Chapter IV

Discussion and Conclusion

1. The Optimum Condition of Fluidized Bed Coater

In this study, one objective was to prepare sustained release theophylline tablets from coated granule. Coating equipment selected for this study was fluidized bed. Among local pharmaceutical manufactures, fluidized bed is well known for drying and granulation. Recently it has received greater attention on its coating applicability.

Fluidized bed coater using different coating method: top spray and bottom spray were studies. Scanning electron microscopy appeared to be a very effective tool for evaluating film coating that have been applied by different coating processes.

The imperfection of coating surface in top spray method could be attributed to the manner in which the liquid is applied. Althrough the spray nozzle was positioned so that it was immersed in fluidized granules,the fluidized pattern was disorganized. As a result, droplets travel random distance before impinging on the substrate. The capacity of droplet to spread to form a continuous film

depends on it viscosity, which changed as the solid content of droplet increases with evaporation. Because in this method the coating was sprayed against the heat air stream. The evaporation of the solvent(which has a low heat of vaporization) was rapid. As a result, the surface of the coating was rough.

Bottom spray or Wurster method was selected to prepare theophylline coated granules because coating by bottom spray were glossy and uniform in appearance when viewed under electron microscopy. The result would be due to the conditions used in the design of the Wurster coater which organizes the granules to be close to the spray nozzle, and arrangement that prevents any appreciable change in the ratio of solid to liquids in the coating droplet. Furthermore, this technique allows each layer of coating to dry more completely before granules were received further coating.

2. The Study of Uncoated Theophylline Granules

The obtained result from release profile of uncoated granule in 0.1N Hcl and phosphate buffer pH 6.8 were similary. Microcrystalline cellulose or Avicel PH101® in granules markedly decrease the amount of release of theophylline. The result can be explained by swelling properties of Avicel PH101®. There may be some gel formation during dissolution test and the gel formed may

retard the releaseof theophylline from the granules.

The USP basket and paddle method for dissolution testing are routinely utilized by scientists to evaluate the release perfomance of conventional and controlled release dosage forms. The differential in amount of drug release from those two methods were found from many studies (Singla and Mediratta,1988; Prasad, Shah, Hunt, Purich, Knight and Cabana,1983; Shenouda, Adams, Alcon and Zoglio, 1986). In this study, uncoated granules containing various fillers were selected to study by those two method in 0.1N Hcl. The basket method gave higher release profiles than the paddle method. Difference in dissolution in these two apparatus used migh be due to full exposure to the medium solution of the total surface area of the granules when the basket was used.

3. The Study of Coated Theophylline Granules

The sustained portions of the sustained release dosage form in this study were prepared by coating the core granules containing solid drug with a water insoluble polymeric material. In this system the water insoluble polymeric material therefore encases the core of drug as illustrated in Figure 75. Drug will partition into the membrane and exchange with the fluid surounding the granules. Additional drug will enter the polymer, diffuse to the periphery, and exchange with the surounding media.

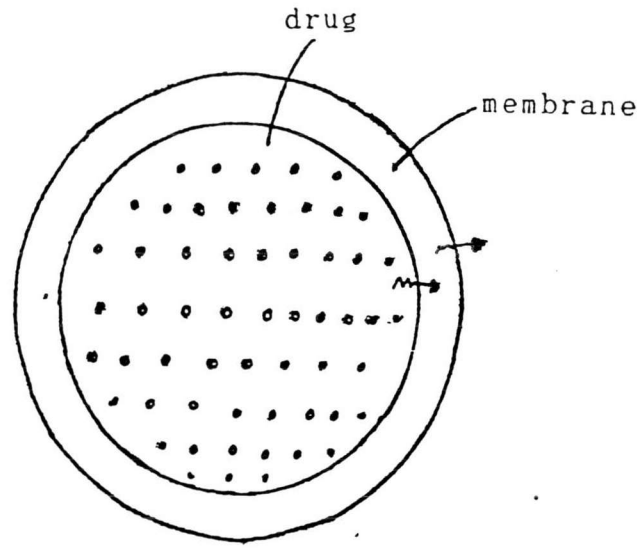


Figure 75 Diffusion Control of Drug Release through a Water Insoluble Polymer (Flynn, Yalkousky and Roseman, 1974)

3.1. Influence of Coating Level on the Drug Release Profiles

The results from scanning electron microscopy (SEM) showed that relatively thicker of film layer was obtained by increasing percent of the film coated. On the other hand, increasing amount of coating solution produced relatively thicker layer of the film coated.

The release profiles from coated granules were found to be dependent on the coating level or amount of coating solutions which were applied to the core granules. Amount of drug release decreases as coating level increases.

The release of theophylline from coated granules could be adjusted by varying the amount of ethylcellulose coating solution

3.2. Influence of Filler Excipients on the Dissolution Profiles of Coated Granules

Colued G. Cauron and James W. McGinty reported the influence of filler excipient on the release properties of theophylline from matrix tablets. But filler excipients affecting theophylline dissolution from coated granule have not been reported.

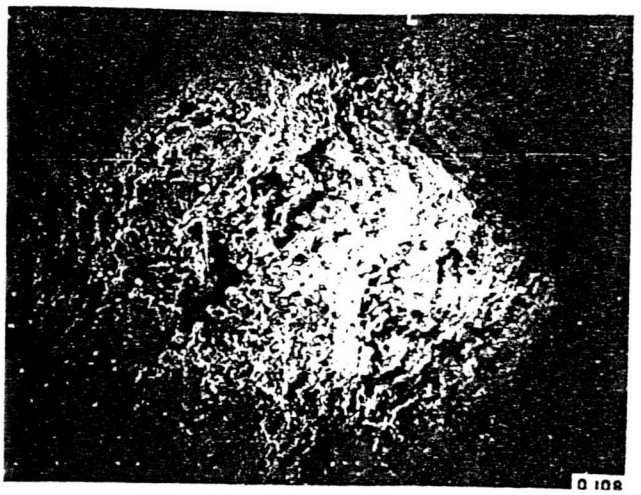
In this study, theophylline coated granules using various diluents were compared for their disolution profiles. Release profiles were found to be highest from granules containing Avicel PH101®. Release profiles of drug from granules containing corn starch, lactose and Emcompress® were second third and fourth, respectively.

The release of theophylline from granules containing microcrystaline cellulose or Avicel PH101® were fairly the highest. The explanation could be that, Avicel PH101® was swelled to rupture the coating film then the dissolution medium could penetrate into the cores faster than the coated granule containing the other fillers. The scanning electron micrographs of various fillers coated with ethylcellulose, after the disslution test were

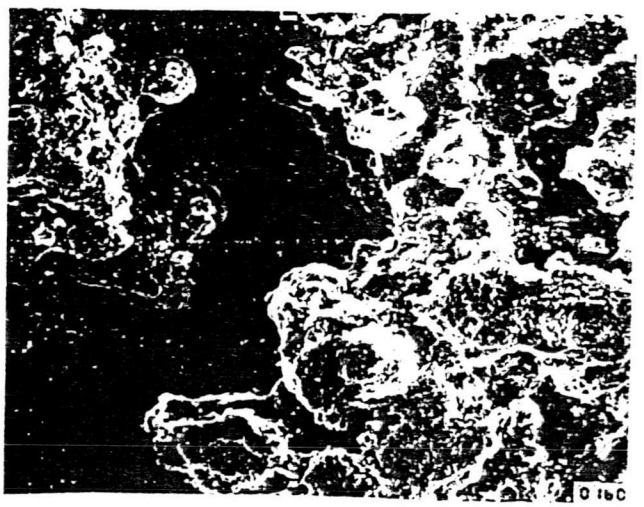
complete, showed there were more rupture on the film coated granules containing Avicel PH101® than other fillers (Figure 76,77,78)

The coat of corn starch granules ruptured during dissolution test similaly to Avicel PH101®. However the ruptures were less marked. Lower degree of broaken film was observed because of swelling of corn starch was not as powerful as Avicel PH101®. The scaning electron micrographs of coated granules containing corn starch as filler after 12 hours dissolution were shown in Figure 79-81. The rupture and pores can be seen but less than that of granules containing Avicel PH101®.

The coated granules containing lactose and Emcompress® gave lower dissolution profiles than Avicel PH101® and corn starch. From the scanning electron micropraph after dissolution of granules as shown in Figure 82-87 there were no rupture of the film coated. So the dissolution medium penetrated into the core at slower rate than the granules containing Avicel PH101® and corn starch. The release profile of coated granules containing lactose seemed higher than Emcompress® because of higher water soluble properties. Emcompress® or Dibasic calcium phosphate is a water insoluble filler. The scaning electron micrographs of coated granules containing Emcompress® as filler after 12 hours dissolution were shown in Figure 82-84.



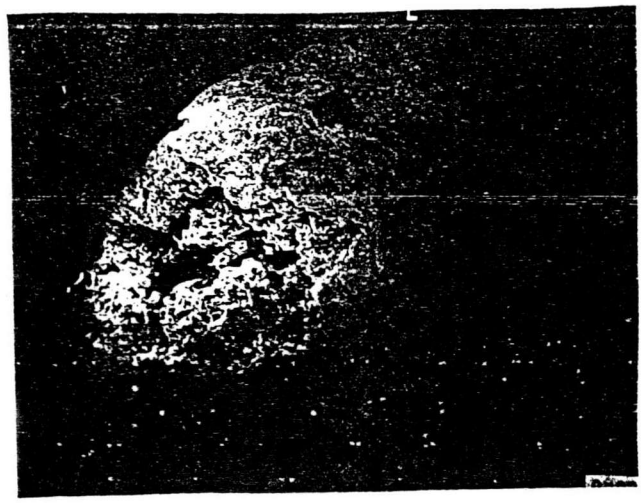
A



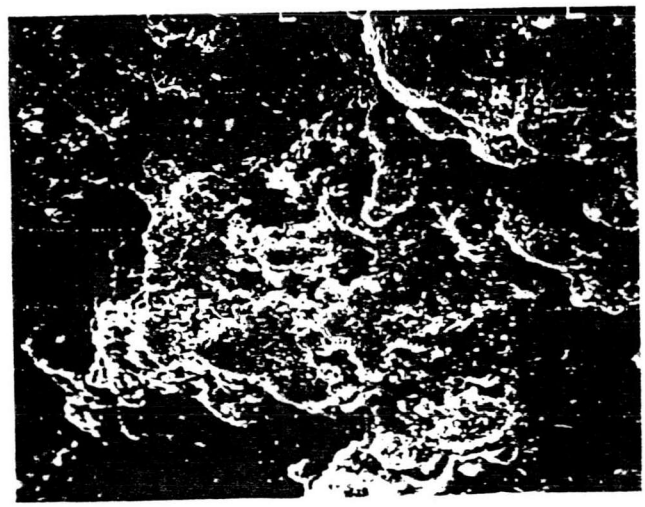
B

Figure 76 The photomicrographs of 10% coated granules containing Avicel PH101® as filler after 12 hours intervals.

(A: magnification 75x, B: magnification 500x)



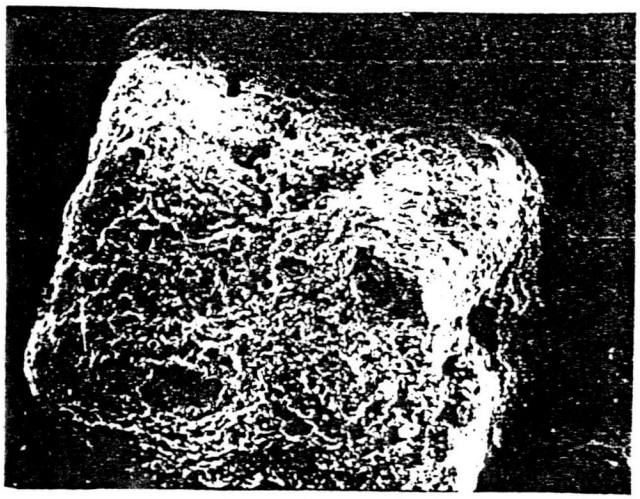
A



B

Figure 77 The photomicrographs of 15% coated granules containing Avicel PH101® as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



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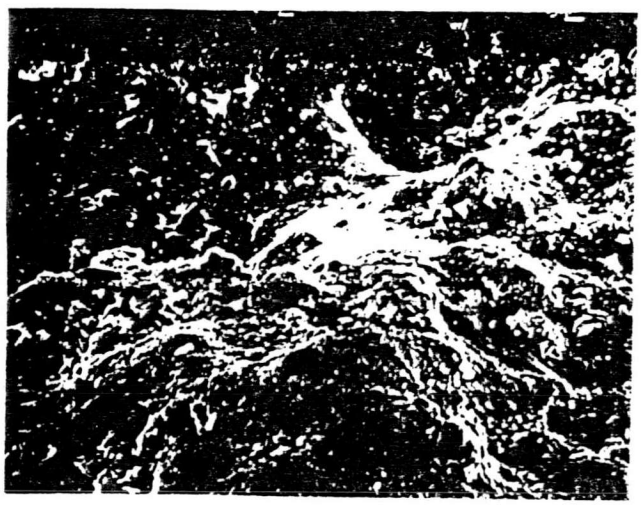
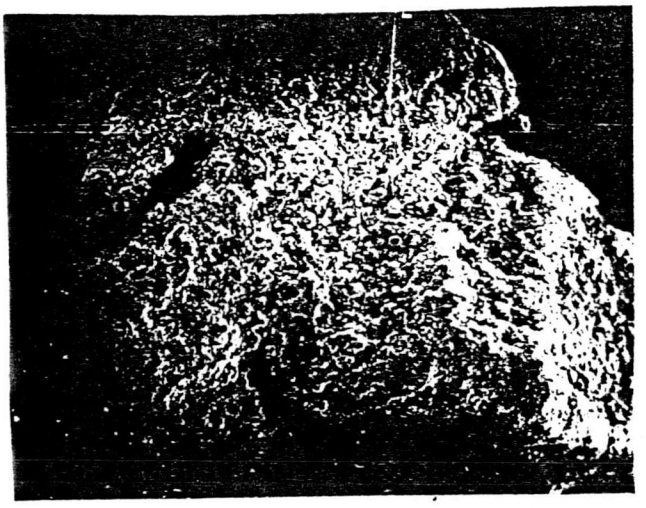


B

Figure 78 The photomicrographs of 20% coated granules containing Avicel PH101® as filler after 12 hours intervals

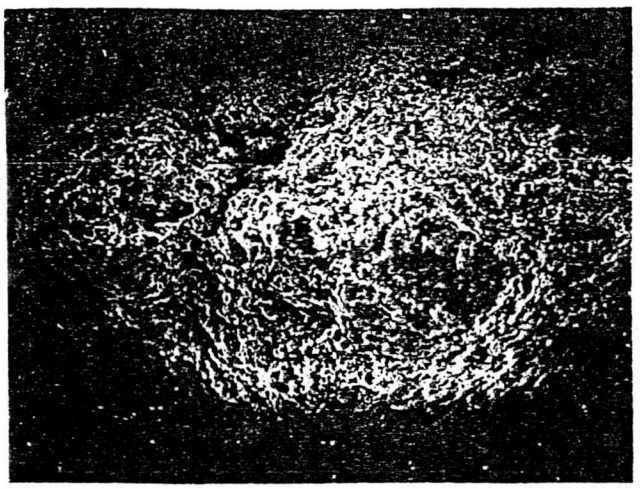
(A: magnification 75x, B: magnification 500x)



A

B

Figure 79 The photomicrographs of 10% coated granules containing corn starch as filler after 12 hours intervals
(A: magnification 75x, B: magnification 500x)



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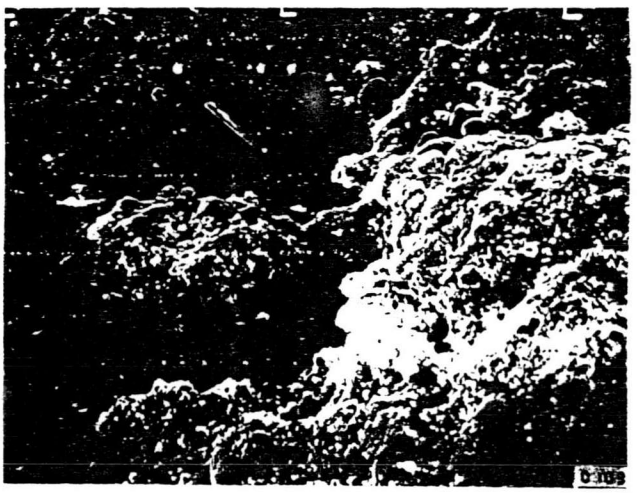
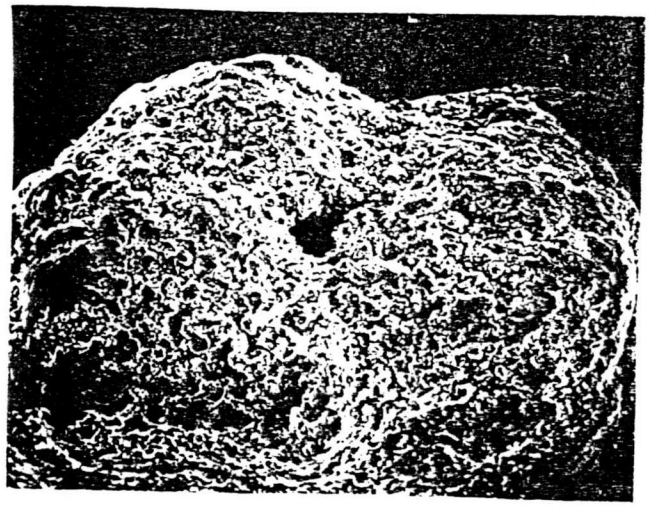


B

Figure 80 The photomicrographs of 15% coated granules containing corn starch as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



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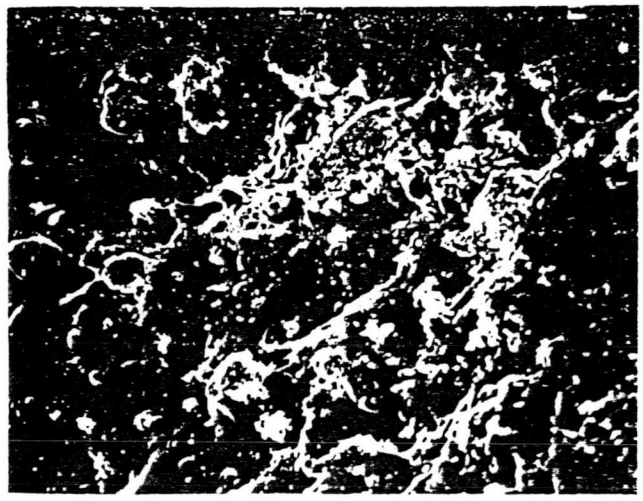
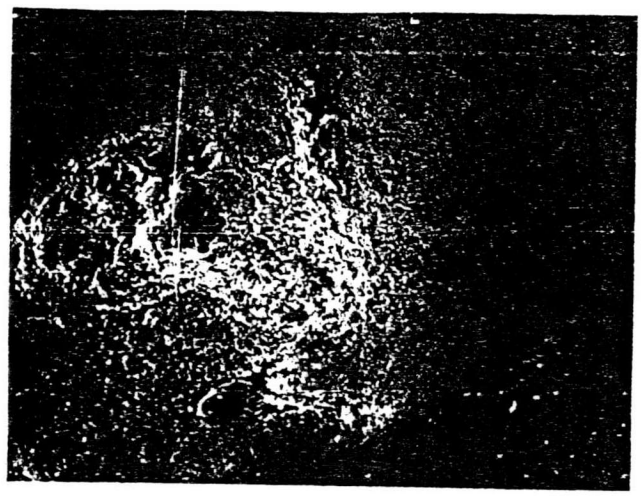


B

Figure 81 The photomicrographs of 20% coated granules containing corn starch as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



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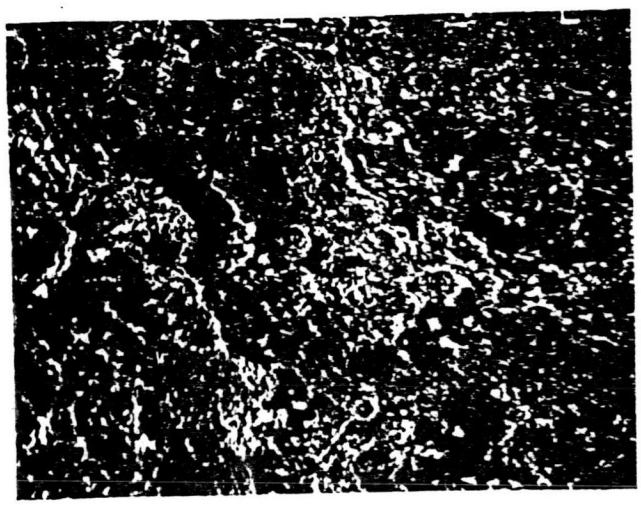
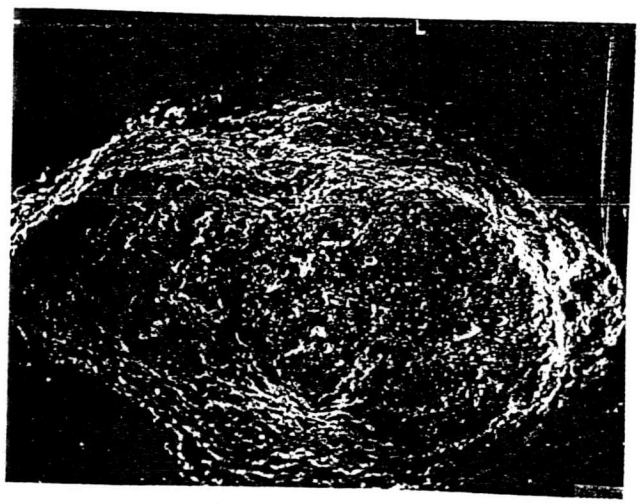


B

Figure 82 The photomicrographs of 10% coated granules containing Emcompress® as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)

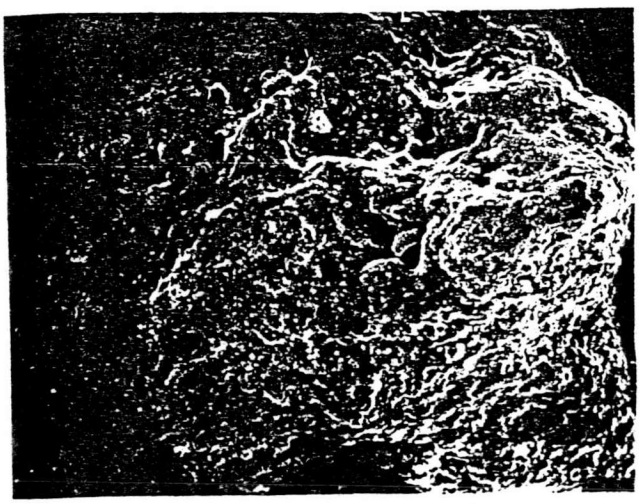


A

B

Figure 83 The photomicrographs of 15% coated granules containing Emcompress® as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)

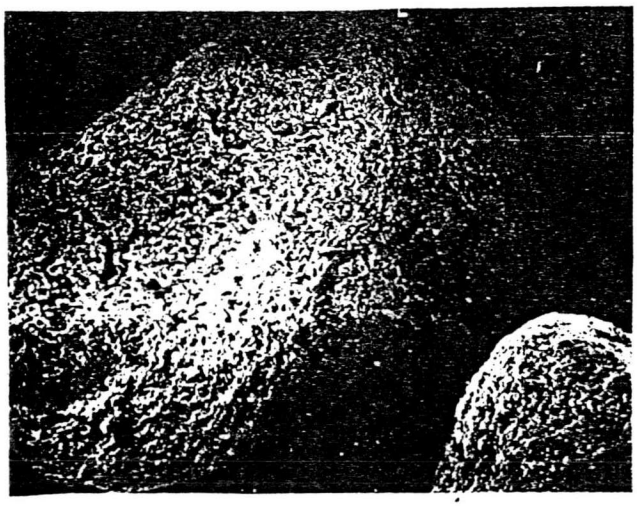


A

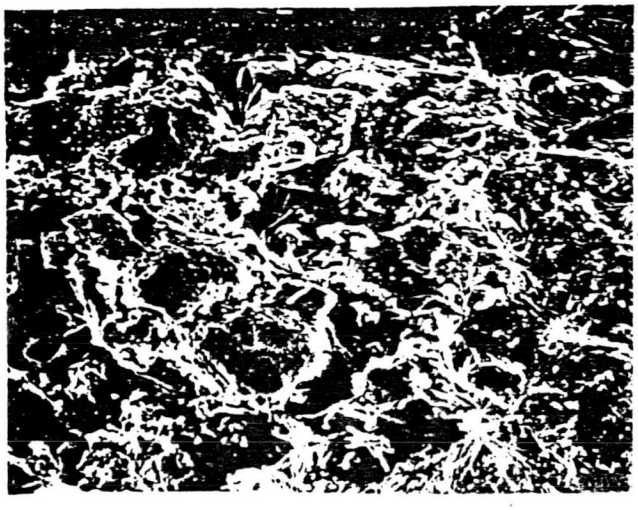
B

Figure 84 The photomicrographs of 20% coated granules containing Emcompress® as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



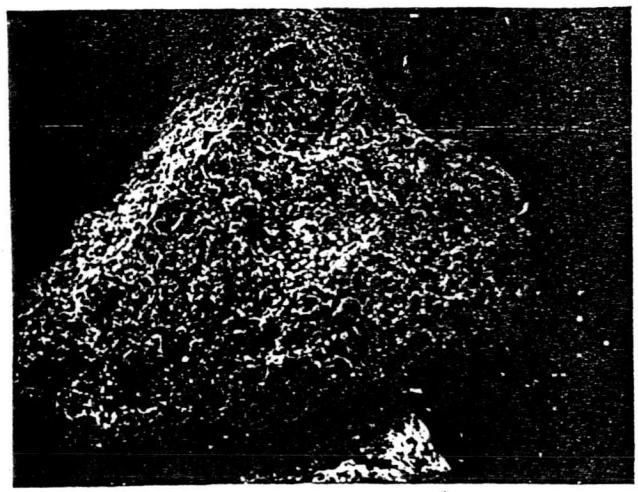
A



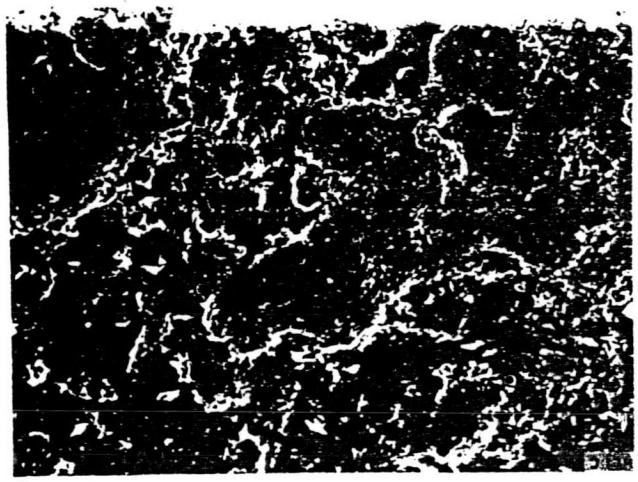
B

Figure 85 The photomicrographs of 10% coated granules containing lactose as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



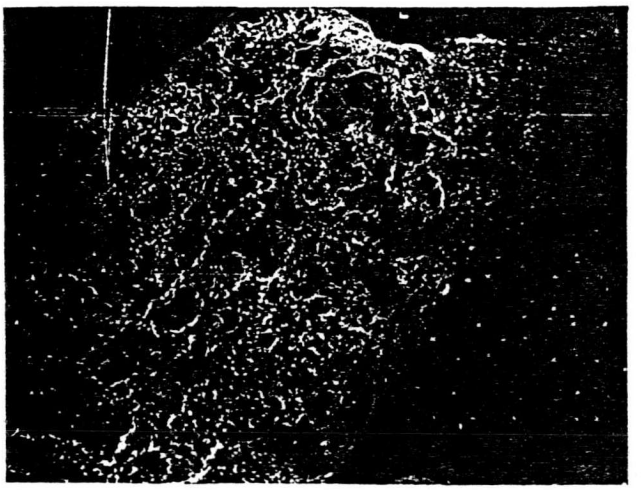
A



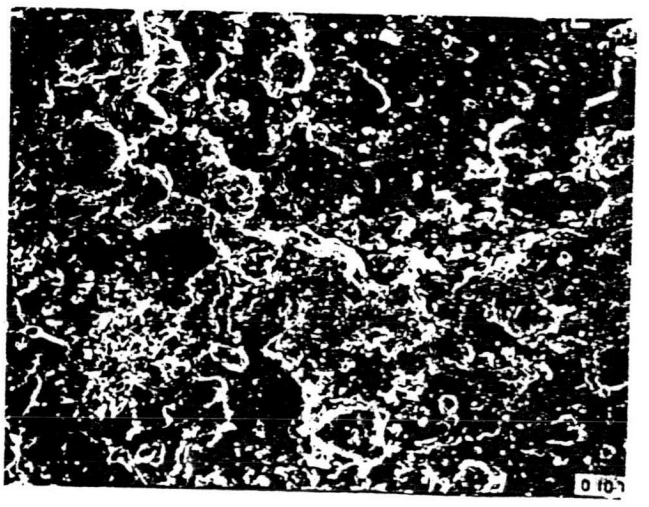
B

Figure 86 The photomicrographs of 15% coated granules containing lactose as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)



A



B

Figure 87 The photomicrographs of 20% coated granules containing lactose as filler after 12 hours intervals

(A: magnification 75x, B: magnification 500x)

4. Study of Theophylline Tablets Prepared from Coated Granules

4.1. Influence of Coating Level of Granules on the Dissolution Profiles of Tablets

The release of theophylline from tablet could be decreased by increasing the amount of ethylcellulose coated on granules in tablet. This would be due to the presence of the ethylcellulose which retard drug dissolution because of its water-insoluble characterestics. The diffusion of the drug through a thicker coating might be inhibited. The dissolution medium penetrated the film more slowly due to less osmotic effect, leading to less drug release. So varying amount of ethylcellulose coating on core granules could directly affect the drug release.

4.2. Influence of Various Fillers of Coated Granules on Dissolution Profiles of Tablets

Dissolution of drug from the tablet was found to be dependent upon the type of filler excipients used. Using microcrystalline cellulose (Avicel PH101®) gave the highest release profile. Corn starch, lactose and Emcompress® were the second, third and fourth, respectively. This result was in agreement with the study of influence of filler excipient on dissolution profiles of coated granule.

4.3. Influence of Disintegrant on the Dissolution of Tablets

Adding Explotab® in tablet formulation gave highter release profile than without explotab®. This might be due to explotab® gave quickly disintergrated tablet which the coated granules could be released to expose to the dissolution medium faster than no explotab®. The obtained data from dissolution study found that there were higher standard deviation from tablet without Explotab®. This would be explained by non homogeneous disintegration of tablets in dissolution medium. The non homogeneous disintegration could affect the exposure of coated granules in tablets to the medium into which the drug was released.

4.4. Influence of Compressional Force on the Dissolution of Tablets

In this studied we found that the dissolution profiles of coated granules were affected by compressional force. However this effect on tablet prepared from each coating level of granules seemed to inconsistent. These would be due to the complicated effect of many variables such as the compaction of granule, the breakage of the wall of coated granules during compressing and the nature of various fillers in granules.

4.5. Dissolution of Tablets Containing Combined Different Coated Granules

The release of drug from 10% coated granules containing Avicel PH101® as filler was highest. The lower release profile was required so 20% coated granules were mixed with 10% coated granules to reduce the release rate.

As was expected, Combined coated granules of 10% and 20% gave lower release profiles. Tablets prepared from combined different coated granules were interesting. The combinations of coated granules containing different fillers might be studied.

4.6. Compared Dissolution profile of Selected Formulation with Commercial Product

The formulation selected to compare with commercial products was tablet containing 15 percent ethylcellulose coated granules with lactose as diluent filler (formulation 15%L5). This formulation gave satisfactory profile such as, less standard deviation, high drug release at 12 hrs and mechanism of drug release closed to zero order.

Theodur® is a product that consisted of two different regions of drug release, a matrix in which some drug was dispersed, and a pellet formulation which was

embedded in the matrix. It is certainly the most succesful of all the sustained release theophylline products.

Nuelin®,the release of Neulin® was relatively fast at the intial stage, followed by a stage with a decrease rate.It consisted of a waxy nondisintegrating bed, the surface of which is coated with cellulose acetate.

Coated granule formulation gave smooth convex curve with the highest amount of drug release at 12 hours

4.7. Reproducibility of Coated Granules by Fluidized Bed Coater

The dissolution profiles of granules coated and tablets found to be reproducible indicating the coating membrane was uniform and completely covered the granule cores even at this level of coating. Evidently, the fluidized bed with Wurster column used for these studies was quite efficient in applying the coating solution to the surface of granules to produce the satisfactory coating.

Conclusion

A sustained release theophylline formulation could be prepared by coating theophylline granules with an appropriate amount of ethylcellulose and the appropriate

types of filler excipient in granule via a Wurster column process.

The coating of ethylcellulose on theophylline granule containing various filler excipients, were shown to retard the release of the drug from the granules. This agree with the result from scanning electron microscopy (SEM) which showed that relatively thicker film layer was obtained by increasing percent of film coat.

In this study, There was a dramatic influence of filler excipients on the drug release characteristic from the coated granules or tablets. Microcystalline cellulose (Avicel PH101®) and corn starch were fillers which their properties could swell in water. The swelling properties could cause the rupture of the coated so the drug release were fairly high. Lactose was the water-soluble filler and thus dissolved in the medium and may, at the same time, increase liquid viscosity inside the core. This inturn would retard dissolution of theophylline within the granules. Dibasic calcium phosphate was the water-insoluble filler and as expected, prevents rapid dispersion of drug particles and subsequent dissolution.

The processing to prepare the tablet such as ingredients and compressional force also affected the release of drug from tablets. For ingredient, adding Explotab® which was a disintergrant, gave higher release

profiles than witout Explotab®.The result may be explained by fast disintegration could disperse granules in the medium more quickly but for compressional force it seemed to be complicated effect and unpredictable.