Chapter III
Results and Discussion

A. Preparation and Evaluation of Modified Starches

1. Preparation of Modified Starches

The modified starches in this study were prepared by three different methods of carboxymethylation reaction using glutinous rice starch as a native starch. This reaction is an etherification reaction. Those three different methods of modification produced the modified starches with different degrees of substitution. These preparation procedures and conditions were modified from methods of Filbert (1952) , since Filbert's methods and conditions of reaction did not give the modified starches with required DS. It was found that slight changes in the reaction conditions or amount of materials used (e.g. monochloroacetic acid , sodium hydroxide) during modification process affected the DS of modified starches (Mishra , Jain and Agrawal , 1990 ; Filbert , 1952). The conditions and amounts of materials used in the modification process are compared and presented in Table 17.

In the presence of strong base , the carboxymethyl substitution reaction mechanism is undoubtedly S_N2 (substitution nucleophilic bimolecular). This means the formation of an intermediate complex. The starch is first converted into an alkaline starch called a starchate nucleophile , followed by a reaction with a nucleophilic agent (Robert , 1965). The etherification of starch with sodium chloroacetate in aqueous sodium hydroxide might take place according to the equation shown in Figure 11.

Monochloroacetic acid or sodium chloroacetate which was used as etherifying agent is a strong electrophile , since it has chlorine as a good leaving

Table 17 Comparison of the conditions and amount of materials used in the preparation of modified glutinous size starches (different 3 DS)

Title	Method		
	A	B	C
Amount of materials			
Solvent	isopropanol; 875 parts	ethanol; 286 parts	anh. methanol; 254 parts
Monochloroacetic acid	59 parts	29.2 parts	27.6 parts
Starch	231 parts	102 parts	109 parts
NaOH	50% ; 238 parts	97% in 69 parts H_2O ;38.4 parts	50% ; 110 parts
Conditions			
Temperature (°C)	75	50	60
Time (min)	30	20	60

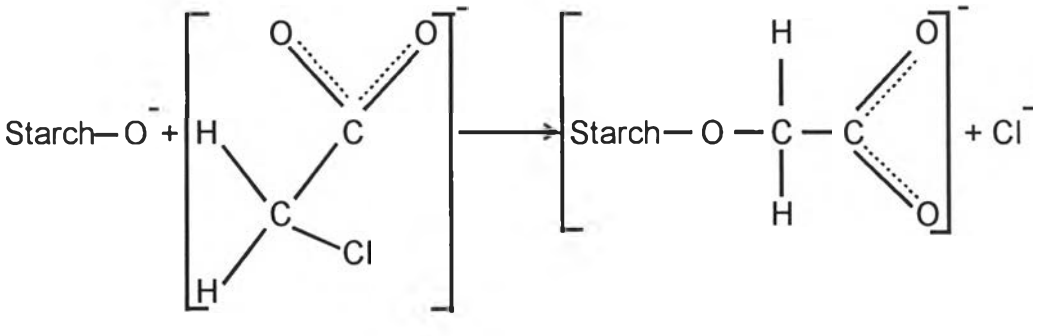


Figure 11 Mechanism of carboxymethyl substitution reaction in the preparation of sodium carboxymethyl starch.

group. The possible reacting positions of each anhydroglucose unit are the primary hydroxyl group on carbon atom 6 ; and the secondary -OH groups on carbon atom 2 and 3 , however carboxymethylation occurs preferentially at the secondary -OH groups (Hofreiter , 1986 ; Radley , 1968 ; Roberts , 1965). It seems reasonable to propose that as carboxymethyl groups are introduced into

the amylose molecule , electrostatic repulsion between the groups disrupts the 3B conformation of polymer chain ; and the secondary -OH groups at carbon atom 3 , no longer hydrogen bonded , become available for etherification.

With a high degree of substitution , products containing hydrophilic groups tend to become cold-water dispersible because the introduction of the substituents weakens the granule structure , so that the granule swells on contact with water. To obtain higher DS cold-water dispersible products in granular form , the reaction may be carried out in a nonswelling solvent like isopropanol (Rutenberg , 1980). In addition , conducting the reaction in a water-miscible solvent containing minor amounts of water is a major improvement in carboxymethylation technique.

2. Evaluation of the Properties of Sodium Carboxymethyl Starches

2.1 Determination of a Degree of Substitution

The degree of substitution of modified glutinous rice starches were determined by acid/base titration. The calculated DS were 0.32 , 0.26 and 0.16 for MGS produced by method A , B and C , respectively , as shown in Table 18. The method of calculation is presented in Appendix I. The DS indicates the average number of hydroxyl groups per anhydroglucose unit on which there are substituent groups. Thus , if all three hydroxyls are substituted , the DS is 3. Most of the available modified starches have low DS values , about or more than 0.1 , which would represent on average 1 substituent group per every 10 anhydroglucose units (Wurzberg , 1986)

The DS was calculated by a summation of degree of acid carboxymethyl substitution (A) and degree of sodium carboxymethyl substitution (S). From this method of calculation , the obtained DS represents the substituent groups in both acid and salt forms. However , the substitution reaction was taken

place in a strong basic condition , so that the major or important part for DS value was the degree of sodium carboxymethyl substitution (S).

The ratio of plain starch to monochloroacetic acid was about 1:0.25 in all methods of preparation. From the results , method A produced modified starch with DS higher than products from method B and C. It might be due to higher temperature and higher amount of sodium hydroxide used in the reaction.

Table 18 Degree of substitution of modified glutinous rice starches

Method of preparation	Various values for calculation of DS.				DS (A+S)
	M	C	A	S	
A (DS ≈ 0.3)	0.0354	11.74	0.0066	0.3093	0.32
B (DS ≈ 0.2)	0.0300	10.00	0.0055	0.2576	0.26
C (DS ≈ 0.1)	0.0615	6.20	0.0108	0.1526	0.16

M = Number of milliequivalent of base required for the neutralization of 1 gm of sodium carboxymethyl starch

C = Percentage of residue on ignition

A = Degree of acid carboxymethyl substitution

S = Degree of sodium carboxymethyl substitution

2.2 Determination of Carboxymethyl Substitution in Modified Starches.

Infrared spectrometer (IR) was easily used to detected the carboxymethyl groups in the obtained modified glutinous rice starches (VANDER Bij , 1976) The infrared spectra of native and modified starches are shown in Figure 12. The carboxymethyl substitution can be confirmed by the presence of carbonyl group (C=O) in the modified starch molecules. From IR spectra , it was illustrated that the spectra of modified starches , different from that of glutinous rice starch , had an intense band near 1600 cm^{-1} represented the CO stretching

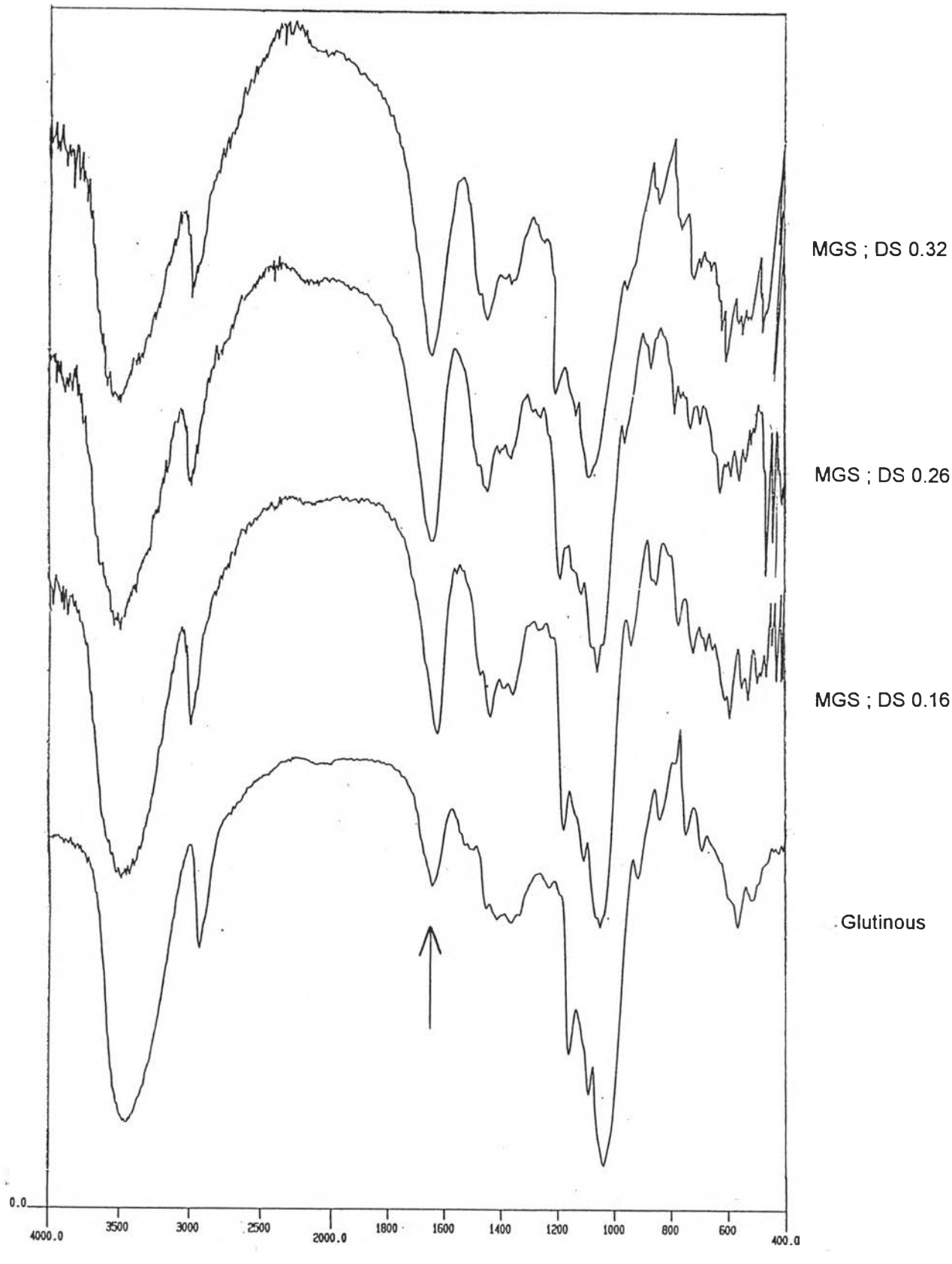


Figure 12 Infrared spectra of native and modified glutinous rice starches .

of carboxyl group. The C=O and C-O of caboxyl salt were replaced by two equivalent C=O bonds which intermediate in force constant between the C=O and C-O (Colthup, Daly and Wiberley, 1975). Thus , it could be concluded that there was a substitution of carboxymethyl groups into the starch molecules.

2.3 Viscosity Measurement

The viscosity measurements of native and modified glutinous rice starches were carried out utilizing Brabender Visco-Amylograph with cartridge 700 cmg. This instrument provides a continuous record of viscosity changes over a controlled heating and cooling cycles. Brabender viscosity curves were illustrated in Figure 13. In the standard of modified starch for food industry , the starch sample suspension is 6% w/w. In order to avoid damage to the sensor shaft which is connected to a coiled torsion spring , the concentration of starch suspension used in this experiment must be decreased to 3% w/w , because the viscosity of some DS of MGS surpassed the measurable range of the catridge. As shown in Figure 13 , the viscosity curves of modified starches were different from that of glutinous rice starch which presented a very low and consistent viscosity throughout the heating , holding and cooling period.

The viscosity of modified glutinous rice starches were more viscous than unmodified starch. It has been suggested that unmodified starch is insoluble and resists swelling in cold water because the intramolecular hydrogen bonding between the polysaccharide macro-molecules creates a rigid and partially crystalline structure which prevents the penetration of water. However , the carboxymethylation of starches introduces strongly hydrophilic anionic groups into the starch molecules which weaken its internal structure and disrupt the hydrogen bonding within the granule , thus enhancing the swelling properties of modified starches when contact with water , and so increasing in the viscosity of starch paste (Baie , et al. 1995 ; BeMiller , 1993 ; Rutenberg , 1980). Furthermore , the swelling of the granules and the viscosity are much more pronounced by the electrostatic repulsion of the carboxymethyl group. When

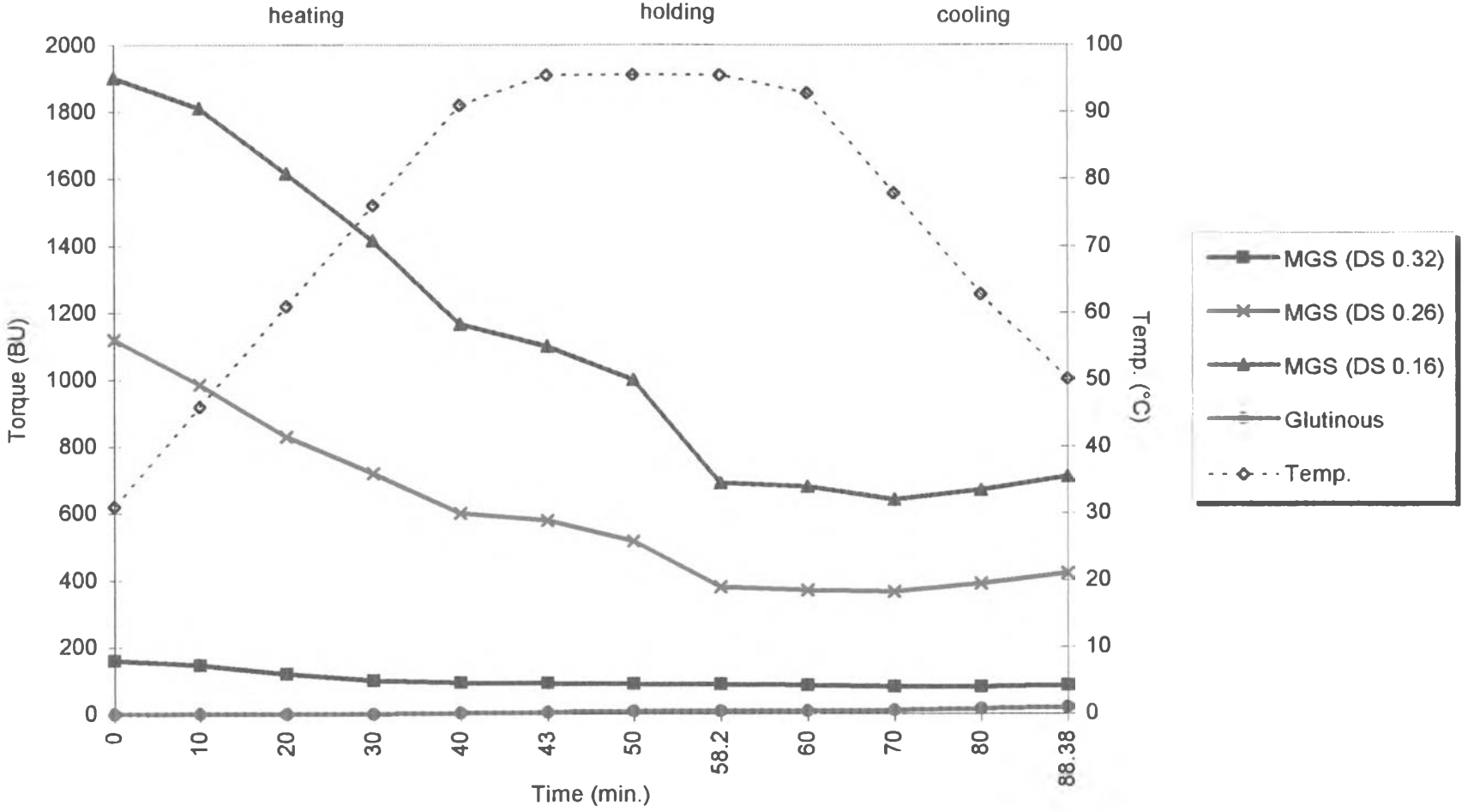


Figure 13 Brabender viscosity curves of glutinous rice starch and MGS at different DS. The concentration was 3 % w/w of dry starches suspended in distilled water. The starch suspension was heated from 30°C to 95°C at a rate of 1.5°C/min. It was then maintained at 95°C for 15 min and then cooled to 50°C at the same rate.

swelling is assisted by electrostatic repulsion , the remaining hydrogen bonds are readily broken and starch molecules are liberated and solubilized. Theoretically , on heating or cooking period , the granules of plain starch start to swell very rapidly with increasing temperature. The temperature at which swelling starts is called the initial gelatinization. The granules begin to lose their birefringence , the solubility of starch increases and the solution becomes viscous (Collisson , 1968). In this experiment , however , the viscosity of unmodified starch was not observed at any temperature which might be due to very low concentration of starch suspension. The temperature at which increasing viscosity occurs depends on the starch concentration because the sharp rise in viscosity occurs when the granules have swollen to such an extent that they occupy a high proportion of the total volume and are in contact with their immediate neighbours. So , in order to observe the first swelling near the initial gelatinization temperature , the concentration must be high enough , for example , at 6% w/w. From a preliminary run , the obvious rise in viscosity was observed at this concentration and the viscosity was about 200-300 BU.

The pattern of viscosity curves of modified starches at various DS were in the same manner in which the viscosity decreased during cooking and holding period and tended to be constant in cooling period. Normally , etherification reaction produces modified starch with lower gelatinization temperature and pronounces granule swelling. If enough substituents are introduced , the gelatinization temperature is lowered to room temperature and become soluble in cold water. When in contact with water , the granules of modified starches swelled many times of their original volume and high viscosity paste was produced. The swollen granules became increasingly susceptible to fragility by heat. As a result , as the temperature increased , the collapse of granules increased and resulting in diminishing of the viscosity (Leach , 1965). Typically , aqueous dispersion of starches tend to increase in viscosity on cooling cycle because of the tendency of the linear amylose molecules to move slowly and reassociate with the adjacent molecules. Whereas , the viscosity of carboxymethyl starch dispersion tended to be constant on cooling cycle due to

the substituent groups along the amylose molecule interfering with the alignment and association process of retrogradation (Rutenberg , 1980).

Baie et al. (1995) found that with increasing in degree of substitution of carboxymethyl tapioca starch , the starch granules disintegrated and became more soluble in cold water. This is accompanied by an increase in viscosity. In this present study , however , the ranked order of viscosity of MGS with different DS was DS 0.16 > DS 0.26 > DS 0.32. These might be due to tapioca starch undergoes a rapid and unrestricted swelling at relatively low temperature , indicative of weak wider range bonding forces , whereas the glutinous rice starch , as a cereal starch , exhibits restricted swelling patterns (Rutenberg , 1980). The more substituent groups introduced into the glutinous rice starch molecules (high DS) resulted in the limited swelling power of starch granule because of less liberated hydroxyl groups to attach with water molecules.

2.4 Moisture Determination

Moisture analyzer was used to determined the moisture content of native and modified glutinous rice starches and the results are depicted in Table 15. The average moisture content ranged between 10-15%. No significant difference of moisture content was observed among native and modified starch with various DS. Thus , it could be concluded that the method of carboxymethyl substitution which produced modified starches with different DS did not influence the moisture content of the products.

B. Application of Sodium Carboxymethyl Starches in the Preparation of Pellets.

The focus of this study was to assess the suitability of carboxymethyl starch with different DS in the production of pellets by extrusion and spheronization process. As shown in other studies , microcrystalline cellulose

was commonly used as an extrusion aid in the preparation of pellets but carboxymethyl glutinous rice starch was introduced as another aid in this study. As a result of swelling power of carboxymethyl starch and increasing in viscosity when in contact with water , it might be used as an extrusion aid which regulated the water content and distribution in the granulation step , modified the rheological properties of the formulation and imparted plasticity to the pellets (Ghrbre-Sellassie , 1995 ; Rutenberg , 1980).

Table 19 Percent moisture contents of native and modified glutinous rice starches.

Starches	% Moisture Content
Glutinous rice starch	13.00
Modified starches	
• DS 0.32	10.21
• DS 0.26	14.97
• DS 0.16	13.06

1. Particle Size of Starting Materials Used in the Production of Pellet.

The particle size of starting materials ,i.e. sucrose powder , hydrous lactose , dicalcium phosphate dihydrate , corn starch and microcrystalline cellulose (Avicel PH101) were determined by particle size analyzer and the results are shown in Table 20.

The particle size distribution curves of these materials are illustrated in Appendix II (Figure 102-106). Between the materials used as pellet bases , average particle size of lactose was higher than that of sucrose and dicalcium phosphate. The particle size distribution of materials were observed from span value , the lower the span value , the narrower the size distribution. The size and size distribution of starting materials could affect the size distribution of pellets.

Table 20 Average particle size of starting materials used in the production of pellets

Starting materials	Average particle size (μm)	Span
Sucrose powder	16.29	1.381
Hydrous lactose	116.11	3.562
Dicalcium phosphate dihydrate	11.25	2.773
Corn starch	14.69	1.408
Avicel PH101	70.58	2.163

Span = The width of volume distribution relative to the volumetric mean diameter = $[D_{90}-D_{10}/D_{50}]$

2. Evaluation of General Characteristics and Physical Properties of Pellets

2.1 Sucrose Pellet Formulations

Sucrose pellets were produced using various amounts of sucrose powder. At first , the different amounts of modified glutinous rice starch with DS 0.32 was employed as an extrusion aid due to , in the recent study (Tasana Tituksuteepong , 1995) , MGS with DS 0.35 was a good tablet binder. However , microcrystalline cellulose (Avicel PH101) was used in some formulations to obtain the pellets with better characteristics , especially in sphericity. Corn starch was used as another pellet filler. Alteration of water content and spheronization process conditions was made to obtain acceptable pellets.

In 65% sucrose pellet formulations , the mixture of starting materials was extruded and spheronized. It was found that spherical particles did not form in any formulations (Figure 14) , particularly when 3.0% w/w of MGS was used (formulations $6S_{31}$ and $6S_{32}$). The outcomes were small cylindrical particles with various lengths , like the dry granules. During the process , the extrudates produced from the extruder were very long , sticky , and then agglomerated and densified. The extrudate that being more rigid in structure might resist to

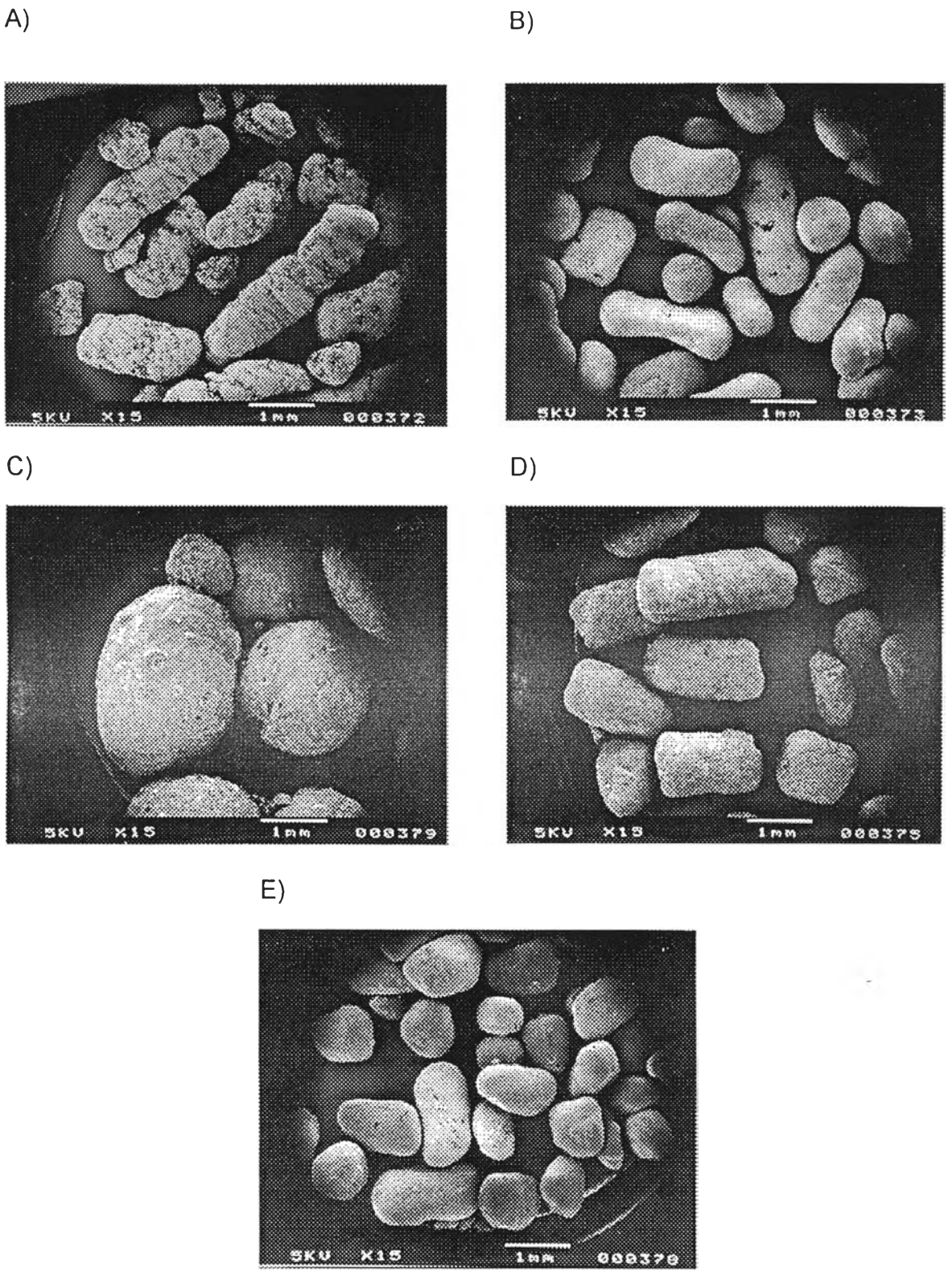


Figure 14 Photomicrographs of some sucrose pellet formulations : A) $6S_{36}$, B) $7S_{34}$, C) $7S_{31}$, D) $8S_{35}$ and E) $9S_{36}$ (x15).

decrease its length and increase its width during spheronization process , hence , the pellet did not form (Newton , et al. , 1995). These might be due to using relatively large amounts of MGS (1.0-3.0% w/w) and added water. MGS could swell many times , its volume and high viscosity was generated when the water was added into the mixtures (Wade and Weller , 1994 ; Rutenberg , 1980). So , the overwet masses were produced and became gluey and long extrudates after extruded through the extruder which created the temperature during processing . Loss of water during extrusion process because of the created heat probably reduced the plasticity of the mass and induced dry and hard extrudates. When MGS at 1% w/w and added water which decreased to 8% were used in formulation $6S_{33}$ and $6S_{34}$, the extrudates were shorter , less rigid and illustrated good appearance but , similar to the previous results , the spheroids were not produced. The spheronizer speed of 800 rpm was applied because rounder particle could be produced when using faster speed (Baert et al. , 1993 ; Bataille et al. , 1993). For the formulation $6S_{35}$ to $6S_{37}$, 17.0-20.0% w/w of Avicel PH101 was used to make more plasticity of extrudates and , hence , the sphericity of the products might be increased. Unfortunately , the spherical particles were not formed , only rod-shaped particles with many size lengths were attained (Figure 14A). The wet mass generated from the mixture composed of 1.0% w/w of MGS was very stiff when passed through the screw of extruder and the obtained extrudates were very long and rigid. Even though the amount of MGS was decreased to 0.5% w/w , the round particles were not formed. From these results, it might be explained that the rod-like fragments did not possess the required plasticity to be converted into spheres because of the crystallized nature of sucrose which became the powdered-texture moist mass when adding the granulation liquid. This granulated mass was more rigid but less cohesive between particles and then generated inappropriate extrudates which resisted forces in spheronizer ; therefore, the spheres could not be produced although Avicel PH101 was used. Generally , the extrudates must be appropriately brittle enough to break down into small cylinders but must be sufficiently cohesive not to be powdered in the spheronizer to form the spheres (Linder and Kleinebudde , 1994).

Similar to the 65% sucrose pellet formulations , the spherical granules were not produced from 70% sucrose formulations due to the same reasons as previously described (Figure 14B). In formulation $7S_{31}$ which composed of 1.0% w/w of MGS , the product was very large and round masses when compared with standard diameter range of appropriate pellets (Figure 14C) due to the exceeding amount of water used in the granulation step. However , whenreducing the amount of water to 10.5% in formulation $7S_{32}$, the large and round masses were still produced but smaller in size. Further decrease in the amount of water and increase in the residence time (10 min) in formulation $7S_{33}$, the small rod-shaped particles were obtained. Because the particles became more spherical with an increase in the residence time (Lucy et al. , 1993 ; Baert et al. , 1993 ; Hellen et al. 1993a) , the longer residence time was applied in this formulation. The higher spheronizer load of 400 gm was used in formulation $7S_{34}$ according to Newton et al. (1995) who found that the higher load eventually produced rounder granules. Unexpectedly , the small granules were still produced. During the extrusion process , the heat was created from the friction forces between the wet mass and the screw of extruder and the warm extrudates were obtained. The relatively hard , long and warm extrudates which reduced its plasticity were obtained in all formulations , hence , the pellets could not be generated.

In 80% sucrose pellet formulations , the initial formulation ($8S_{31}$) employing 2.0% w/w of MGS produced long and conglomerate extrudates ; then the large agglomerates which stuck inside the spheronizer were gained. It was due to the exceeding amount of water resulting in aggregation during spheronization. The shorter extrudates with good appearance were made from using lower water content in formulation $8S_{32}$; however , the outcomes were fines and small granules. In further studies , the quantity of MGS was decreased to 0.5-1.0% w/w while the amount of water was increased depending on the nature of wet mass for processing in extruder. It was found that pellets with good characteristics were not formed ; only small rod-shaped granules , granules with round ends in formulation $8S_{35}$ and large spherical masses in formulation $8S_{36}$

were obtained (Figure 14D). The crystallized powder of sucrose that generated coarse-nature and less cohesive wet masses with low plasticity was the main cause that pellets were not formed.

From the previous results , round end granules with less aggregation were produced from some formulations when 0.5% w/w of MGS was employed. Thus , this amount of MGS was used in all 90% sucrose pellet formulations. The example of product was shown in Figure 14E. The fines and very small brittle granules were produced in formulations $9S_{31}$ and $9S_{32}$ because these formulations were moistened with relatively low amount of water (3.5 and 6%). Further addition of granulated water (7.5-8%) resulted in aggregate extrudates which became agglomerate particles sticking inside the spheronizer and , consequently , large masses and small rod-shaped particles were obtained. Decreasing the amount of added water to 7% in formulation $9S_{34}$ resulted in fines , small cylindrical particles , dumbbell-shaped particles and less aggregate masses. In formulations $9S_{36}$, $9S_{37}$ and $9S_{38}$ which were moistened with 7.5% of added water , the slower spheronizer speed (300-400 rpm) and longer residence time (10-15 min) were applied. The obtained products were slightly round , rod and dumbbell-shaped particles accompanied with large masses. The speed of friction plate was then increased (to 500 rpm) to eliminate the aggregation of particles during processing in spheronizer. The outcomes were , however , the same as previously described. Further experiments were carried on by using Avicel PH101 in the formulations $9S_{310}$ to $9S_{313}$ with the expectation that the plasticity of wet powder masses would become greater. Unfortunately , the spherical particles still did not form although 9.5% w/w of Avicel PH101 was used.

It might be concluded that pellet or spherical particle could not be produced from all sucrose pellet formulations. Utilization of sucrose powder with crystalline character was attributed to coarse texture of the wet mass when moistened with water, resulting in rigid , less cohesive and low plasticity extrudates , and then only rod- or dumbbell-shaped particles were formed after spheronization process. Sometimes the warm extrudates were obtained from

friction of the coarse nature of wet mass especially when using large amount of MGS. This warm extrudate might lose more water and, hence, the plasticity of the mass was decreased (Linder and Kleinebudde , 1994).

2.2 Lactose Pellet Formulations

In this experiment , hydrous lactose was used as a soluble pellet base. As shown in Table 5-8 , changes in amount of materials and processing conditions were performed to produce pellet with good appearances. In the first step, MGS with DS 0.32 was used. Then , three formulations with different amounts of water and exhibited good characteristics were selected for employing MGS with DS 0.26 and 0.16 , to determine the effect of degree of substitution of MGS on the physical properties of pellets.

For 65% lactose pellet formulations , microcrystalline cellulose (Avicel PH101) was used in all formulations. Since , in the preliminary study , the appropriate pellet was not formed without Avicel PH101. The relatively low amounts of 5.0-10.0% w/w of Avicel PH101 produced pellet with unacceptable characteristics i.e., with aggregation and agglomeration , as shown in Figure 15, whereas the more appropriate characteristic pellets could be formed in the formulations using 15.0% w/w of Avicel PH101. It was noted that the quantity of Avicel PH101 used in the formulation utilizing MGS could be reduced when compared with pellet formulations in the previous research (Intira Coowanitwong , 1997 ; Linder and Kleinebudde , 1994 ; Wan et al. , 1993 ; Fielden et al. , 1993; Newton et al. , 1995). The concentration of MGS was mostly fixed at 0.5% w/w because the large amount of MGS (1.0-3.0% w/w) generated very sticky wet masses and , consequently , the suitable pellets could not be formed. In addition , round end granules and sphere-like particles were observed by using 0.5% of MGS in sucrose pellet formulations , as previously mentioned. However , the lower amounts of MGS , 0.1-0.3% w/w , were employed as it was expected that more spherical granules with less aggregation and without large masses might be formed. However , the aggregation of extrudates and sticking around the

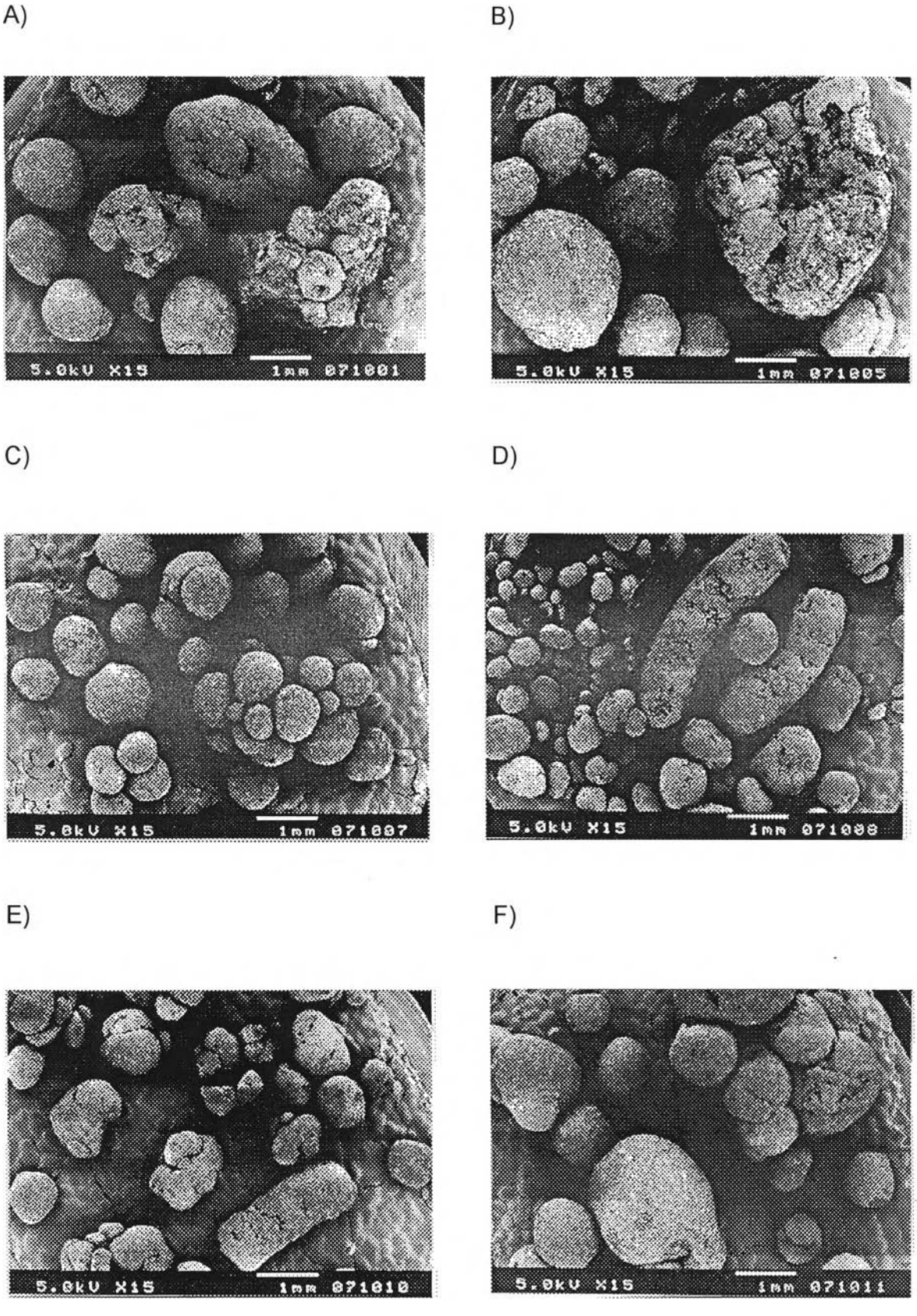


Figure 15 Photomicrographs of some 65% lactose pellet formulations : A) $6L_{31}$, B) $6L_{33}$, C) $6L_{35}$, D) $6L_{36}$, E) $6L_{311}$ and F) $6L_{312}$ (x15).

spheronizer were observed , then the large masses were produced and accompanied with inappropriate pellets. So , the amount of 0.5% w/w of MGS was used in further studies. Changes in amount of water were performed by observation of the nature of wet powder mass for processing in extruder and characteristics of the outcome. Moisture content of granulated mass have been found to have a significant influence on spheroid characteristics. Water has two major roles in the granulation and spheronization process. It is required to bind the powder mix during granulation. Its plasticizing and lubricating properties also aid the extrusion process (O'Connor and Schwartz. 1989 ; Wan et al. , 1993). For the spheronization process conditions , the faster speed of friction plate (800-900 rpm) and the longer residence time (8 , 10 min) were applied to generate more spherical pellet (Hellen and Yliruusi , 1993 ; Hileman et al. , 1993 ; Lucy et al., 1993) whereas the smaller load in spheronizer was used to reduce aggregation and agglomeration of particles including sticking of particles around the spheronizer. It was observed that the spheronizer speed higher than 500 rpm could not produce the improvable characteristic of pellets , hence , the speed of 500 rpm was employed. As expected , utilization of 8 min of residence time generated satisfactory rounder pellets than using 2 or 5 min Newton et al. (1995) found that too low load appeared to give poor particle/particle interaction , thus less round pellets or rod-like particles were made when using low load of 150 gm (Figure 15D). Furthermore , the spheronizer load of 200-250 gm produced pellet appearance similar to that of 300 gm Therefore , the spheronizer load of 300 gm was utilized in further experiments.

Moreover , it was surprisingly found that leaving the extrudates for 10 minutes before processing in spheronizer (formulations $6L_{314}$-$6L_{318}$) could produce less aggregation of individual pellet. This might be explained that surface moisture content of extrudates was slightly reduced and resulted in diminishing of the cohesion of each particle including adhesions of pellet to spheronizer. The appropriate appearance of pellets was produced from formulation $6L_{317}$ (37% of granulated water), and then the amount of water was changed (to 36 and 38%) to investigate the effect of added water on physical

properties of pellets , but using the same amount of other materials and processing conditions as formulation $6L_{317}$. The variation of added water which was lower or more than this range could not produce pellets with good appearances. After that MGS with DS 0.26 and 0.16 were used instead of DS 0.32 and employing the compositions and processing conditions similar to the formulations containing MGS DS 0.32.

For 80% lactose pellet formulations , the utilization of 15% w/w of Avicel PH101 , 0.5% w/w of MGS with DS 0.32 and spheronization process conditions (Table 6) were based on the acceptable appearance of pellet formulations in 65% lactose model. The first formulation ($8L_{31}$) resulted in overwet and very sticky mass which difficultly passed through the screw of extruder since the high concentration of water was used. The final product was very large spherical mass. Thus , the lower amounts of water were used and good characteristic of pellets was obtained. Three levels of water , 31 , 30 and 29% , were focused to study the effect of added water on physical properties of pellets. Consequently , MGS with DS 0.26 and 0.16 were used , similar to 65% lactose pellets.

In lactose blank pellet formulations , B.1 to B.6 employing the amount of materials and processing conditions similar to those of 65% and 80% lactose pellets except without MGS produced smaller size and more aggregation of products when compared with lactose pellets. The aggregation of individual pellets resulted in less round appearance. Wet powder mass with low plasticity , resulting from using the same amount of added water as lactose pellets , difficultly passed through the screw of extruder. It might be due to lack of MGS which could form a high viscosity jelly when in contact with water and using low amount of Avicel PH101. This could not confer a degree of plasticity that allowed the wet mass not to be readily extruded.

Evaluation of physical properties of 65% and 80% lactose pellets containing various DS of MGS and amounts adding of water , compared with their blank pellets , were as follows.

2.2.1 Particle Size Distribution

The particle size distribution of pellets was examined by sieve analysis which is a suitable method for the analysis of round or nearly round particles and the results are depicted in Figures 16-23 and in Appendix III. In order to determine geometric mean diameter (D_{50}) , the percent cumulative undersize of pellet in probability scale was plotted against sieve size and these plots are illustrated in Appendix III. D_{50} of 65% and 80% lactose pellets using different DS of MGS and amounts of water including lactose blank pellets are shown in Figures 24-25. The values of D50 and geometric standard deviation (σ_g) are presented in Table 21. In addition , the data in statistical processes are shown in Appendix V (Table 54-55 and 58-59).

For 65% lactose pellets , the size distribution of pellets containing MGS at different DS and using the same amount of water was comparable , but slightly narrower than those of blank pellets. Because geometric standard deviation of pellets prepared with MGS at various DS exhibited slight difference but was mostly lower than that of blank pellets (Table 21). Mostly , σ_g of pellets using MGS at DS 0.26 was lower than that of using other DS. D_{50} of pellets using modified starches was larger than that of blank pellets , in all quantities of water. Using various DS of MGS yielded the pellets with non-significant difference of D_{50}. In comparison between formulations prepared with different amounts of water in each series DS of MGS , it was found that slight increase in amount of water resulted in a great increase in size of pellets , whereas slight increase in size of blank pellets was observed. D_{50} of pellets prepared with 38% of water was greater than those utilizing 37% and 36% of water (Figure 24). Geometric standard deviation (σ_g) of pellets was affected by different amounts of water was , it was decreased with increasing added water level. It could be indicated that size distribution of pellets using the highest amount of added water (38%) was narrower than using the lower amount of added water.

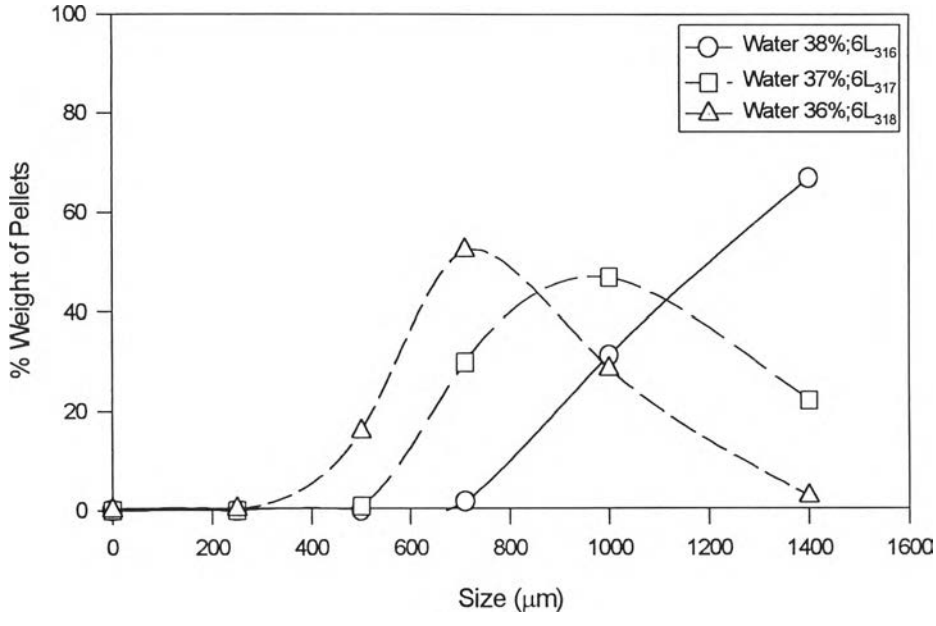


Figure 16 Particle size distribution curves of 65 % lactose pellets prepared with DS 0.32 of MGS at different amounts of water .

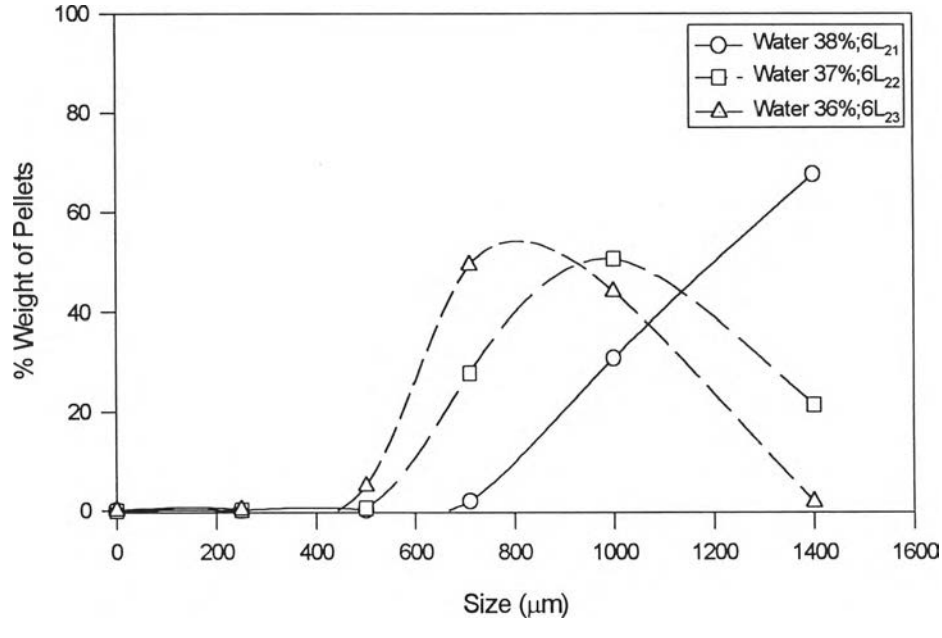


Figure 17 Particle size distribution curves of 65 % lactose pellets prepared with DS 0.26 of MGS at different amounts of water .

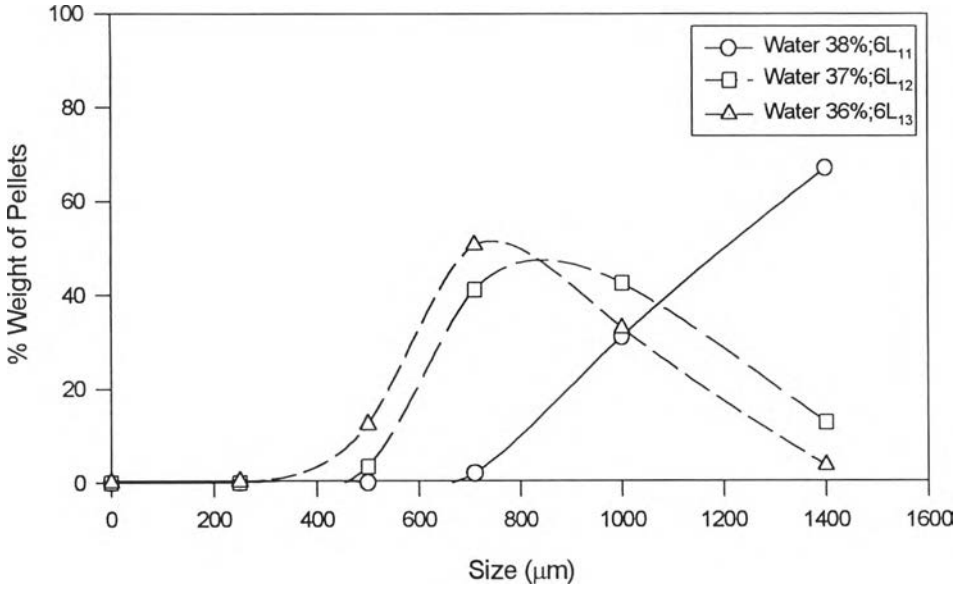


Figure 18 Particle size distribution curves of 65 % lactose pellets prepared with DS 0.16 of MGS at different amounts of water .

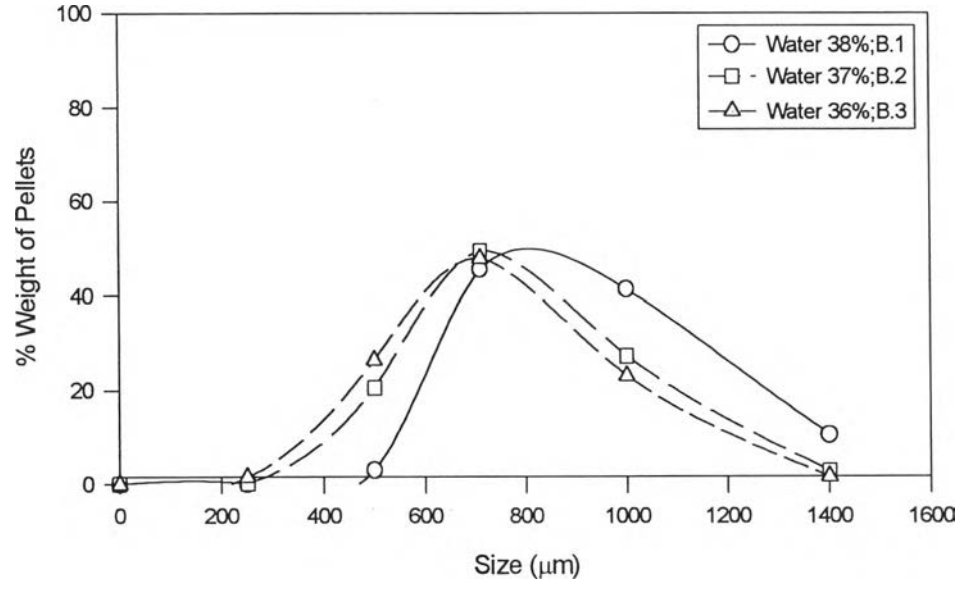


Figure 19 Particle size distribution curves of 65 % lactose blank pellets prepared with different amounts of water .

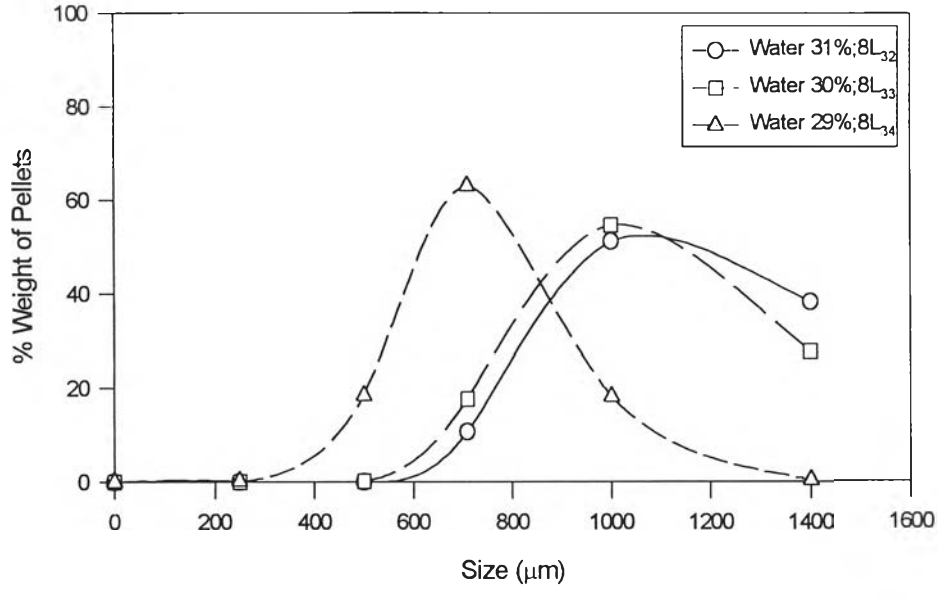


Figure 20 Particle size distribution curves of 80 % lactose pellets prepared with DS 0.32 of MGS at different amounts of water .

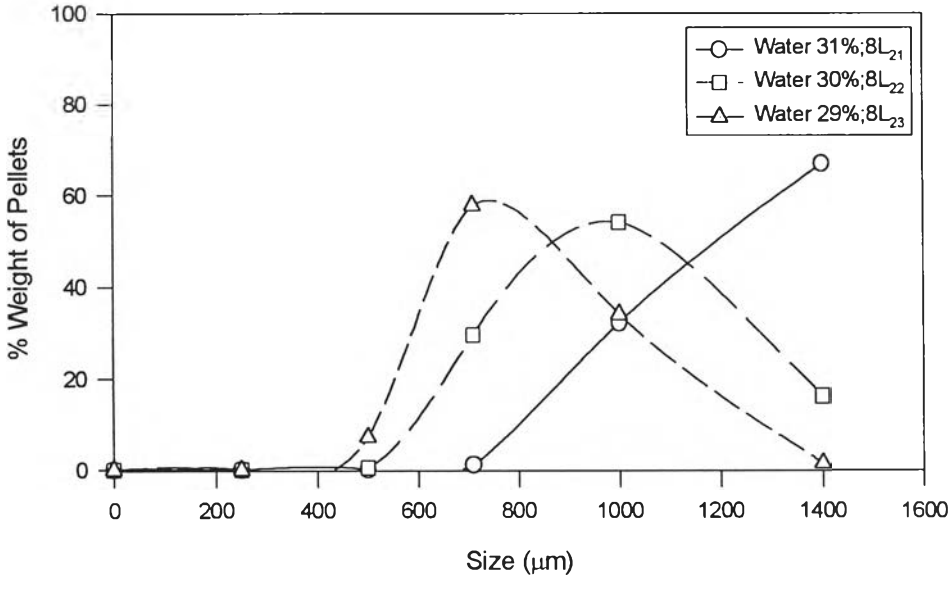


Figure 21 Particle size distribution curves of 80 % lactose pellets prepared with DS 0.26 of MGS at different amounts of water .

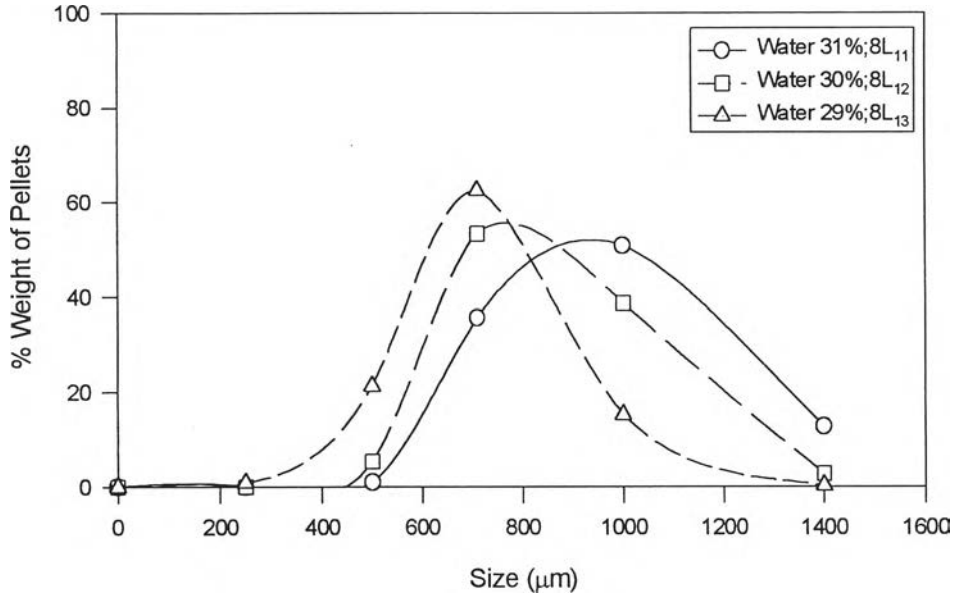


Figure 22 Particle size distribution curves of 80 % lactose pellets prepared with DS 0.16 of MGS at different amounts of water .

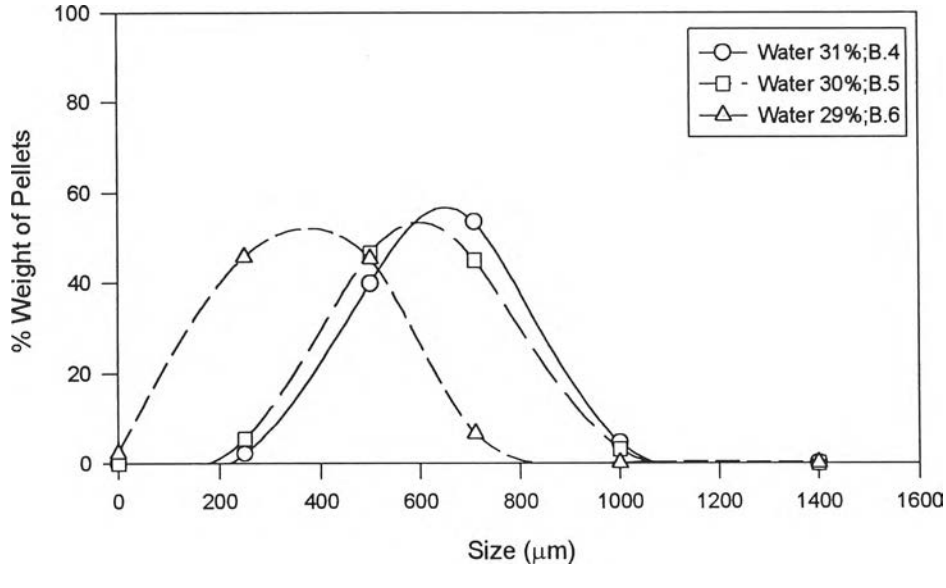


Figure 23 Particle size distribution curves of 80 % lactose blank pellets prepared with different amounts of water .

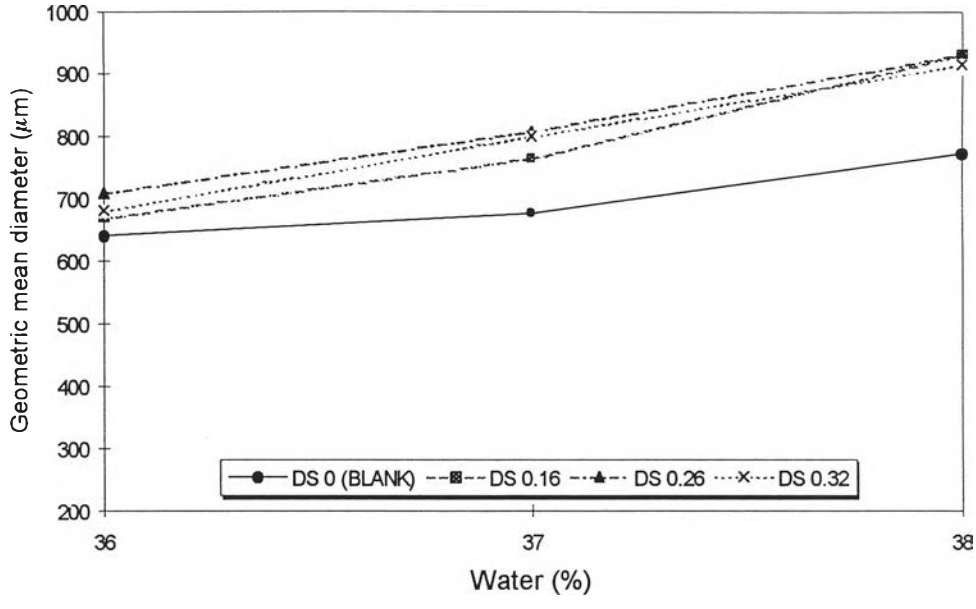


Figure 24 Geometric mean diameter (D_{50}) profiles of 65% lactose pellets prepared with different DS of MGS and amounts of water.

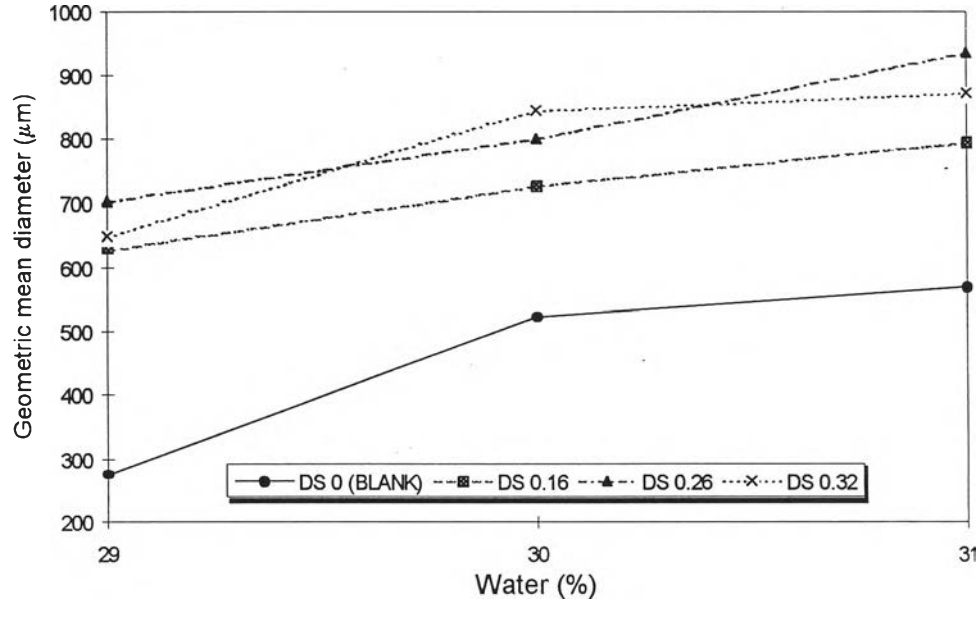


Figure 25 Geometric mean diameter (D_{50}) profiles of 80% lactose pellets prepared with different DS of MGS and amounts of water.

Table 21 Geometric mean diameter (D_{50}) and geometric standard deviation (σ_g) of 65 % and 80 % lactose pellets prepared with different DS of MGS and amounts of water.

DS	MGS	65% Lactose Pellets				80% Lactose Pellets			
	(% w/w)	Water (%)	Formulation	D_{50} (μm)	σ_g	Water (%)	Formulation	D_{50} (μm)	σ_g
0.32	0.5	38	$6L_{316}$	914.96	1.2251	31	$8L_{32}$	871.51	1.2195
		37	$6L_{317}$	800.00	1.2497	30	$8L_{33}$	845.04	1.2252
		36	$6L_{318}$	680.39	1.3120	29	$8L_{34}$	646.73	1.3143
0.26	0.5	38	$6L_{21}$	931.23	1.2114	31	$8L_{21}$	936.43	1.2102
		37	$6L_{22}$	806.23	1.2459	30	$8L_{22}$	799.75	1.2453
		36	$6L_{23}$	707.57	1.2847	29	$8L_{23}$	703.08	1.2792
0.16	0.5	38	$6L_{11}$	929.66	1.2116	31	$8L_{11}$	793.91	1.2387
		37	$6L_{12}$	764.15	1.2614	30	$8L_{12}$	725.84	1.2674
		36	$6L_{13}$	667.14	1.3583	29	$8L_{13}$	626.12	1.3389
0 *	-	38	B.1	770.44	1.2480	31	B.4	568.31	1.3852
		37	B.2	675.53	1.3143	30	B.5	521.18	1.4778
		36	B.3	640.34	1.3481	29	B.6	273.37	5.9589

* Blank pellets

In 80% lactose pellet formulations , the comparable size distribution of pellets prepared with MGS at various DS and any amounts of water were observed excluding the utilization of DS 0.26 with 31% of water (formulation 8 L_{21}) which gave a great increase in size (Figure 21). Since geometric standard deviation (σ_g) of pellet formulations using modified starches was lower than that of blank pellets. Therefore size distributions of MGS containing pellets were narrower than those of blank pellets (see σ_g in Table 21). Similar to 65% formulations , the lower σ_g was found from pellets containing MGS with DS 0.26. Size of blank pellets obviously reduced when compared with the formulations using modified starches. It was clearly seen from D_{50} values , D_{50} of pellets employing modified starches at any DS was significantly greater than that of blank pellets in all quantities of water. In comparison between different DS of MGS , the ranked order of D_{50} was : D_{50} of pellets using DS 0.26 $\geq$ DS 0.32 $\approx$ DS 0.16 at 29% of water , D_{50} of pellets using DS 0.32 $\approx$ DS 0.26 > DS 0.16 at 30% of water and D_{50} of pellets using DS 0.26 > DS 0.32 > DS 0.16 at 31% of water (Figure 25). However , D_{50} of pellets using MGS at DS 0.26 and 0.16 was significantly different (Table 59 in Appendix V). Different D_{50} of pellets could also be seen from using various quantities of added water . Utilization of 31% of water produced pellets with higher D_{50} , in respective comparison to using 30% and 29%. The ranked order of σ_g of pellets prepared with different amounts of MGS was : σ_g of pellets using 31% water < 30% water < 29% water .

From the results , it could be implied that utilization of modified starch in pellet formulation affected the size distribution and D_{50} of pellet. The modified starch which blended together with other starting materials could swell many time its volume and form high viscosity paste when granulated with water. This properties of MGS could improve the plasticity and cohesive nature of wet powder mass for passing through the extruder. This characteristic was also conferred from microcrystalline cellulose (Avicel PH101). Modified starch imparted a degree of plasticity and cohesive character to the obtained extrudates and when processed in spheronizer , cohesive forces between particles withstanded the destructive forces from spinning motion of the friction plate

resulting in promote growth of pellets. Therefore , an increase in pellet size were observed and this could be obviously seen in D_{50} value. But the plasticity and cohesiveness of wet mass and extrudate of blank pellets were only given from low amount of Avicel PH101. The uniform distribution of MGS in mixing powder might better regulate the water content and distribution in the granulation and control the plasticity of whole wet mass when compared to blank pellets. It might result in slightly narrower size distribution of pellet prepared with modified starch. In comparison of the effect of different DS of MGS on size distribution of pellet , it could be concluded that degree of substitution slightly affected the size distribution but did not affect D_{50} of pellets. This result agreed with the previous research (Tasana Pituksuteepong , 1995). It was found from σ_g values that using MGS at DS 0.26 yielded the pellets with slightly narrower size distribution than using other DS. As can be seen from the data , there was a significant influence of water content on the pellet size. A minimum amount of granulation liquid was essential before spheroids could be formed. This quantity was needed to form a moist , cohesive and plastic mass for spheronization. With further additions of water , e.g. 37% to 38% in 65% lactose pellets or 29% to 30% in 80% lactose pellets , the pellets grew in size and the greater D_{50} value was observed. In fact the water content at the die wall during extrusion (and presumably at the surface during subsequent spheronization) was found to be important. However , a slight excess of moisture on the surface of extrudates enhances deformation and promotes coalescence and pellet growth (Wans et al. , 1993 ; Pinto et al. ,1992). Moreover , the narrower size distribution was found when increasing the amount of added water.

2.2.2 Bulk and Tapped Densities

Bulk and tapped densities of pellets were determined by cylinder method and the results of 65% and 80% lactose pellets are displayed in Table 22. The bulk and tapped densities of pellets containing modified starches were slightly higher than those of blank pellets. Slight difference of bulk and tapped densities could be observed when using different DS of MGS and amounts of

Table 22 Bulk density and tapped density of lactose pellet formulations prepared with different DS of MGS and amounts of water.

DS	MGS (%w/w)	65 % Lactose Pellets				80 % Lactose Pellets			
		Water (%)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Water (%)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)
0.32	0.5	38	$6L_{316}$	0.752 (0.008*)	0.765 (0.012)	31	$8L_{32}$	0.767 (0.009)	0.788 (0.006)
		37	$6L_{317}$	0.738 (0.003)	0.774 (0.003)	30	$8L_{33}$	0.758 (0.006)	0.779 (0.007)
		36	$6L_{318}$	0.741 (0.003)	0.771 (0.010)	29	$8L_{34}$	0.745 (0.003)	0.777 (0.004)
0.26	0.5	38	$6L_{21}$	0.737 (0.000)	0.785 (0.004)	31	$8L_{21}$	0.769 (0.006)	0.786 (0.004)
		37	$6L_{22}$	0.727 (0.003)	0.768 (0.003)	30	$8L_{22}$	0.754 (0.003)	0.777 (0.004)
		36	$6L_{23}$	0.738 (0.000)	0.788 (0.004)	29	$8L_{23}$	0.750 (0.003)	0.779 (0.004)
0.16	0.5	38	$6L_{11}$	0.734 (0.003)	0.776 (0.006)	31	$8L_{11}$	0.746 (0.000)	0.769 (0.000)
		37	$6L_{12}$	0.724 (0.006)	0.748 (0.003)	30	$8L_{12}$	0.735 (0.000)	0.767 (0.003)
		36	$6L_{13}$	0.726 (0.000)	0.769 (0.003)	29	$8L_{13}$	0.756 (0.003)	0.785 (0.004)
0 **	-	38	B.1	0.715 (0.003)	0.756 (0.007)	31	B.4	0.737 (0.003)	0.769 (0.000)
		37	B.2	0.713 (0.003)	0.745 (0.003)	30	B.5	0.716 (0.003)	0.763 (0.000)
		36	B.3	0.714 (0.003)	0.767 (0.003)	29	B.6	0.713 (0.003)	0.754 (0.003)

* Standard deviation ** Blank pellets

granulated water. The bulk and tapped densities of pellets containing MGS at DS 0.16 tended to be the lowest. With increase in the amount of added water , the densities tended to be increased. Moreover , the densities of 65% lactose pellets were lower than those of 80% formulations.

According to Vervaet et al. (1995) , the bulk and tapped densities of pellets are determined to gain an idea of the uniformity of the particle size distribution. The very uniform pellets had the great bulk and tapped density. In addition , bulk density is indicative of the packing properties of spheres and is greatly dependent on the diameter of pellets (Hellen et al. , 1993b ; Sonaglio et al. , 1995 ; Woodruff and Nuessle , 1972). From the results it could be concluded that increase in uniformity of particle size and packing properties of pellets were obtained by using the modified starches in the pellet formulation. This did not related to the average diameter of pellets , D_{50} , that of pellets containing modified starches was greater than blank pellets. Because it was generally known that small size pellets of blank formulations were able to form a closer packing and resulted in high bulk density. It might be elucidated that the pellets without modified starches or blank pellets formed loosely agglomerates , thus lower bulk density was observed. The uniformity of particle size distribution was slightly affected by various DS of MGS because slight difference in bulk and tapped densities of pellets containing MGS with different DS were observed. The slight better uniform size distribution of pellets prepared with MGS at DS 0.32 and 0.26 than DS 0.16 was seen. MGS at DS 0.16 showed the highest viscosity so it could not spread uniformly in the mixture and resulted in wider size distribution.

The quantity of added water also influenced bulk and tapped densities of pellets. Mostly , increment of added water would lead to increase in bulk and/or tapped densities and resulted in more uniform size distribution of spheres (Malinowski and Smith , 1975). The greater bulk and tapped densities of 80% lactose pellets in comparison with 65% formulations indicated the more uniformity of size distribution. This might be due to the more uniform particle size

of powder mixture because of increasing the amount of lactose which showed the largest average particle size (see Table 20).

2.2.3 Hardness

The hardness values at various size fractions of 65% and 80% lactose pellets are illustrated in Figures 26-31 and Appendix IV (Tables 42-43). The statistical treatment of hardness data are presented in Appendix V (Tables 86-87 and 90-95). It could be seen that the hardness at any size fractions of pellets containing modified starches was significantly higher than their blank pellets. This was obviously seen in 80% lactose formulations (Figures 29-30). Generally , the strength or hardness of pellets increase with particle size increased (Vervaet et al. , 1995). This was confirmed by hardness at size fraction of 1000-4000 μm > 710-1000 μm > 500-710 μm. When comparison was taken between different amount of water , it could be seen that the higher the quantity of granulated water , the greater the hardness of the obtained pellets. However , unpredictable trend of the effect of water added on hardness of pellets at 500-710 μm was found (Figures 28 and 31). In 65% lactose pellet formulations , the hardness at 1000-1400 μm size fraction of pellets prepared by MGS with different DS , in all amounts of water , was comparable (Table 88 in Appendix V) whereas the ranked order of hardness at other sizes was as follows : hardness of using MGS with DS 0.26 > DS 0.32 > DS 0.16. In 80% lactose pellets , the effect of DS on hardness of spheres at 1000-1400 and 710-1000 μm size fractions was ranked in the order as follows :hardness of using MGS with DS 0.26 ≥ DS 0.32 > DS 0.16. However , At 500-710 μm size , the ranked order was as follows : hardness of using DS 0.32 > DS 0.26 ≈ DS 0.16 (Figure 31).

Comparison of pellet hardness between formulations containing modified starches and blank formulations revealed that the former produced pellets with greater hardness. This could be explained that modified starch upon wetting with added water gradually became a highly viscous gel and exerted the greater binding force between particles during the granulation step (Baie et al. ,

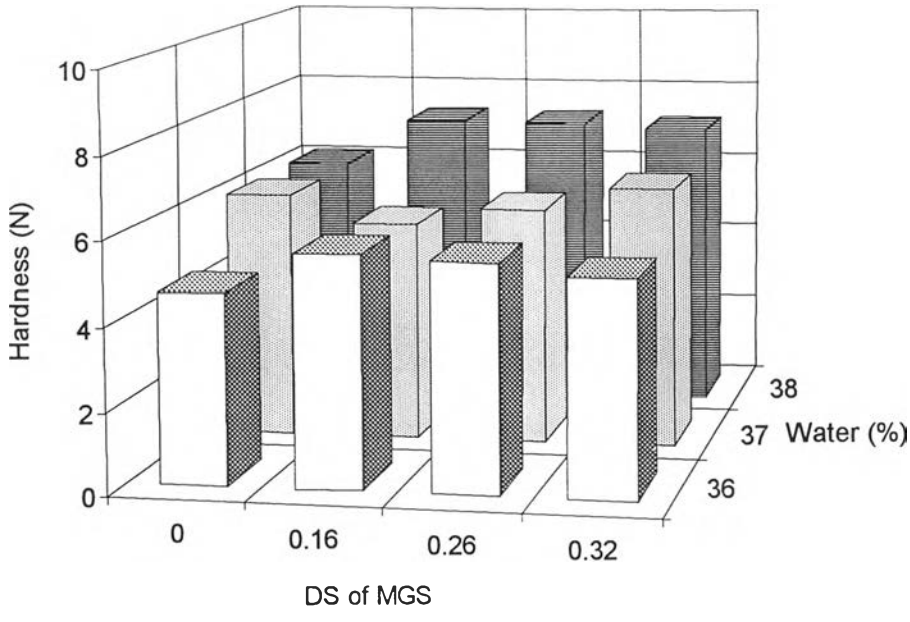


Figure 26 Histograms for hardness at 1000-1400 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

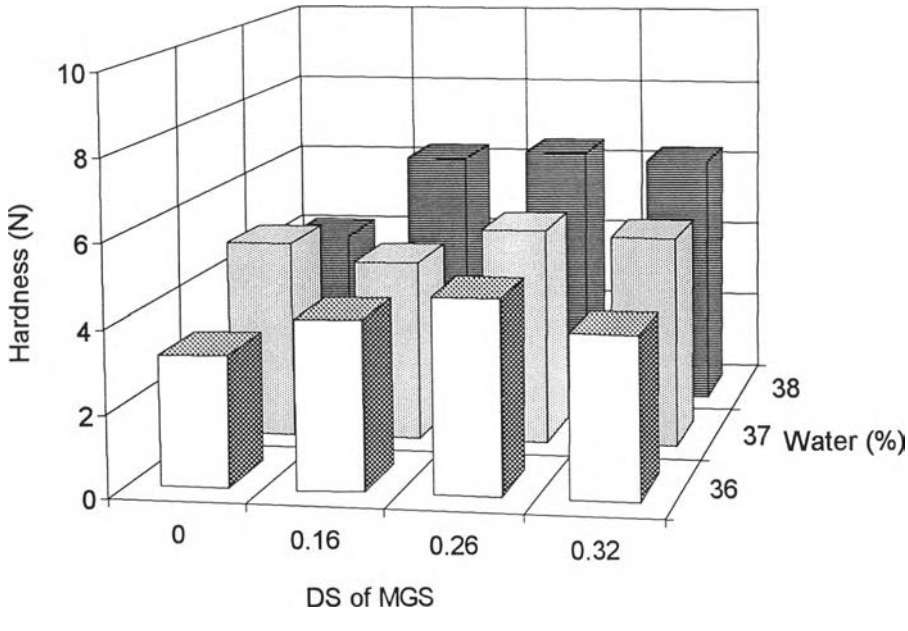


Figure 27 Histograms for hardness at 710-1000 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

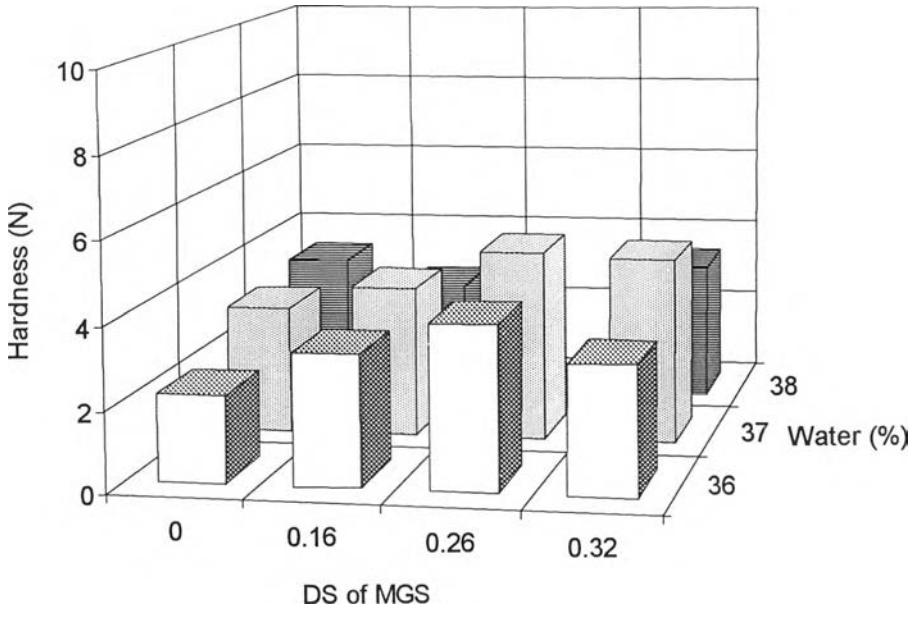


Figure 28 Histograms for hardness at 500-710 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

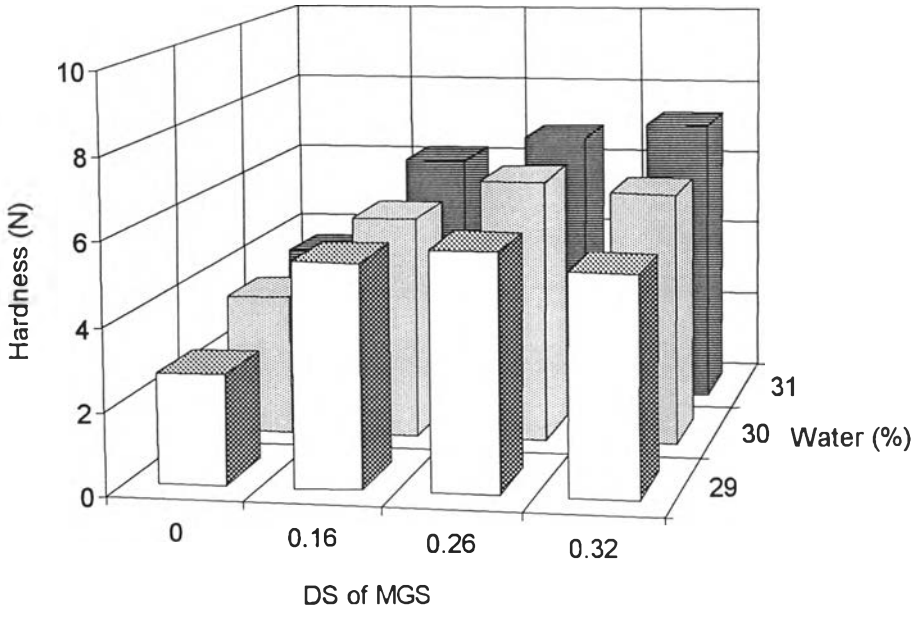


Figure 29 Histograms for hardness at 1000-1400 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

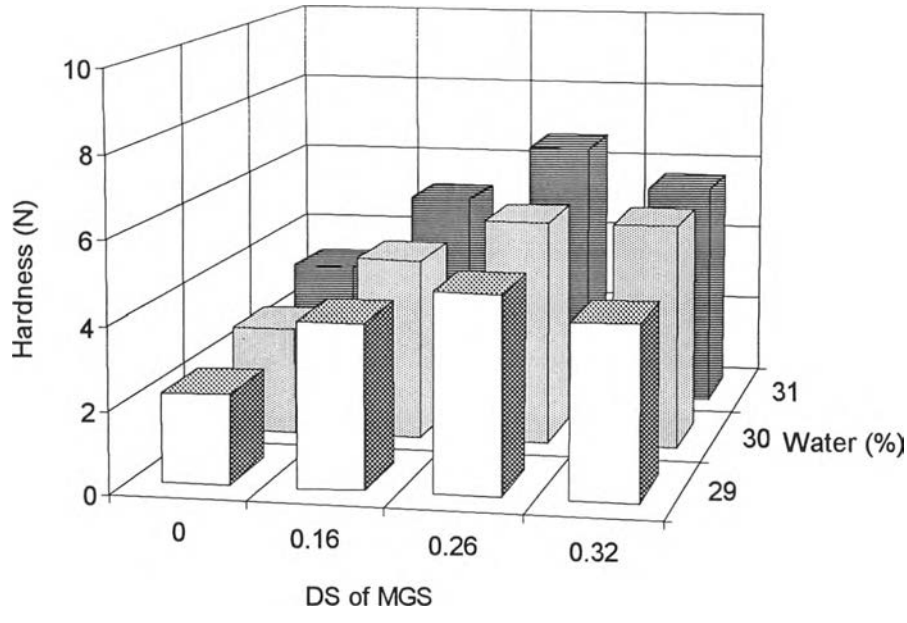


Figure 30 Histograms for hardness at 710-1000 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

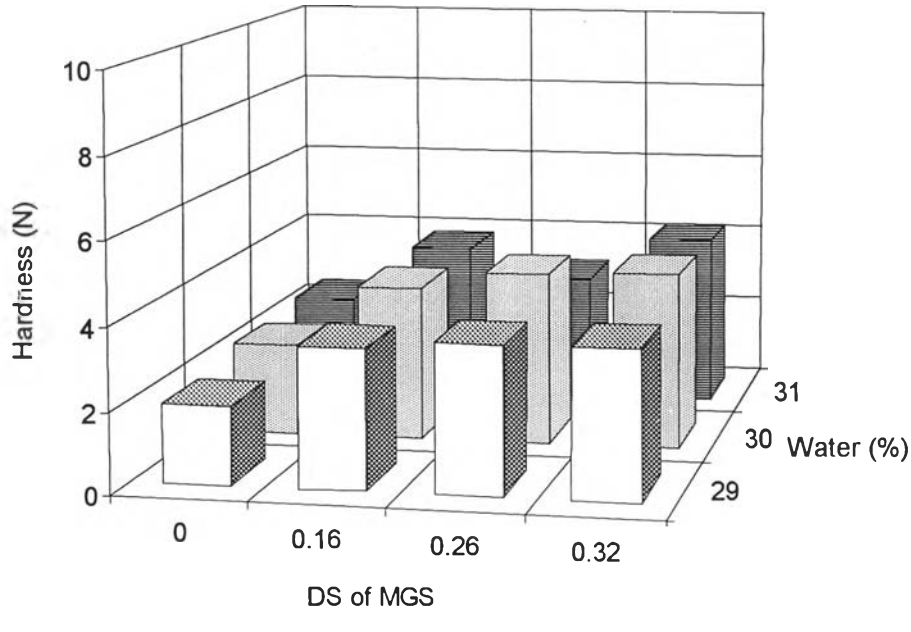


Figure 31 Histograms for hardness at 500-710 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

1995 , Tasana Pituksuteepong , 1995). As a result , the interparticular binding strength in extrudates and obtained pellets was consequently increased when compared with blank pellets. In both 65 and 80% lactose models , it was found that , in most cases , pellets containing MGS with DS 0.26 had the highest hardness whereas those containing MGS with DS 0.16 had the lowest. It might be due to the high viscosity of MGS at DS 0.16 when contacted with water influenced the homogeneity of distribution of MGS through the whole powder mixture. The material with higher viscosity could distribute less uniform than the lower one (Dingwall and Ismail , 1977). So , the greater binding force of the highest viscous MGS could not spread uniformly and resulted in less mechanical strength of spheres. In spite of the very low viscosity of MGS at DS 0.32 , its binding strength was not enough for being a part of the greater hardness. In other words , the relatively medium viscosity of MGS at DS 0.26 could disperse uniformly in the powder mixture and had enough binding force to produce pellets with higher mechanical strength.

For the different amounts of water , it might be noted that the hardness of pellets increased with increasing water level. This result are in accordance with data reported by Baert and Remon (1993) , and Otsuka et al. (1994). This could be explained that the high level of water resulted in the high binding bridges between particles built up by MGS and recrystallization of lactose particles which were responding for the mechanical strength of pellets , thus the greater hardness was obtained. However , in some cases , the hardness was increased by reducing the amount of water. This was apparent in 500-710 μm size of pellets. A possible explanation was that greater interparticular contact and bonding during processing in extruder was also obtained in lower water level because it required greater extrusion forces.

The pharmaceutical pellets in the size range of 710-1000 μm is commonly employed. In this experiment it was found that the effect of DS on hardness of pellets of 710-1000 μm size range was similar at all levels of added granulated water. In addition , the influence of water on hardness of 710-1000

μm fraction was also similar at all DS of MGS. Therefore , the pellets of that size range was a representative of the resulting pellets.

2.2.4 Friability

Percent friability of various size fraction of 65% and 80% lactose pellets are shown in Figures 32-37 and in Appendix IV (Tables 48-49) . Some percent friability values was not available due to the little amount of some size fractions was obtained during size classification and was not enough for friability tests. The test method chosen for these experiments put mechanical stress on the pellets. Percent friability varied between 0.65-1.47% and 0.03-1.31% for 65% lactose formulations prepared with or without modified starches , respectively. For 80% lactose model , percent friability of pellets containing modified starches was in the range of 1.02-1.41% whereas of blank pellets was in the range of 1.38-3.73%. It could be observed that friability values of lactose pellets were less than 2% except 80% lactose blank pellets at the lowest amount of adding water which showed the friability value up to 3.75% (Figure 37). Furthermore , the percent friability did not related to the size or diameter of pellets.

In 65% lactose pellet formulations , blank pellets at 1000-1400 μm size exhibited slightly more friable pellets when compared with the formulations containing modified starches (Figure 32). However , in other size fractions , the comparable or less percent friability of blank pellets was obtained. In comparison between pellets prepared by different DS of modified starch , at 1000-1400 μm size fraction , MGS with DS 0.16 led to produce slightly less friable pellets than other DS but the conclusion could not be made about the effect of different DS of MGS on pellet friability at other size fractions. Consideration on the effect of various amounts of water on pellet friability at any size fractions was mostly in the following order : friability of pellets using 37% water < 36% water ≤ 38% water. However , percent friability of blank pellets using 38% of added water was the lowest. As can be seen from the testing results of 80% lactose pellets , percent friability values of modified starches containing pellets was slightly

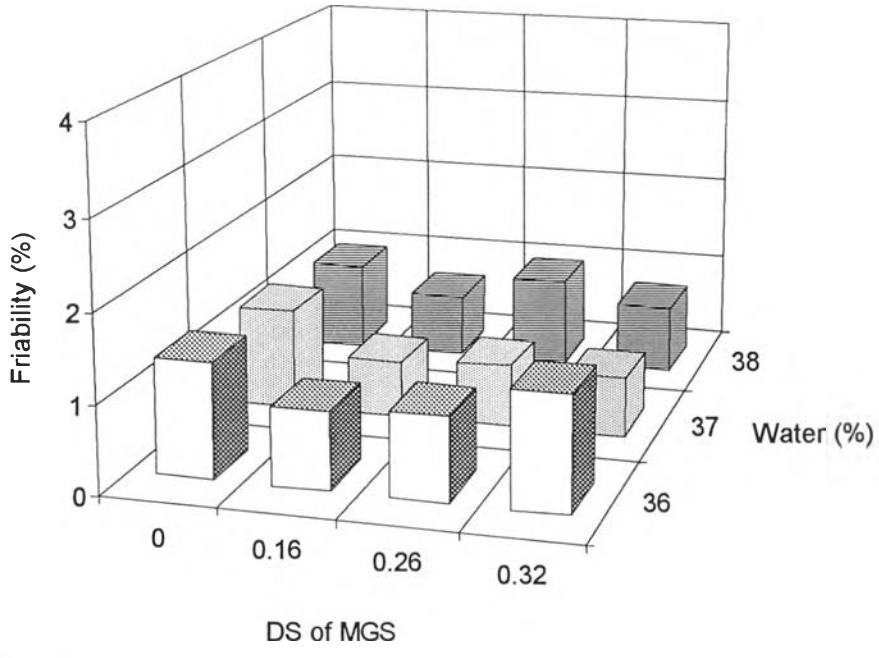


Figure 32 Histograms for percent friability at 1000-1400 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

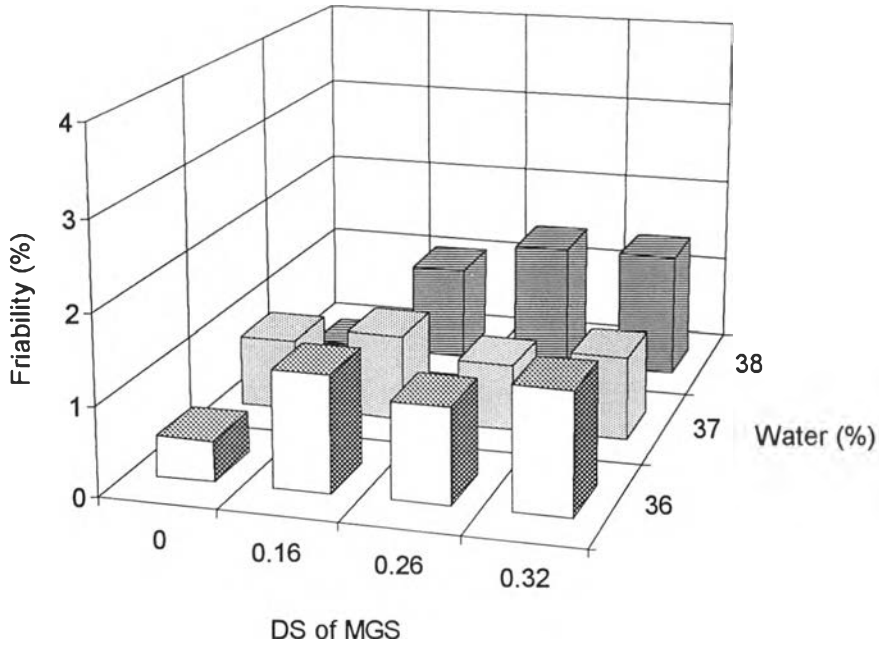


Figure 33 Histograms for percent friability at 710-1000 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

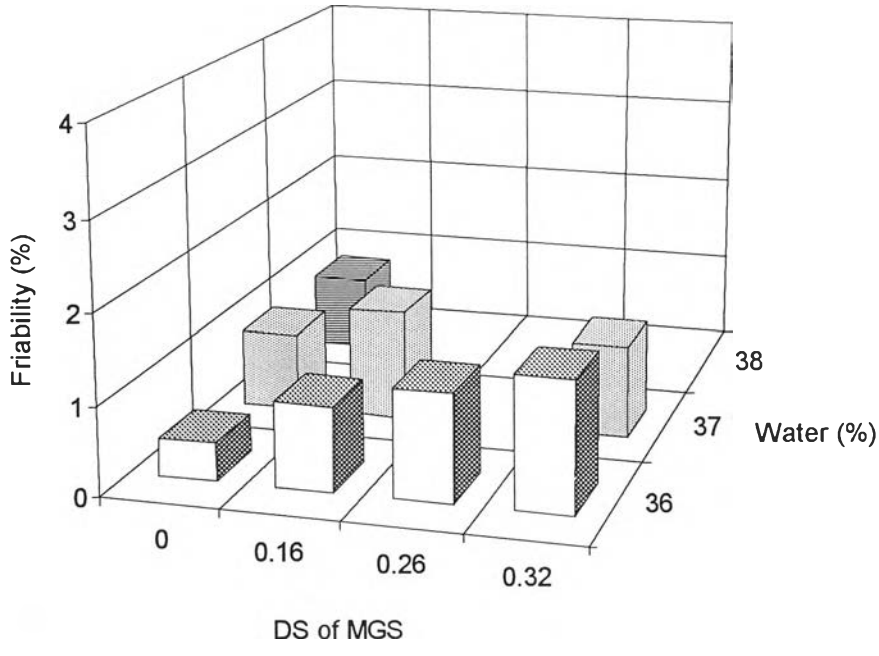


Figure 34 Histograms for percent friability at 500-710 μm-size fraction of 65% lactose pellets prepared with different DS of MGS and amounts of water.

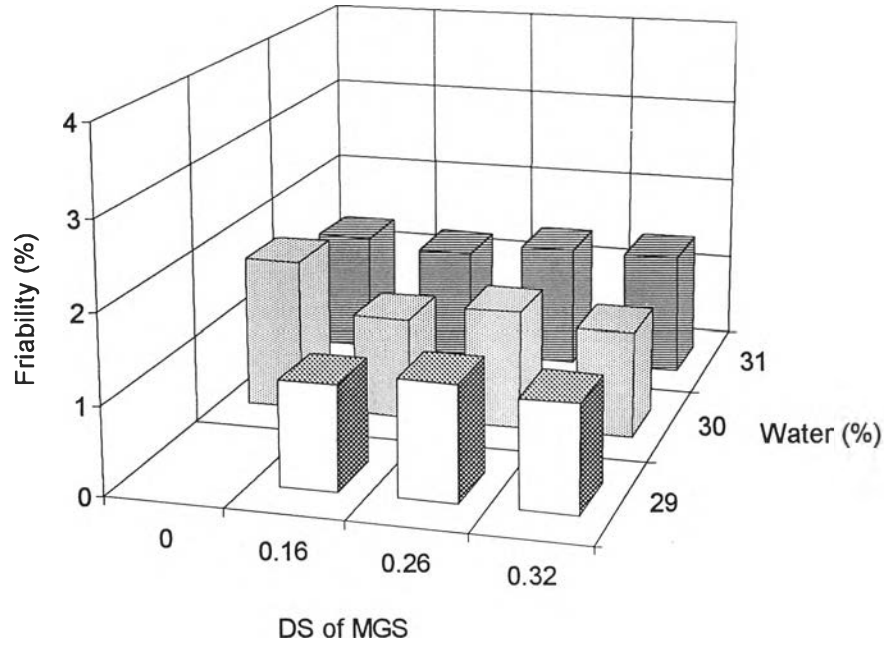


Figure 35 Histograms for percent friability at 1000-1400 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

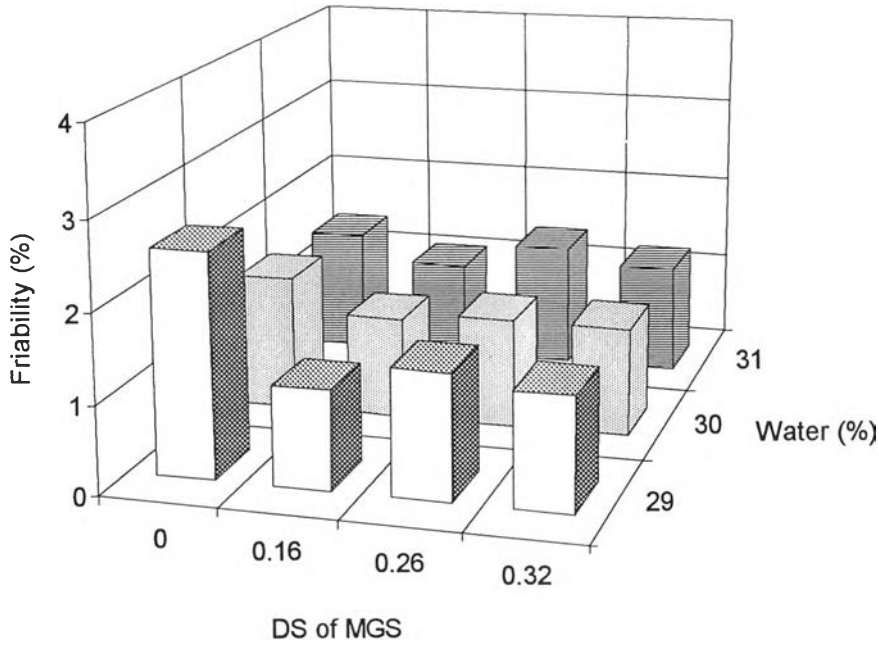


Figure 36 Histograms for percent friability at 710-1000 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

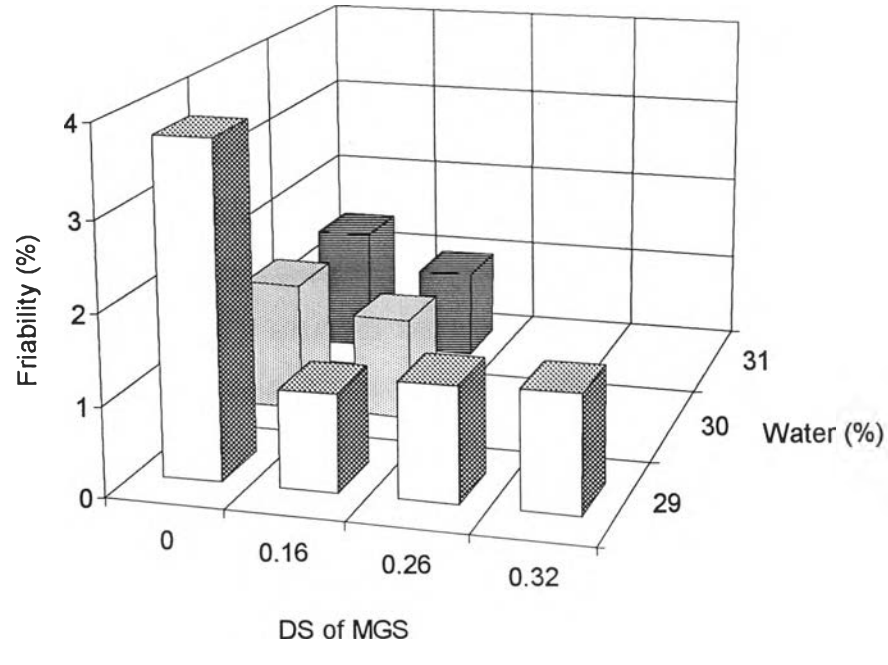


Figure 37 Histograms for percent friability at 500-710 μm-size fraction of 80% lactose pellets prepared with different DS of MGS and amounts of water.

different and less than those of blank pellets (Figures 35-37). Percent friability of pellets at 1000-1400 μm size and using 31% water was higher than that using 29% and 30% water but the effect of added water on friability in other size fractions could not be concluded . On the other hand , the ranked order of blank pellet friability influenced by the amount of water was : friability of using 31% water < 30% water < 29% water .

As previously mentioned , percent friability of modified starches containing pellets was less than 2% which were mechanically acceptable , e.g. for coating purposes. Although the numerical values of pellets friability in some cases , particular in blank pellets of 80% lactose formulation , seemed to be high due to the robust test method used (Hellen et al. , 1993b). In general , friability is an indication of pellet strength or hardness. Thus , the negative correlation of hardness and friability should be observed , i.e. the more pellet hardness was , the less friability obtained (Eerikainen , 1991 ; Reynold , 1970 ; Vervaet et al. , 1995). However , no correlation was found between these two properties in this experiment. Because the friability of the pellets with more hardness prepared by MGS with DS 0.26 was greater in comparison to those prepared by other DS. In addition , the higher the amount of added water , the greater the hardness and friability of pellets , especially at 38% water of 65% lactose model or 31% water of 80% lactose model. This result did not agreed with Millili and Schwartz (1990) who noted that as the amount of water in the mixture used for granulation increased , the resultant pellets was generally less friable. Nevertheless , this correlation between amount of added water and percent friability was found in blank pellet formulations. Based on the above results , however , it could be concluded that the friability of pellets prepared with modified starches was mostly lower than blank pellets.

2.2.5 Sphericity

In this study , degree of sphericity of pellets was derived from some parameters as aspect ratio and form factor which based on a two-dimensional

image of the particle. Image analysis method was used to obtain these parameters and the results at various size fractions are depicted in Tables 23-24 and Appendix V (Analysis of variance data in Tables 106-107 , 110-114). For optimal round particles , aspect ratio and form factor close to unity are obtained so , from the Table , the high values are expected. Aspect ratio of modified starches containing pellets was significantly higher than or closer to unity than that of blank pellets except aspect ratio of pellet at 500-710 μm size which exhibited no difference when compared with blank pellets. Comparison between pellets using MGS with different DS but the same amount of water , non-significant difference of aspect ratio was found. Slight difference was observed between aspect ratio of pellets prepared with various amounts of added water. For 65% lactose pellets , the rank of aspect ratio of pellets at 1000-1400 μm size when using different quantities of water was ordered as : aspect ratio of pellets using 38% water > 37% water > 36% water. However , only significant difference between 38% and 37% of water was obtained. The difference of aspect ratio at the other size fractions was also non-significant. It could be observed that the aspect ratio of spheroids prepared by 37% of granulated water exhibited slight difference among different three size groups and it was also considered in the same manner , i.e. aspect ratio of size 710-1000 ≥ 500-710 ≥ 1000-1400 μm. In 80% lactose formulations , the influence of added water level on aspect ratio was similar to 65% lactose pellets. The aspect ratio of formulations using different amounts of water in all DS of MGS mostly illustrated non-significant difference. Moreover , the aspect ratio of spheres manufactured with 30% of water presented the similar values among various size fractions.

As can be seen from the Tables 23-24 , form factor of pellets containing modified starches particular in 1000-1400 μm size fraction was slightly higher than that of blank pellets , although no difference was observed in the other sizes. Furthermore , using different DS of MGS or amounts of added water produced pellets with similar value of form factor.

Table 23 Sphericity values at various size fractions of 65% lactose pellets prepared with different DS of MGS and amounts of water.

DS	MGS (%w/w)	Water (%)	Formulation	Aspect ratio			Form factor		
				1000-1400 μm	710-1000 μm	500-710 μm	1000-1400 μm	710-1000 μm	500-710 μm
0.32	0.5	38	$6L_{316}$	0.91 (0.04*)	0.90 (0.04)	0.87 (0.05)	0.97 (0.02)	0.97 (0.02)	0.97 (0.02)
		37	$6L_{317}$	0.90 (0.05)	0.91 (0.03)	0.89 (0.04)	0.97 (0.02)	0.97 (0.01)	0.97 (0.01)
		36	$6L_{318}$	0.86 (0.05)	0.88 (0.05)	0.90 (0.04)	0.96 (0.02)	0.97 (0.02)	0.96 (0.02)
0.26	0.5	38	$6L_{21}$	0.91 (0.03)	0.90 (0.03)	0.88 (0.06)	0.98 (0.01)	0.98 (0.01)	0.94 (0.04)
		37	$6L_{22}$	0.89 (0.05)	0.91 (0.03)	0.90 (0.03)	0.97 (0.01)	0.98 (0.02)	0.97 (0.02)
		36	$6L_{23}$	0.87 (0.04)	0.91 (0.04)	0.87 (0.06)	0.97 (0.02)	0.98 (0.01)	0.97 (0.02)
0.16	0.5	38	$6L_{11}$	0.90 (0.04)	0.92 (0.04)	0.88 (0.05)	0.97 (0.01)	0.97 (0.02)	0.95 (0.04)
		37	$6L_{12}$	0.89 (0.05)	0.91 (0.02)	0.90 (0.03)	0.97 (0.02)	0.96 (0.02)	0.97 (0.04)
		36	$6L_{13}$	0.89 (0.05)	0.90 (0.04)	0.87 (0.05)	0.96 (0.02)	0.98 (0.01)	0.97 (0.01)
0**	-	38	B.1	0.88 (0.05)	0.87 (0.07)	0.91 (0.06)	0.97 (0.01)	0.97 (0.02)	0.97 (0.03)
		37	B.2	0.84 (0.05)	0.87 (0.06)	0.89 (0.05)	0.94 (0.05)	0.97 (0.02)	0.97 (0.02)
		36	B.3	0.85 (0.05)	0.86 (0.06)	0.88 (0.05)	0.93 (0.02)	0.95 (0.02)	0.95 (0.03)

* Standard deviation ** Blank pellets

Table 24 Sphericity values at various size fractions of 80% lactose pellets prepared with different DS of MGS and amounts of water.

DS	MGS (%w/w)	Water (%)	Formulation	Aspect ratio			Form factor		
				1000-1400 μm	710-1000 μm	500-710 μm	1000-1400 μm	710-1000 μm	500-710 μm
0.32	0.5	31	$8L_{32}$	0.90 (0.02*)	0.91 (0.03)	0.85 (0.07)	0.96 (0.03)	0.98 (0.01)	0.96 (0.02)
		30	$8L_{33}$	0.91 (0.04)	0.91 (0.04)	0.88 (0.04)	0.98 (0.01)	0.98 (0.01)	0.96 (0.02)
		29	$8L_{34}$	0.88 (0.05)	0.89 (0.05)	0.88 (0.04)	0.96 (0.03)	0.96 (0.01)	0.96 (0.02)
0.26	0.5	31	$8L_{21}$	0.89 (0.05)	0.90 (0.04)	0.82 (0.08)	0.97 (0.01)	0.98 (0.01)	0.95 (0.03)
		30	$8L_{22}$	0.90 (0.04)	0.90 (0.04)	0.88 (0.05)	0.98 (0.01)	0.98 (0.01)	0.97 (0.01)
		29	$8L_{23}$	0.89 (0.04)	0.90 (0.04)	0.86 (0.06)	0.96 (0.02)	0.98 (0.01)	0.97 (0.01)
0.16	0.5	31	$8L_{11}$	0.89 (0.04)	0.90 (0.04)	0.88 (0.04)	0.97 (0.02)	0.98 (0.01)	0.97 (0.01)
		30	$8L_{12}$	0.89 (0.04)	0.89 (0.05)	0.87 (0.06)	0.97 (0.02)	0.98 (0.01)	0.97 (0.01)
		29	$8L_{13}$	0.88 (0.05)	0.90 (0.05)	0.85 (0.07)	0.96 (0.02)	0.97 (0.01)	0.96 (0.02)
0**	-	31	B.4	0.85 (0.06)	0.86 (0.05)	0.86 (0.06)	0.94 (0.03)	0.95 (0.02)	0.97 (0.02)
		30	B.5	0.87 (0.04)	0.86 (0.04)	0.87 (0.05)	0.94 (0.03)	0.96 (0.02)	0.96 (0.02)
		29	B.6	0.80 (0.01)	0.86 (0.06)	0.86 (0.04)	0.91 (0.05)	0.93 (0.05)	0.95 (0.03)

* Standard deviation ** Blank pellets

Generally , the roundness or sphericity of the pellets is important for successfully coating , for improving the flowability and , thus , is optimal for controlled release products (Baert et al. , 1993 ; Hellen and Yliruusi , 1993). The applicability of pellets for those purposes can be increased by using the high spherical particle. For both 65% and 80% lactose formulations , it could be concluded that modified starches at any DS containing pellets were significantly rounder than blank pellets. This was obviously seen from aspect ratio. Modified starch containing extrudates might have the more appropriate surface plasticity and binding properties to be converted into rounder spheres than blank extrudates. This was probably due to the modified starch when wetted with granulated water formed a thin film around the extrudate , therefore , it could be easily spheronized. The formation of thin film at the surface might also be due to the moisture which forced out from the interior to the outer surface as the extrudates were spun on the rotating plate (Wan et al. , 1993). These plasticizing and binding properties might increased besides those received from microcrystalline cellulose. However , the different degree of substitution of modified starches did not influence the aspect ratio and consequent sphericity of the pellets. In previous studies , the amount of granulation liquid have been found to has a pronounced effect on the sphericity of pellets where pellets with more water content were rounder (Hellen and Yliruusi, 1993 ; Linder and Kleinebudde, 1994 ; Wan et al. , 1993). But the amount of water used in this study slightly affected the shape parameters . The difference in results might due to the plastic properties of wet mass was not sensitive to the 1% difference in added water content.

In all formulations of 65 and 80% lactose pellets , it could not be seen the significant difference of form factor of the obtained pellets , even in pellets prepared by modified starches when compared with blank pellets. It was observed that the measured values for form factor exhibited the same dependencies as the values for aspect ratio but closer to one than aspect ratio. However , Linder and Kleinebudde (1994) suggested that the form factor does not distinguish between round or less round pellets as exactly as the aspect ratio.

The form factor is an important factor in the case of irregularly shaped particles. Moreover , aspect ratio could be detected more precisely than form factor by image analysis , especially for small particles as pellets (Kleinebudde , 1993).

2.2.6 Pellets Characteristics , Surface and Internal Structure by SEM.

The general characteristic of pellet including pellet shape at various size fractions were examined using scanning electron microscope (SEM) at different magnifications (x15 and x35). The surface and cross-sectioned morphology of pellets representing by pellets at 710-1000 μm size fraction were also observed at x750 and x150 magnifications. These results of 65% lactose formulations are shown in Figures 38-45 and these of 80% lactose pellets are depicted in Figures 46-53. Three formulations which prepared with the same water content (37% water for 65% lactose pellets and 29% water for 80% lactose pellets) were chosen from each of three degree of substitution to represent the characteristics and shape of pellets in each model. Since no difference of general characteristics and shape among pellets using different quantities of added water was observed except the size or average diameter. These three formulations were compared with one formulation of blank pellets. In both 65% and 80% lactose pellets , it could be seen from the figures that modified starch containing pellets were more spherical , larger size and slightly less agglomeration than blank pellets (Figures 38A-41A and 46A-49A). Comparison between the unsized pellets prepared by MGS at different DS , DS 0.26 produced pellets with the largest particle size (Figure 39A) , however , the roundness of pellets at any size fractions exhibited no difference. These results were in accordance with the previous described in particle size distribution and sphericity determinations.

For surface and internal structure , all pellet formulations in each model were compared. The surface conditions of 65% and 80% model showed the same characters. In general , pellets with smooth surface were suitable for coating purposes. Anyhow , in this study , perfectly smooth surface was not obtained in all pellet formulations , small crumbs were found. It could be assumed

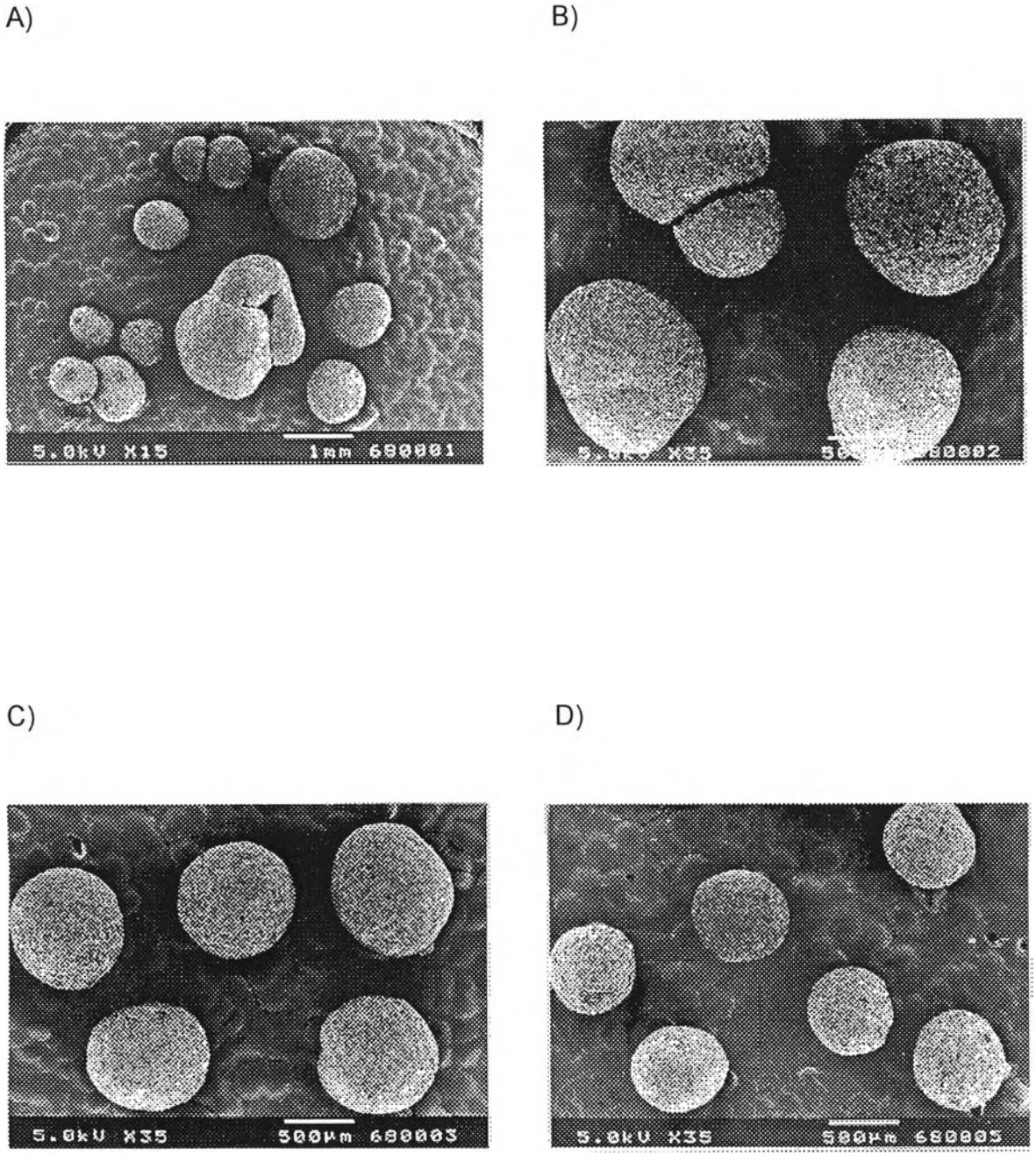


Figure 38 Photomicrographs presenting pellet characteristics of $6L_{317}$ using 0.5% w/w of MGS with DS 0.32 and 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

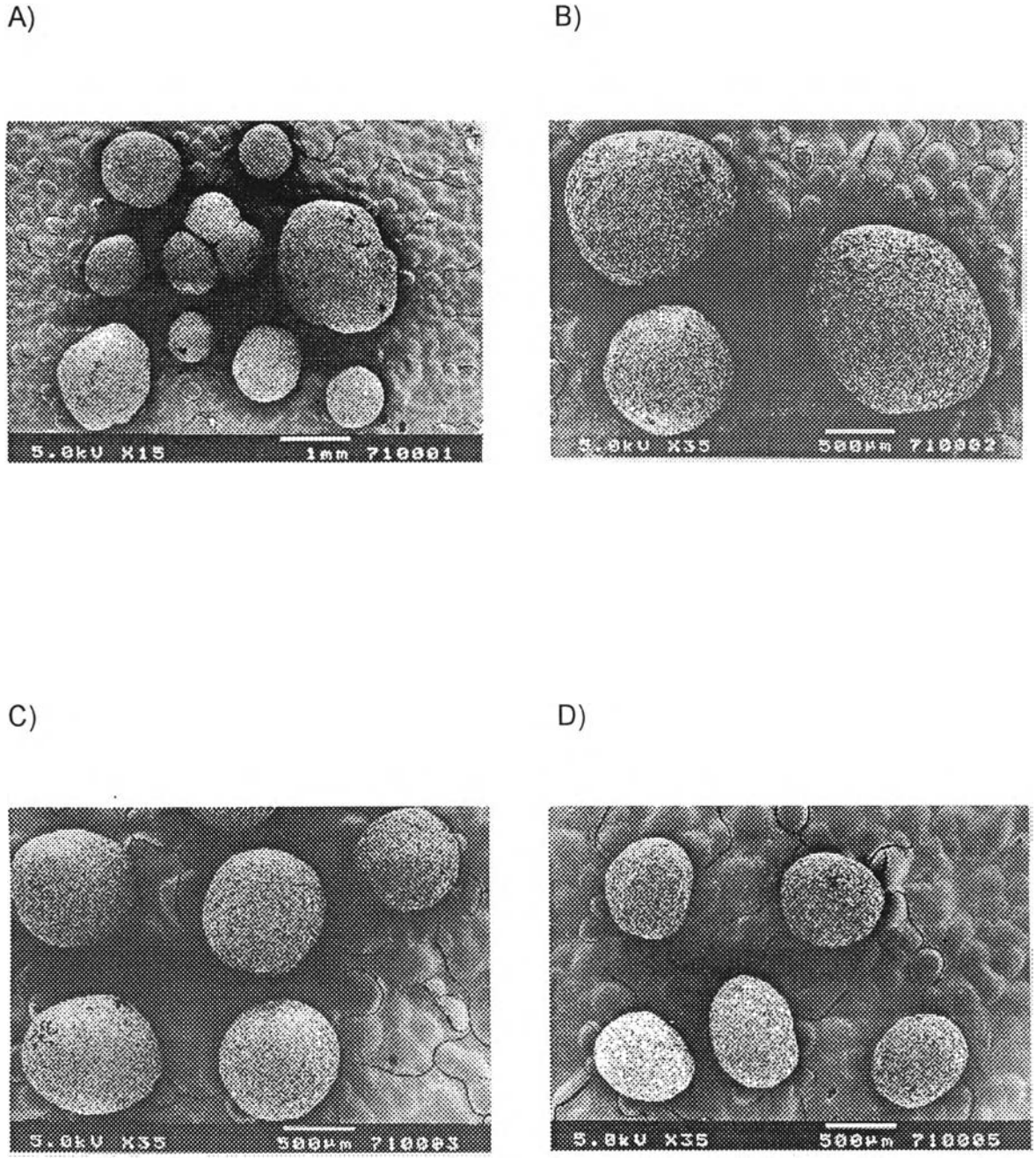
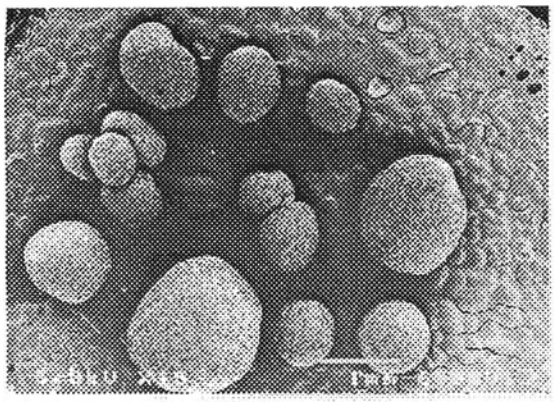
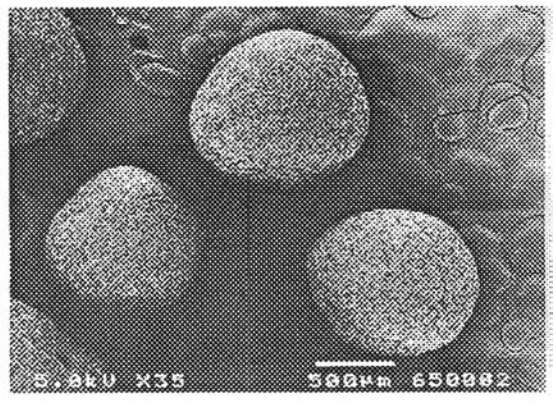


Figure 39 Photomicrographs presenting pellet characteristics of $6L_{22}$ using 0.5% w/w of MGS with DS 0.26 and 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

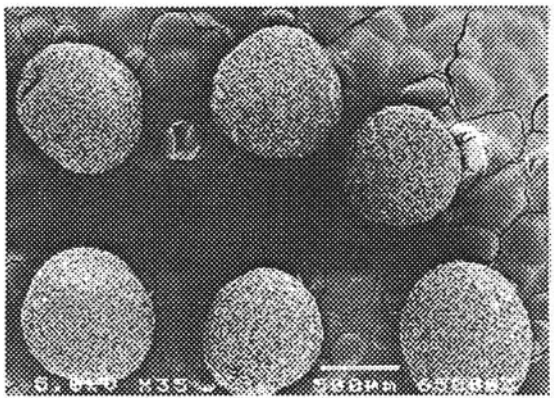
A)



B)



C)



D)

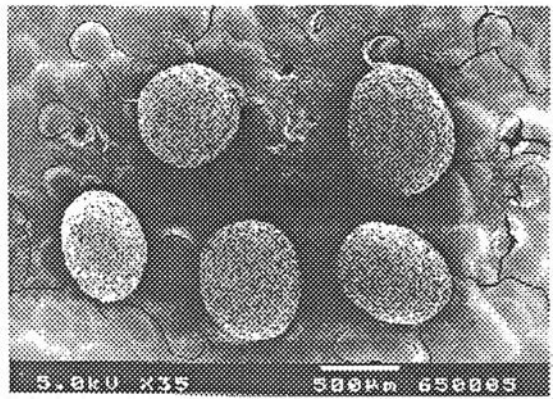
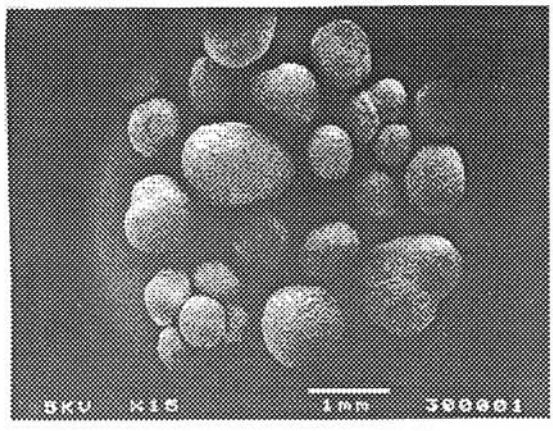
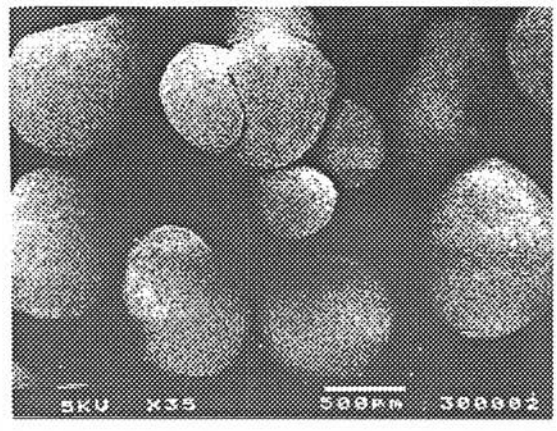


Figure 40 Photomicrographs presenting pellet characteristics of $6L_{12}$ using 0.5% w/w of MGS with DS 0.16 and 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

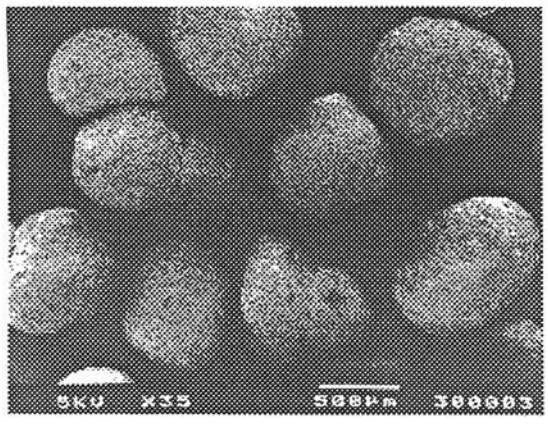
A)



B)



C)



D)

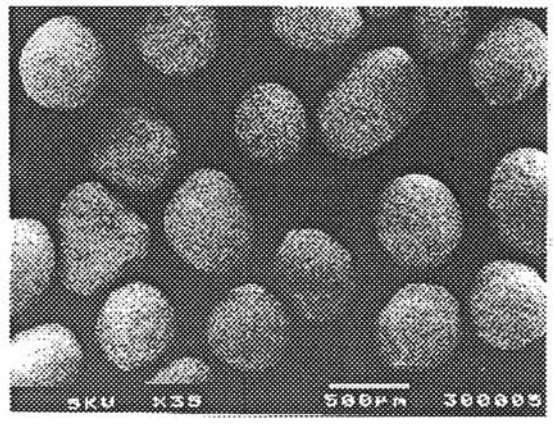
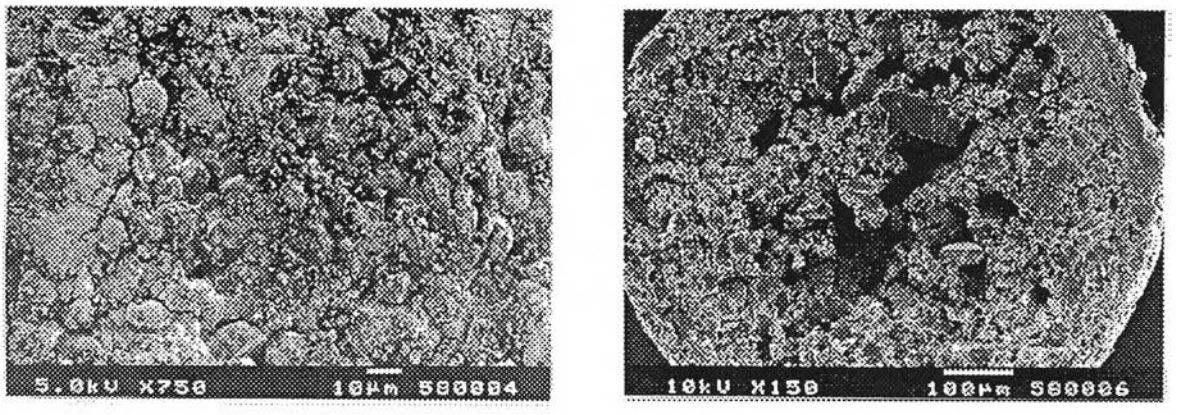
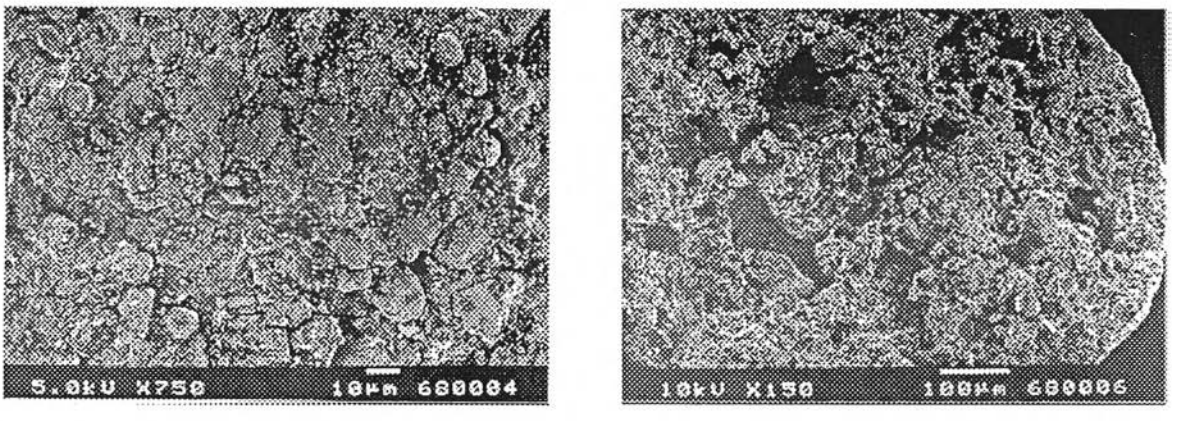


Figure 41 Photomicrographs presenting characteristics of 65% lactose blank pellet (B.2) using 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

A)



B)



C)

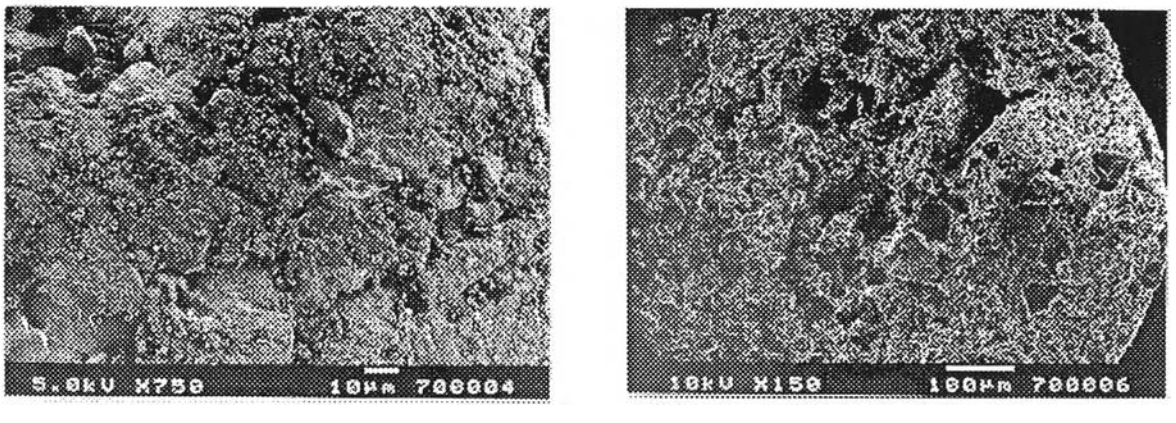
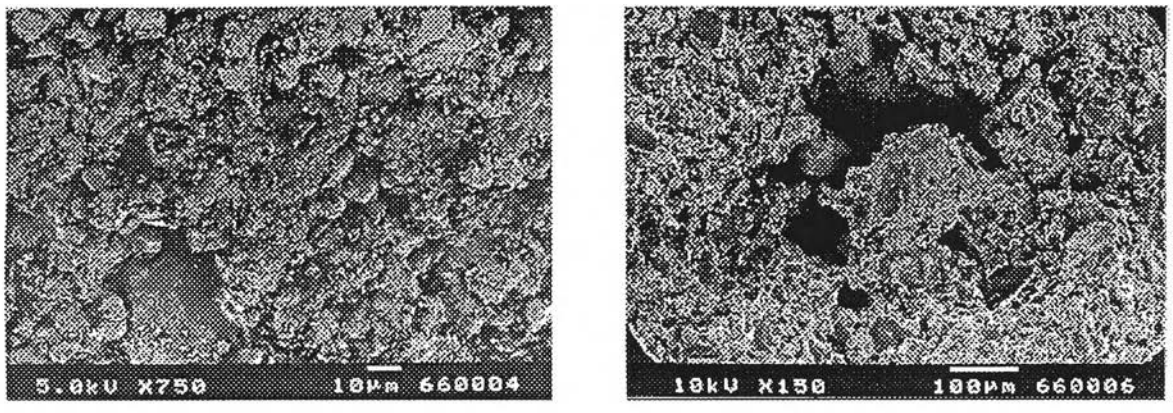
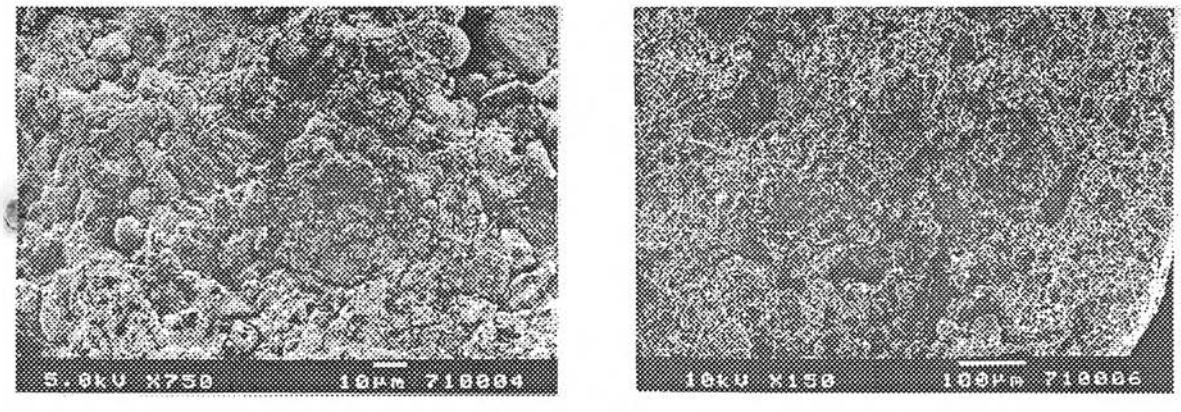


Figure 42 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% lactose pellet formulations using 0.5% w/w of MGS with DS 0.32 and different amounts of water : A) $6L_{316}$ (38%), B) $6L_{317}$ (37%), C) $6L_{318}$ (36%)

A)



B)



C)

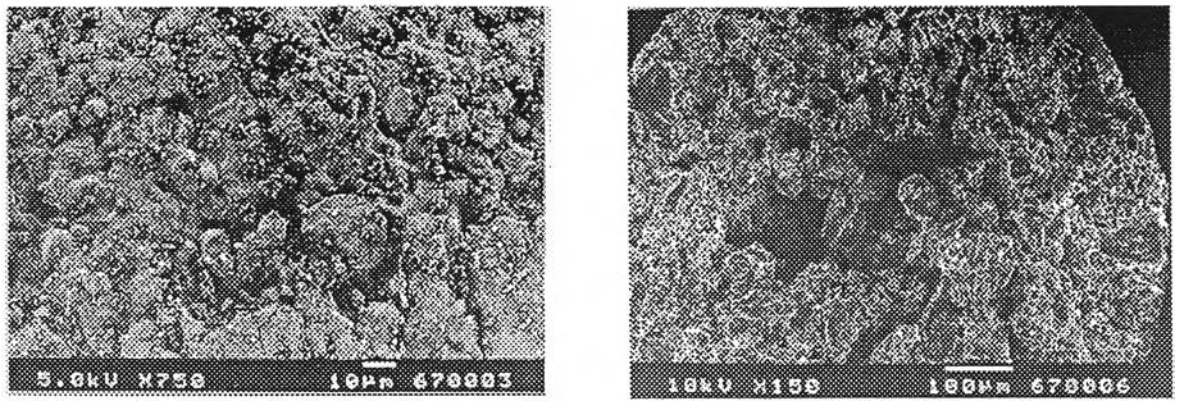
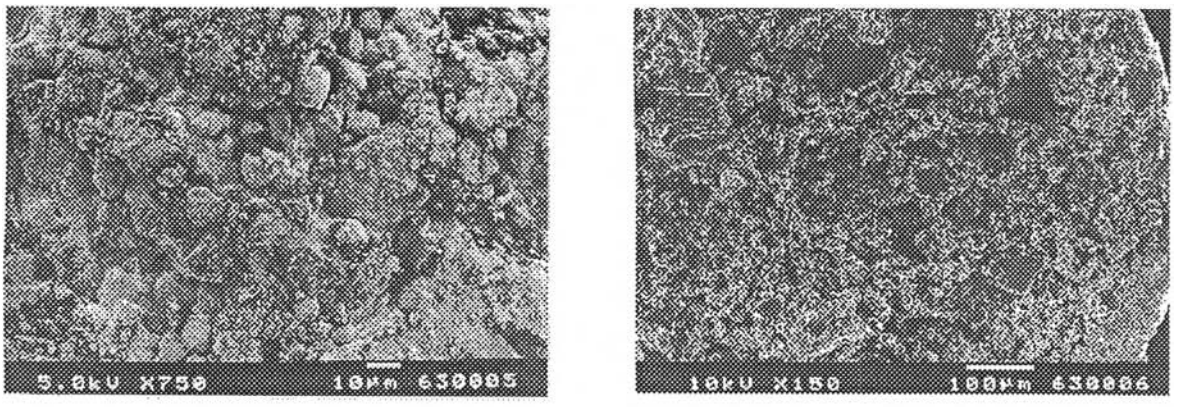
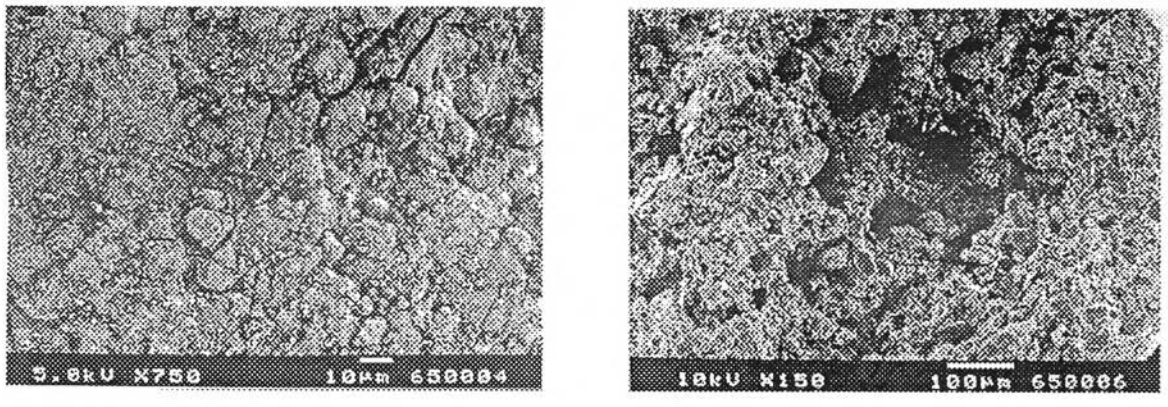


Figure 43 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% lactose pellet formulations using 0.5% w/w of MGS with DS 0.26 and different amounts of water : A) $6L_{21}$ (38%), B) $6L_{22}$ (37%), C) $6L_{23}$ (36%)

A)



B)



C)

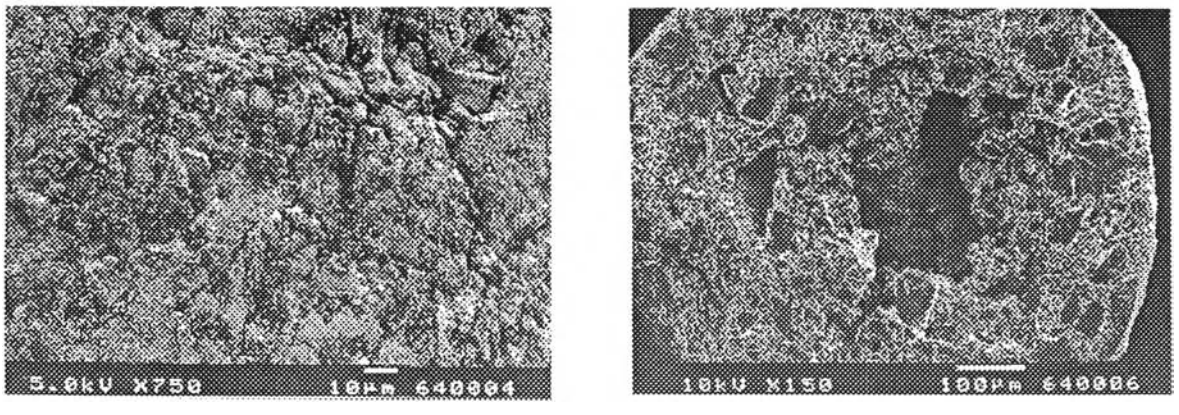
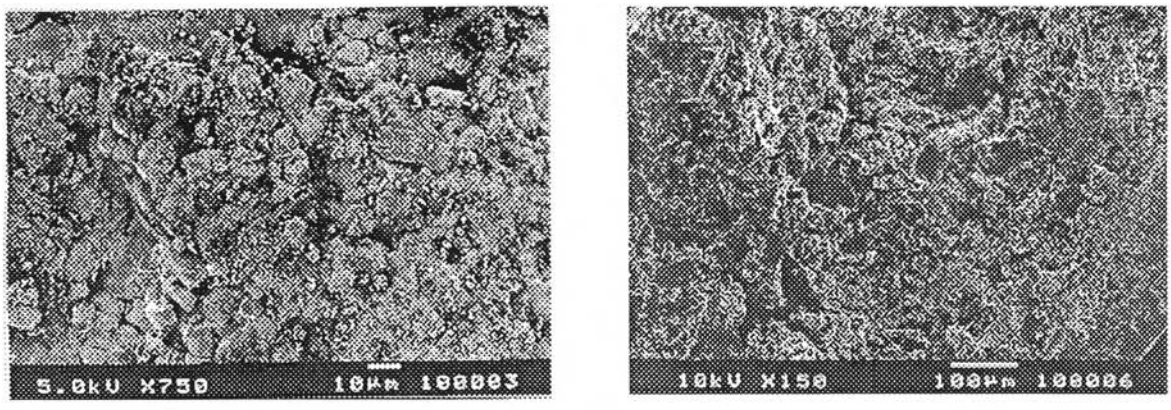
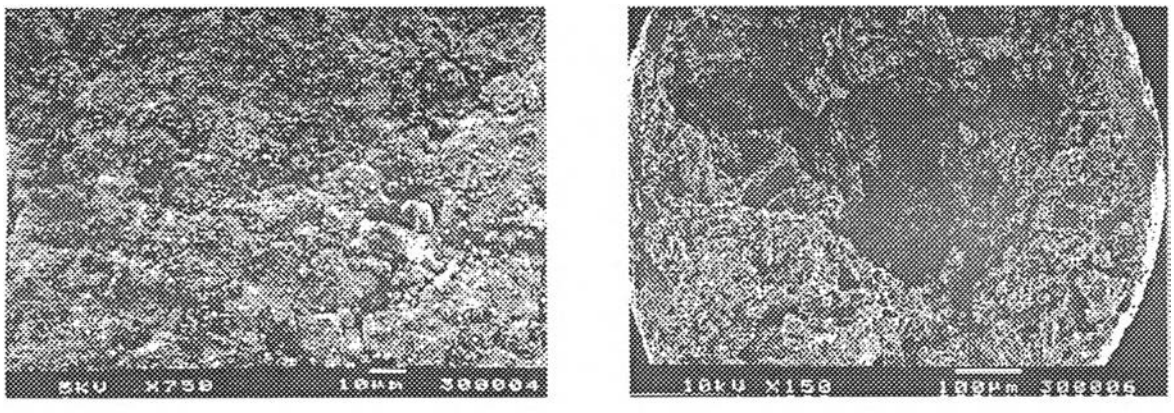


Figure 44 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% lactose pellet formulations using 0.5% w/w of MGS with DS 0.16 and different amounts of water : A) $6L_{11}$ (38%), B) $6L_{12}$ (37%), C) $6L_{13}$ (36%)

A)



B)



C)

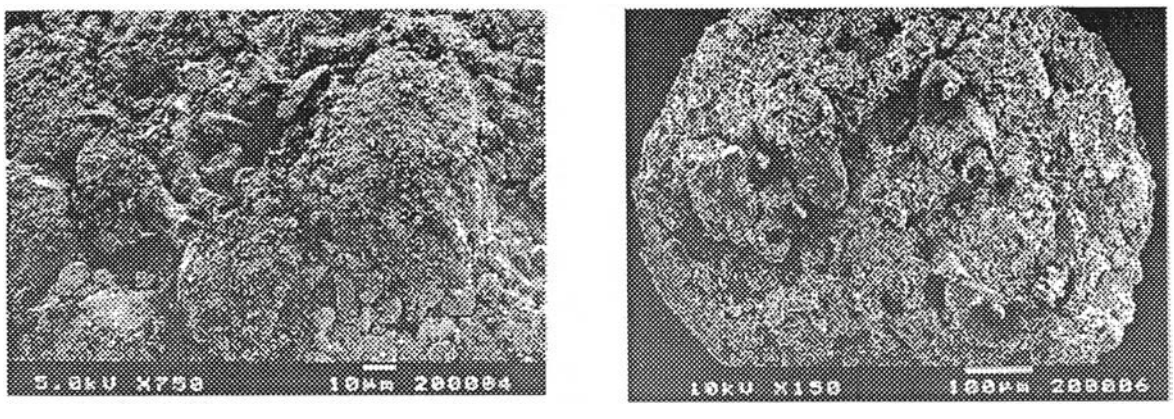


Figure 45 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% lactose blank pellets using different amounts of water : A) B.1 (38%), B) B.2 (37%), C) B.3 (36%)

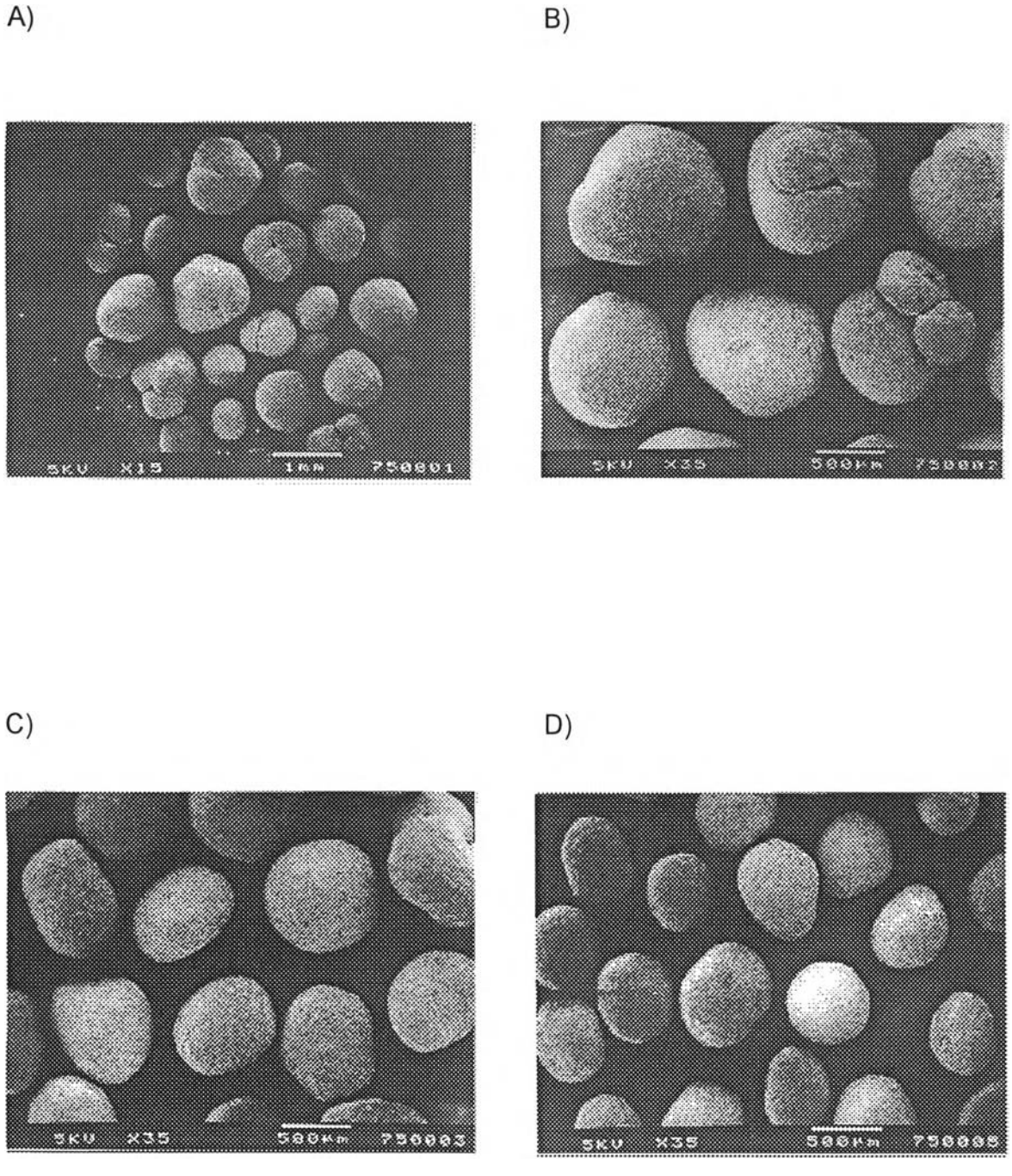


Figure 46 Photomicrographs presenting pellet characteristics of $8L_{34}$ using 0.5% w/w of MGS with DS 0.32 and 29% of water : A) Unsized pellets x 15, B) Size 1000-1400 μm x 35, C) Size 710-1000 μm x 35 and D) Size 500-710 μm x 35.

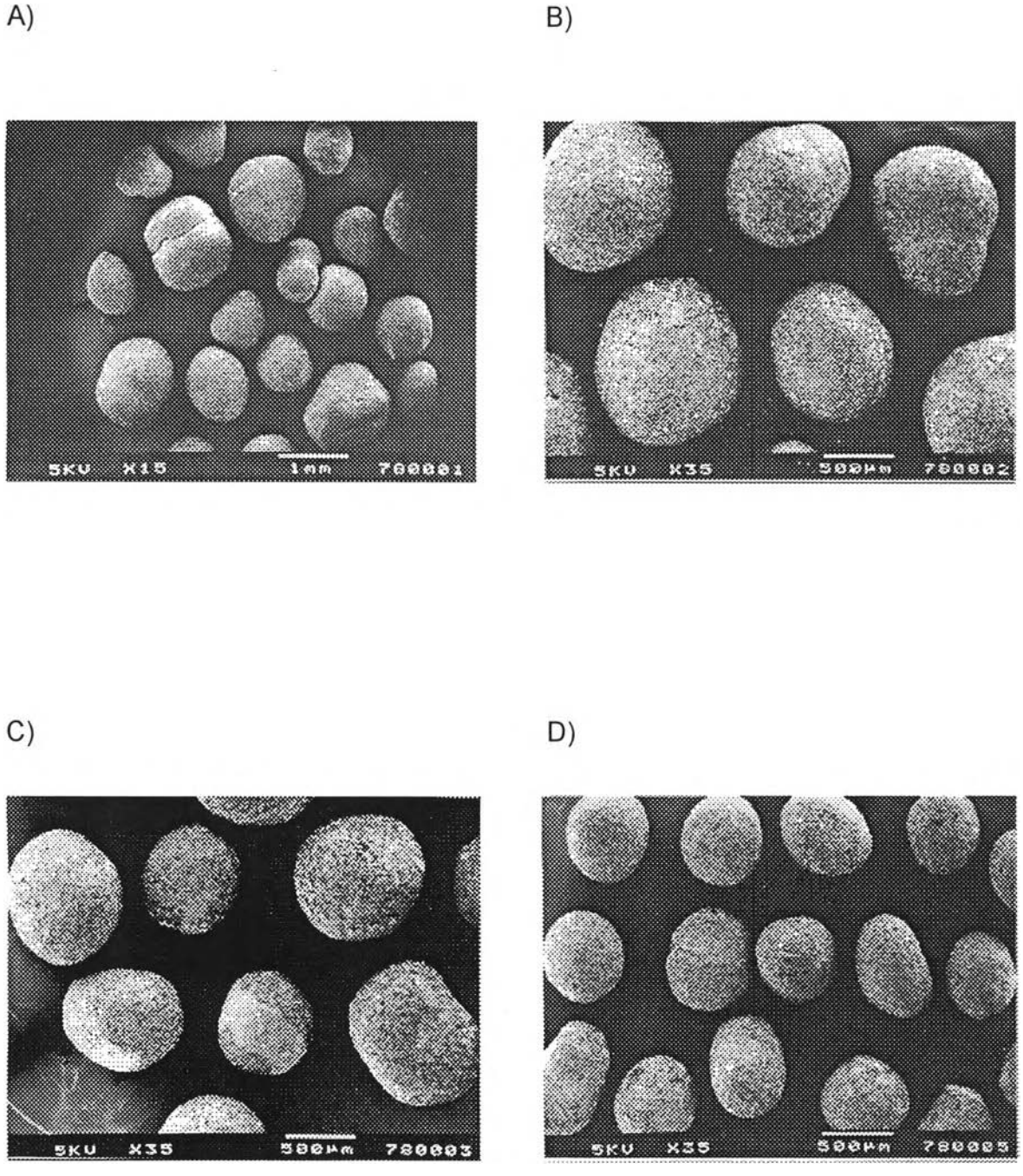


Figure 47 Photomicrographs presenting pellet characteristics of $8L_{23}$ using 0.5% w/w of MGS with DS 0.26 and 29% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

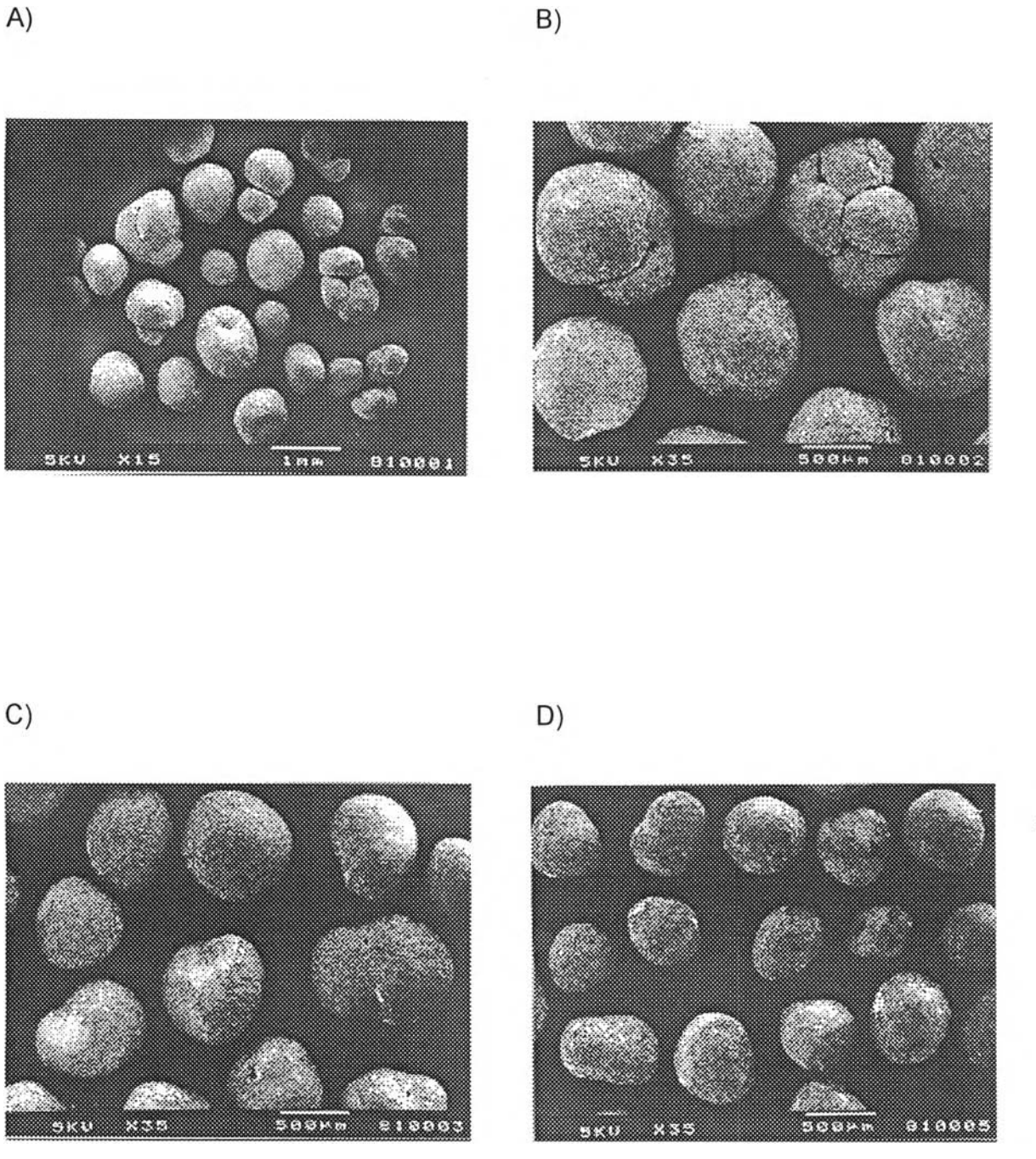


Figure 48 Photomicrographs presenting pellet characteristics of $8L_{13}$ using 0.5% w/w of MGS with DS 0.16 and 29% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

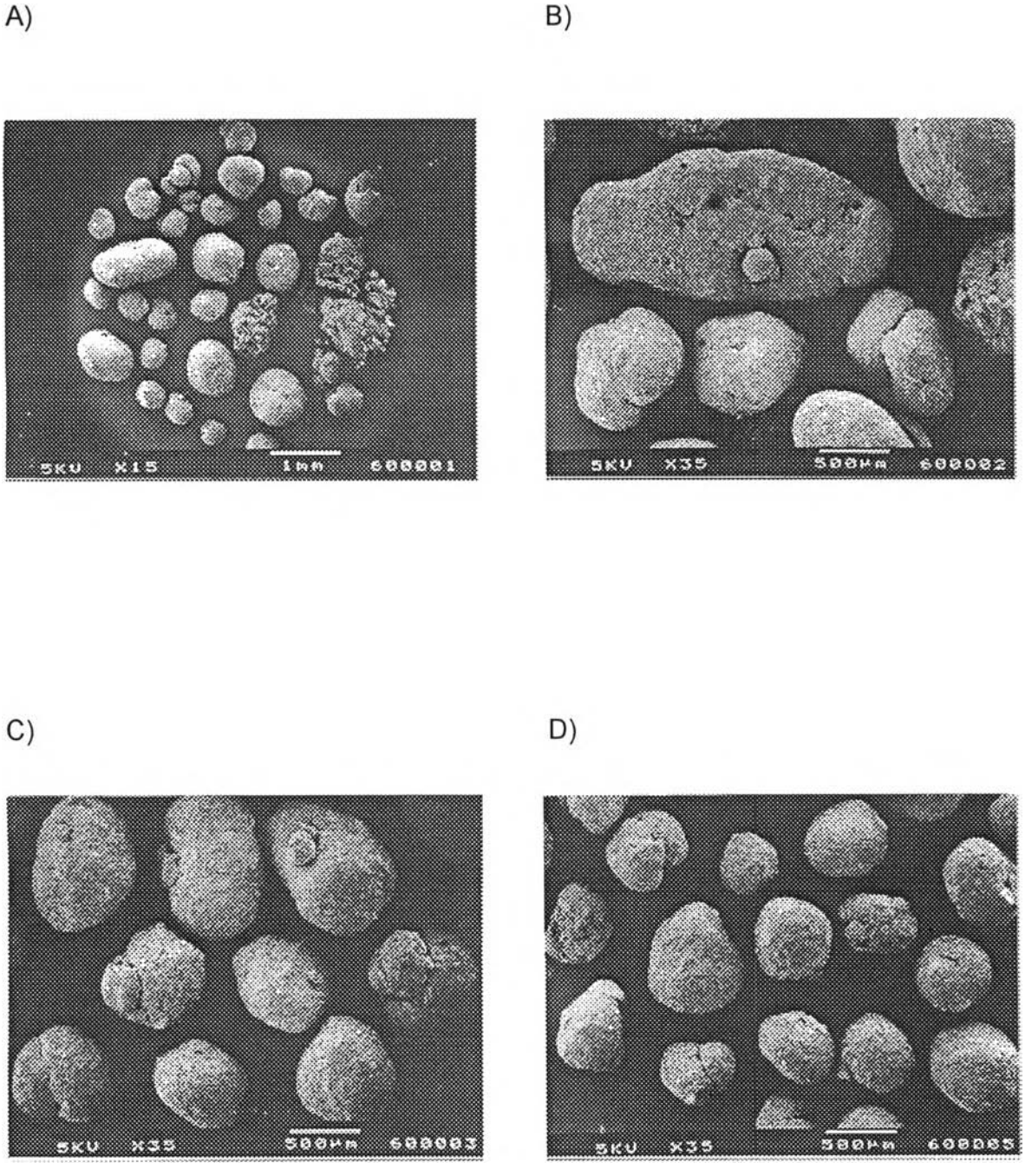
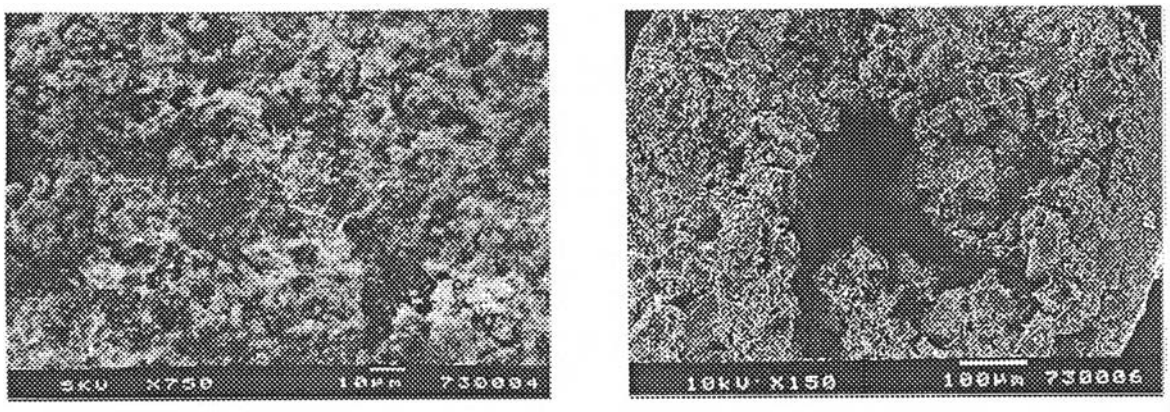
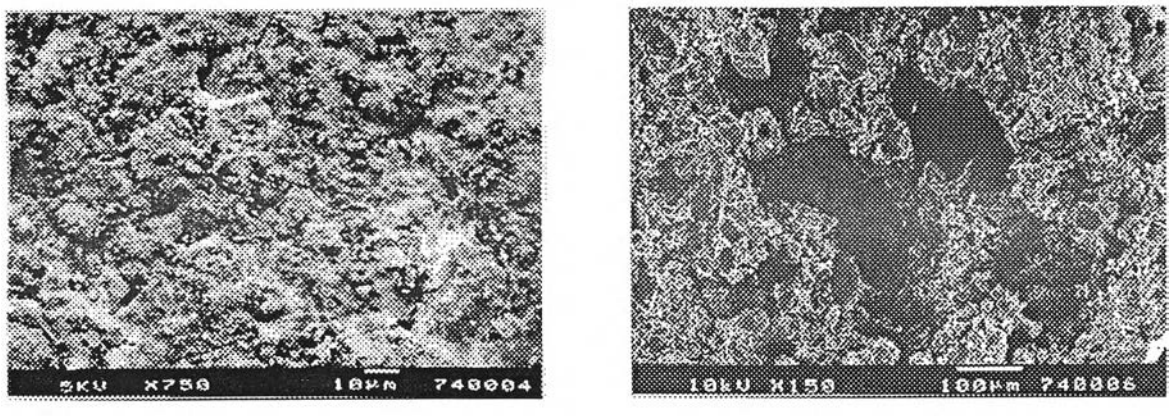


Figure 49 Photomicrographs presenting characteristics of 80% lactose blank pellet (B.6) using 29% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

A)



B)



C)

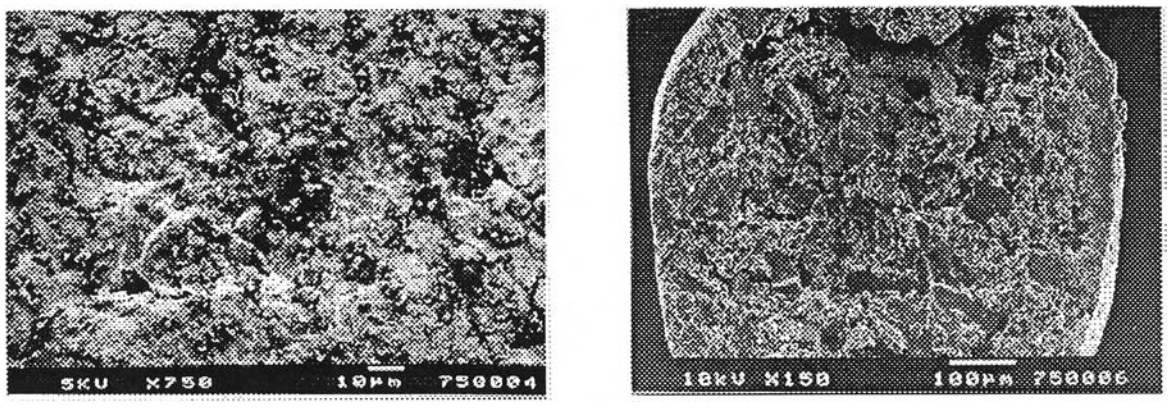
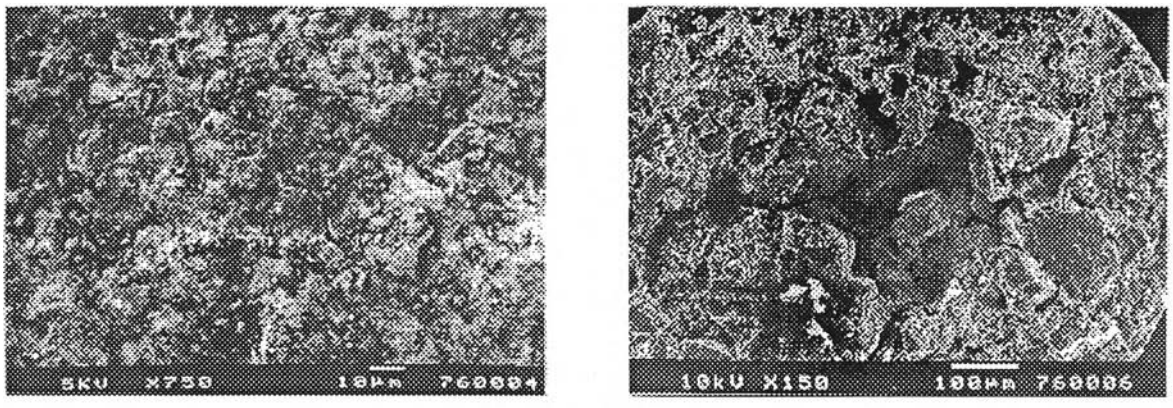
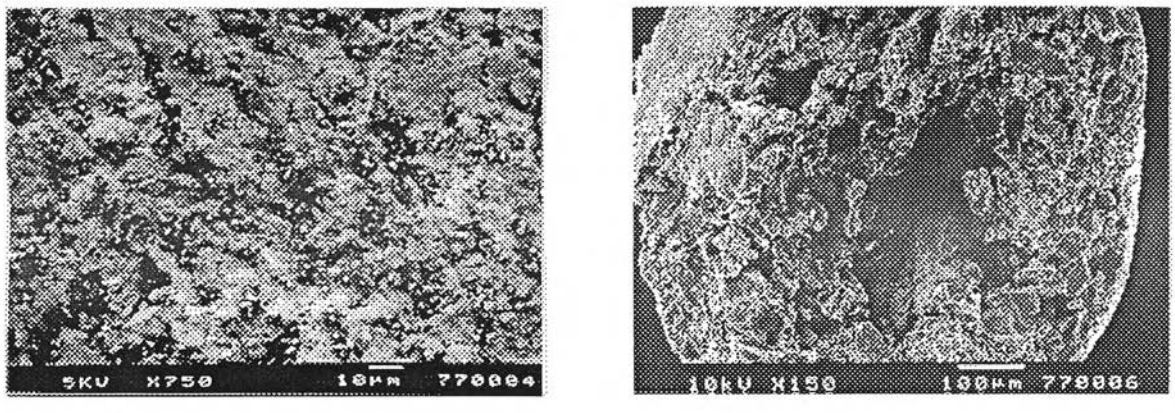


Figure 50 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% lactose pellet formulations using 0.5% w/w of MGS with DS 0.32 and different amounts of water : A) $8L_{32}$ (31%), B) $8L_{33}$ (30%), C) $8L_{34}$ (29%)

A)



B)



C)

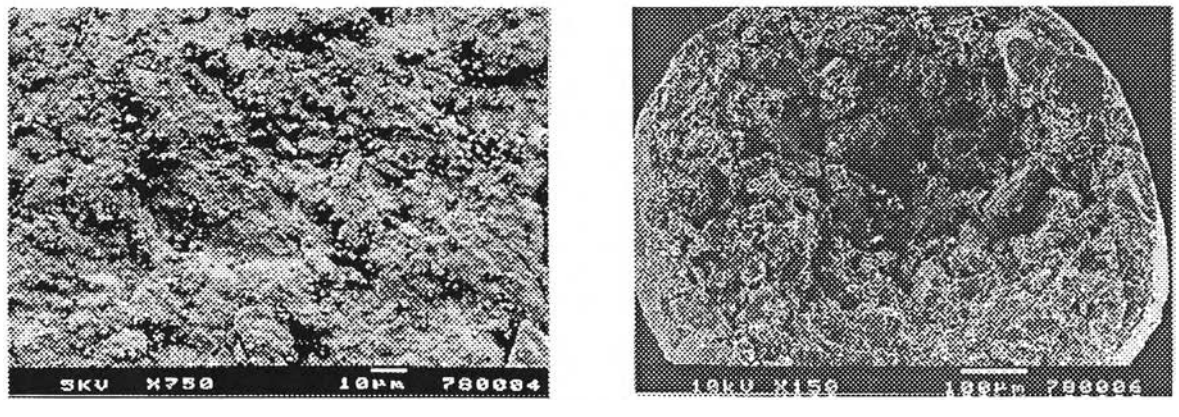
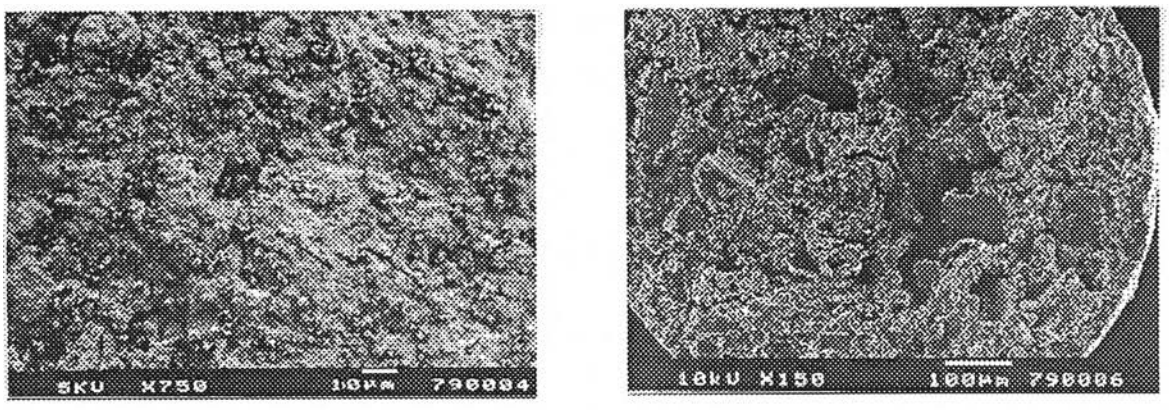
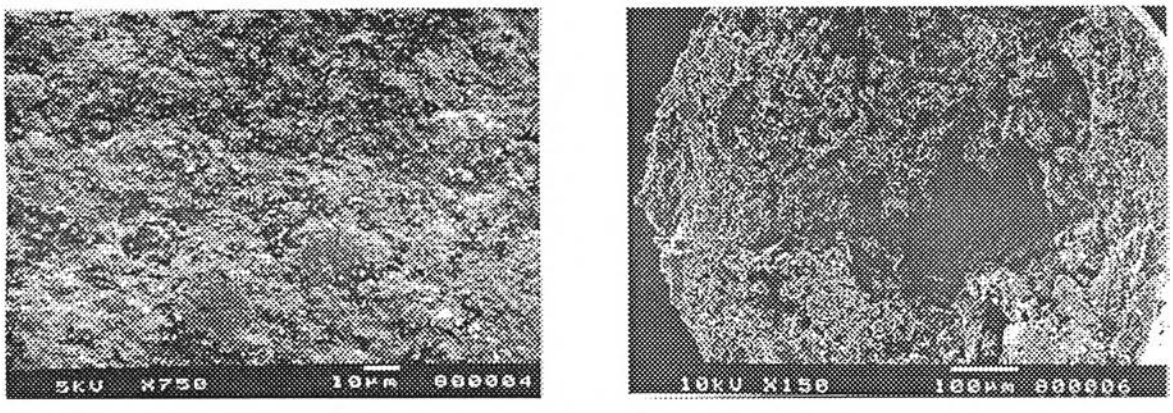


Figure 51 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% lactose pellet formulations using 0.5% w/w of MGS with DS 0.26 and different amounts of water : A) $8L_{21}$ (31%), B) $8L_{22}$ (30%), C) $8L_{23}$ (29%)

A)



B)



C)

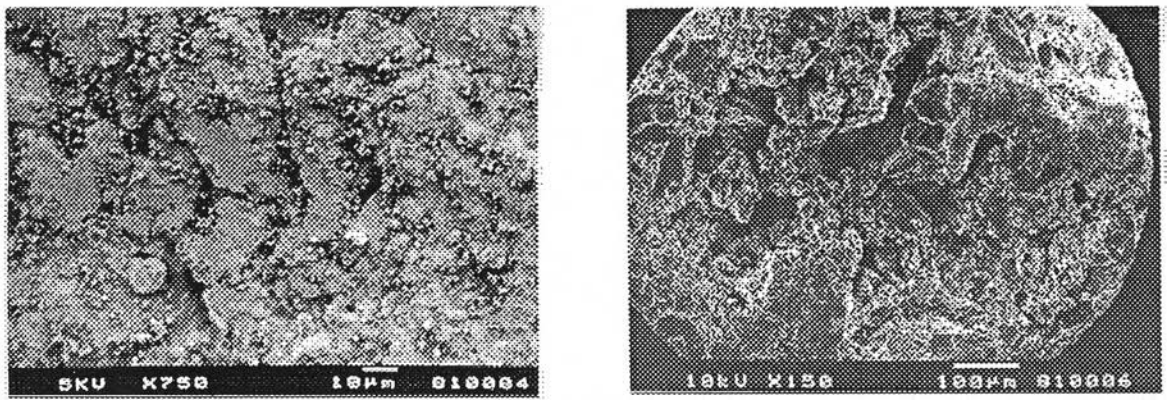
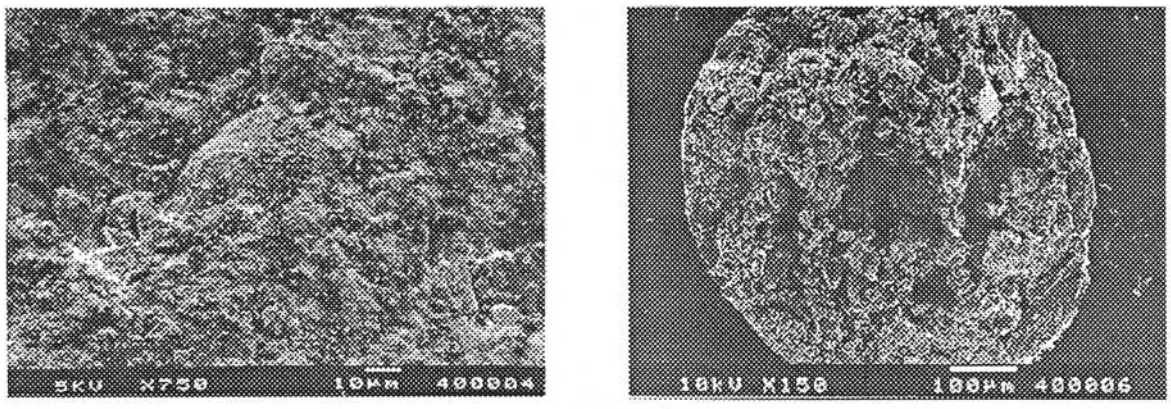
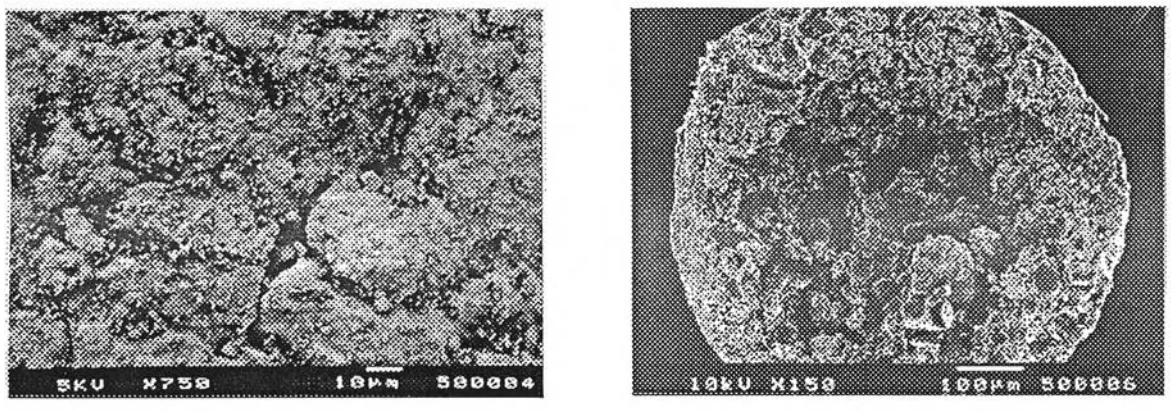


Figure 52 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% lactose pellet formulations using 0.5% w/w of MGS with DS 0.16 and different amounts of water : A) $8L_{11}$ (31%), B) $8L_{12}$ (30%), C) $8L_{13}$ (29%)

A)



B)



C)

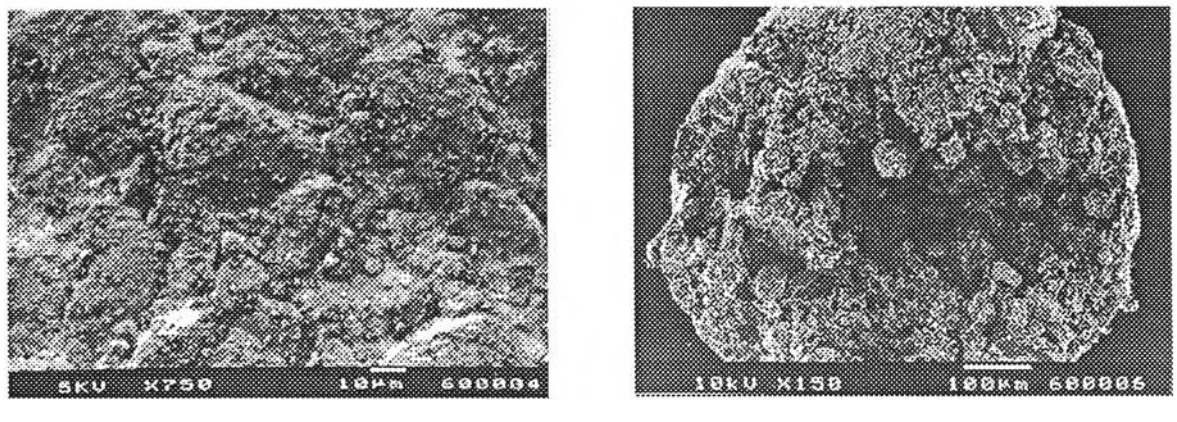
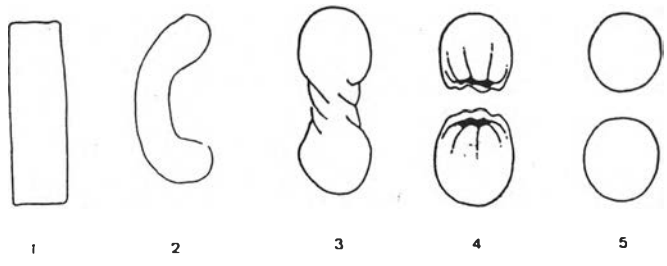


Figure 53 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% lactose blank pellets using different amounts of water : A) B.4 (31%), B) B.5 (30%), C) B.6 (29%)

that the plasticity of the wet mass was adequate to produce spherical particles , but insufficient to produce a smooth surface (Hellen et al. , 1993b). Utilization of modified starch with any DS yielded the pellets with slightly smoother surface than blank formulations which had a larger crevice-cavities. These agreed with the prior results of sphericity in section 2.2.5 which noted that MGS containing pellets were rounder than blank pellets since the smooth surface condition was mostly occurred with a round sphere, although some authors reported that the surface smoothness was not dependent on the pellet shape (Hellen et al. , 1993 b). It might be explained that the higher plasticity and binding strength of MGS containing extrudates might be appropriate to form rounder and smoother surface of spheres when compared with blank extrudates. It was observed that DS of MGS had played no effect on surface condition of the pellets as well as their sphericity which has been previously mentioned. The effect of the added water level on the surface structure has been reported (Baert and Remon , 1993 ; Hellen et al. , 1993b ; Otsuka et al. , 1994). It was found that the greater the amount of water , the smoother the surface of pellets. But , in this experiment , the roughness of surface tended to be increased with greater amount of water. It might be discussed that the cohesive force between particles was increased with the highest amount of water and this cohesive force might resist the friction force which spheronized and smoothed the surface during spheronization step. However , the difference in surface conditions due to various water level was less because the plastic properties of wet mass was less sensitive to 1% difference in water content.

Almost in the cross-sections of the pellets in both 65% and 80% lactose formulations showed the spheres having a cavity in the internal structure (e.g. Figures 42-45 and 50-53). Baert and Remon (1993) described the mechanism of pellet formation from this cavity. They suggested that the cavities were not formed by aggregation of small particles during spheronization process but some type of twisting might occur. The model of sphere forming mechanism was as follow :



Mechanism of pellet formation (Baert and Remon , 1993)

In the first step , rope-folding (2) of the extrudate (1) occurred followed by twisting, resulting in the formation of a kind of dumb-bell (3). A further twist resulted in the breaking of the dumbbell into two parts with a central cavity (4). Finally , this cavity closed and spheres were formed (5). The formation of internal cavity of lactose pallets might be postulated that , during the process , the migration of liquid from the interstices between particles to the surface of the sphere is almost always accompanied by the migration of chemical in the formulation that are soluble in the liquid (Chien and Nuessle , 1985). Thus , lactose which was soluble in the added water could migrate to the surface of pellets resulting in the formation of internal cavity. In comparison of the internal structure among pellets prepared with various DS of MGS and amounts of added water , no difference was observed. The internal structure of all pellet formulations seemed to be porous. It might be due to fluidized-bed drying which gave a fast and uniform evaporation of liquid as a result of turbulent motion of the fluidized particles (Dyer et al. , 1994).

2.3 Dicalcium Phosphate Pellet Formulations

Dicalcium phosphate dihydrate was used in pellet formulations as an insoluble pellet model. Changes in amount of materials and spheronization process conditions were carried out , as shown in Table 9-12 , to generate good appearance pellets. For 65% dicalcium phosphate pellets , formulations $6D_{31}$ to

$6D_{33}$ which prepared without Avicel PH101 could not produce satisfactory pellets. The spheronized products were only the lump of moist mass when using relatively high amounts of water (about 39-41%). In spite of reducing water content to 36% , the wet mass passed through the screw of extruder with difficulty and resulting in masses with various size including small relatively round particles. During the extrusion process , the water acts as a die wall lubricant (Pinto et al. , 1992) , and thus it is possible that too low amount of water in wet mass resulted in less effective lubrication for passing through the screw of extruder. Furthermore , the low plasticity of extrudates was obtained from lack of using Avicel PH101. The relatively low mounts of Avicel PH101 , 5.0-10.0% w/w , produced pellet with aggregation and large mass from agglomeration. It was found that aggregation of extrudates and sticking around the spheronizer disappeared when using higher amount of Avicel PH101 (10.0-15.0% w/w). The amount of MGS with DS 0.32 was fixed at 0.5% w/w , based on lactose pellet formulations. Changes in amount of water was performed by observation of the nature of wet mass for processing in extruder and appearance of product. In formulation $6D_{311}$, spheronizer speed was increased to 800 rpm for diminishing the aggregation of individual pellet and non spherical mass which was appeared in the former formulations ($6D_{31}$-$6D_{310}$). Using longer residence time (8 min) and leaving the extrudates for 15 min before spheronization (in formulation $6D_{312}$) was performed due to those previously mentioned reasons , then the appropriate appearance pellet was found to be produced , however , a small amount of non spherical masses still appeared. Changes in amount of water from 50% (formulation $6D_{312}$) to 52 and 48% were carried out to study the effect of added water on physical properties of pellets. The variation of added water which was lower or more than this range could not produce the acceptable pellets. After that MGS with DS 0.26 and 0.16 were used in these three interesting formulations instead of DS 0.32 to investigate the effect of degree of substitution in modified starches on physical properties of pellets.

For 80% dicalcium phosphate pellets , the amount of Avicel PH101 , MGS and processing conditions (Table 8) were similar as those of 65%

formulations which produced the acceptable pellets. It was found that the higher the amount of water , the lower the amount of large and non spherical particles. During processing , the wet mass could easily pass through screw of extruder and the obtained extrudate spun freely in spheronizer when compared with 65% dicalcium phosphate model. Three levels of water , 48 , 46 and 44% , were used to study the effect of water on physical properties of pellet.

It was observed that the amount of granulated water used in the preparation of dicalcium phosphate pellets was greater than that of lactose pellets. Baert et al. (1992) reported that lower limit of microcrystalline cellulose concentration used in order to obtain good spheres of dicalcium phosphate was higher than of lactose spheres. This lower limit depended on the solubility of pellet base material. The higher amount of microcrystalline cellulose was essential for improving the plasticized property of wet mass and resulted extrudates. In this study , the concentration of microcrystalline cellulose used in the productions of lactose and dicalcium phosphate pellets was equal , thus the amount of added water employed to obtain dicalcium phosphate pellets with good characteristic must be increased.

In blank pellet formulations , B.7 to B.12 , which using the same amount of materials and processing conditions as of 65% and 80% dicalcium phosphate pellets except without MGS produced smaller size pellet including higher amount of large and non spherical particles. The possible reasons were similar as previously mentioned in lactose pellet formulations (in section 2.2).

Evaluation of physical properties of 65% and 80% dicalcium phosphate pellets prepared with various DS of MGS and amount of water , compared with their blank pellets , were as follows.

2.3.1 Particle size distribution

The procedures used to determine the size and size distribution were similar as previously described for lactose pellets. The results of size

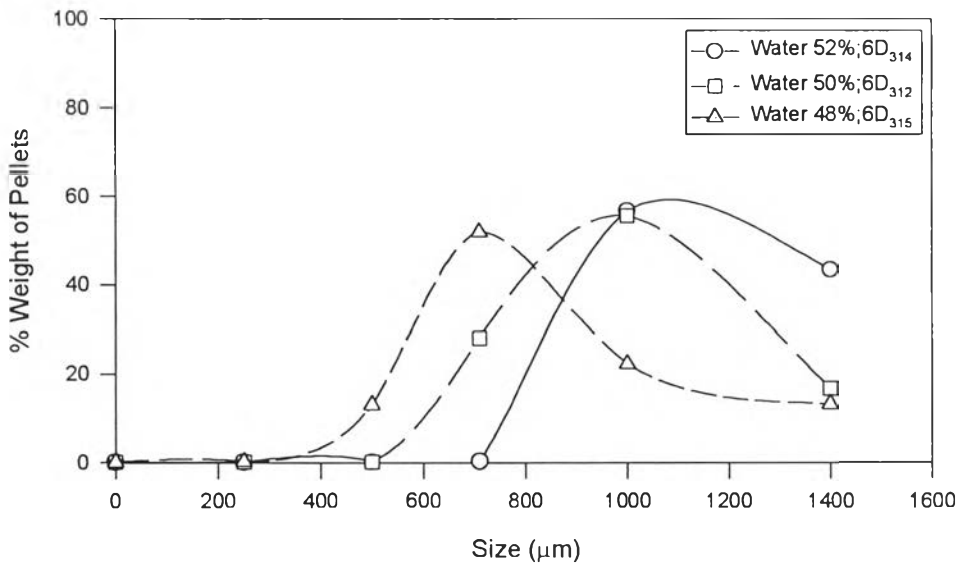


Figure 54 Particle size distribution curves of 65 % dicalcium phosphate pellets prepared with DS 0.32 of MGS at different amounts of water

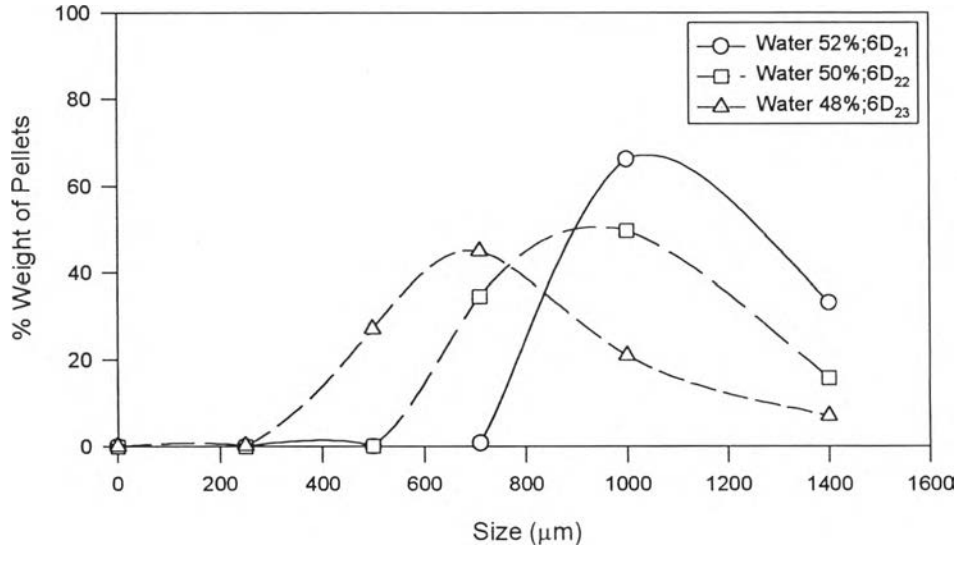


Figure 55 Particle size distribution curves of 65 % dicalcium phosphate pellets prepared with DS 0.26 of MGS at different amounts of water

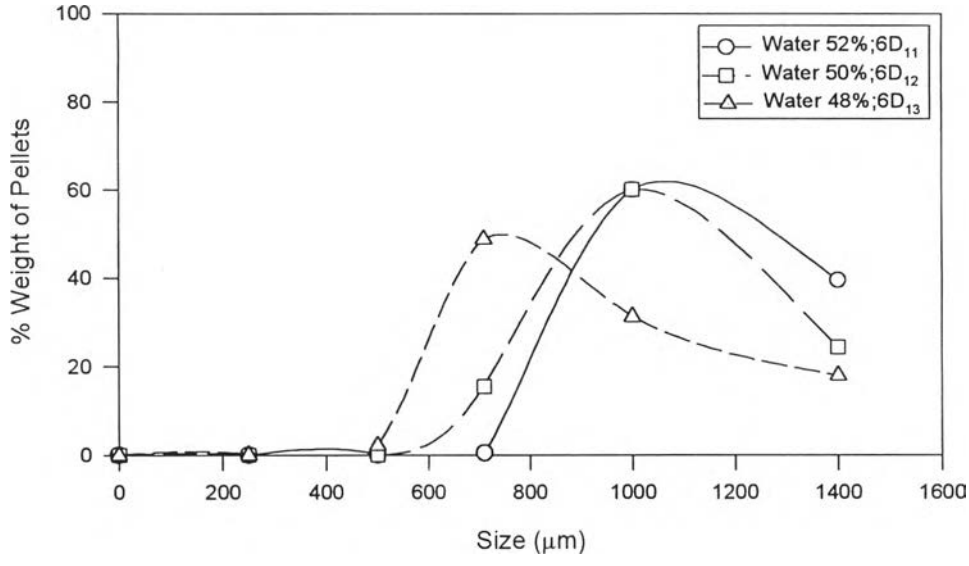


Figure 56 Particle size distribution curves of 65 % dicalcium phosphate pellets prepared with DS 0.16 of MGS at different amounts of water

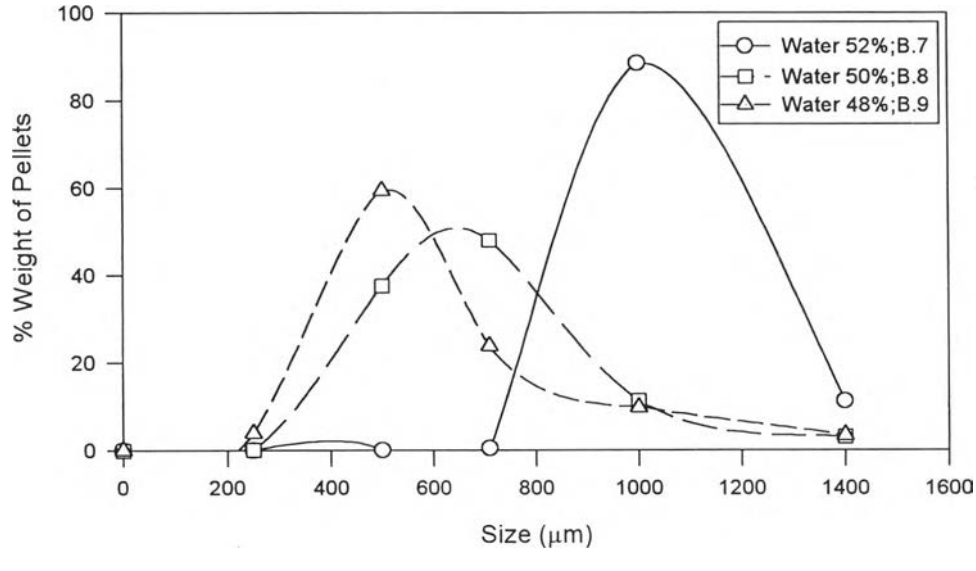


Figure 57 Particle size distribution curves of 65 % dicalcium phosphate blank pellets prepared with different amounts of water .

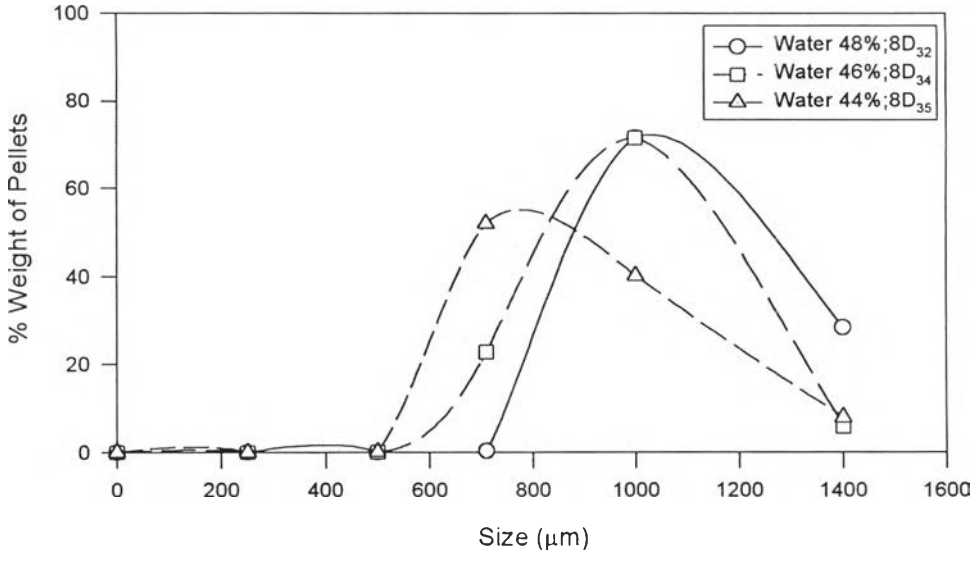


Figure 58 Particle size distribution curves of 80 % dicalcium phosphate pellets prepared with DS 0.32 of MGS at different amounts of water

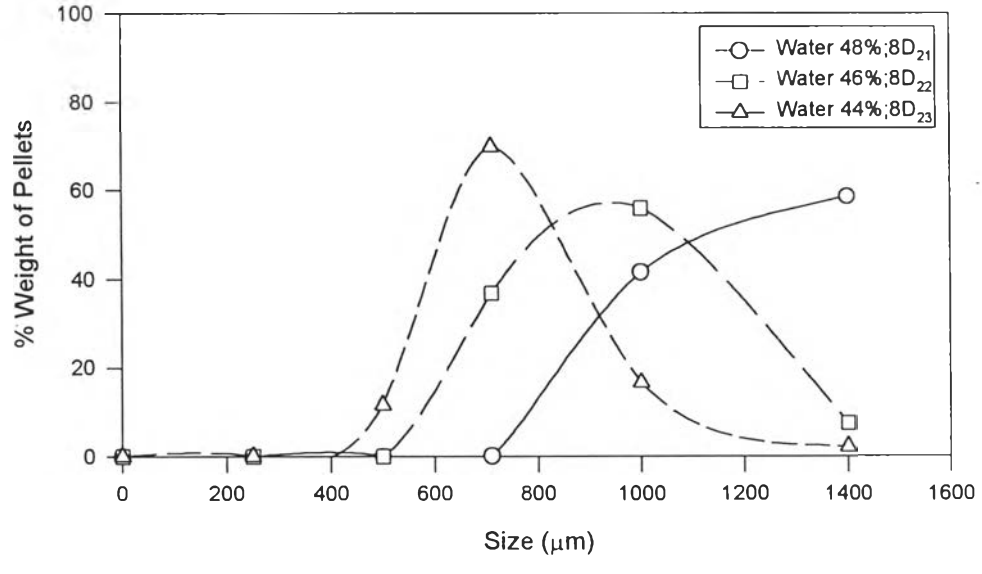


Figure 59 Particle size distribution curves of 80 % dicalcium phosphate pellets prepared with DS 0.26 of MGS at different amounts of water

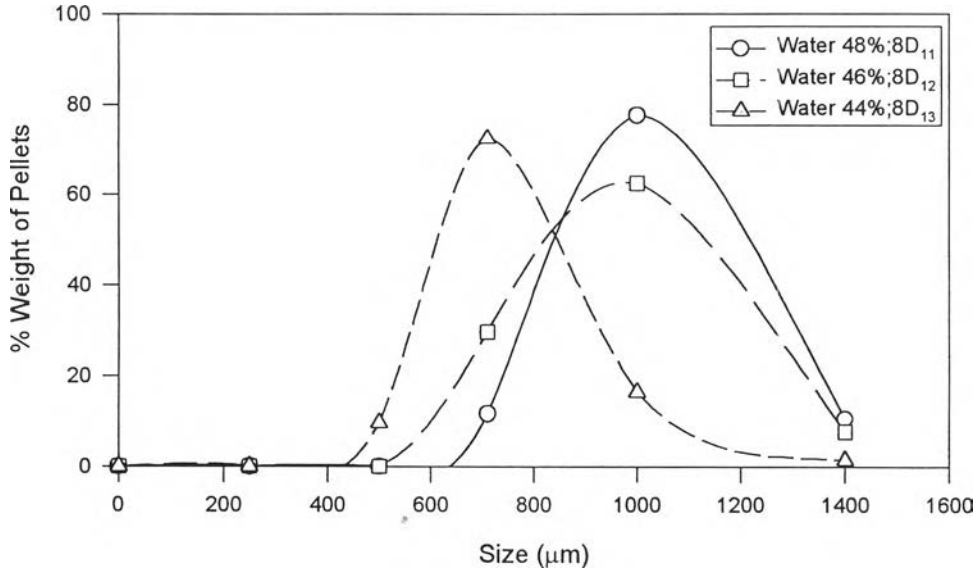


Figure 60 Particle size distribution curves of 80 % dicalcium phosphate pellets prepared with DS 0.16 of MGS at different amounts of water

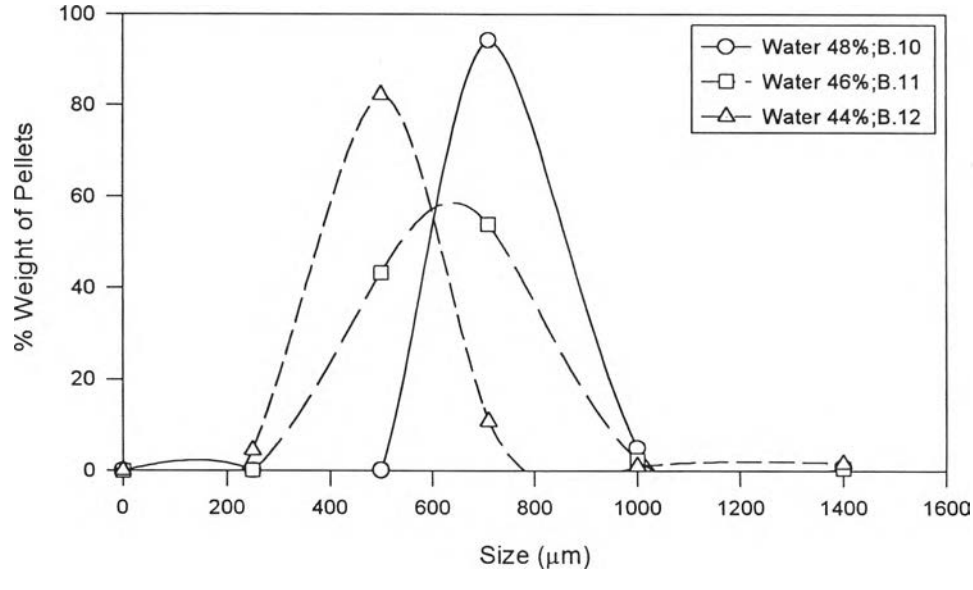


Figure 61 Particle size distribution curves of 80 % dicalcium phosphate blank pellets prepared with different amounts of water .

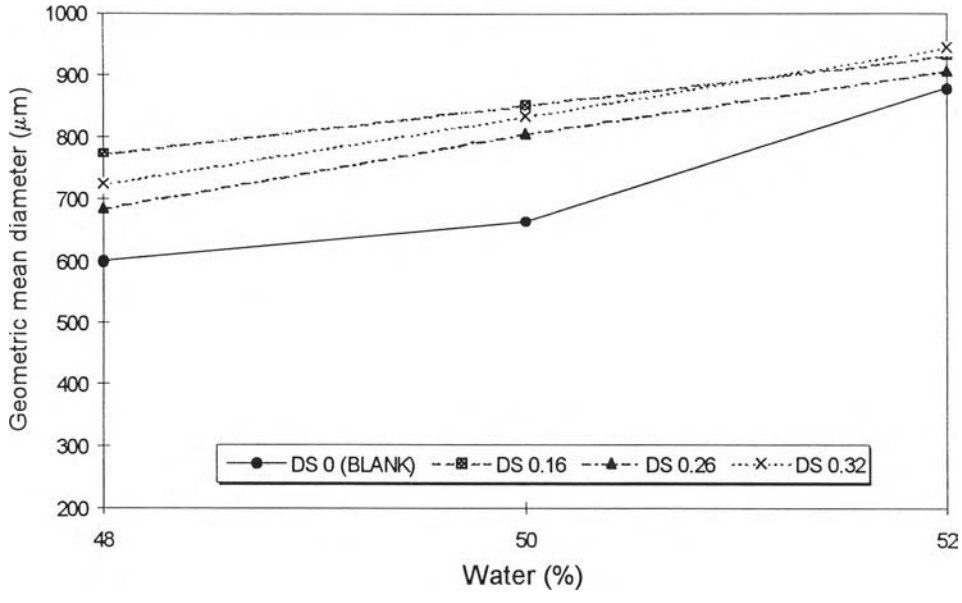


Figure 62 Geometric mean diameter (D_{50}) profiles of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

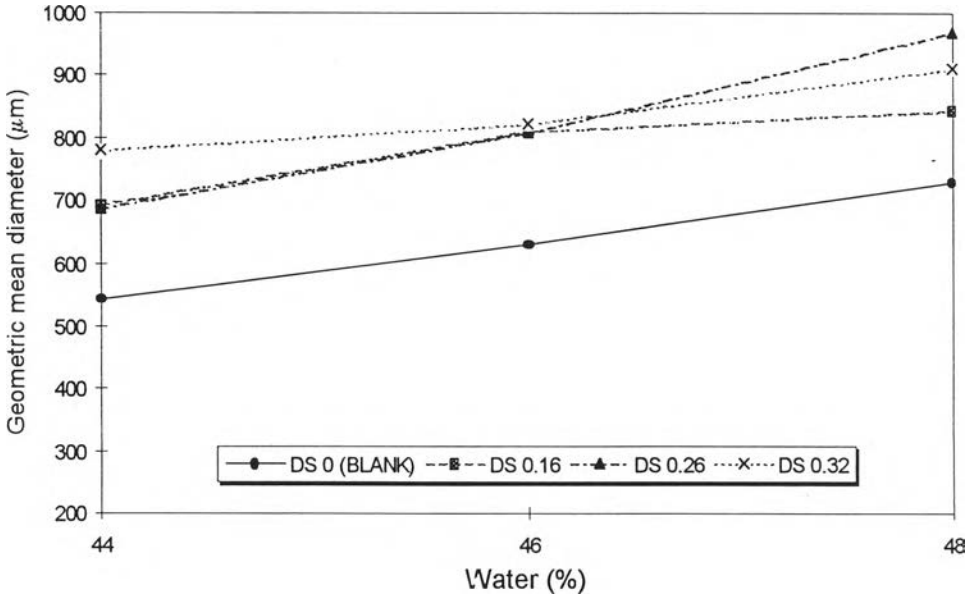


Figure 63 Geometric mean diameter (D_{50}) profiles of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

Table 25 Geometric mean diameter (D_{50}) and geometric standard deviation (σ_g) of 65 % and 80 % dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

DS	MGS (% w/w)	65% Dicalcium Phosphate Pellets				80% Dicalcium Phosphate Pellets			
		Water (%)	Formulation	D_{50} (μm)	σ_g	Water (%)	Formulation	D_{50} (μm)	σ_g
0.32	0.5	52	$6D_{314}$	943.95	1.2006	48	$8D_{32}$	910.90	1.2069
		50	$6D_{312}$	832.21	1.2223	46	$8D_{34}$	821.23	1.2188
		48	$6D_{315}$	723.32	1.2911	44	$8D_{35}$	780.33	1.2436
0.26	0.5	52	$6D_{21}$	905.42	1.2092	48	$8D_{21}$	967.53	1.1993
		50	$6D_{22}$	803.97	1.2414	46	$8D_{22}$	807.94	1.2249
		48	$6D_{23}$	682.56	1.3191	44	$8D_{23}$	686.13	1.2928
0.16	0.5	52	$6D_{11}$	930.12	1.2024	48	$8D_{11}$	843.09	1.2161
		50	$6D_{12}$	849.18	1.2218	46	$8D_{12}$	809.28	1.2260
		48	$6D_{13}$	771.76	1.2596	44	$8D_{13}$	692.57	1.2799
0 *	-	52	B.7	876.83	1.2105	48	B.10	727.10	1.2402
		50	B.8	661.15	1.3169	46	B.11	692.11	1.3152
		48	B.9	598.66	1.4108	44	B.12	541.29	1.4723

* Blank pellets

distribution are illustrated in Figures 54-61 and Table 38-39 (in Appendix III). Appendix III show the percent cumulative undersize of pellet in probability scale plotted against sieve size. Calculated geometric mean diameter (D_{50}) of 65% and 80% dicalcium phosphate pellets using different DS of MGS and amounts of water including blank pellets are depicted in Figures 62-63. The values of D_{50} and geometric standard deviation (σ_g) are shown in Table 25. Appendix V (Tables 56-57 and 60-61) present the results from analysis of variance of D_{50}.

For 65% dicalcium phosphate pellets , the size distribution of pellets prepared with MGS at different DS and using the same amount of added water was slightly different but narrower than that of blank pellets. Since slight difference of geometric standard deviation (σ_g) of spheres containing MGS with different DS was observed but these were lower than that of blank pellets (Table 25). With increase in amount of granulated water in each series of DS of MGS , including in blank pellets , resulted in a considerable increase in size of pellets. D_{50} of spheres prepared with modified starches was significantly greater than that of blank pellets at any added water levels (Figure 62). In each water level , using various DS of MGS yielded the pellets with negligible difference in D_{50}. In comparison between pellets prepared with different amounts of water , the rank of D_{50} was as follows : D_{50} of pellets using 52% water > 50% water > 48% water . Geometric standard deviation (σ_g) of pellets containing MGS with DS 0.16 was mostly the lowest (Table 25). The ranked order of σ_g affected by water level was as follows : σ_g of pellets using 52% water < σ_g of pellets using 50% water < σ_g of pellets using 48% water.

In consideration of 80% dicalcium phosphate pellets , the comparable size distribution of pellets prepared with MGS at DS 0.26 and 0.16 was observed except with 48% of water which mainly large particles were produced from DS 0.26 (Figure 59). Size distribution of pellets using MGS with DS 0.32 was slightly different from the pellets prepared using MGS with DS 0.26 and 0.16. These size distributions of modified starch containing pellets were narrower than those of blank pellets. Average particle size of blank pellets considerably decreased when comparison to MGS containing pellets. This was

obviously seen from D_{50} values (Figure 63). The effect of degree of substitution of MGS on D_{50} of pellets was inconsistent. It depended upon the amount of added water. However , data from statistical treatment showed non-significant difference. The obviously different D_{50} could be seen from using different quantities of added water. Utilization of 48% of added water yielded pellets with higher D_{50} when comparison to 46% and 44% . In the case of σ_g , the lowest σ_g was mostly found from formulations using MGS at DS 0.32. The rank of σ_g affected by different amounts of water used was : σ_g of pellets using 48% water < σ_g of pellets using 46% water< σ_g of pellets using 44% water.

From the results , it could be concluded that utilization of modified starch had an influence on size distribution and D_{50} of pellets. At the same amounts of water used , employing modified starch produced pellets with greater particle size when compared with blank pellets. The different DS of MGS slightly affected the size distribution but did not affect D_{50} of pellets. In addition , the quantity of added water in granulation step showed a significant effect on the pellet size : the higher the amount of water , the greater the D_{50} of pellet. The possible explanations of these results were similar to as described in size distribution of lactose pellets (Section 2.2.1). The narrower size distribution of MGS containing pellets than blank pellets might be explained that uniform distribution of MGS in mixing powder might better regulate the water content and distribution in the granulation and control the plasticity of whole mass when compared with blank pellets. It was found from the σ_g values that utilization of MGS at DS 0.16 in 65 % dicalcium phosphate formulations and MGS at DS 0.32 in 80% formulations produced pellets with slightly narrower size distribution than using other DS. Moreover , the narrower size distribution of pellets was obtained when using the higher amount of granulated water.

2.3.2 Bulk and Tapped Densities

The bulk and tapped densities of 65% and 80% dicalcium phosphate pellets are illustrated in Table 26. In 65% formulations , the bulk and

Table 26 Bulk density and tapped density of dicalcium phosphate pellet formulations prepared with different DS of MGS and amounts of water.

DS	MGS	65 % Dicalcium Phosphate Pellets				80 % Dicalcium Phosphate Pellets			
	(%w/w)	Water (%)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Water (%)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)
0.32	0.5	52	$6D_{314}$	0.857 (0.004*)	0.875 (0.004)	48	$8D_{32}$	0.873 (0.004)	0.901 (0.008)
		50	$6D_{312}$	0.857 (0.004)	0.898 (0.005)	46	$8D_{34}$	0.875 (0.004)	0.912 (0.012)
		48	$6D_{315}$	0.852 (0.008)	0.888 (0.005)	44	$8D_{35}$	0.877 (0.000)	0.915 (0.005)
0.26	0.5	52	$6D_{21}$	0.852 (0.008)	0.896 (0.005)	48	$8D_{21}$	0.873 (0.009)	0.891 (0.012)
		50	$6D_{22}$	0.857 (0.004)	0.907 (0.005)	46	$8D_{22}$	0.883 (0.009)	0.929 (0.013)
		48	$6D_{23}$	0.865 (0.004)	0.929 (0..005)	44	$8D_{23}$	0.891 (0.005)	0.932 (0.005)
0.16	0.5	52	$6D_{11}$	0.845 (0.004)	0.875 (0.004)	48	$8D_{11}$	0.881 (0.005)	0.910 (0.000)
		50	$6D_{12}$	0.848 (0.000)	0.885 (0.000)	46	$8D_{12}$	0.885 (0.008)	0.926 (0.017)
		48	$6D_{13}$	0.831 (0.004)	0.893 (0.000)	44	$8D_{13}$	0.878 (0.000)	0.930 (0.005)
0 **	-	52	B.7	0.850 (0.004)	0.872 (0.004)	48	B.10	0.866 (0.004)	0.884 (0.005)
		50	B.8	0.850 (0.004)	0.909 (0.000)	46	B.11	0.867 (0.009)	0.896 (0.005)
		48	B.9	0.850 (0.004)	0.904 (0.005)	44	B.12	0.878 (0.000)	0.912 (0.005)

* Standard deviation ** Blank pellets

tapped densities of pellets prepared with MGS at DS 0.16 were the lowest. It could be noted that bulk and tapped densities of modified starch containing pellets were slightly lower than those of blank pellets. Slight difference of bulk density could be observed from using different amounts of granulated water. Tapped density of pellets utilizing various amounts of added water possessed uncorresponding relationship. However , it was found that 52% of water produced pellets with the lowest tapped density.

Consideration of 80% dicalcium phosphate pellets , unlike the 65% formulations , the greater bulk and tapped densities of pellets prepared with modified starches were observed when compared with blank pellets. Among using various DS of MGS , the same character of bulk and tapped densities was observed , that was using MGS with DS 0.26 and 0.16 exhibited no difference but mostly higher than using DS 0.32. Pellets prepared by 48% of water possessed the lowest bulk and tapped densities. In comparison between 65% and 80% formulations , it was found that the densities of 80% pellets was higher than those of 65% pellets.

As previously described for lactose pellet formulations , the bulk and tapped densities are examined to gain an idea of the uniformity of size distribution and packing properties of spherical particles (Hellen et al. , 1993b ; Sonaglio et al. , 1995 ; Vervaet et al. ,1995 ; Woodruff and Nuessle , 1972). For 65% formulations , it could be concluded that the degree of uniformity and packing properties of MGS containing pellets were slightly lower than those of blank pellets. This did not agree with the narrower size distribution of MGS pellets than blank pellets. The modified starch with DS 0.16 produced pellets with the lowest bulk density in comparison to DS 0.26 and 0.32. This was related to the average diameter or D_{50} of pellets. From the previous results , D_{50} of pellet containing MGS at DS 0.16 was slightly higher than that of using the others. It is generally known that small size pellets are able to form a close packing resulting in high bulk density. Hence , the lowest bulk density possibly occurred from the higher size of pellets using MGS at DS 0.16. But it did not agree with the

narrower size distribution of MGS at DS 0.16 containing pellets (Section 2.3.1). On the other hand , the degree of uniformity of size distribution and packing properties of 80% dicalcium phosphate pellets prepared by using modified starches were slightly higher than those of blank pellets since the bulk and tapped densities of the former were slightly greater than the later. It was in accordance with the results of size distribution (Section 2.3.1) which was noted that the narrower size distribution of MGS containing pellets was observed. Utilization of various DS of modified starch led to produce pellets with slight difference in bulk and tapped densities in that increase in degree of substitution resulted in lower densities. It was hard to concluded that the lower densities when using high DS indicated the poor uniformity of size distribution since it was not in accordance with size distribution which found that MGS at DS 0.32 yielded pellets with narrower size distribution. The quantity of granulated water also affected the bulk and tapped densities. Contrary to those of lactose pellets (Section 2.2.2) , bulk and tapped densities of dicalcium phosphate pellets seemed to be decreased with increasing the amount of added water. It was probably due to the water insoluble character of dicalcium phosphate dihydrate which inhibited the liquid or moisture distribution in the mixture. The localized agglomeration of particles in powder mixture was obtained and tended to be increased with increasing the amount of liquid. Thus , the degree of uniformity of particle size distribution might be reduced and caused less densities.

2.3.3 Hardness

The hardness at various size fractions of 65% and 80% dicalcium phosphate pellets are shown in Figures 64-69 and Appendix IV (Tables 44-45). The statistical analysis results are presented in Tables 88-89 and 96-101 of Appendix V. Because the little quantity of pellets in 500-710 μm size fraction was obtained during size classification which was not adequate for hardness tests , some hardness values in that size range might be not available (Figure 66 , 69). As can be seen from the results , it could be noted that utilization of modified starches yielded the pellets with significantly higher hardness at any size range

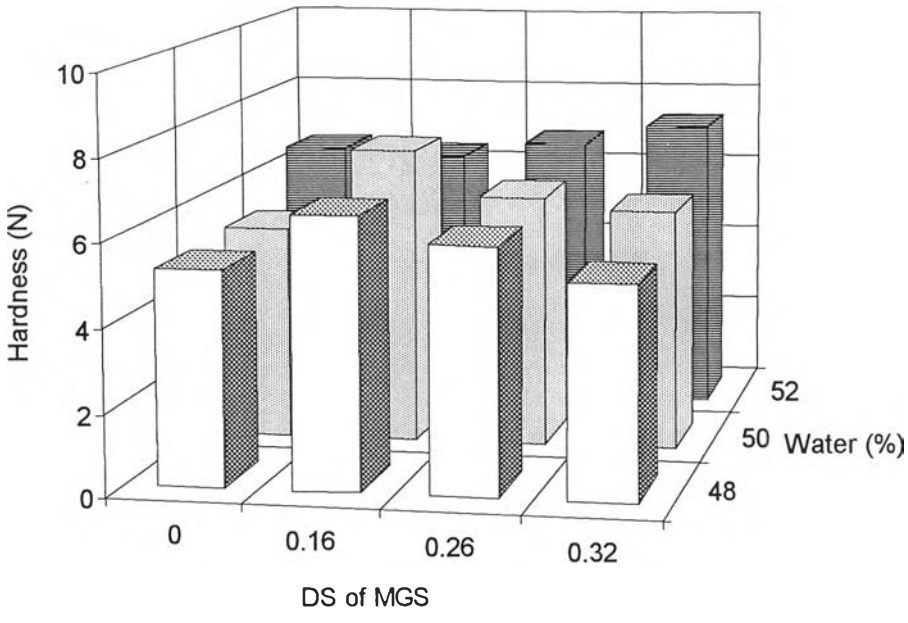


Figure 64 Histograms for hardness at 1000-1400 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

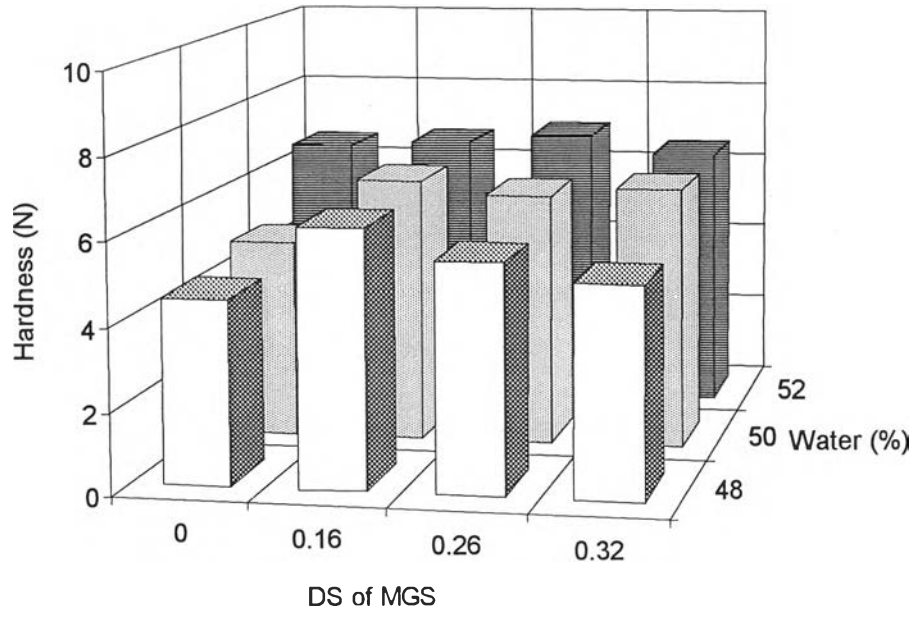


Figure 65 Histograms for hardness at 710-1000 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

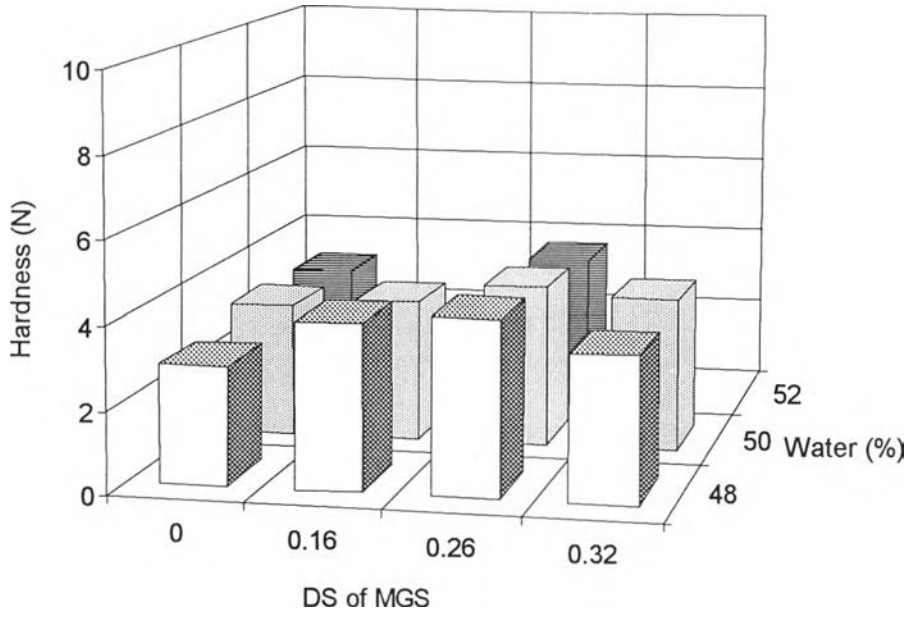


Figure 66 Histograms for hardness at 500-710 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

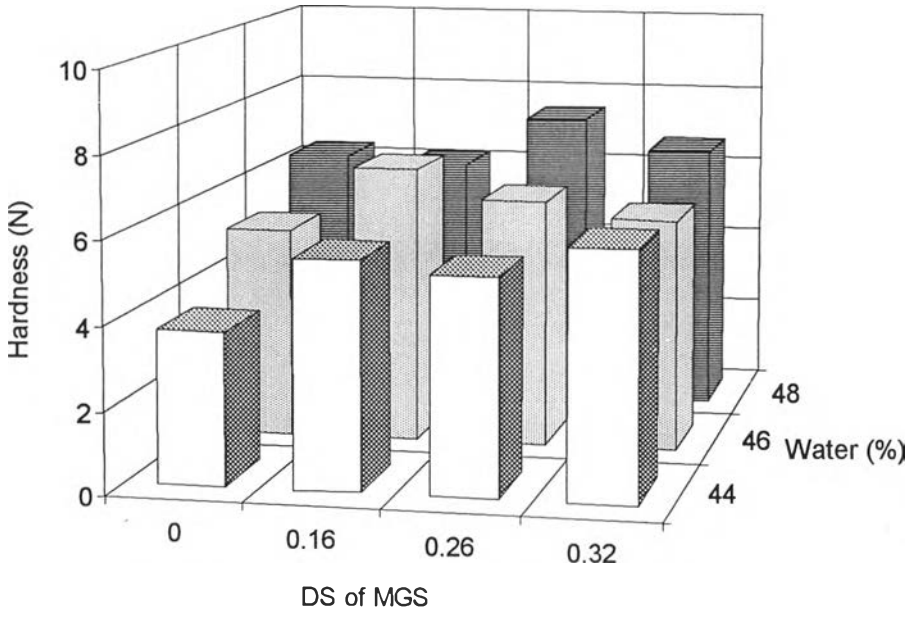


Figure 67 Histograms for hardness at 1000-1400 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

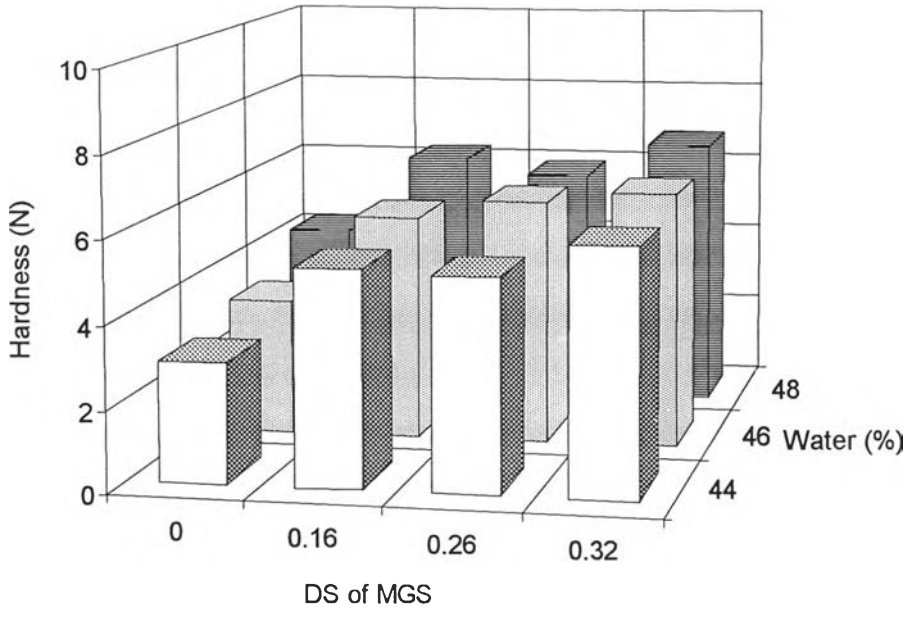


Figure 68 Histograms for hardness at 710-1000 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

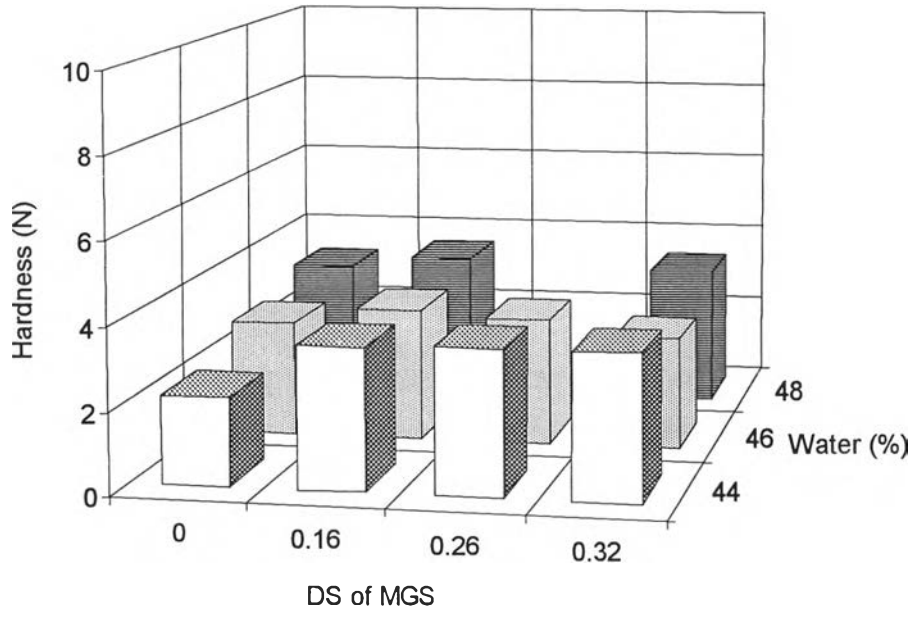


Figure 69 Histograms for hardness at 500-710 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

than blank pellets. In general , the hardness of pellets has a positive correlation with pellet size or diameter (Vervaet et al. , 1995). In this study , the ranked order of hardness was : hardness of size 1000-1400 μm > 710-1000 μm > 500-710 μm , which similar to lactose formulations. With the different water level , it could be seen that the hardness tended to be increased with increasing water levels. This influence of granulated water was obviously seen in 710-1000 μm size fraction (Figures 65 and 68) , which also previously noted in lactose pellets that it was a representative of the resulting pellets (see section 2.2.3). For other size fractions , however , the no relationship of hardness was observed. For 65% dicalcium phosphate pellets , the ranked order of hardness of 1000-1400 μm and 710-1000 μm size fractions which using various DS of MGS was : hardness of pellets using DS 0.16 > DS 0.26 ≥ DS 0.32 , and these values were mostly greater than that of blank pellets (Figures 64-65). But the hardness of pellets in the size fraction of 500-710 μm that affected by DS of MGS used was ranked in the order as : using DS 0.26 > DS 0.32 ≈ DS 0.16 (Figure 66).

In 80% formulations , it was found that the hardness of 1000-1400 μm size pellets prepared with different DS of MGS was not significantly different. At 710-1000 μm fraction , the hardness of pellets using modified starches with DS 0.26 and 0.16 exhibited no difference but lower than that using DS 0.32 (Figure 68). The inconsistent relationship of hardness was observed in 500-710 μm size fraction when compared between various water levels.

Comparison of pellet hardness between formulations containing modified starches and blank formulations revealed that the former mostly produced pellets with greater hardness. The possible explanations were similar as previously described in lactose pellet formulations (Section 2.2.3). Degree of substitution of MGS had an influence on the hardness of 65% and 80% formulations in different manners. Pellets using MGS at DS 0.16 and 0.32 mainly possessed the highest hardness for 65% and 80% dicalcium phosphate pellets , respectively. Although the high viscosity of MGS at DS 0.16 influenced on the distribution of MGS through the whole powder mixture , the obtained extrudates

could spheronize to form close packing particles due to the great binding strength of MGS with DS 0.16. It might be suggested that the uniformity of distribution of MGS in 65% dicalcium phosphate system did not affected the hardness of pellets. It indicated that when the amount of insoluble dicalcium phosphate increased from 65 % to 80% , the effect of MGS viscosity on the distribution in powder mixture became more significant. The MGS with lower viscosity , when in contact with added water , could distribute more uniform than that with the higher one (Dingwall and Ismail , 1977). Thus , the binding force produced from the lowest viscosity of MGS at DS 0.32 could spread uniformly resulting in the greatest hardness.

Similar to lactose pellets , it was clearly concluded that the hardness of pellets tended to be increased with increasing the quantity of added water. However , in some size fractions or series of DS , the higher hardness was observed when water level was reduced , The possible reasons of these results has been previously described in lactose pellets formulations.

2.3.4 Friability

Percent friability of various size fractions of 65% and 80% dicalcium phosphate pellets are depicted in Figures 70-75 and Tables 50-51 (in Appendix IV). Some percent friability values might not be available since the amount of pellets of those size fractions was very little after size classification and was not enough for friability tests. It could be seen from the figures that percent friability were less than 2% and did not related to the size of pellets. For 65% dicalcium phosphate pellets , utilization of modified starches mostly produced more friable pellets when compared with blank formulations. Comparison between using various DS of modified starch , the rank of percent friability at any size range was mainly ordered as follows : friability of pellets using DS 0.16 < DS 0.26 < DS 0.32 (Figures 70-71). With the different amounts of granulated water , the friability of pellets prepared with 50% of water was the lowest and with 48% was usually the highest. The greater friability of 80% dicalcium phosphate pellets was obtained in

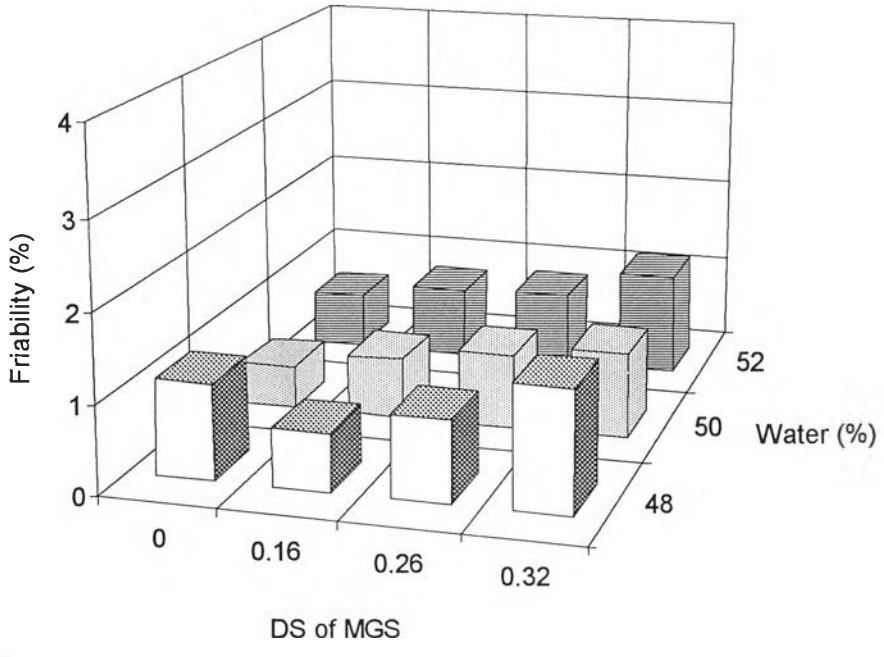


Figure 70 Histograms for percent friability at 1000-1400 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

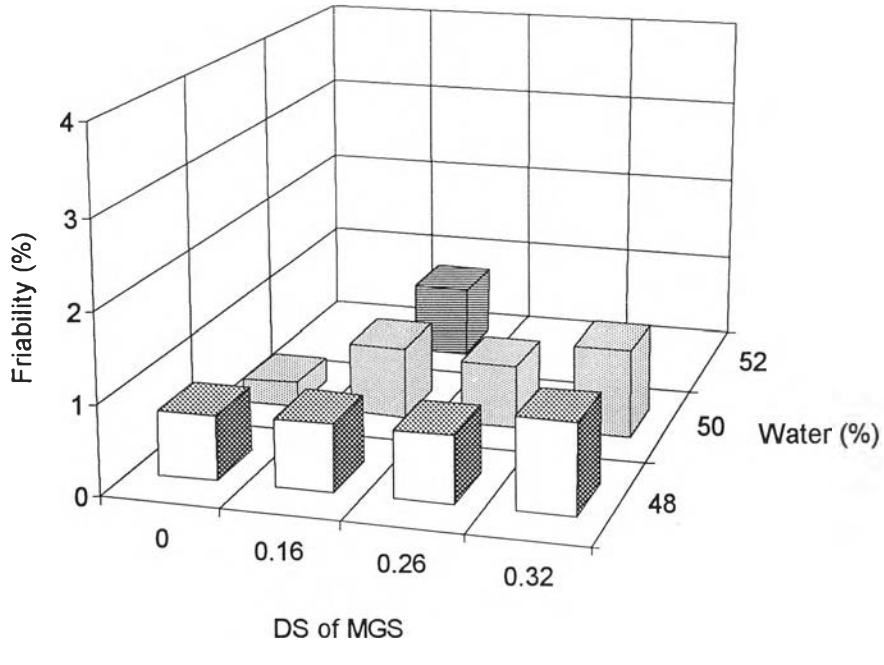


Figure 71 Histograms for percent friability at 710-1000 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

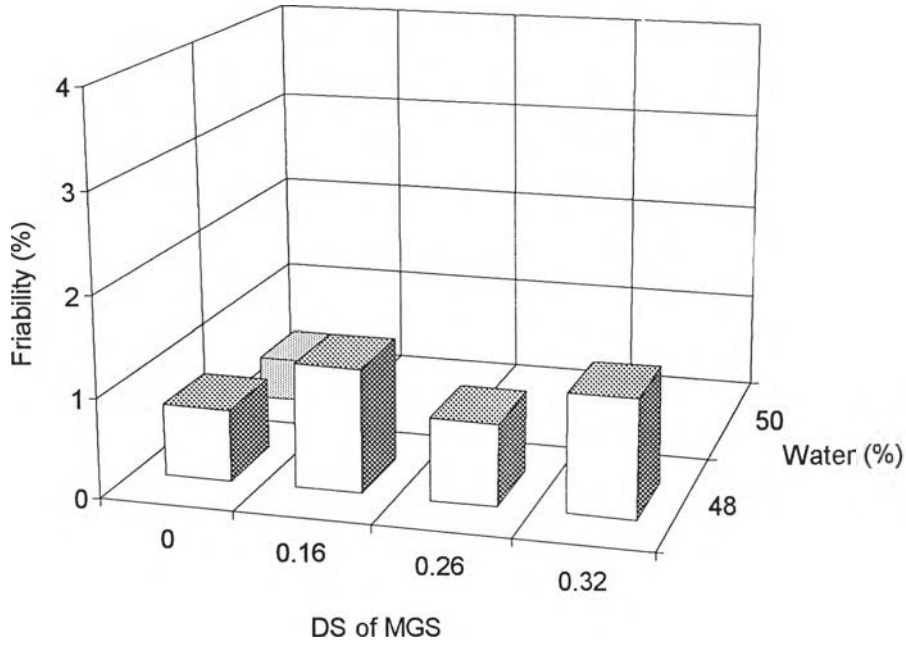


Figure 72 Histograms for percent friability at 500-710 μm-size fraction of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

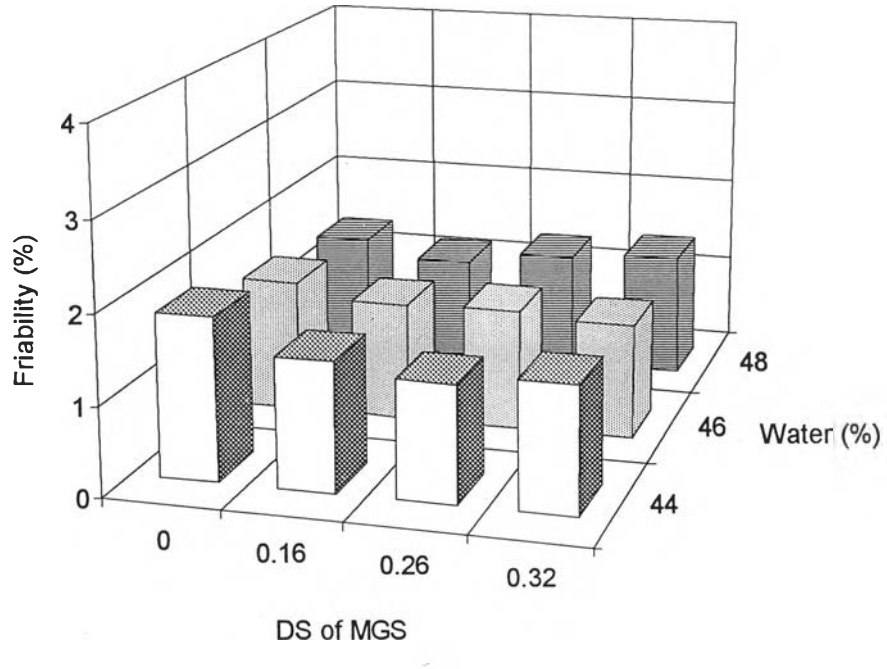


Figure 73 Histograms for percent friability at 1000-1400 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

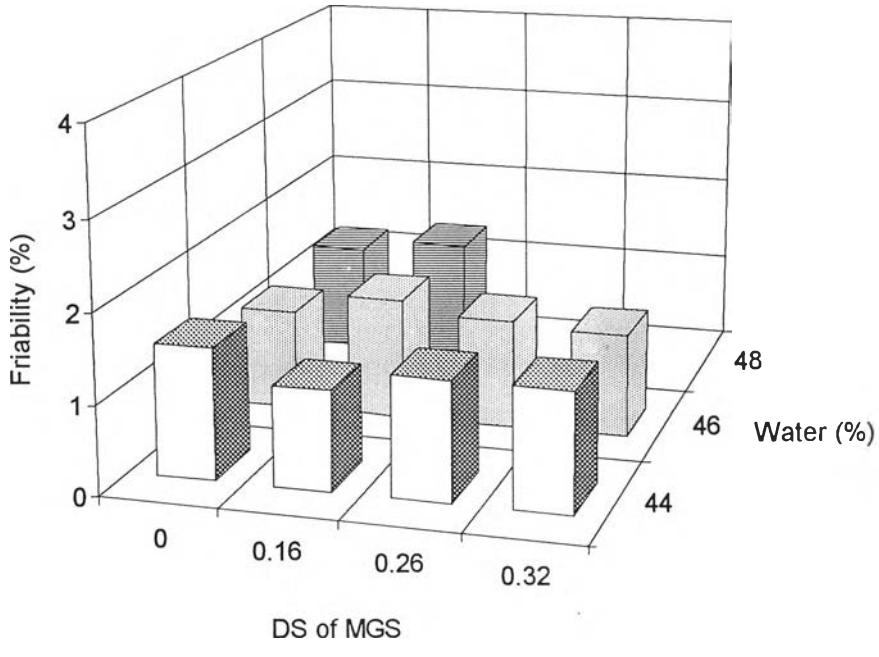


Figure 74 Histograms for percent friability at 710-1000 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

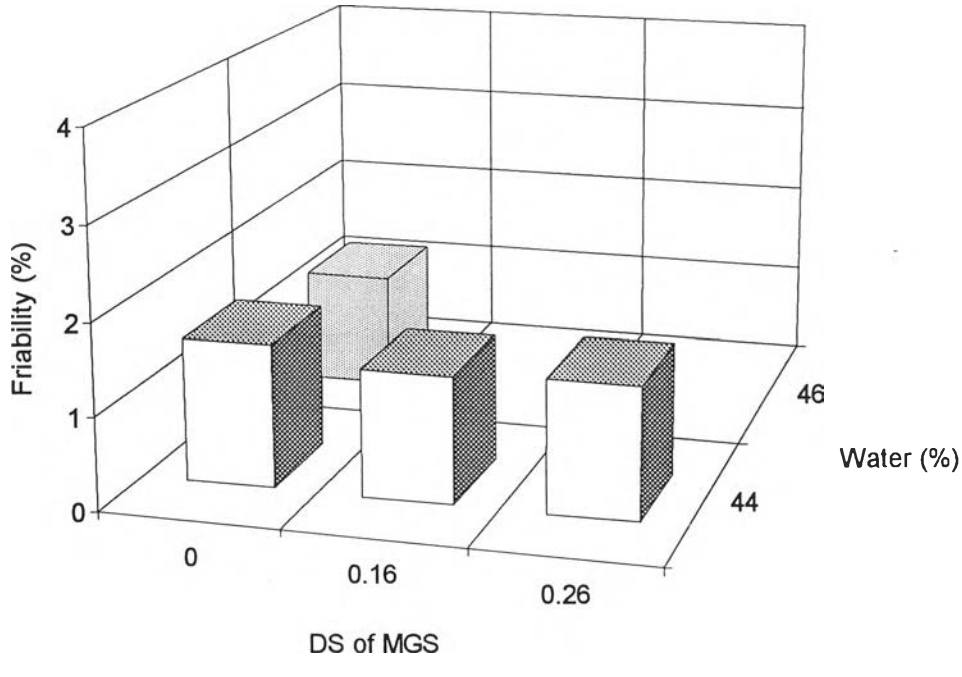


Figure 75 Histograms for percent friability at 500-710 μm-size fraction of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

comparison to 65% formulations. Percent friability at 1000-1400 μm size of modified starches containing pellets was slightly different and mostly less than those of blank pellets (Figure 73). The influence of different DS of MGS on friability of pellets depended upon water level and pellet size. The friability of pellets affected by various amounts of water was slightly different.

As previously noted in lactose pellets , friability which less than 2% was mechanically acceptable , e.g. for coating purpose. The friability is an indication of pellet strength or hardness that is the greater the hardness , the lesser the friability (Erikainen , 1991 ; Reynold , 1970 ; Vervaet et al. , 1995). In this study , such correlation between these two properties did not found because the friability of MGS pellets in 65% formulations which had the greater hardness was higher than blank pellets. Although percent friability which was affected by degree of substitution was mostly related to pellet hardness , the rank of friability of 65% dicalcium phosphate pellets was ordered as : friability of pellets using DS 0.16 < DS 0.26 < DS 0.32 whereas the rank of hardness was ordered as : hardness of pellets using DS 0.16 > DS 0.26 > DS 0.32. For 80% formulations , it could not have any conclusions on the effect of degree of substitution on the friability of pellets. Millili and Schwartz (1990) suggested that as the amount of water increased , the obtained pellets are generally less friable. Inversely , utilization of 52% of water produced pellets with more friable than 50% . But the highest percent friability still observed from using the lowest quantity of added water. The amount of granulated water slightly affected pellet friability of 80% dicalcium phosphate pellets.

2.2.5 Sphericity

As previously described for lactose pellets , degree of sphericity of pellets , in this experiment , was determined from two parameters which were aspect ratio and form factor. These parameters were obtained from image analysis and the results varied by the size fractions are illustrated in Tables 27-28. Statistical analysis data are shown in Appendix V (Tables 108-109 , 115-119).

Table 27 Sphericity values at various size fractions of 65% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

DS	MGS (%w/w)	Water (%)	Formulation	Aspect ratio			Form factor		
				1000-1400 μm	710-1000 μm	500-710 μm	1000-1400 μm	710-1000 μm	500-710 μm
0.32	0.5	52	$6D_{314}$	0.92 (0.02*)	0.90 (0.03)	-	0.97 (0.02)	0.97 (0.01)	-
		50	$6D_{312}$	0.92 (0.04)	0.93 (0.02)	0.88 (0.04)	0.98 (0.01)	0.98 (0.01)	0.97 (0.01)
		48	$6D_{315}$	0.89 (0.05)	0.92 (0.04)	0.90 (0.05)	0.97 (0.02)	0.97 (0.02)	0.97 (0.02)
0.26	0.5	52	$6D_{21}$	0.92 (0.03)	0.90 (0.04)	0.91 (0.04)	0.97 (0.02)	0.97 (0.01)	0.97 (0.03)
		50	$6D_{22}$	0.92 (0.04)	0.93 (0.02)	0.90 (0.04)	0.98 (0.01)	0.97 (0.01)	0.98 (0.01)
		48	$6D_{23}$	0.89 (0.05)	0.90 (0.05)	0.92 (0.03)	0.94 (0.06)	0.98 (0.01)	0.98 (0.02)
0.16	0.5	52	$6D_{11}$	0.94 (0.02)	0.91 (0.04)	-	0.98 (0.01)	0.97 (0.02)	-
		50	$6D_{12}$	0.92 (0.03)	0.92 (0.02)	0.90 (0.05)	0.98 (0.01)	0.97 (0.01)	0.97 (0.02)
		48	$6D_{13}$	0.90 (0.04)	0.93 (0.02)	0.91 (0.03)	0.98 (0.02)	0.98 (0.02)	0.97 (0.01)
0**	-	52	B.7	0.93 (0.03)	0.92 (0.02)	0.91 (0.04)	0.97 (0.01)	0.98 (0.01)	0.97 (0.02)
		50	B.8	0.83 (0.07)	0.91 (0.05)	0.92 (0.02)	0.95 (0.04)	0.98 (0.01)	0.97 (0.01)
		48	B.9	0.83 (0.07)	0.85 (0.07)	0.94 (0.03)	0.94 (0.03)	0.96 (0.03)	0.98 (0.02)

* Standard deviation ** Blank pellets

Table 28 Sphericity values at various size fractions of 80% dicalcium phosphate pellets prepared with different DS of MGS and amounts of water.

DS	MGS (%w/w)	Water (%)	Formulation	Aspect ratio			Form factor		
				1000-1400 μm	710-1000 μm	500-710 μm	1000-1400 μm	710-1000 μm	500-710 μm
0.32	0.5	48	$8D_{32}$	0.92 (0.03*)	0.88 (0.03)	0.88 (0.05)	0.98 (0.01)	0.97 (0.01)	0.97 (0.02)
		46	$8D_{34}$	0.93 (0.02)	0.92 (0.02)	0.90 (0.03)	0.97 (0.02)	0.98 (0.01)	0.96 (0.02)
		44	$8D_{35}$	0.90 (0.05)	0.96 (0.03)	0.91 (0.03)	0.97 (0.01)	0.97 (0.03)	0.97 (0.01)
0.26	0.5	48	$8D_{21}$	0.92 (0.03)	0.87 (0.05)	-	0.96 (0.02)	0.97 (0.01)	-
		46	$8D_{22}$	0.92 (0.03)	0.93 (0.02)	0.90 (0.05)	0.98 (0.01)	0.98 (0.02)	0.98 (0.01)
		44	$8D_{23}$	0.89 (0.06)	0.91 (0.05)	0.91 (0.03)	0.97 (0.02)	0.98 (0.01)	0.92 (0.01)
0.16	0.5	48	$8D_{11}$	0.92 (0.04)	0.92 (0.02)	0.92 (0.03)	0.97 (0.02)	0.97 (0.04)	0.97 (0.01)
		46	$8D_{12}$	0.92 (0.03)	0.92 (0.03)	0.92 (0.02)	0.98 (0.01)	0.98 (0.01)	0.98 (0.01)
		44	$8D_{13}$	0.88 (0.06)	0.92 (0.02)	0.92 (0.03)	0.97 (0.01)	0.97 (0.02)	0.98 (0.02)
0**	-	48	B.10	0.91 (0.04)	0.93 (0.02)	0.92 (0.03)	0.97 (0.01)	0.98 (0.01)	0.97 (0.02)
		46	B.11	0.83 (0.06)	0.91 (0.04)	0.92 (0.02)	0.94 (0.04)	0.97 (0.02)	0.97 (0.01)
		44	B.12	0.81 (0.07)	0.87 (0.06)	0.87 (0.10)	0.94 (0.04)	0.97 (0.02)	0.97 (0.03)

* Standard deviation ** Blank pellets

For appropriately round pellets , aspect ratio and form factor close to unity are obtained. It could be observed that aspect ratio of modified starches containing pellets was almost closer to unity or higher than that of blank pellets. This obviously seen in pellets at 1000-1400 μm size fraction. But aspect ratio of 500-710 μm fraction exhibited no difference from blank pellets. At 710-1000 μm fraction , MGS pellets prepared with highest amount of water , i.e. 52% and 48% for 65% and 80% formulations , respectively , possessed the lower aspect ratio than blank pellets. Comparison between pellets using MGS with different DS but similar amount of water , non-significant difference of aspect ratio was found. Only slight difference was observed among aspect ratio of pellets prepared with various amounts of added water. In 65% dicalcium phosphate pellets , the ranked order of aspect ratio of pellets at 1000-1400 μm size fraction was : aspect ratio of pellets using 52% water > 50% water > 48% water (Table 27). However , the ranked order of others size fractions were dissimilar that was : aspect ratio of pellets using 48% water > 50% water > 52% water in 500-710 μm fraction and inconsistent order in 710-1000 μm fraction. It could be observed that the aspect ratio of spheres prepared by 48% of granulated water showed negligibly different among three size groups.

In consideration of 80% dicalcium phosphate formulations , the aspect ratio of pellets at 1000-1400 μm size tended to be increased with increasing amount of water (Table 28). But nearly similar value of aspect ratio at 500-710 μm fraction and uncorresponding ranked order at 710-1000 μm fraction were observed. In addition , the aspect ratio at various size fractions of spheres manufactured with 44% of added water and any DS of MGS showed similar trend.

In general , the high spherical particle is suitable for successfully coating , improving the flowability and , consequently , controlled release products. From the results , it could be concluded that modified starch containing pellets were significantly more spherical than blank pellets. The possible reasons were the same as described in sphericity of lactose pellets (Section 2.2.5). However , MGS pellets using the great quantity of water , in some formulations ,

might less round than blank pellets. It might be explained that using modified starch and great amount of water resulted in high cohesive force of wet mass and more elastic extrudates which resisted to spinning motion of friction plate to form rounder spheres (Linder and Kleinebudde , 1994). The influence of degree of substitution on the aspect ratio and consequent sphericity of pellets was almost negligible. In previous studies , the amount of granulation liquid had been found to have a pronounced effect on the sphericity of pellets where pellets with greater water content were rounder (Hellen and Yliruusi , 1993 ; Linder and Kleinebudde , 1994 ; Wan et al. , 1993). In this study , the pronounced effect of liquid level on pellet sphericity was seen especially in size fraction of 1000-1400 μm but the sphericity of other size factions were inconsistent. This might be described that the particles with small size could easily spun in spheronizer and formed optimal pellets by independent upon the great amount of water. The slight difference of aspect ratio affected by the various amounts of added water might be due to the plastic properties of wet mass which was less sensitive to the 2% difference in water content.

As can be seen from the Tables 27-28 , the form factor of pellets containing modified starches particular in 1000-1400 μm size fraction was slightly higher than that of blank pellets but no difference was observed of other sizes. Comparison between using various DS of MGS or amounts of added water , form factor exhibited approximately the same value. This was in agreement with Linder and Kleinebudde (1994) who indicated that the form factor could not distinguish between round or less round pellets as exactly as the aspect ratio.

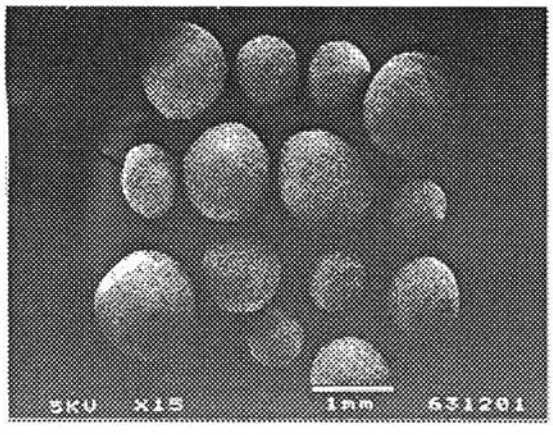
2.3.6 Pellet Characteristics , Surface and Internal Structure by SEM

The general characteristics of pellet including pellet shape at various size fractions were studied by scanning electron microscope (SEM) at two magnifications (x15 and x35). The surface and cross-sectioned morphology of pellets representing by 710-1000 μm fraction of pellets were also studied at x750 and x150 magnifications. The obtained photomicrographs of 65% and 80%

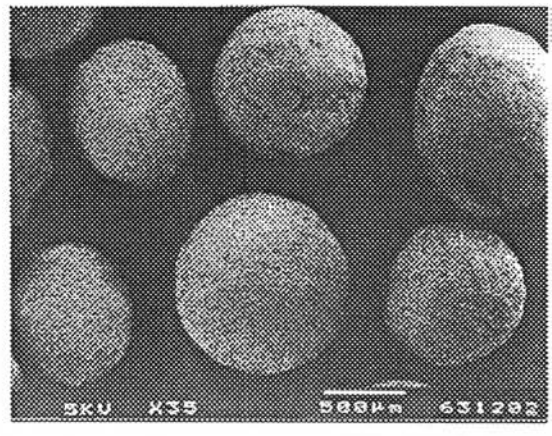
formulations are shown in Figures 76-83 and Figures 84-91 , respectively. Three formulations of each model which prepared with the same water level (50% water for 65% formulations and 44% water for 80% formulations) were chosen from each group of degree of substitution to represent the characteristics and shape of pellets. No difference of general characteristics and shape of pellets caused by different added water was found except the size or average diameter. These three formulations were compared with formulation of blank pellets. For 65% and 80% dicalcium phosphate pellets , it could be seen from the figures 76-79 and 84-87 that modified starch containing pellets were more spherical, larger in size and slightly less agglomeration than blank pellets. In comparison among the unsized 65% dicalcium phosphate pellets , DS 0.16 produced pellets with the largest particle size (Figure 78A). However , the sphericity of pellets at any size fractions illustrated no difference. In consideration of 80% dicalcium phosphate pellets , the characteristics and shape of pellets had the same character of 65% formulations but the particle size of pellets using various DS of MGS exhibited no difference (Figures 84-86A). These results were in accordance with the prior results of size distribution and sphericity (Section 2.3.1 and 2.3.5). It could also be concluded that DS of MGS did not play a significant effect on particle size of pellets.

The surface conditions of 65% and 80% pellet formulations were not different . As previously described for lactose pellets , very smooth surface was not obtained. Small crumbs were found on the surface of all formulations . The surface property of spheres containing modified starches was smoother than blank pellets. These were in accordance with the sphericity results (Section 2.3.5) which noted that MGS pellets were rounder than blank pellets since a rounder sphere mostly formed with smoother surface. The possible reasons of these results were based on as described for lactose pellets in section 2.2.5. Comparison of the surface between pellets using different DS of MGS , it was found that DS 0.16 produced pellets with rougher surface than other DS (Figures 82 and 90). This finding could confirm the previous study which suggested that the surface smoothness did not depend on the pellet shape (Hellen et al. , 1993

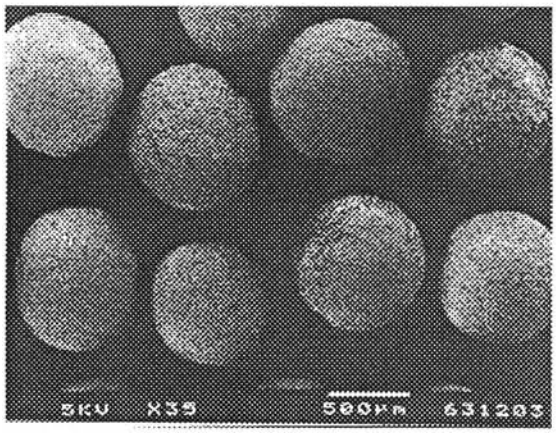
A)



B)



C)



D)

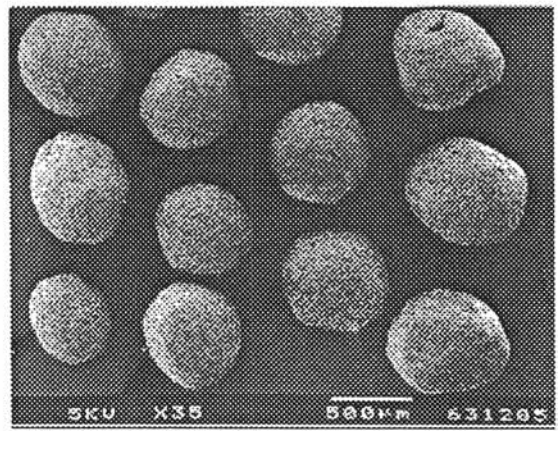
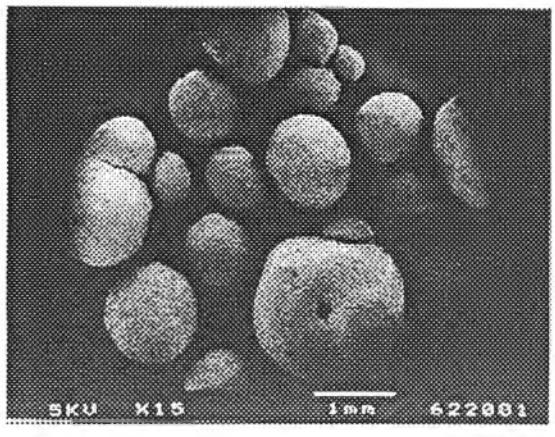
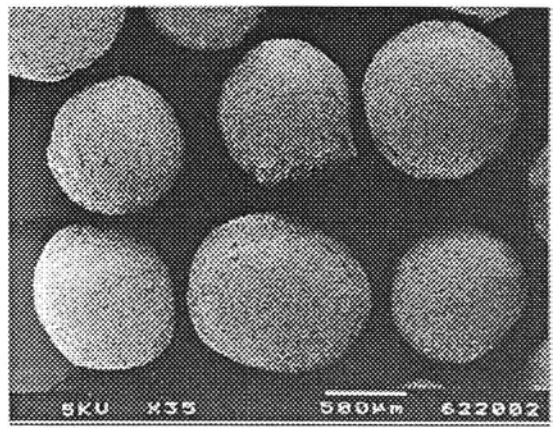


Figure 76 Photomicrographs presenting pellet characteristics of $6D_{312}$ using 0.5% w/w of MGS with DS 0.32 and 50% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

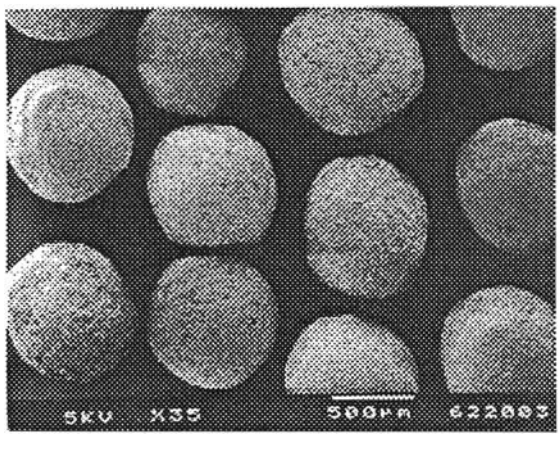
A)



B)



C)



D)

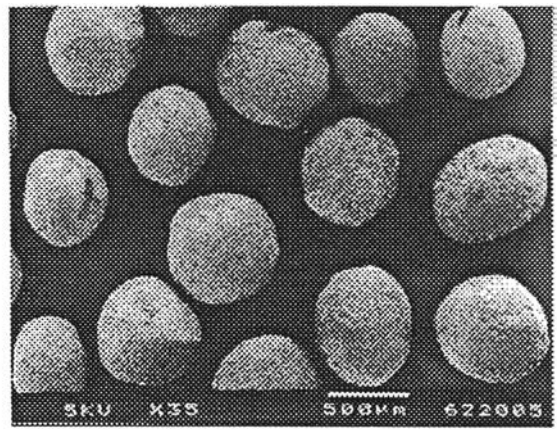


Figure 77 Photomicrographs presenting pellet characteristics of $6D_{22}$ using 0.5% w/w of MGS with DS 0.26 and 50% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

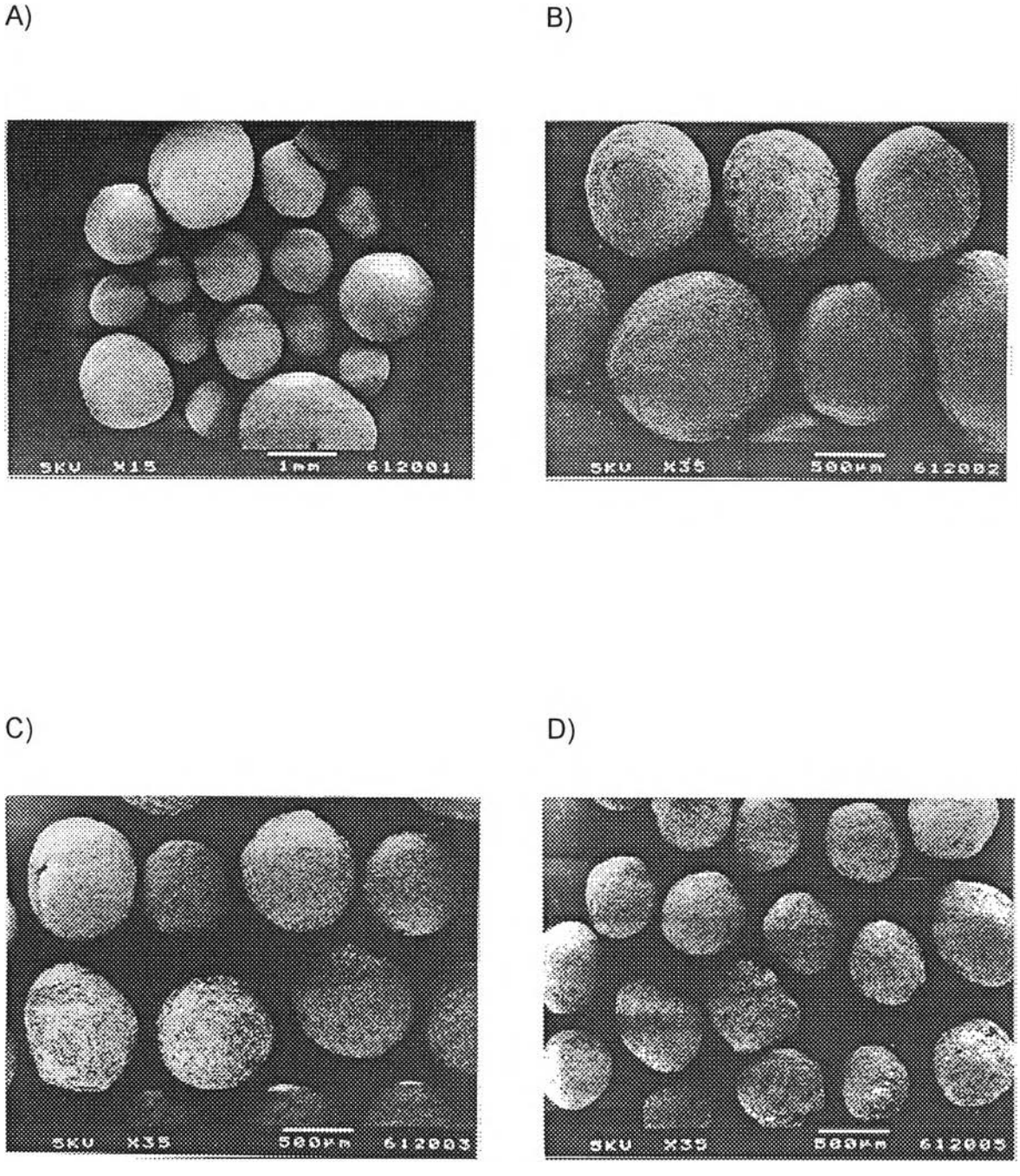


Figure 78 Photomicrographs presenting pellet characteristics of $6D_{12}$ using 0.5% w/w of MGS with DS 0.16 and 50% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

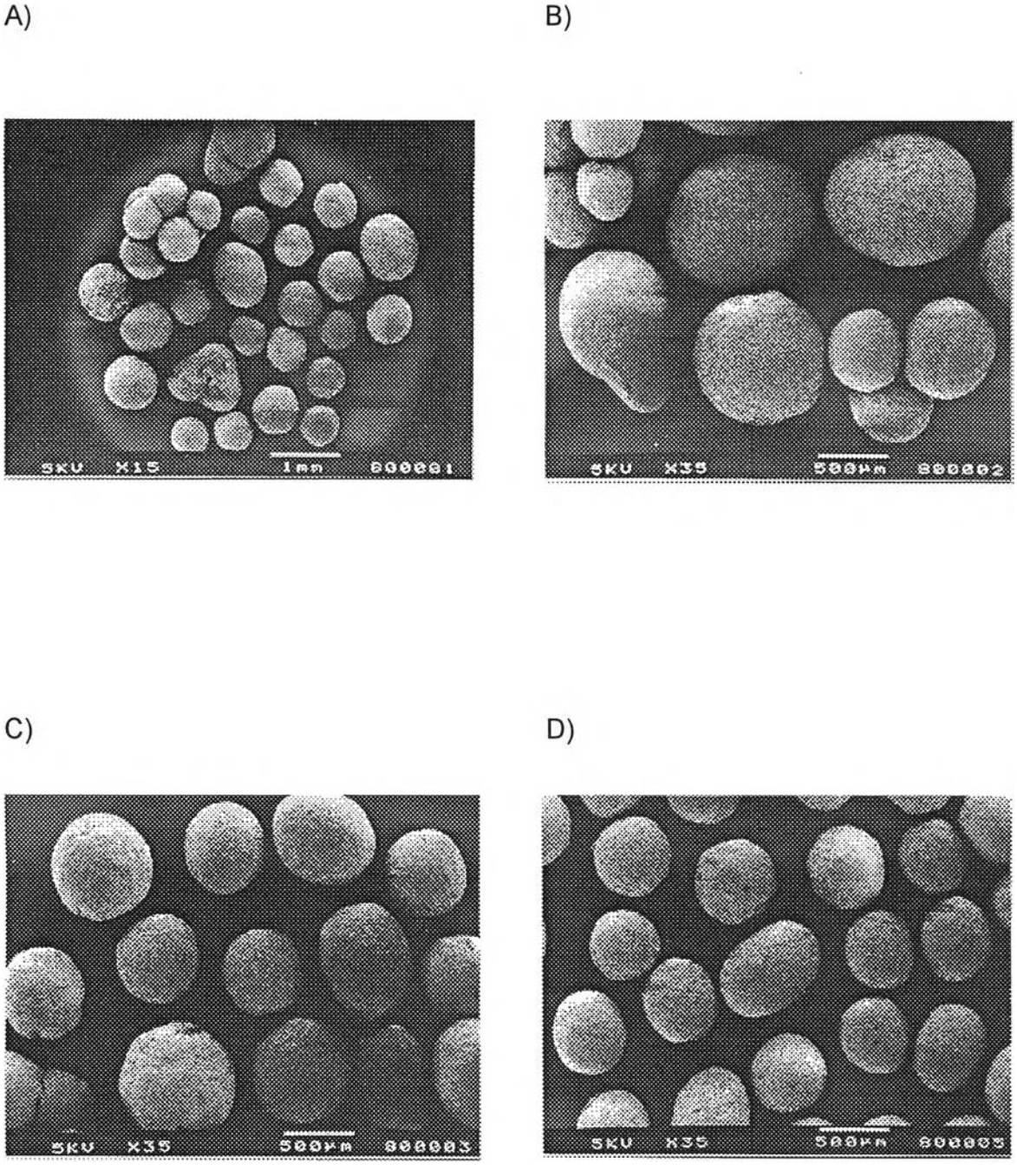
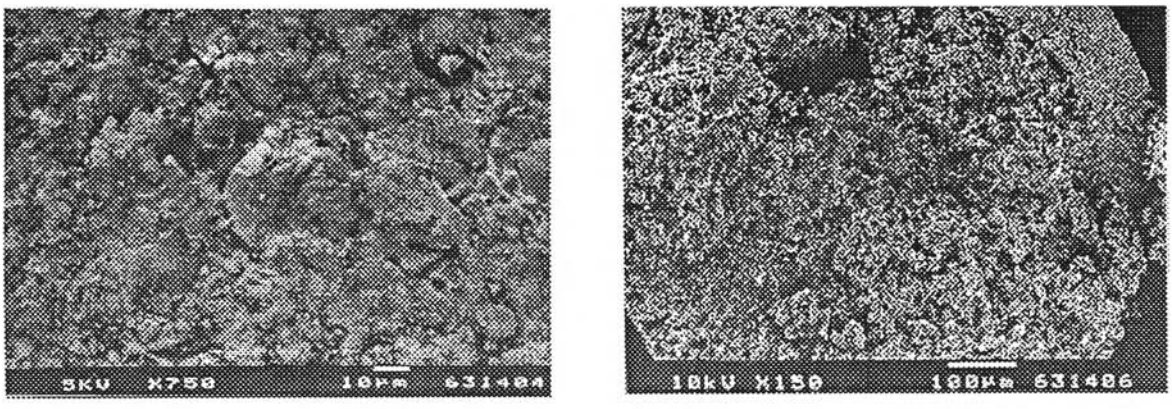
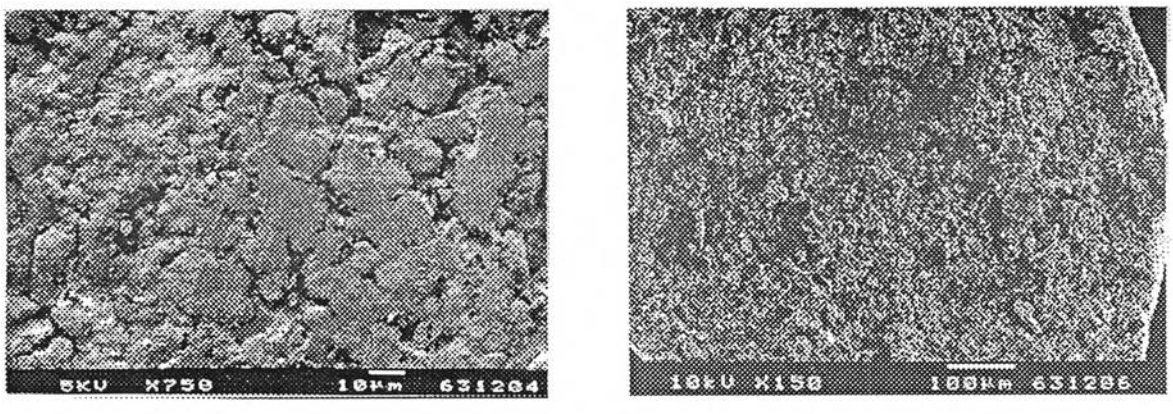


Figure 79 Photomicrographs presenting characteristics of 65% dicalcium phosphate blank pellet (B.8) using 50% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

A)



B)



C)

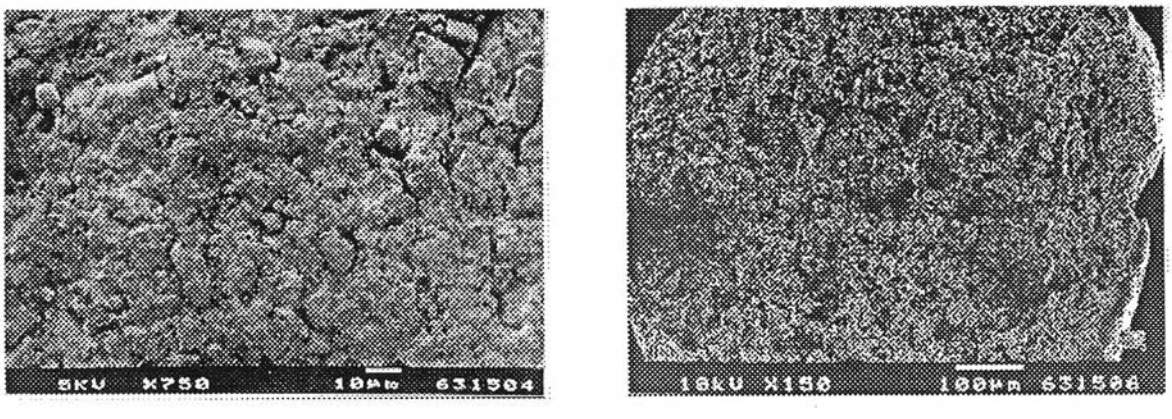
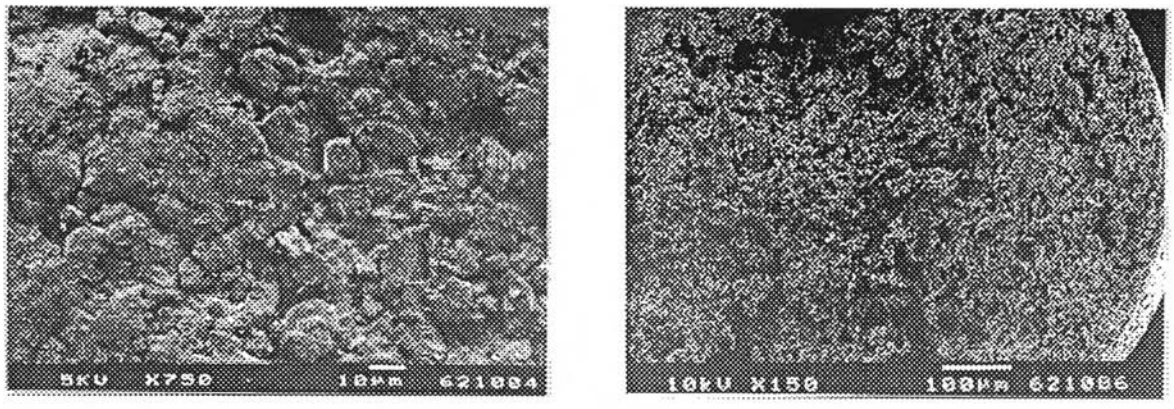
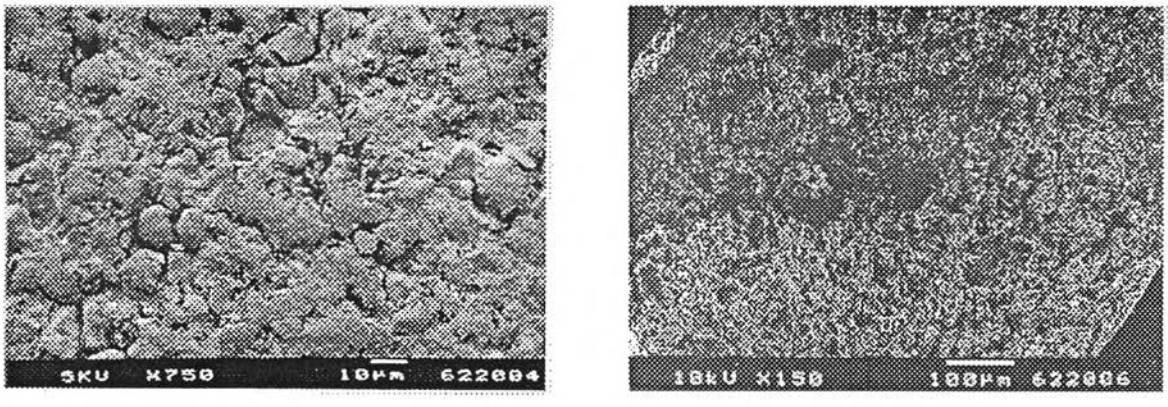


Figure 80 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.32 and different amounts of water : A) $6D_{314}$ (52%), B) $6D_{312}$ (50%), C) $6D_{315}$ (48%)

A)



B)



C)

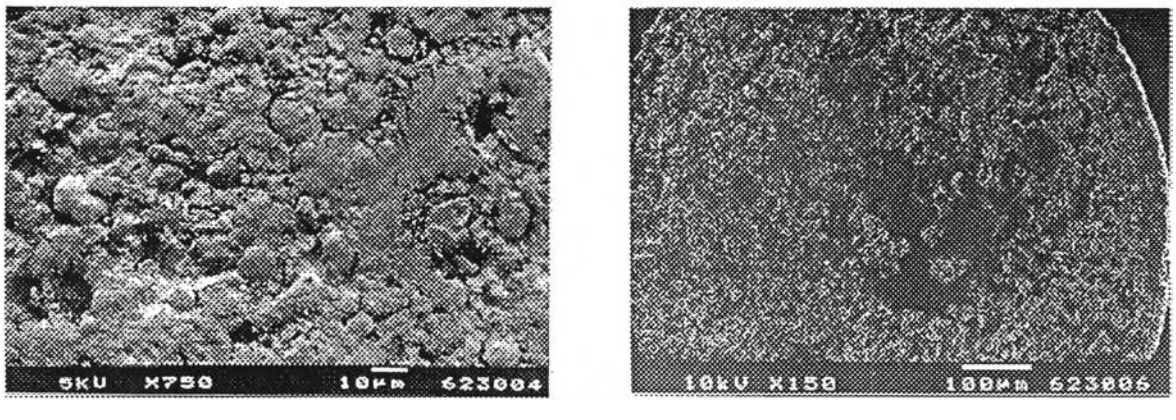
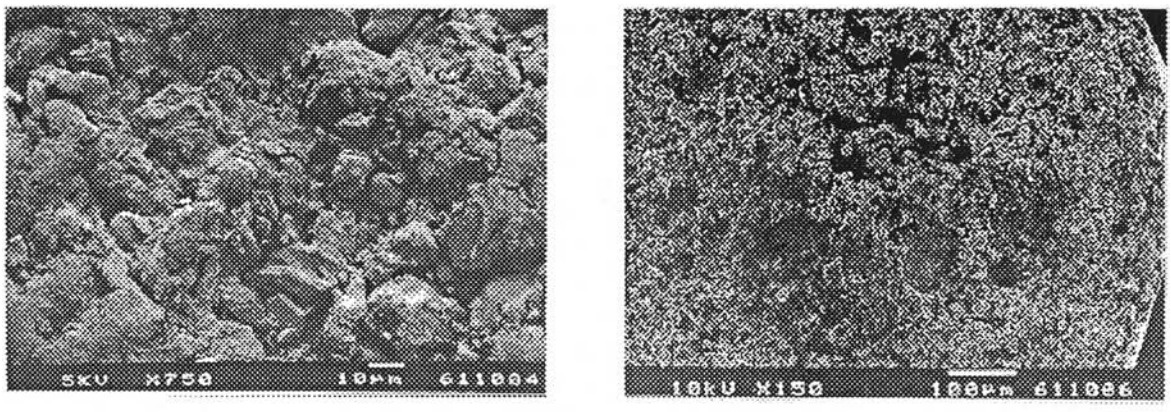
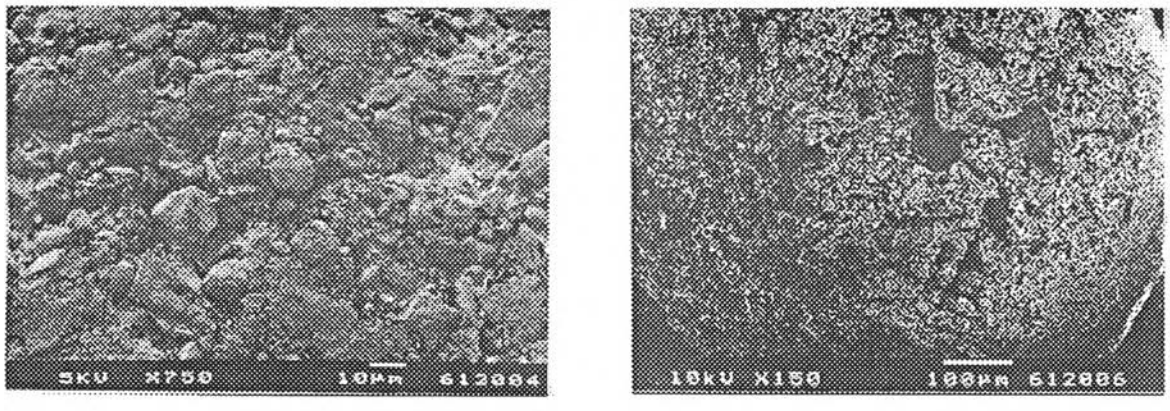


Figure 81 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.26 and different amounts of water : A) $6D_{21}$ (52%), B) $6D_{22}$ (50%), C) $6D_{23}$ (48%)

A)



B)



C)

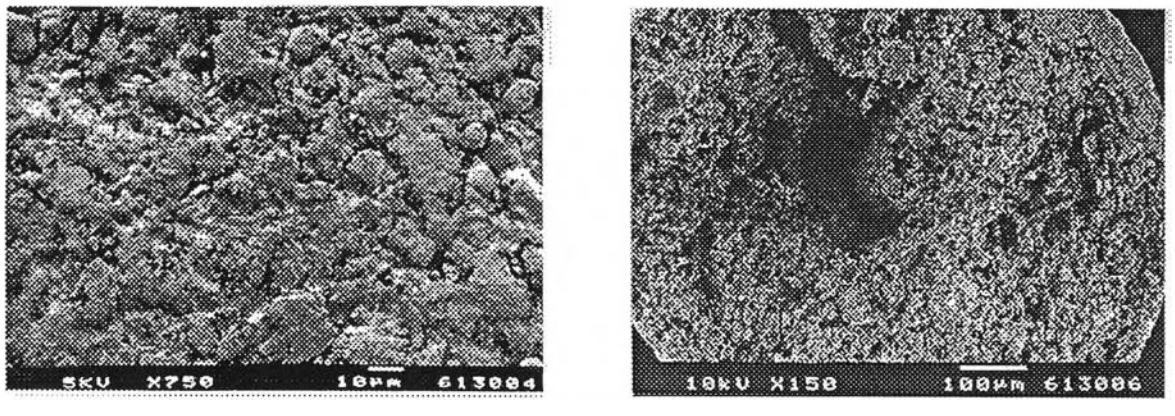
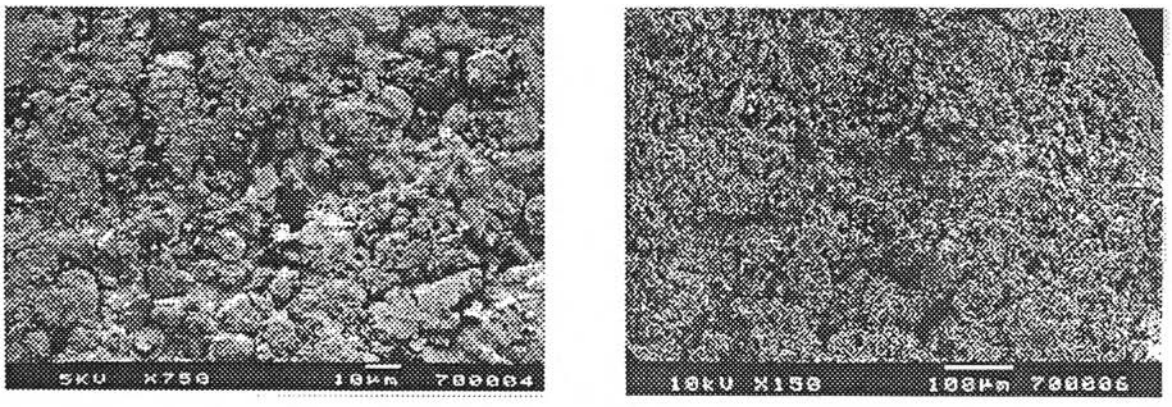
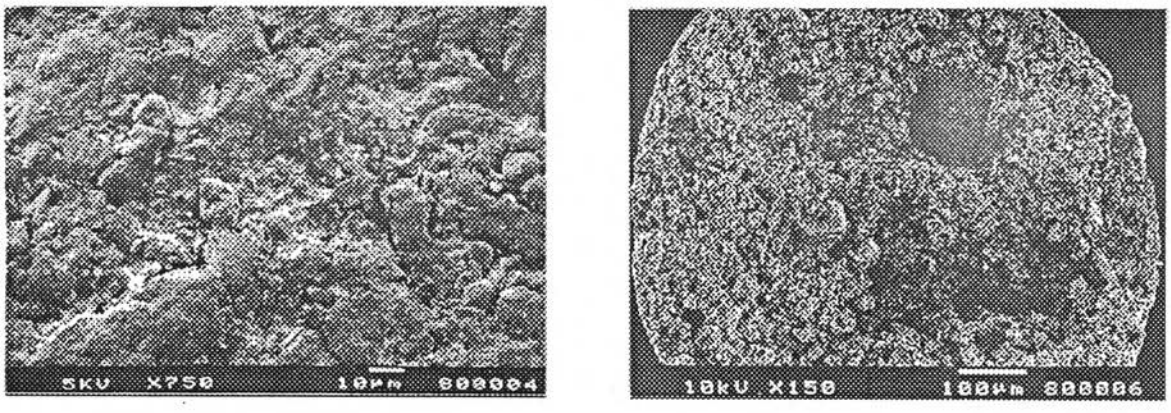


Figure 82 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.16 and different amounts of water : A) $6D_{11}$ (52%), B) $6D_{12}$ (50%), C) $6D_{13}$ (48%)

A)



B)



C)

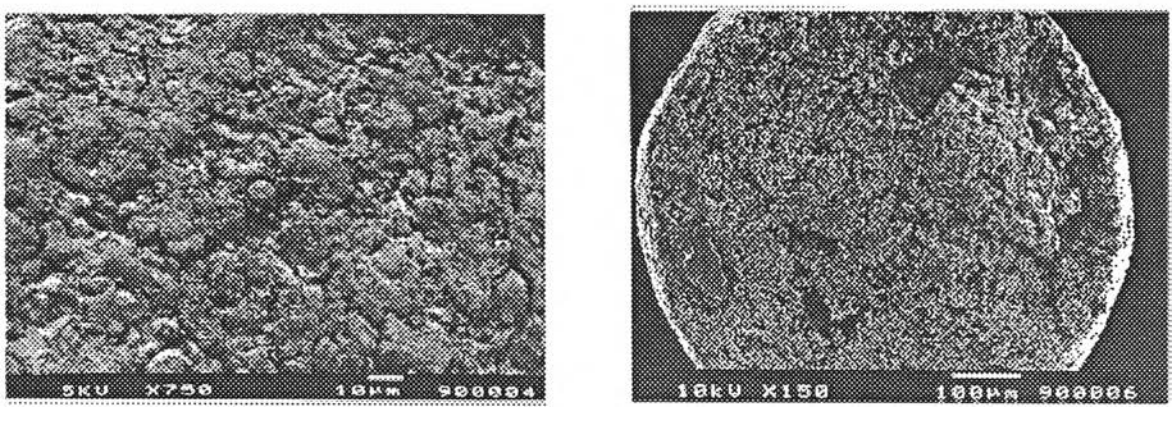
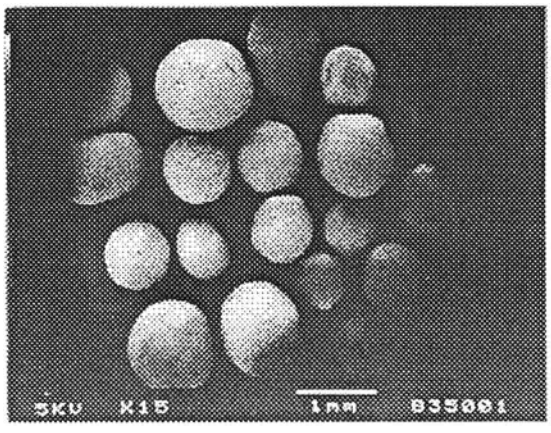
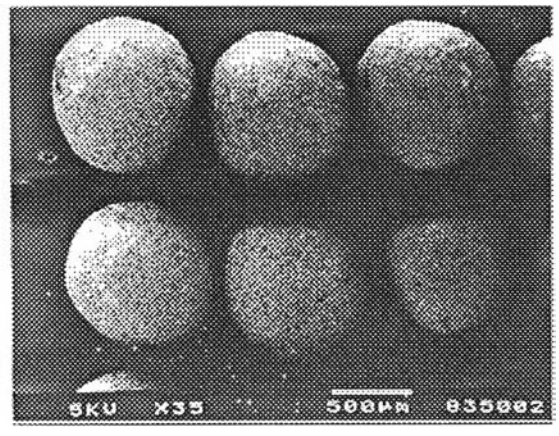


Figure 83 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 65% dicalcium phosphate blank pellets using different amounts of water : A) B.7 (52%), B) B.8 (50%), C) B.9 (48%)

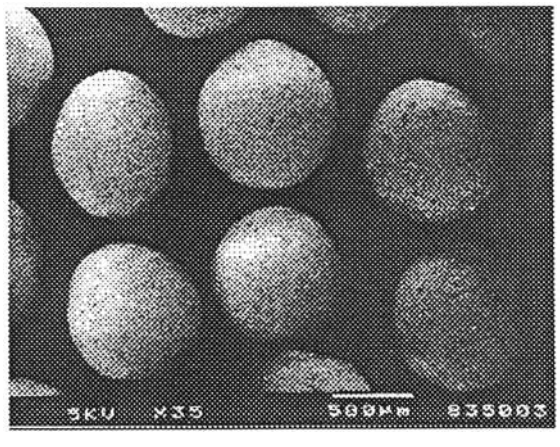
A)



B)



C)



D)

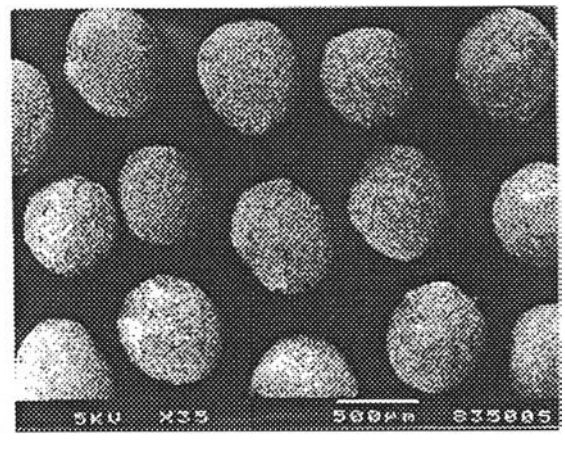


Figure 84 Photomicrographs presenting pellet characteristics of $8D_{35}$ using 0.5% w/w of MGS with DS 0.32 and 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

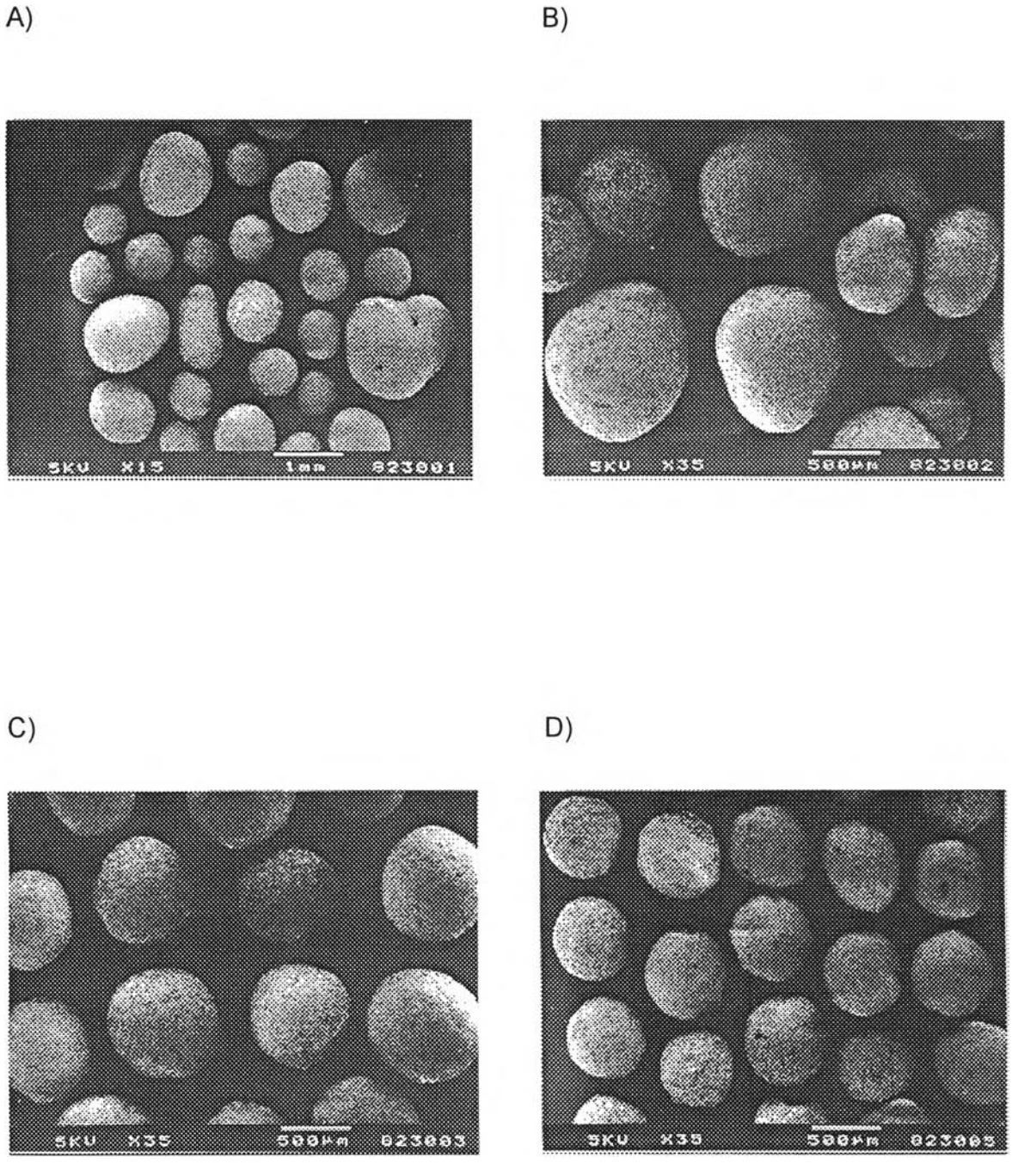


Figure 85 Photomicrographs presenting pellet characteristics of $8D_{23}$ using 0.5% w/w of MGS with DS 0.26 and 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

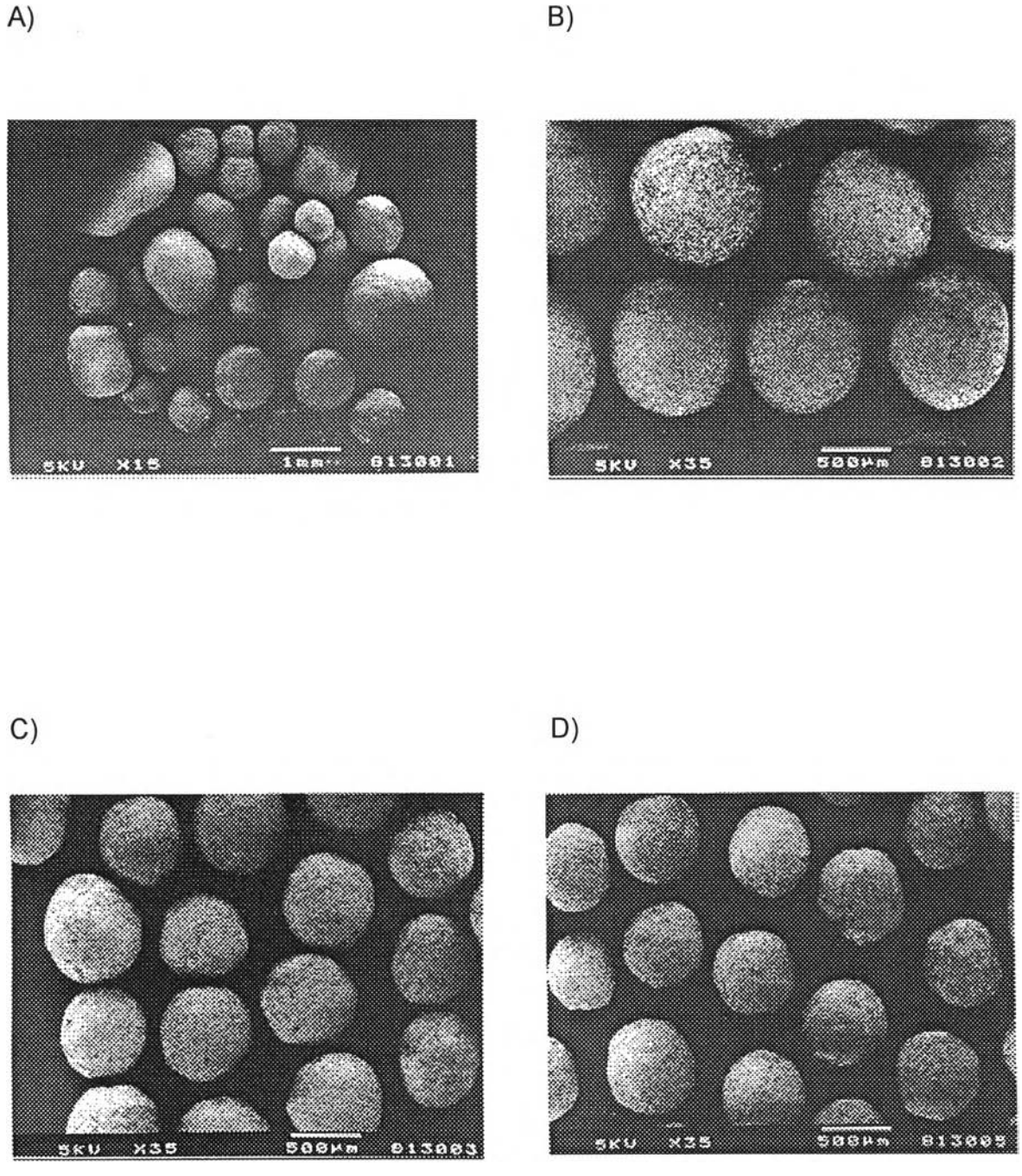


Figure 86 Photomicrographs presenting pellet characteristics of $8D_{13}$ using 0.5% w/w of MGS with DS 0.16 and 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

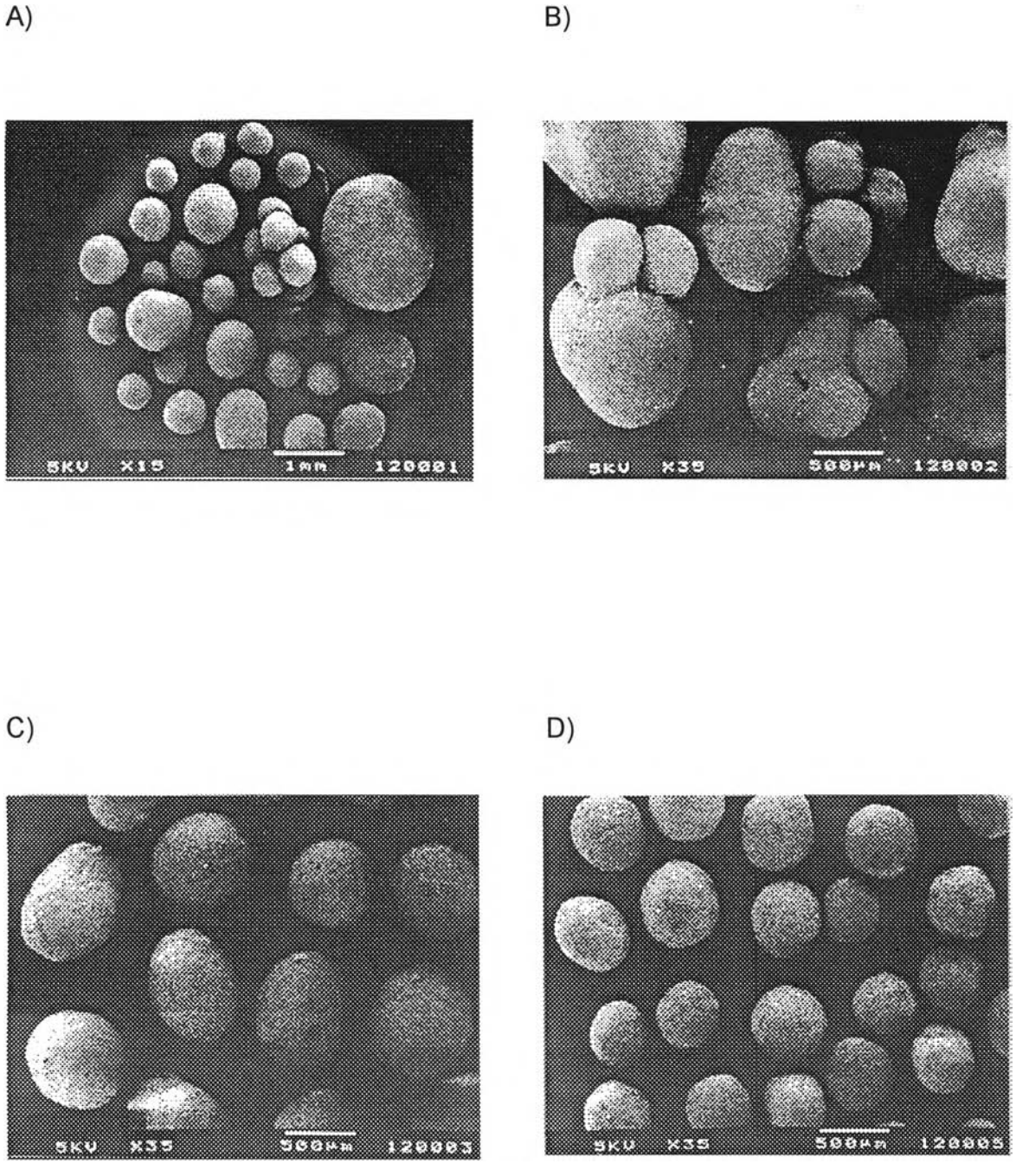
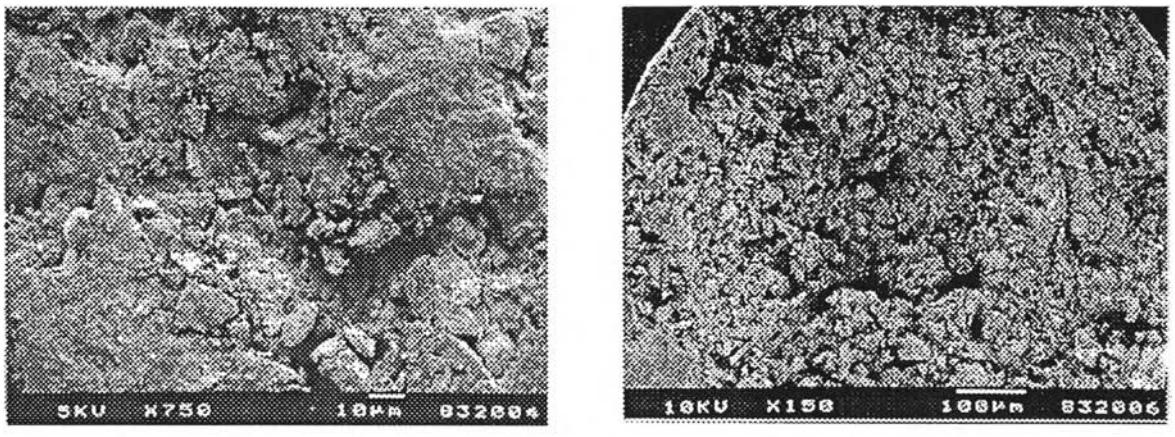
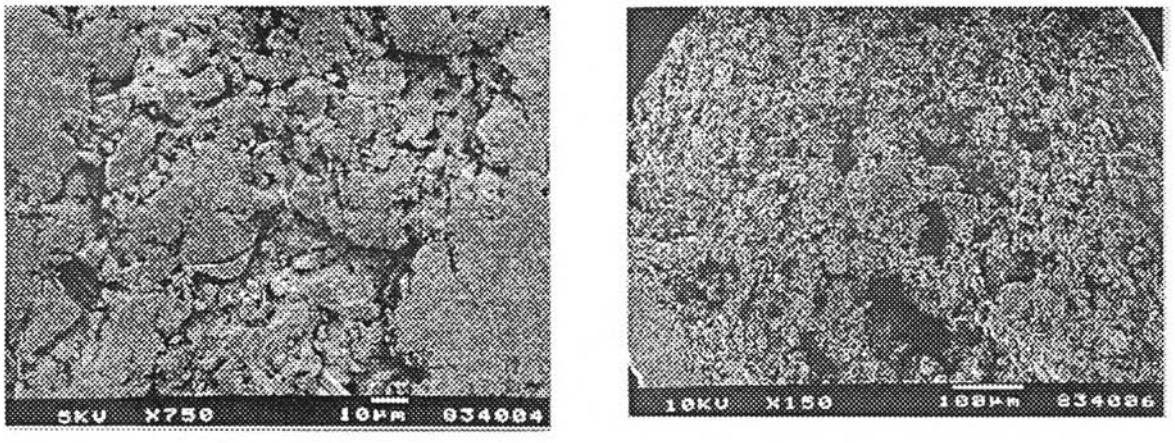


Figure 87 Photomicrographs presenting characteristics of 80% dicalcium phosphate blank pellet (B.12) using 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 35, C) Size 710-1000 µm x 35 and D) Size 500-710 µm x 35.

A)



B)



C)

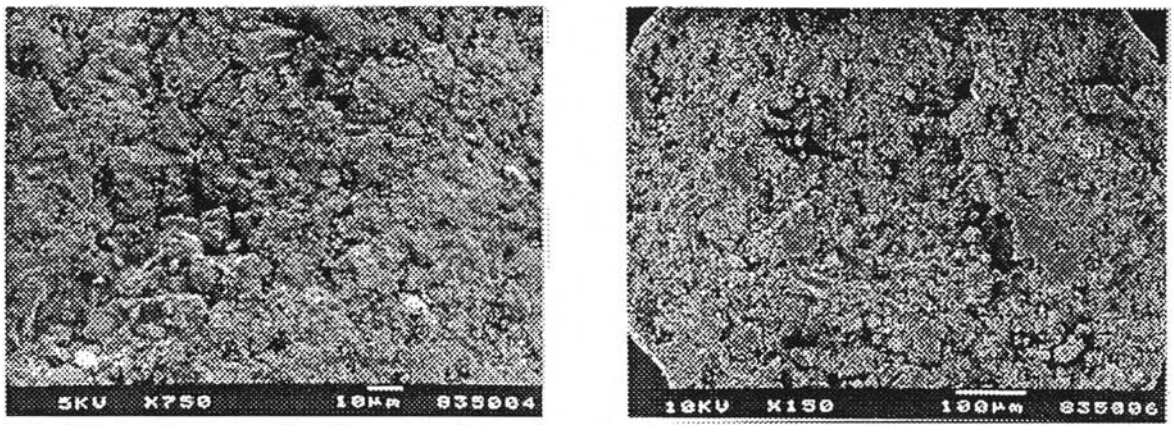
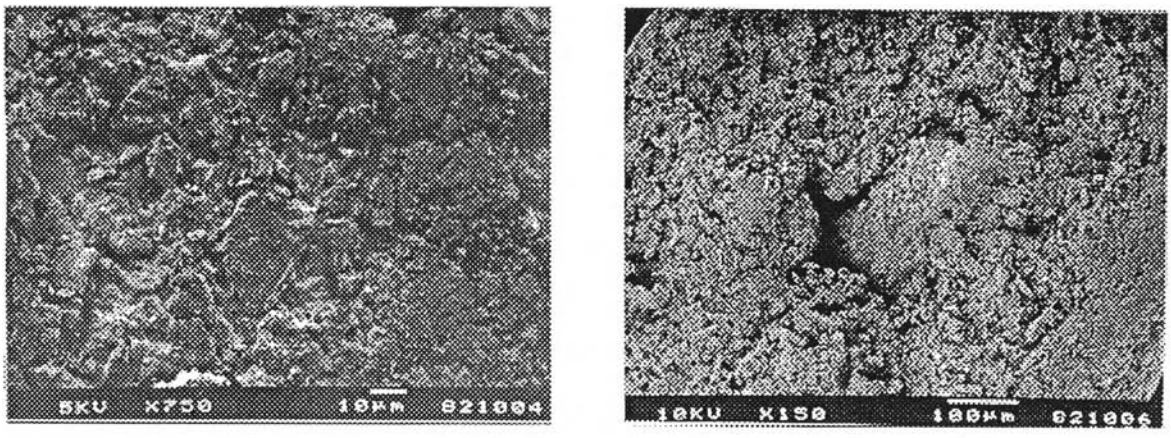
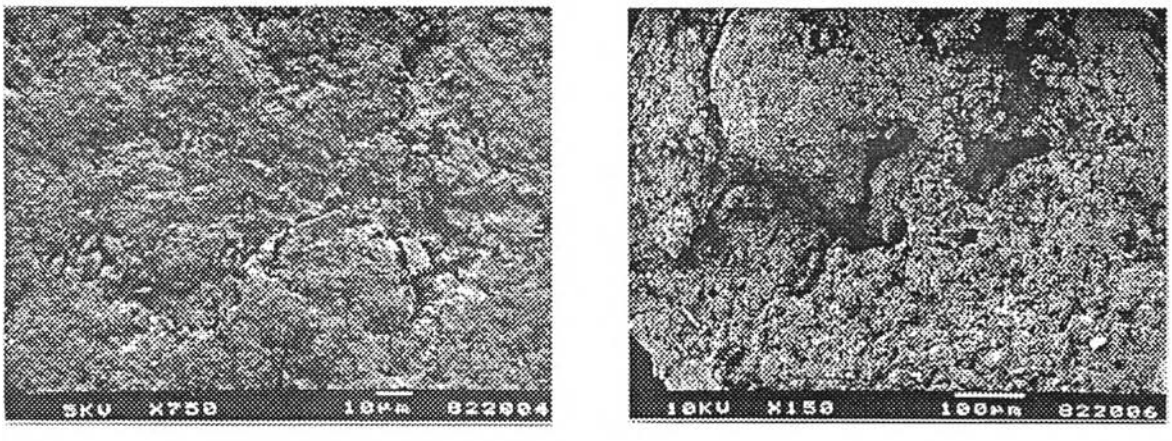


Figure 88 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.32 and different amounts of water : A) $8D_{32}$ (48%), B) $8D_{34}$ (46%), C) $8D_{35}$ (44%)

A)



B)



C)

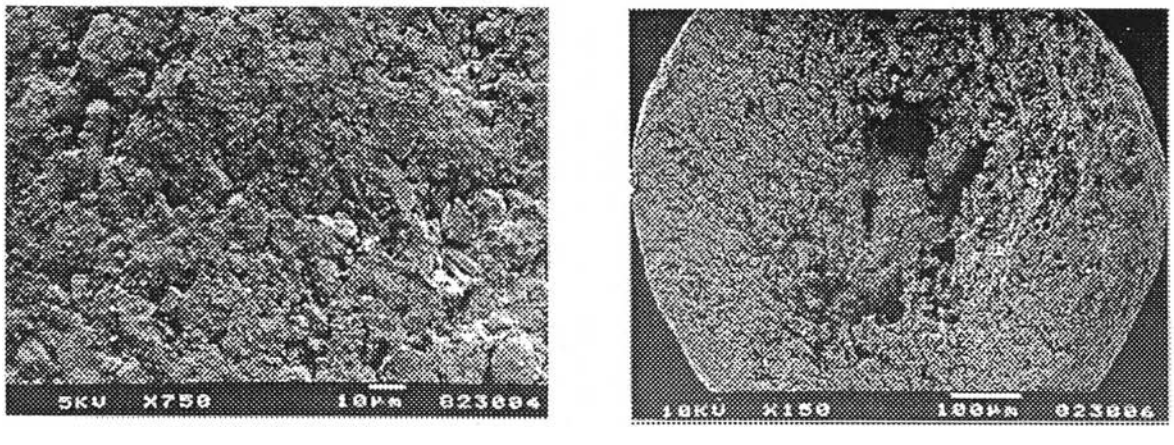
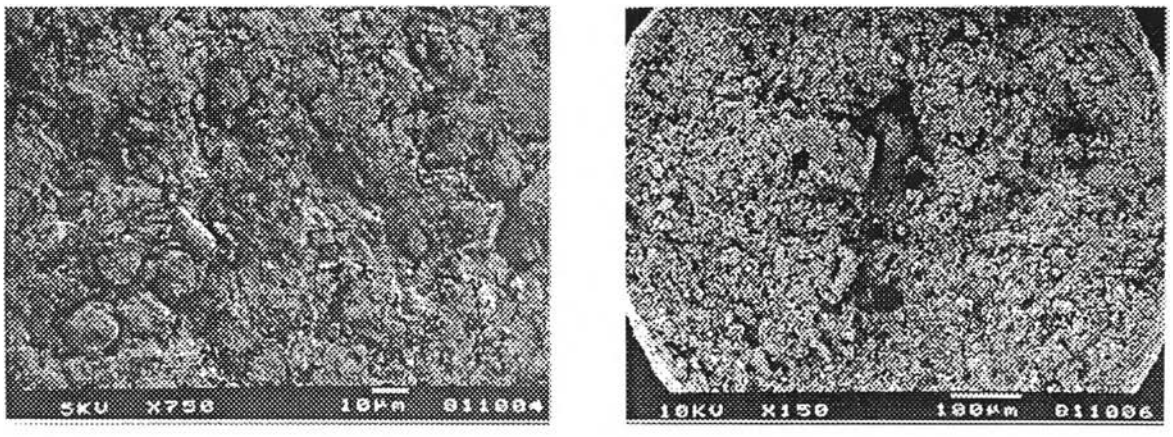
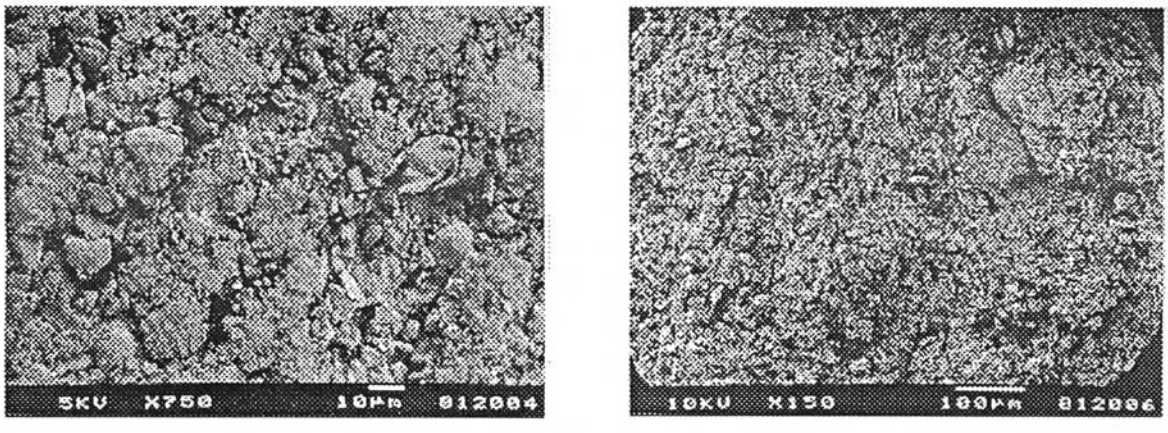


Figure 89 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.26 and different amounts of water : A) $8D_{21}$ (48%), B) $8D_{22}$ (46%), C) $8D_{23}$ (44%)

A)



B)



C)

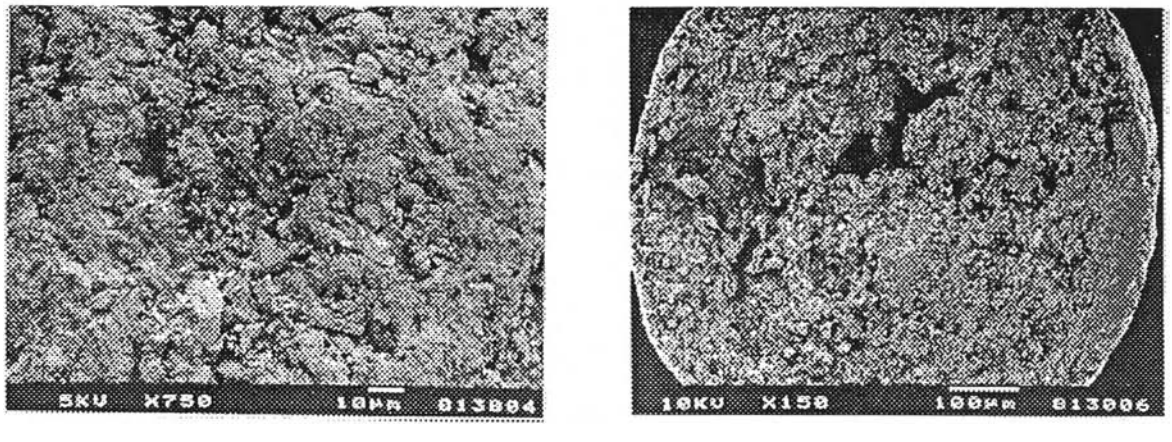
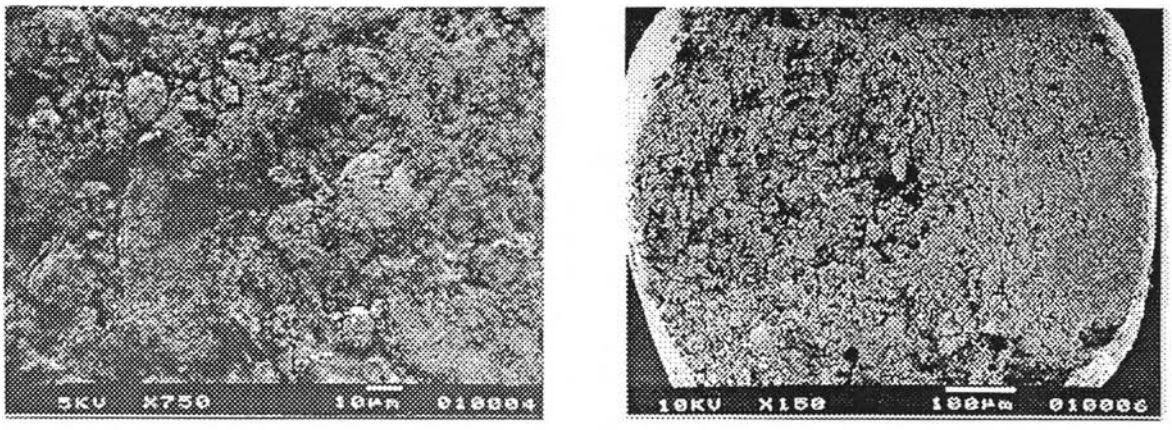
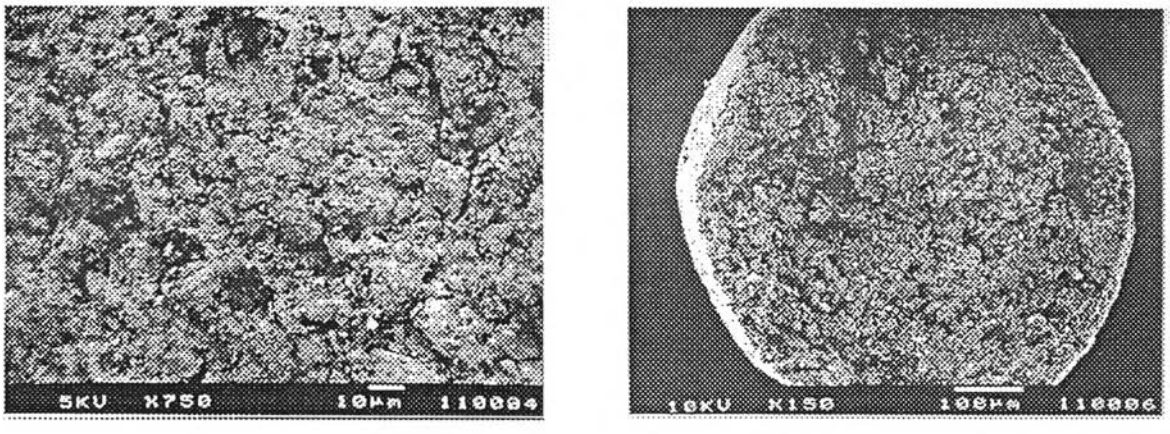


Figure 90 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% dicalcium phosphate pellet formulations using 0.5% w/w of MGS with DS 0.16 and different amounts of water : A) $8D_{11}$ (48%), B) $8D_{12}$ (46%), C) $8D_{13}$ (44%)

A)



B)



C)

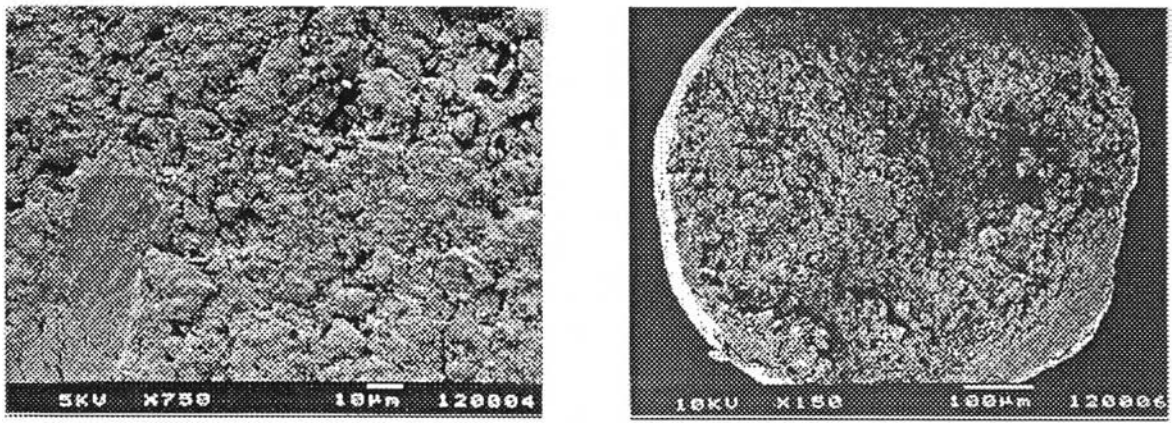


Figure 91 Photomicrographs presenting pellet surfaces (Left, x750) and internal structures (Right, x150) of 80% dicalcium phosphate blank pellets using different amounts of water : A) B.10 (48%), B) B.11 (46%), C) B.12 (44%)

b). Since , in this study , no significant influence of degree of substitution on pellet shape but surface of pellet prepared with DS 0.16 was slightly different from with other DS. It might be assumed that highest viscosity of MGS at DS 0.16 when in contact with water increased the cohesive force in the mass and the resulting extrudates. This force would be resistant to the force occurring in spheronization process , thus smooth surface was not easily produced. The effect of added water level on the surface characteristic was similar as described for lactose pellets. The roughness of surface tended to be increased with increasing the amount of added water.

Baert and Remon (1993) described the mechanism of pellet formation from the occurrence of cavity in the photomicrographs of cross-sectioned pellet. The internal cavity was obviously seen in lactose pellet formulations but it could not be found in dicalcium phosphate pellets. From the particle size of starting materials (Table 20), it was found that the average particle size of dicalcium phosphate dihydrate , in comparison to lactose , was very small. The forces in the spheronizer were sufficient and easy to compact fine particles together and the cavity might be filled with this fine particles (Fielden et al. , 1992 a). Hence , the interior cavity of dicalcium phosphate pellets almost disappeared. Moreover , it might be also postulated that , during the process , the migration of liquid from the interstices between particles to the surface of the sphere is almost always accompanied by the migration of chemical in the formulation that are soluble in the liquid (Chien and Nuessle , 1985). Thus , lactose which was soluble in the added water could migrate to the surface of pellets at higher degree than the insoluble dicalcium phosphate dihydrate , resulting in the formation of internal cavity of lactose pellets.

3. Selection of the Pellet Formulations Which Exhibited Good Physical Properties

This step concerned about the selection of the most satisfactory formulations from lactose and dicalcium phosphate pellets which were evaluated

in the previous part of this work. The selected formulations were used to study the effect of the amount of modified glutinous rice starch on the various pellet properties . To select the formulation , some important physical properties of pellet were considered.

For all lactose pellet formulations , 65% lactose pellets were more appropriate for further studies than 80% lactose pellets because percent friability of 65% formulations were lower and the wet mass easily passed through screw of extruder. The wet powder mass of 80% formulations difficultly passed through the screw of extruder although using the same amount of Avicel PH101 as that of 65% formulations. This might be explained by that the higher the amount of lactose which possessed the largest particle size was (Table 20) , the greater the friction force during processing in extruder was created. Thus , the formulation $6L_{22}$ which employed MGS at DS 0.26 and 37% of added water was chosen The possible reasons were as follows :

1. Pellets containing MGS with DS 0.26 and using any added water level possessed the highest hardness.
2. MGS with DS 0.26 produced pellets with the lowest geometric standard deviation (σ_g) of size distribution.
3. Average particle size or D_{50} of pellets using 37% of water was suitable for pharmaceutical application.
4. The aspect ratio of spheres manufactured with 37% of water presented the similar values among various size fractions.

For all dicalcium phosphate pellets , the 80% formulations were suitable for further studies. Because the wet mass of 80% formulations was easier passed through the screw of extruder and the obtained extrudates were more freely spun in spheronizer when compared with 65% formulations , even when the high or low water level was used. Thus , the formulation $8D_{35}$ with MGS at DS 0.32 and 44% of adding water was selected. The main reasons were as follows :

1. Mostly , the hardness of pellets using MGS with DS 0.32 was higher than that of using other DS.
2. MGS with DS 0.32 almost yielded pellets with the lowest σ_g of size distribution.
3. Utilization of MGS with DS 0.32 and 44% of added water in formulation produced pellets with the greater hardness when compared with using the other added water levels.
4. The aspect ratio of pellets prepared with 44% of water showed similar tendency of ranked order among various size fractions.

4. Evaluation of the Physical Properties of Pellets Containing Different Amounts of Modified Starches.

The above formulations , $6L_{22}$ and $8D_{35}$ were the basic formulas for investigation of the effect of various modified starch quantities on pellet properties . The basic formulas composed of 0.5% w/w of modified starch , so this quantity was changed to 0.3 and 0.8% w/w whereas the amount of other starting materials and process variables were kept constant. The acceptable pellets could not be produced when the greater amount of MGS ($\geq$ 1% w/w) was used. The physical properties of the obtained pellets in comparison to basic formulations and their blank pellets were as follows.

4.1 Particle Size Distribution

The particle size distribution of lactose and dicalcium phosphate pellets prepared with various amounts of MGS are shown in Figure 92-93 and Table 40-41 (in Appendix III). The percent cumulative undersize plots are depicted in Figure 111-112 of Appendix III. Tables 29-30 illustrates the geometric mean diameter (D_{50}) and geometric standard deviation (σ_g).

For lactose pellets , the size distribution of pellets using different amounts of MGS were narrower and the particle size were larger than of blank pellets (Figure 92). With increasing the amount of MGS , the particle size of

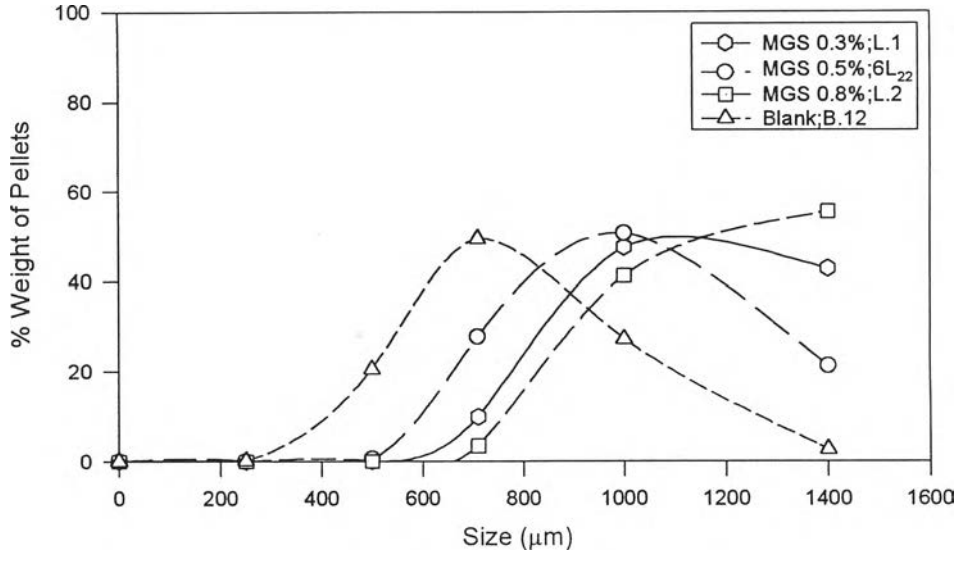


Figure 92 Particle size distribution curves of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37 % of water.

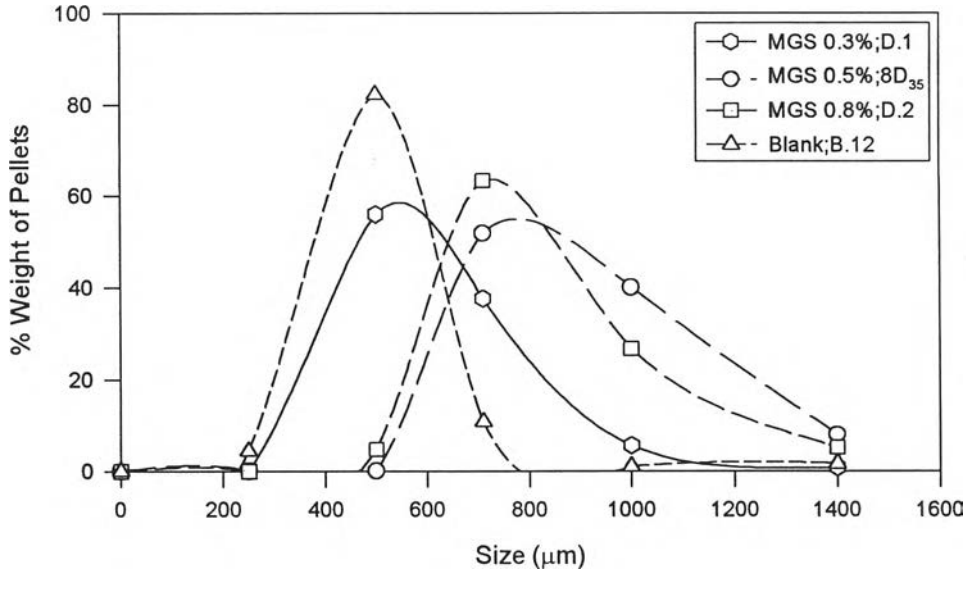


Figure 93 Particle size distribution curves of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

Table 29 Geometric mean diameter (D_{50}) and geometric standard deviation (σ_g) of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37 % of water.

MGS (% w/w)	Formulation	Geometric mean diameter (D_{50} ; μm)	Geometric standard deviation (σ_g)
0.3	L.1	875.26	1.2202
0.5	$6L_{22}$	806.23	1.2459
0.8	L.2	922.78	1.2071
0 *	B.2	675.53	1.3143

* Blank pellets

Table 30 Geometric mean diameter (D_{50}) and geometric standard deviation (σ_g) of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

MGS (% w/w)	Formulation	Geometric mean diameter (D_{50} ; μm)	Geometric standard deviation (σ_g)
0.3	D.1	616.16	1.3433
0.5	$8D_{35}$	780.33	1.2436
0.8	D.2	740.45	1.2554
0 *	B.12	541.29	1.4723

* Blank pellets

pellets (D_{50}) containing 0.3% and 0.5% w/w of MGS showed no difference but lower than of those containing 0.8% w/w (Table 29). However , the size distribution were comparable. In dicalcium phosphate pellets , the size distribution of modified starches containing pellets were slightly narrower and particle size were greater than those of blank pellets (Figure 93). However , as above described , the size distribution of pellets prepared with various amounts of MGS exhibited no difference. D_{50} values of pellets using 0.5% and 0.8% w/w of MGS were non-significant different but higher than that of using 0.3% w/w (Table 30).

The characteristic of size distribution and the larger size of pellets when compared with blank formulations were the same as previously described in the former lactose and dicalcium phosphate pellets (in section 2.2.1 and 2.3.1). Using various amounts of MGS in the range of 0.3-0.8% w/w gave a little effect on the average particle size of pellets but no effect on the size distribution. For lactose pellets , MGS at 0.8% w/w produced pellets with the largest particle size when compared with using MGS at 0.3% and 0.5% w/w. On the other hand , MGS at 0.5% and 0.8% w/w in dicalcium phosphate pellets generated pellets with nearly equal of average particle size but slightly larger than of 0.3% w/w. In fact , D_{50} should be increased upon increasing MGS quantity. Because the higher amount of MGS , when in contact with water , could improve the plasticity and cohesive force of wet mass and extrudates resulting in withstanding the destructive forces from friction plate and promoting the growth of pellets. In this study , it might be implied that D_{50} and size distribution were less sensitive to 0.2-0.3% difference of MGS quantity.

4.2 Bulk and Tapped Densities

Table 31 and 32 display the bulk and tapped densities of lactose and dicalcium phosphate pellets. The bulk and tapped densities of pellets containing modified starches were higher than those of blank pellets. This was in accordance with the prior discussion in the section for lactose and dicalcium

Table 31 Bulk density and tapped density of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37%of water.

MGS (% w/w)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)
0.3	L.1	0.742 (0.009*)	0.768 (0.009)
0.5	$6L_{22}$	0.727 (0.003)	0.768 (0.003)
0.8	L.2	0.740 (0.003)	0.768 (0.003)
0 **	B.2	0.713 (0.003)	0.745 (0.003)

* Standard deviation

** Blank pellets

Table 32 Bulk density and tapped density of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

MGS (% w/w)	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)
0.3	D.1	0.899 (0.004*)	0.924 (0.005)
0.5	$8D_{35}$	0.877 (0.000)	0.915 (0.005)
0.8	D.2	0.907 (0.005)	0.945 (0.000)
0 **	B.12	0.878 (0.000)	0.912 (0.005)

* Standard deviation

** Blank pellets

phosphate pellets. It could be seen from the results that bulk and tapped densities of pellets containing different amounts of modified starch showed no difference. However , bulk and tapped densities of lactose pellets were significantly lower than those of dicalcium phosphate pellets.

This could be concluded that the uniformity of size distribution and close packing property of MGS containing pellets were higher degree than those of blank pellets. The different amounts of MGS used in the formulation did not affect bulk and tapped densities of pellets and resulting in the comparable uniformity of size distribution and close packing property.

4.3 Hardness

The hardness profiles at various size fractions of lactose and dicalcium phosphate pellets containing different amounts of MGS are illustrated in Figures 94-95 and the hardness data are shown in Tables 46-47 (Appendix IV). The statistical analysis are shown in Appendix V (Table 102-105) . Utilization of different amounts of modified starch in the formulations produced pellets with the higher hardness than blank pellets. The hardness affected by various quantities of MGS was obviously seen in dicalcium phosphate pellets (Figure 95). But the slight difference of hardness was observed in lactose pellets (Figure 94). In some size fractions , the hardness of lactose pellets containing 0.8% w/w of MGS was the highest . It was found that the hardness at various size fractions of pellets manufactured by using 0.5% MGS showed nearly similar value. In consideration of dicalcium phosphate formulations , the pellets using MGS at 0.8% w/w possessed the higher hardness than using 0.5% and 0.3%.

From the above results , it could be concluded that the increase in pellet hardness was obtained when the higher amount of modified starch.was employed This was apparently observed in dicalcium phosphate pellets. It might be discussed that the binding and cohesive forces between particles which were responding for the mechanical strength were also increased with increasing the

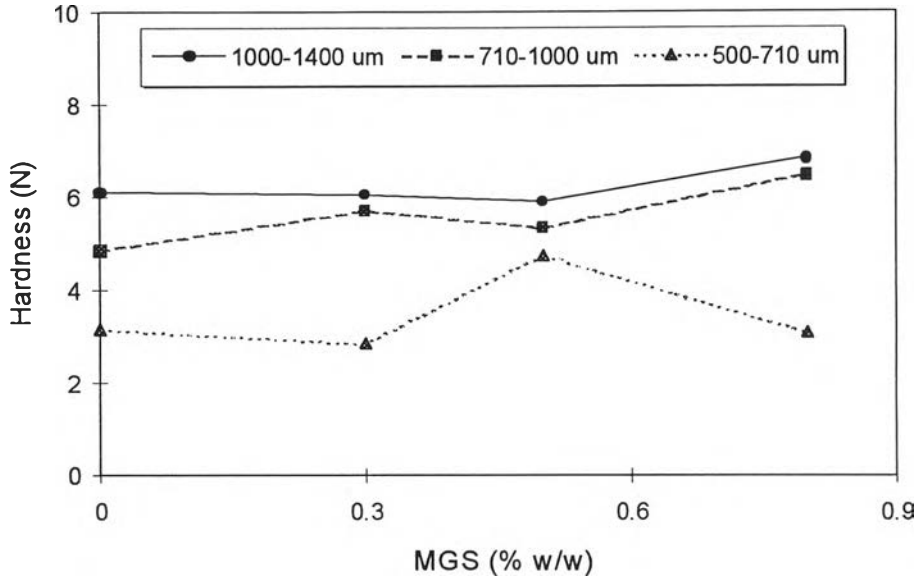


Figure 94 Hardness profiles of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37 % of water.

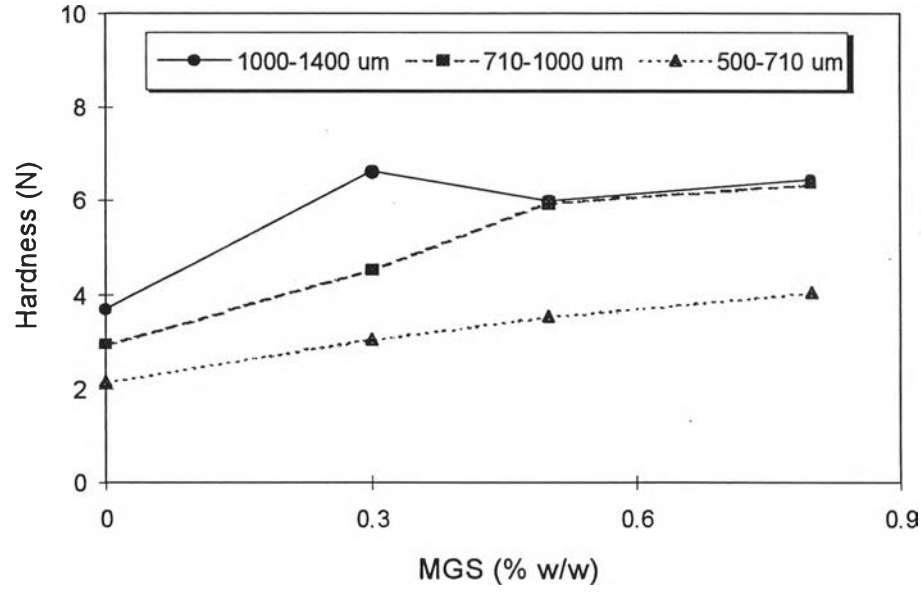


Figure 95 Hardness profiles of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

amount of modified starch resulting in the great interparticular binding strength in extrudates and the obtained pellets. However , the hardness in all quantities of MGS was also affected by different size fractions of pellets.

4.4 Friability

Percent friability of each size fraction of lactose and dicalcium phosphate pellets prepared by using various amounts of MGS are displayed in Figures 96-97 and Tables 52-53 (Appendix IV). Some percent friability values might not be available since inadequate amount of pellets of 500-710 μm size fraction for friability tests was obtained during size classification. The friability of both lactose and dicalcium phosphate pellets at any size fractions were lower than that of blank pellets. In addition , dicalcium phosphate pellets was more friable than lactose pellets. From the figures 96-97 , it was found that the friability of lactose and dicalcium phosphate pellets containing various amounts of modified starch possessed inconsistent relationship depending upon different size fractions. Moreover , the correlation of pellet friability and hardness (the greater the hardness , the lower the friability) was not found . In this study , It could not be indicated that the friability of pellet was an indication of pellet strength or hardness.

4.5 Sphericity

Table 33 and 34 presents the sphericity values , aspect ratio and form factor , of lactose and dicalcium phosphate pellets which prepared by different MGS quantities. Analysis of variance of aspect ratio are displayed in Tables 120-123 (Appendix V). It was found that the aspect ratio at any size fractions of pellets prepared with different amounts of MGS exhibited non-significant difference , except using 0.3% w/w of MGS which yielded the pellets with relatively low of aspect ratio at 1000-1400 μm size fraction. Similar to previously described for lactose and dicalcium phosphate pellets (Section 2.2.5 and 2.3.5) , the aspect ratio of all formulations using modified starches were

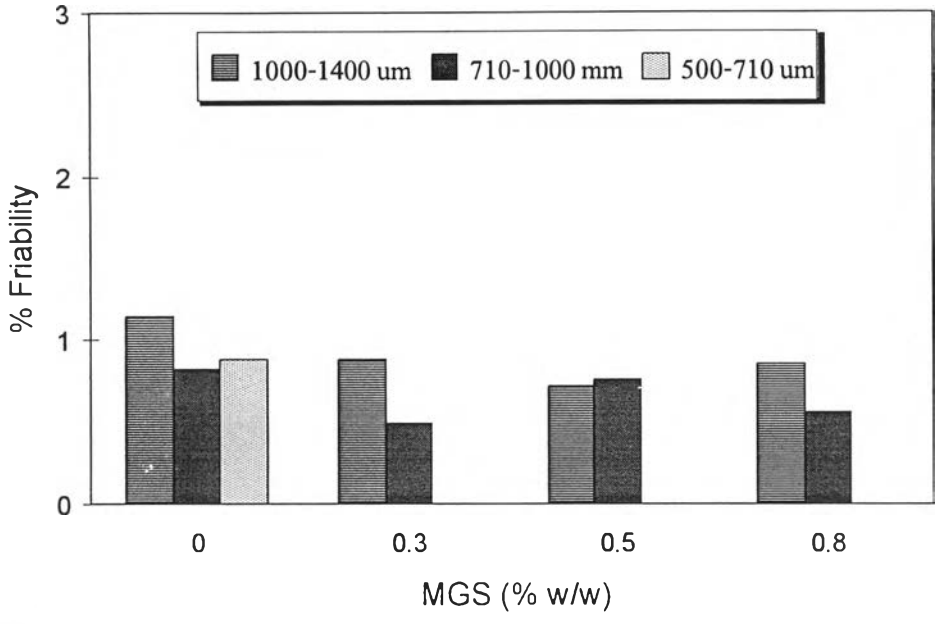


Figure 96 Histograms for percent friability of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37 % of water.

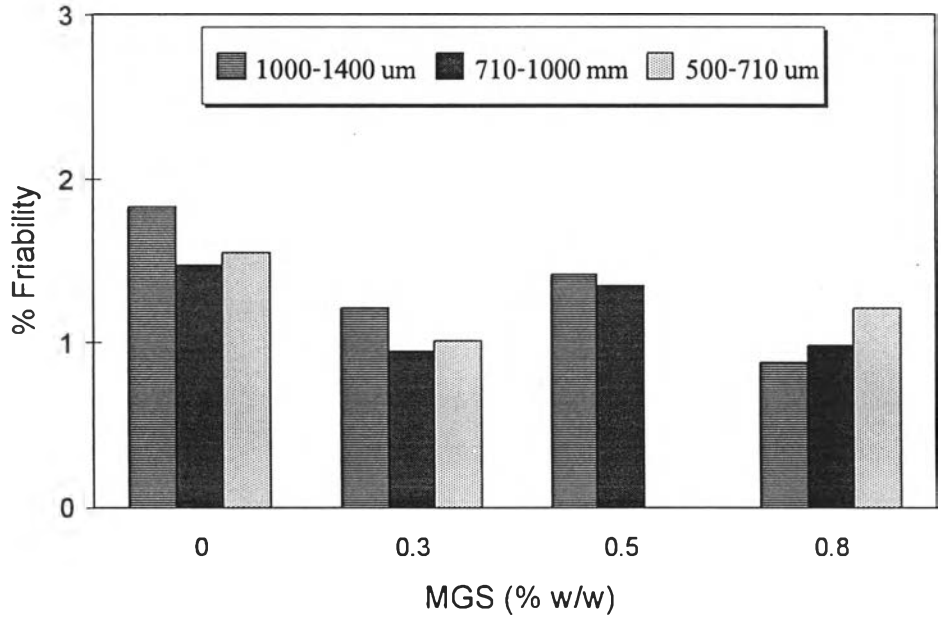


Figure 97 Histograms for percent friability of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

Table 33 Sphericity values at various size fractions of lactose (65%) pellets prepared with different amounts of MGS (DS 0.26) and 37 % of water.

MGS (%w/w)	Formulation	Aspect ratio			Form factor		
		1000-1400μm	710-1000 μm	500-710 μm	1000-1400μm	710-1000 μm	500-710 μm
0.3	L.1	0.87 (0.06*)	0.90 (0.04)	0.91 (0.03)	0.97 (0.01)	0.97 (0.01)	0.96 (0.03)
0.5	$6L_{22}$	0.89 (0.05)	0.91 (0.03)	0.90 (0.03)	0.97 (0.01)	0.98 (0.02)	0.97 (0.02)
0.8	L.2	0.91 (0.04)	0.91 (0.04)	0.90 (0.04)	0.98 (0.01)	0.98 (0.01)	0.98 (0.01)
0**	B.2	0.84 (0.05)	0.87 (0.06)	0.89 (0.05)	0.94 (0.04)	0.97 (0.02)	0.97 (0.01)

* Standard deviation

** Blank pellets

Table 34 Sphericity values at various size fractions of dicalcium phosphate (80%) pellets prepared with different amounts of MGS (DS 0.32) and 44 % of water.

MGS (%w/w)	Formulation	Aspect ratio			Form factor		
		1000-1400μm	710-1000 μm	500-710 μm	1000-1400μm	710-1000 μm	500-710 μm
0.3	D.1	0.85 (0.06*)	0.92 (0.03)	0.93 (0.02)	0.96 (0.03)	0.98 (0.01)	0.97 (0.01)
0.5	$8D_{35}$	0.90 (0.05)	0.93 (0.03)	0.91 (0.03)	0.97 (0.01)	0.97 (0.03)	0.97 (0.01)
0.8	D.2	0.91 (0.03)	0.92 (0.01)	0.92 (0.04)	0.96 (0.04)	0.97 (0.02)	0.97 (0.02)
0**	B.12	0.81 (0.07)	0.87 (0.06)	0.87 (0.10)	0.94 (0.04)	0.97 (0.02)	0.97 (0.03)

* Standard deviation

** Blank pellets

greater than that of blank pellets. As can be seen from the Tables , form factor of pellets containing various amounts of MGS were comparable and indicated no difference when compared with blank pellets.

It could be concluded that the different amounts of modified starch used in pellet formulations did not affect the roundness of pellets. However , the less sphericity of pellets at 1000-1400 μm when using 0.3% of MGS might be postulated that the larger particles were more anisometric or due to the more agglomeration of particles resulting in decrease of the sphericity of larger particles (Kleinebudde , 1993). Additionally , 0.3% w/w of MGS produced pellets with inadequate plasticity to generate more spherical particles at that size. From the form factor values , it could also be concluded that various amounts of MGS did not affect pellet sphericity. The preceding study suggested that the form factor could not distinguish between round or less round pellets as exactly as the aspect ratio (Linder and Kleinebudde , 1994). The form factor is an only important factor in the case of irregularly shaped particles.

4.6 Pellet Characteristics , Surface and Internal Structure by SEM

The general characteristics of pellet and pellet shape at various size fractions were examined by scanning electron microscope (SEM) at different magnifications (× 15 and × 35). The surface and cross-sectioned morphology of pellets at 710-1000 μm size fraction were also studied at × 750 and × 150 magnifications. The photomicrographs of lactose pellets prepared by using different amounts of MGS are shown in Figures 98-99 and those of dicalcium phosphate pellets are illustrated in Figures 100-101. These results were also compared with the basic lactose and dicalcium phosphate formulations ($6L_{22}$ and $8D_{35}$) in Figures 39 , 43 in section 2.2.6 and Figures 84 , 88 in section 2.3.6.

In lactose pellets , it could seen from the unsized pellets that utilization of 0.8% w/w of MGS (Figures 99A) yielded the pellets with most large particle size when compared with using 0.3 % and 0.5% w/w (Figure 98A and 39

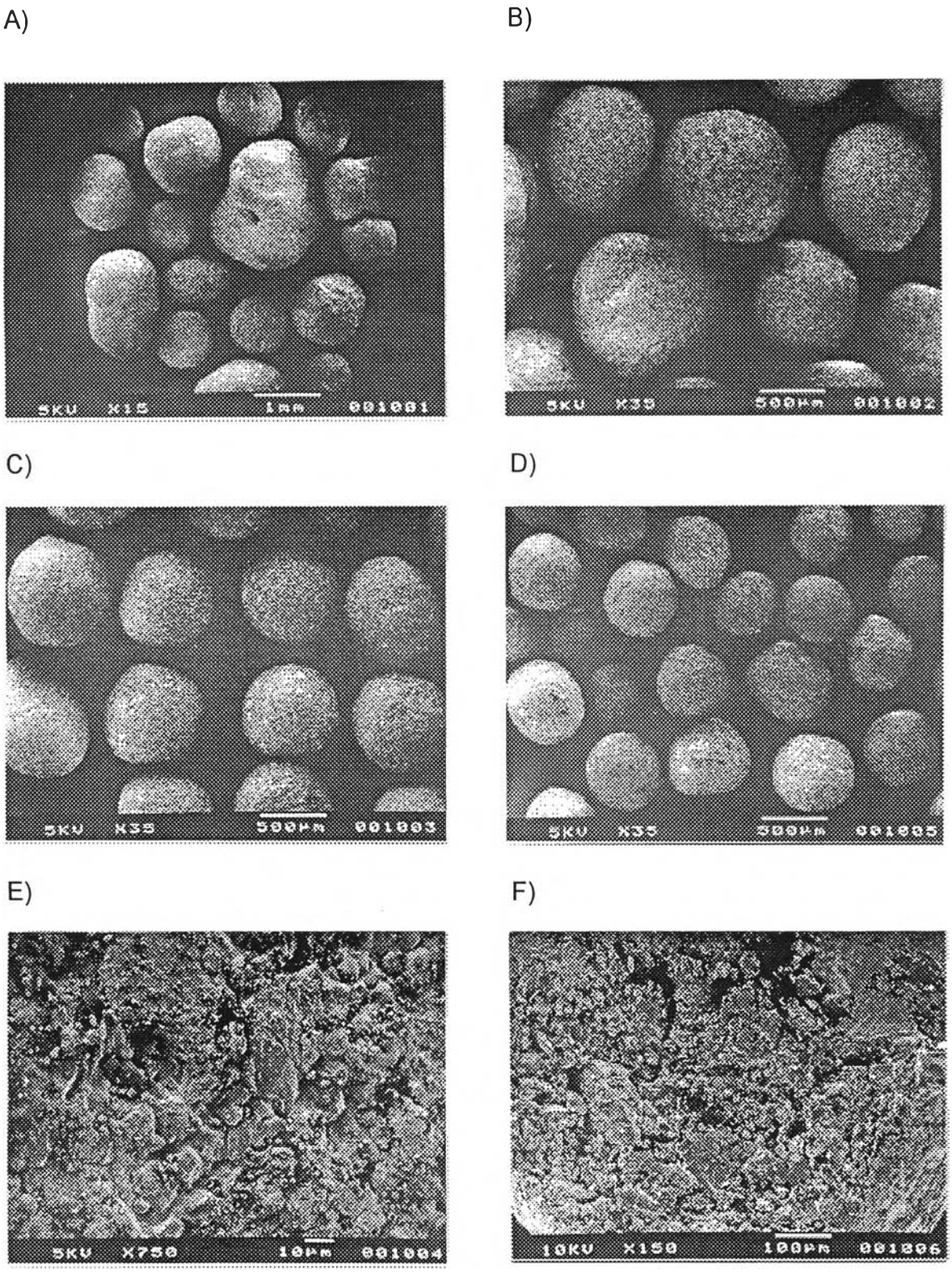


Figure 98 Photomicrographs of 65% lactose pellets (L.1) using 0.3% w/w of MGS (DS 0.26) and 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 15, C) Size 710-1000 µm x 15, D) Size 500 -710 µm x 15, E) Surface x 750, and F) Internal structure x 150.

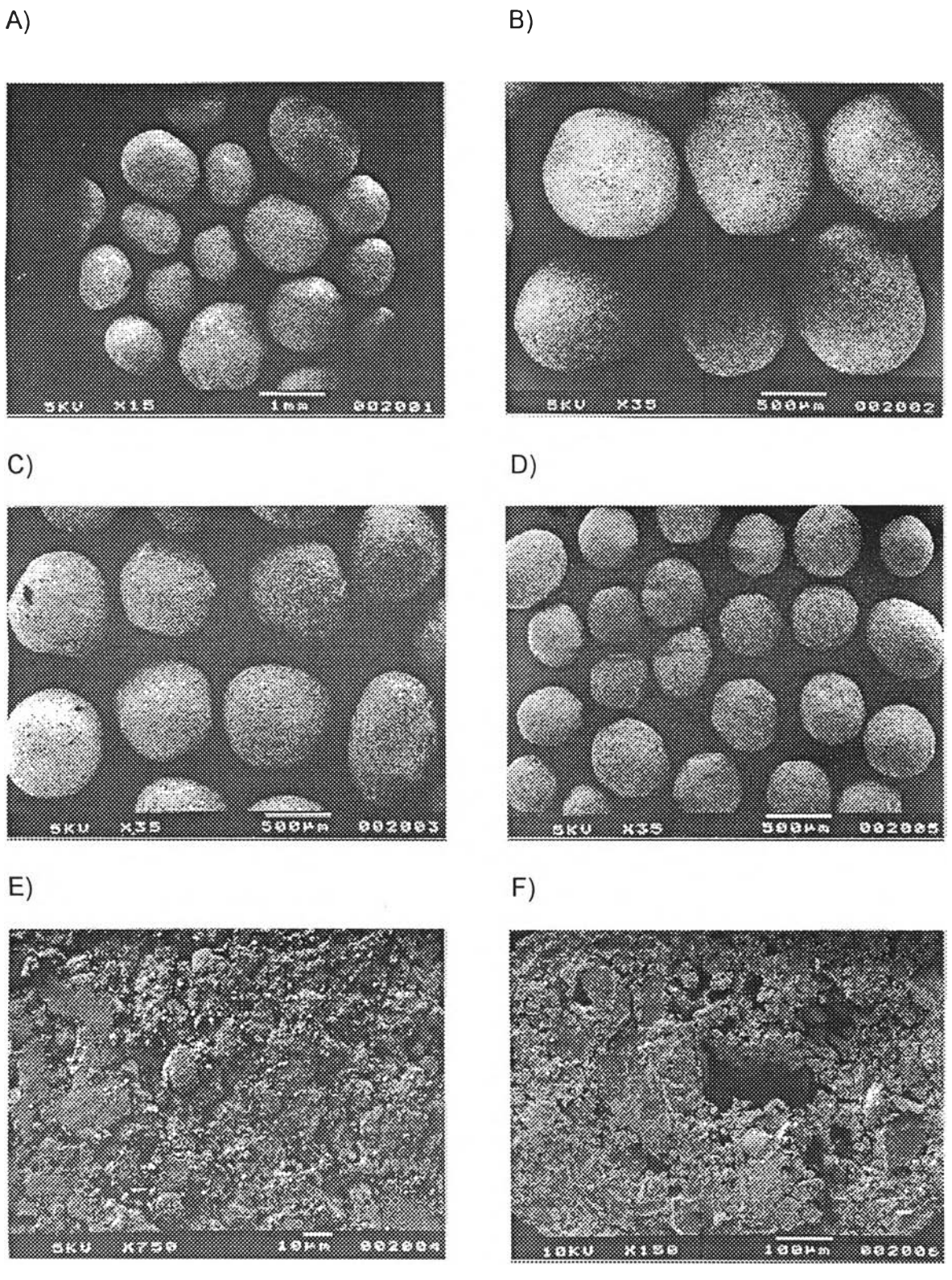


Figure 99 Photomicrographs of 65% lactose pellets (L.2) using 0.8% w/w of MGS (DS 0.26) and 37% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 15, C) Size 710-1000 µm x 15, D) Size 500 -710 µm x 15, E) Surface x 750, and F) Internal structure x 150.

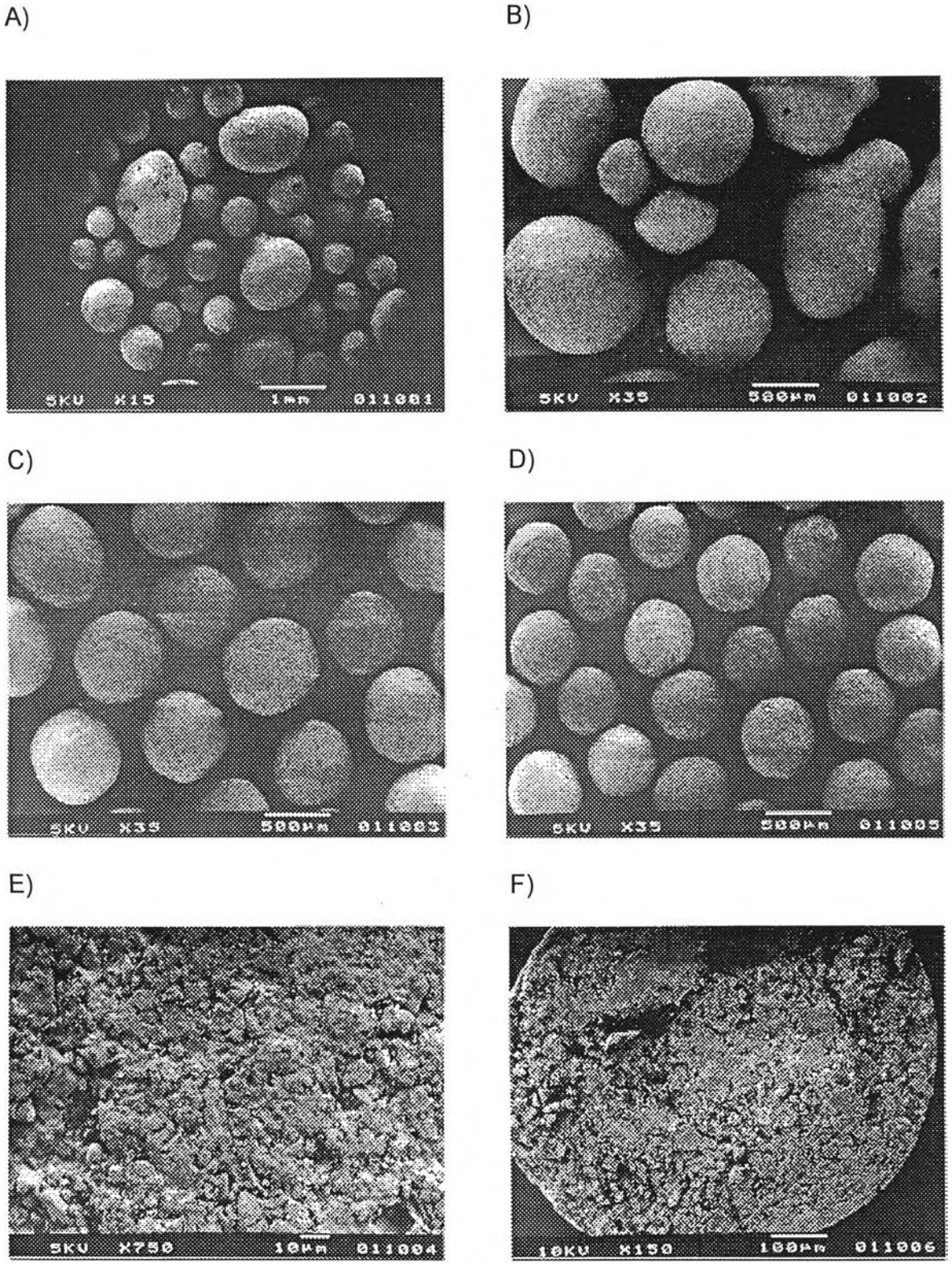


Figure 100 Photomicrographs of 80% dicalcium phosphate pellets (D.1) using 0.3% w/w of MGS (DS 0.32) and 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 15, C) Size 710-1000 µm x 15, D) Size 500 -710 µm x 15, E) Surface x 750, and F) Internal structure x 150.

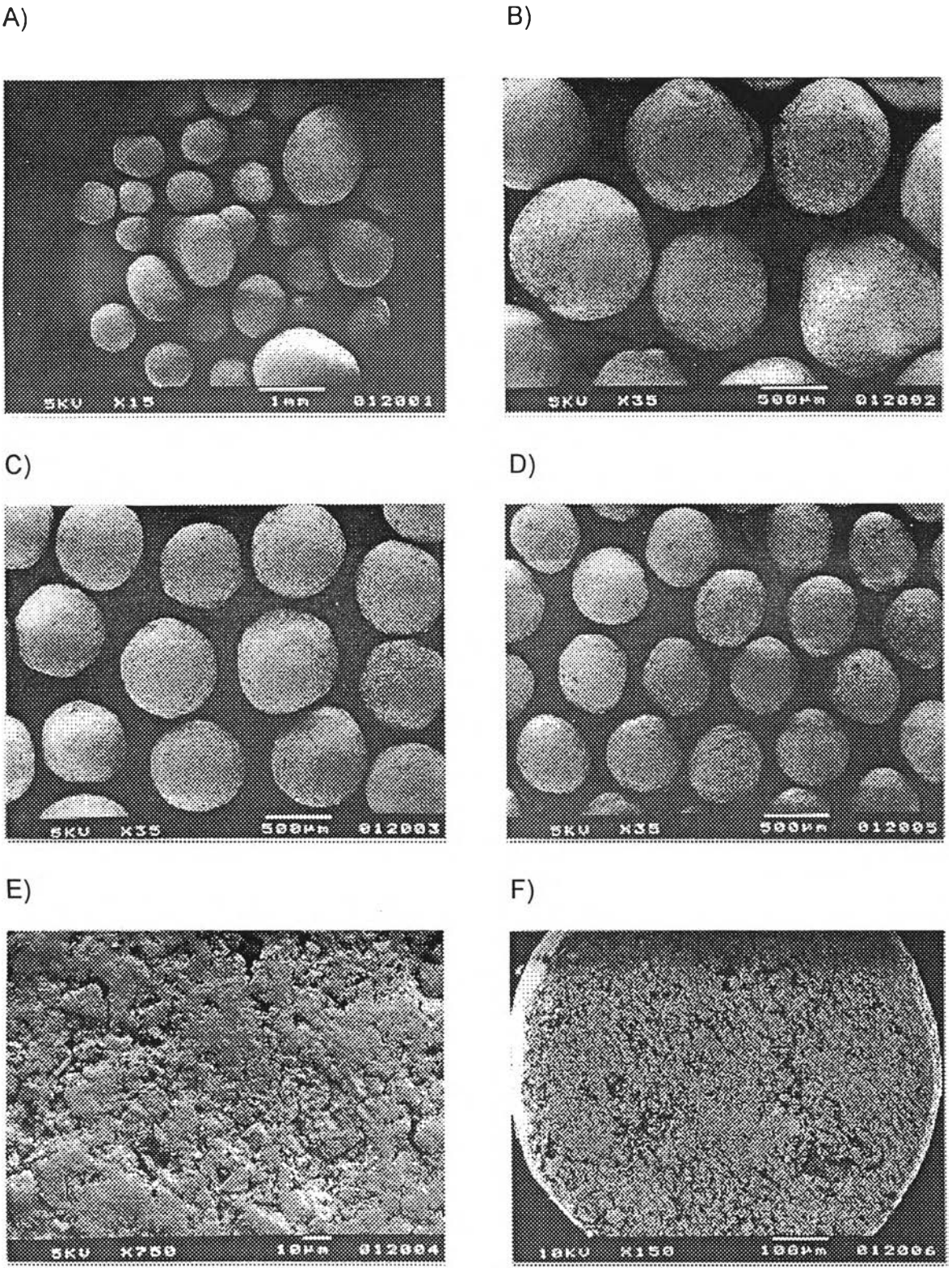


Figure 101 Photomicrographs of 80% dicalcium phosphate pellets (D.2) using 0.8% w/w of MGS (DS 0.32) and 44% of water : A) Unsized pellets x 15, B) Size 1000-1400 µm x 15, C) Size 710-1000 µm x 15, D) Size 500 -710 µm x 15, E) Surface x 750, and F) Internal structure x 150.

A) , however , the roundness at any size fractions appeared no difference. These results were in accordance with previously described in particle size distribution and sphericity. The surface morphology of pellets containing MGS at 0.3% (Figure 98E) and 0.5% ($6L_{22}$ in Figure 43B) indicated no difference but were rougher than those containing 0.8%. It could be assumed that the degree of plasticity and binding strength of 0.8% MGS containing extrudates were high and suitable to form smoother surface of spheres. This was suggested by Hellen et al. (1993b) that surface smoothness was not dependent on the pellet shape because the sphericity of pellets prepared by various amounts of modified starch was not different. In consideration of the cross-sectioned morphology , it could not be observed the difference between pellets using different amounts of MGS. However , it showed a cavity in the internal structure of the pellets. The formation of the cavity inside has been described in section 2.2.6.

Unsized pellets of dicalcium phosphate formulations indicated that 0.3% w/w of MGS containing pellets had smaller in size and more agglomeration , which was obviously seen in 1000-1400 μm size fraction (Figure 100A) , than pellets using 0.5% and 0.8% of MGS. The roundness of pellets at any size fractions was not different except D.1 (0.3% of MGS) at 1000-1400 μm fraction which was relatively less round. It might be due to the agglomeration of individual particles. As described in lactose pellets , the surface condition of pellets containing 0.3% (Figure 100E) and 0.5% w/w ($8D_{35}$ in Figure 88C) of MGS presented no difference but were rougher than those using 0.8% w/w. The possible explanation was the same as above discussion for lactose pellets. Moreover , the internal structure of D.2 (0.8% ; Figure 101F) was more dense than D.1 (0.3% ; Figure 100F) and $8D_{35}$ (0.5% ; Figure 88C , Right). This might be due to the more cohesive and binding strength between particles of the highest amount of MGS containing pellets. The internal cavity which was seen in lactose pellets could not be found in these formulations. The feasible reason was also discussed in the previous dicalcium phosphate pellets (Section 2.3.6).

To study the effect of employing modified starch in the formulation on porosity of pellets , formulations $6L_{22}$ and $8D_{35}$ which were representative of lactose and dicalcium phosphate pellets were chosen for further porosity determinations.

4.7 Porosity

Porosity of pellet was determined utilizing mercury intrusion porosimeter and the results of formulations $6L_{22}$ and $8D_{35}$ are shown in Table 35 in comparison to their blank pellets (B.2 and B.12). Percent porosity of $6L_{22}$ and its blank pellets (B.2) were nearly comparable. But , percent porosity of $8D_{35}$ was slightly greater than its blank pellets (B.12).

In lactose pellets , it was noted that modified starch did not affect the porosity of pellets. Chien and Nuessle (1985) suggested that there was a migration of materials that were soluble in the added liquid to the surface of spheres accompanied with the migration of liquid during the process. Lactose and carboxymethyl starch which were soluble in added water could migrate to the surface and induced the large internal pores. These could be seen from cross-sectioned characteristic (Section 2.2.6) and average pore diameter of lactose pellets. Additionally , microcrystalline cellulose did not affect the formation of pores since the microcrystalline cellulose itself took up the water ; when the water evaporated this material shrank and no pores were left (Linder and Kleinebudde , 1994 ; Kleinebudde , 1993). The formation of large pores resulted in the less total pore area and percent porosity when compared with dicalcium phosphate pellets.

In the case of dicalcium phosphate pellets , modified starch had an influence on the pellet porosity. Dicalcium phosphate dihydrate was insoluble material while carboxymethyl starch was soluble. When the soluble modified starch migrated to the surface of pellet as well as the migration of water , the pores with small size were formed because of using the low amount of modified starch. Moreover , the small pores also formed when modified starch migrated

Table 35 Porosity of lactose and dicalcium phosphate pellet formulations compared with blank pellets.

Porosity	65% Lactose Pellets		80% Dicalcium Phosphate Pellets	
	$6L_{22}$ *	B.2 ***	$8D_{35}$ **	B.12 ***
Total pore area (m^2/gm)	1.512	2.451	8.281	5.765
Average pore diameter (μm)	0.174	0.128	0.053	0.062
Percent porosity	18.02	20.55	46.83	38.83

* Using 0.5% w/w of MGS (DS 0.26) and 37% of water

** Using 0.5% w/w of MGS (DS 0.32) and 44% of water

*** Blank pellet formulations

through insoluble and non-migrated parts of pellet. It could be seen the formation of small pores from the lesser average pore diameter in comparison to lactose pellets. These occurrence possessed the higher total pore area and percent porosity. For blank pellets , the formation of pore was not assisted by modified starch , hence , the lesser percent porosity was obtained.

The pore structure of pellet can affect the capillary action of the dissolved drug and consequently influence the rate of release of drug from pellets. The high porosity might have been the reason for the faster dissolution time (Dyer et al. , 1994 ; Linder and Kleinebudde , 1994 ; Millili and Schwartz , 1990).