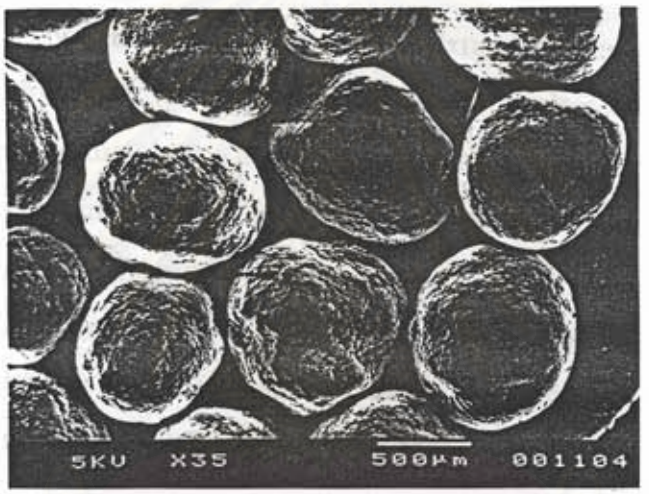
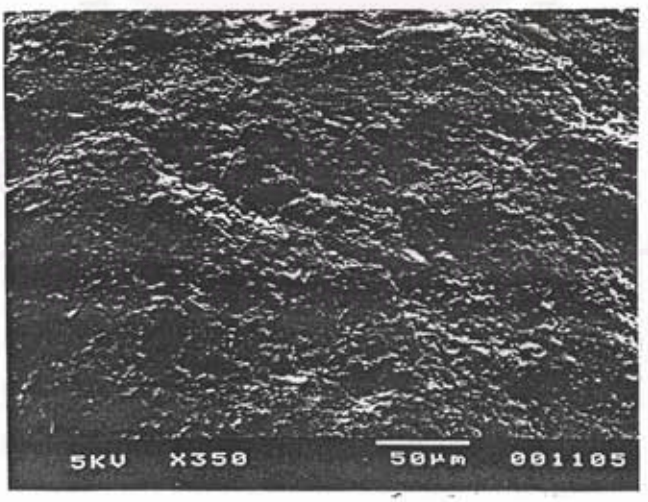



Figure 178 Comparison of release profile of Inderal®LA160 with developed sustained release propranolol hydrochloride capsules in pH change method.

After the dissolution test by pH-change method, the morphology from scanning electron microscope (SEM) of Inderal®LA160 is shown in Figure 179. Although the Inderal®LA160 compositions was not known, the shrunk residue observed from SEM were similar to the formula developed in this experiment. This evidence was a significant reveal that this work was successful in term of drug release when compared with the successful product Inderal®LA160.




A




B

Figure 179 Photomicrographs of Inderal®LA160 in pH change method.
(Key : A × 35 magnification , B × 350 magnification )