CHAPTER V

SCALE UP AND REPRODUCIBILITY IN PREPARATION OF COMPOSITE PARTICLES OF RICE STARCH AND MICROCRYSTALLINE CELLULOSE

Introduction

In order to investigate the reproducibility of the preparation of composite particles by this technique and prepared the larger amount of powders for further study concerning the application of this coprocessed excipient in the manufacturing of tablets of drug products which are presented in chapter VI, then the selected formulation and spray drying conditions which have been described in previous chapter were employed for scale up production at various quantity feeding suspension of 1, 2, 3, and 4 kg. Then the obtained products from different lot were tested for theirs physical properties of powder and tablets prepared to confirm that the process is reproducible. Therefore, the objective of the study that reported in this chapter is to examine the reproducibility of scale up production of selected formulation on the physical and tabletting properties. Moreover, the bulk of composite particles which combining from various lots was also investigated for the physical properties of powder and tabletting.

Materials and Methods

Materials

Rice starch	(Cho Heng Co., Ltd., Thailand)
Microcrystalline cellulose	(Vivapur®101, Lot No. 5610102917, J. Rettenmaier & Söhne, Germany)
Deionized water	

Methods

1. Formulation Scale Up

Rice starch (RS) and VJM at ratio 7 : 3 were weighed and mixed with deionized water to obtain the final concentration of 20 % w/w. Then the suspension was mixed thoroughly with the aid of homoginizer for 10 minutes to get homogeneous suspension. The suspension was subsequently spray dried. The conditions used were: inlet temperature of 130 °C, atomizing pressure of 1 bar and feed rate at about 30-32 g/min.

The suspension quantity of 1, 2, 3, and 4 kg were performed to study the formulation scale up.

1.1 Powder Evaluation

Spray dried powders were subjected to evaluation for LOD, morphology, flow property and particle size & particle size distribution. Equipments and conditions were the same as previously described.

1.2 Tablet Evaluation

Spray-dried powders were compressed for tabletting evaluation. The equipment and conditions were the same as mentioned earlier. The resultant tablets were evaluated for hardness, thickness, diameter, % friability and disintegration time.

2. The Reproducibility Study

The formulation of rice starch and VJM at ratio of 7 : 3 was used to study the

reproducibility of the preparation. The suspension quantity of 4 kg was repeatedly prepared for 4 lots. The procedure of the preparations and conditions of spray drying were the same as those presented in 1.

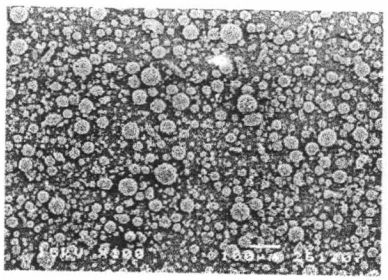
The resultant preparations were subjected to determinations for powder and tabletting properties. The procedures were the same as in 1.1 and 1.2.

Results and Discussion

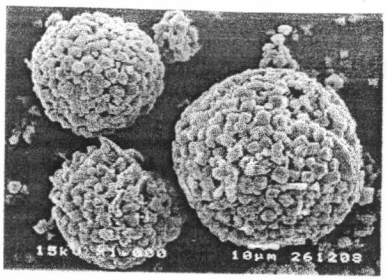
From experimental design study only F4 (see chapter IV) was selected for further investigation on formulation scale up and the reproducibility of the preparations.

1. Formulation Scale Up

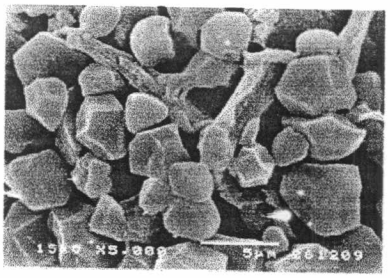
The suspension quantities of 1- 4 kg were prepared and spray dried. The Spray dried powders obtained were evaluated for the powder characteristics and tabletting properties. These scale up formulations are designated as F41 to F44. SEM photomicrographs of powder are shown in Figure 5-1. The resultant powder was in spherical form in all preparations and at higher magnification, the aggregated particles were composed of rice starch and cellulose whose parts of the surface were fused together. The particle size and size distribution of the scale up preparations are tabulated in Table 5-1. Particle sizes of the F41 are similar to that of F4. Mean particle sizes (D50) and D90 of all preparations are similar and has the value of 49.65 to 53.12 μm and 88.30 to 92.04 μm, respectively while D10 values decreased from 22.94 to 17. 78 μm indicated that more fine particles were attained. This led to the high span values in larger quantity of production. This is due to during the processing, some parts of atomization droplets stuck to the chamber wall of the spray dryer and some of them especially for small particles were dried when contact to the hot air, might be drop down in the collecting bottle. The higher quantity of preparation, the longer time of contact to the hot air and the more small particles would produce and blown into the collecting bottle resulting in higher small particles in the spray dried powder of large quantity. Powder physical properties of all preparations are exhibited in Table 5-2. Percent LOD of all preparations are similar and in the range of 5.59 to 6.12 %. When increasing the volume of the spray dried formulation resulted in an increasing of % Yield. This is because of the more contact to hot air of the stuck particles which was dried and blown into the collecting bottle. When the powder was subjected to powder characteristics test, the flow properties slightly decreased with an increasing of the quantity of the preparation due to more fine particles. However, flowability index values were resemble and in the range of



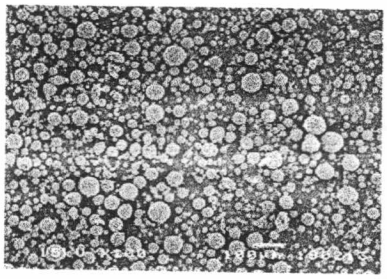
F4 X 100



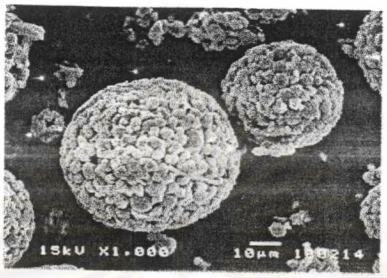
F4 X 1000



F4 X 5000



F41 X 100



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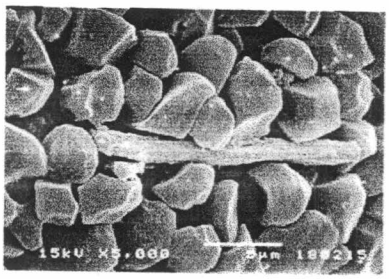
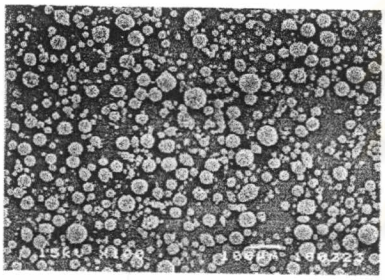
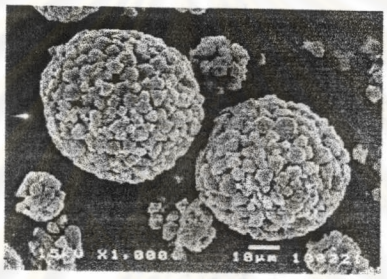


F41 X 5000



F42 X 100



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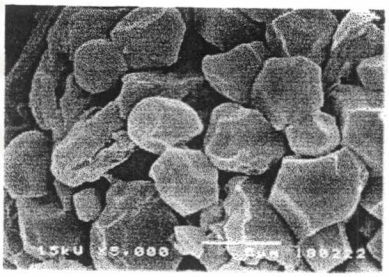

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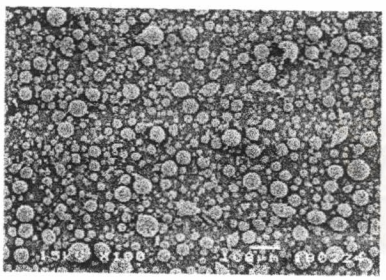
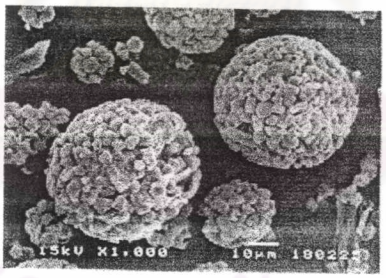


F43 X 100



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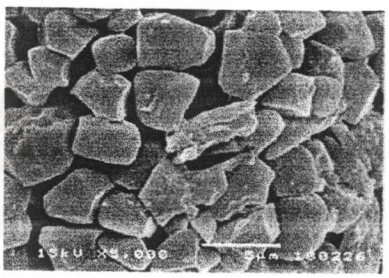
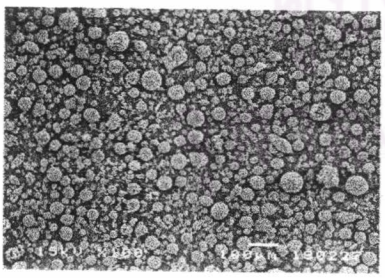
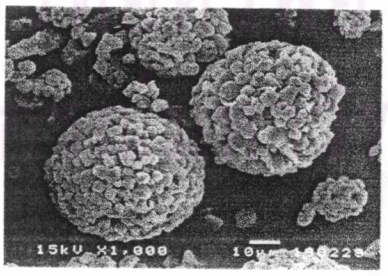


F43 X 5000



F44 X 100



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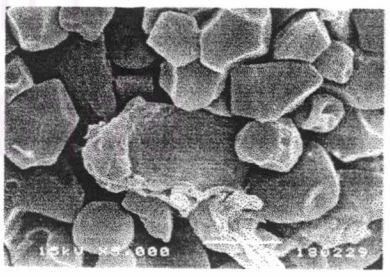


F44 X 5000

Figure 5-1 SEM photomicrographs of F4 and F41 to F44.

Table 5-1 Particle size distribution of scale up preparation.

Formula	D (v, 0.1) (μm) average (SD)	D (v, 0.5) (μm) average (SD)	D (v, 0.9) (μm) average (SD)	Span = (D90 - D10) / D50 average (SD)
F4	22.94 (0.14)	52.10 (0.08)	88.30 (0.65)	1.25 (0.01)
F41	21.72 (0.10)	53.12 (0.30)	88.92 (1.44)	1.26 (0.02)
F42	18.57 (0.36)	51.03 (0.22)	90.47 (1.12)	1.41 (0.02)
F43	19.45 (0.05)	51.43 (0.20)	92.04 (0.68)	1.41 (0.01)
F44	17.78 (0.20)	49.65 (0.28)	89.68 (0.88)	1.45 (0.02)

Table 5-2 Physical properties of powder of scale up preparations.

Formula	Yield (%)	LOD (%) average (SD)	Angle of Repose (degree) average (SD)	Angle of Spatula (degree) average (SD)	Bulk Density (g/ml) average (SD)	Packed Density (g/ml) average (SD)	Compressibility (%) average (SD)	Cohesion (%) average (SD)	Flowability Index average (SD)
F4	48.33	6.12 (0.23)	28.2 (1.50)	59.9 (2.94)	0.441 (0.01)	0.536 (0.00)	17.72 (1.24)	3.6 (0.00)	70.7 (2.08)
F41	47.04	6.00 (0.01)	31.9 (1.71)	54.7 (1.49)	0.439 (0.01)	0.543 (0.01)	19.29 (1.51)	4.4 (0.01)	70.3 (1.15)
F42	48.41	5.90 (0.18)	32.0 (0.55)	59.4 (1.87)	0.435 (0.01)	0.526 (0.01)	17.36 (1.28)	7.2 (0.01)	69.2 (1.04)
F43	55.76	6.01 (0.30)	31.8 (1.89)	58.1 (2.30)	0.433 (0.00)	0.526 (0.01)	17.73 (0.47)	6.3 (0.02)	70.3 (0.58)
F44	61.27	5.59 (0.12)	32.3 (0.26)	58.7 (1.97)	0.425 (0.01)	0.524 (0.00)	18.88 (1.31)	7.6 (0.01)	68.7 (0.76)

68.7 to 70.7. This indicated no change of the flowability when scale up the formulations. Physical properties of tablets were examined and shown in Table 5-3. The results of all preparations were resemble and gave the hardness, %friability, and disintegration in the range of 189.2 to 196.7 N, 0.36 to 0.40 %, and 2.44 to 2.71 minutes, respectively. From the results above, this preparation could be reproduced and gave consistent properties of the powder characteristics and tabletting properties.

2. Reproducibility Study

To obtain the large amount of powder for characterization of tabletting properties reported in next chapter (chapter VI), the preparation of F44 were performed several times to get the sufficient amount of powder. This preparation was sprayed for another 4 times to examine the reproducibility study and designated as F44-1 to F44-4. SEM photomicrographs are shown in Figure 5-2 and got the similar result. Physical properties of the powder and that of tablets are tabulated in Table 5-4. Percent Yield was slightly decrease and gave the value around 54.96 to 58.06%. Percent LOD and hardness of the tablets were similar in all preparations. From the above results, this meant that this formulation could be reproduced to get the consistent powder and tablets physical properties. Then the F44 were produced several times to obtain the spray dried powder of about 7 kg. The resultant powder was collected and mixed in the V-shape blender to obtain homogeneous powder. This preparation is assigned as RS/MCC. After mixing, RS/MCC powder was sampling for testing the physical properties and the results are exhibited in Table 5-5 to 5-7. Flow properties of bulk RS/MCC powder gave the higher value of angle of repose than each scale up preparations but the result of percent compressibility and flowability index were similar. When sampling powder at the top, middle, and bottom of the bulked powder, it was found that the particle size distribution, % LOD, and physical properties of tablets also gave the similar results.

Conclusion

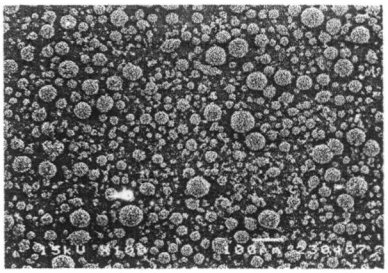
Composite particles of rice starch and MCC could be scale up and reproduced with the consistency in the powder and tabletting properties as in the lab-scale studies previously reported.

Table 5-3 Physical properties of tablets of scale up preparations using hydraulic press at compression force 2000 lb.

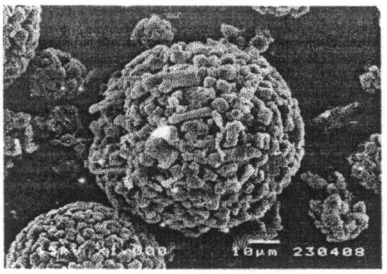
Formula	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)	Friability (%)	DT (min) average (SD)
F4	189.2 (15.89)	12.88 (0.06)	3.52 (0.09)	0.40	2.56 (0.26)
F41	191.2 (8.83)	12.91 (0.02)	3.38 (0.05)	0.40	2.71 (0.18)
F42	196.7 (14.91)	12.90 (0.03)	3.35 (0.05)	0.36	2.56 (0.58)
F43	191.2 (10.59)	12.91 (0.02)	3.37 (0.06)	0.39	2.44 (0.19)
F44	190.6 (10.30)	12.90 (0.03)	3.39 (0.03)	0.39	2.49 (0.20)

Table 5-4 Physical properties of reproduced preparations.

Formula	Yield (%)	LOD (%) average (SD)	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)
F44	61.27	5.59 (0.12)	190.6 (10.30)	12.90 (0.03)	3.39 (0.03)
F44-1	56.94	6.10 (0.10)	200.5 (10.69)	12.84 (0.02)	3.53 (0.05)
F44-2	54.94	6.80 (0.11)	202.6 (10.50)	12.83 (0.04)	3.45 (0.06)
F44-3	58.06	6.96 (0.15)	213.0 (7.65)	12.82 (0.02)	3.50 (0.07)
F44-4	57.88	5.88 (0.18)	196.8 (12.56)	12.82 (0.02)	3.48 (0.04)



F44-1 X 100



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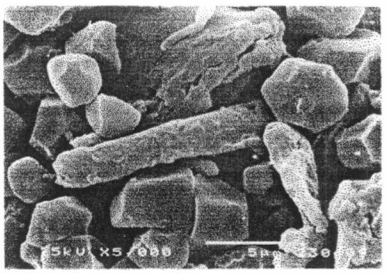

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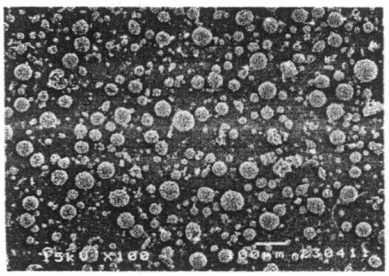
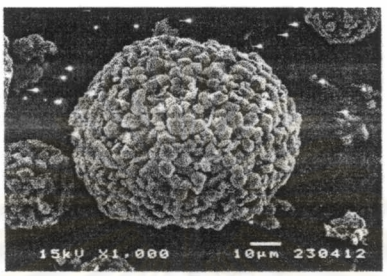


F44-2 X 100



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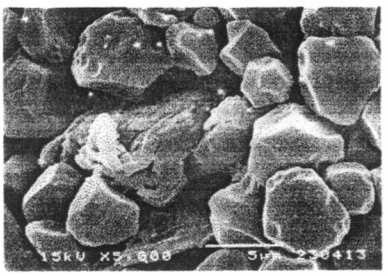

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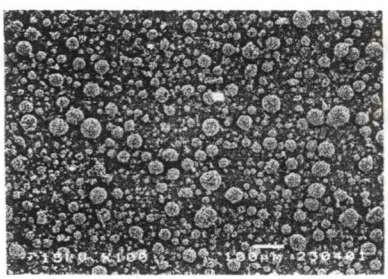
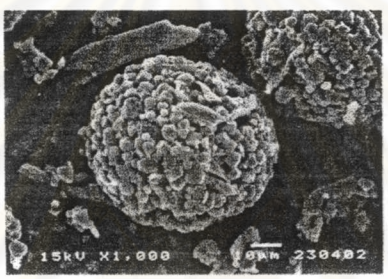


F44-3 X 100



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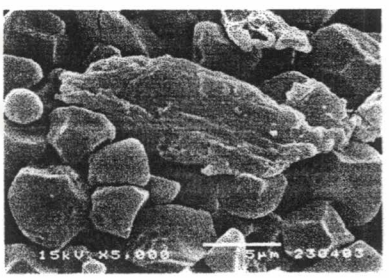

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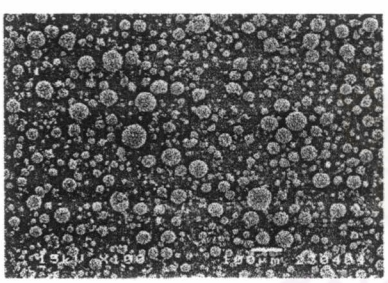
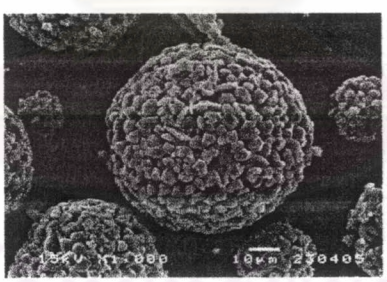


F44-4 X 100



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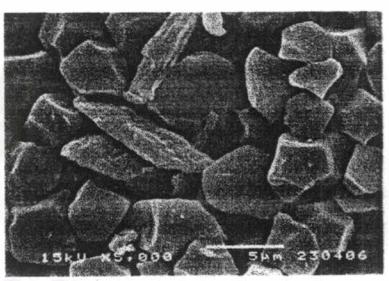

F44-4 X 5000

Figure 5-2 SEM Photomicrographs of F44-1 to F44-4

Table 5-5 Physical properties of powder of bulk preparation (RS/MCC).

Topic	Value average (SD)
Angle of Repose (degree)	34.6 (2.89)
Angle of Spatula (degree)	59.5 (1.27)
Bulked Density (g/ml)	0.427 (0.00)
Packed Density (g/ml)	0.521 (0.01)
Compressibility (%)	17.92 (0.22)
Cohesion (%)	6.2 (0.01)
Flowability Index	69.0 (0.87)

Table 5-6 Physical properties of bulk preparation (RS/MCC).

Sampling	LOD (%) average (SD)	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)
Top	6.82 (0.21)	190.7 (12.91)	12.81 (0.03)	3.44 (0.04)
Middle	6.67 (0.24)	208.9 (6.47)	12.80 (0.03)	3.43 (0.06)
Bottom	6.79 (0.21)	197.5 (10.40)	12.81 (0.03)	3.44 (0.05)

Table 5-7 Particle size distribution of bulk preparation (RS/MCC).

Sampling	D (v, 0.1) (μm) average (SD)	D (v, 0.5) (μm) average (SD)	D (v, 0.9) (μm) average (SD)	Span = (D90 – D10) / D50 average (SD)
Top	17.80 (0.21)	52.76 (0.52)	97.43 (1.17)	1.51 (0.02)
Middle	18.74 (0.25)	52.54 (0.14)	95.91 (2.27)	1.47 (0.05)
Bottom	18.92 (0.04)	52.50 (0.34)	93.35 (1.10)	1.42 (0.01)