CHAPTER IV

RESULTS AND DISCUSSION

1. Material characterization

1.1 Scanning electron microscope (SEM)

Lactose, dibasic calcium phosphate and diclofenac sodium were examined under a scanning electron microscope (SEM) for morphological evaluation. The shape and surface topography of theirs were presented in Figures 12 - 14.

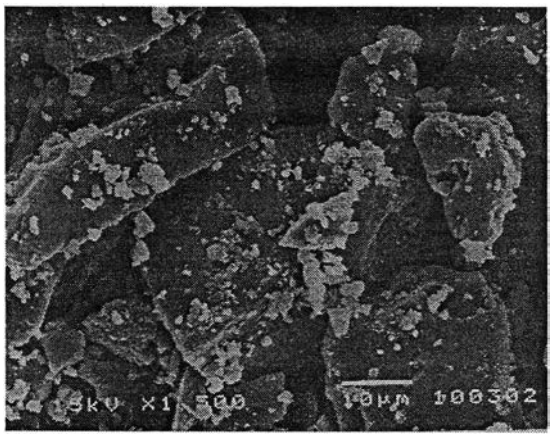


Figure 12 Scanning electron photomicrographs of lactose in magnification of x 1,500

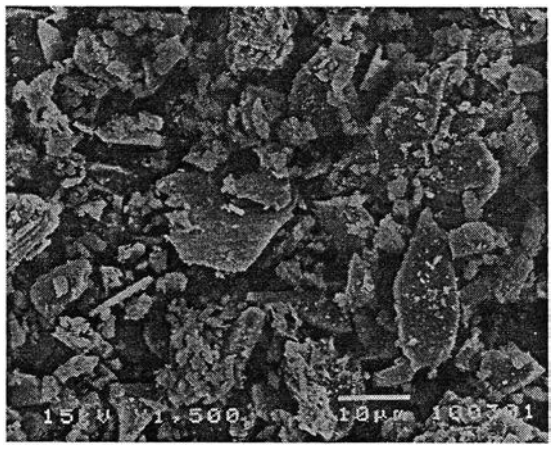


Figure 13 Scanning electron photomicrographs of dibasic calcium phosphate in magnification of x 1,500

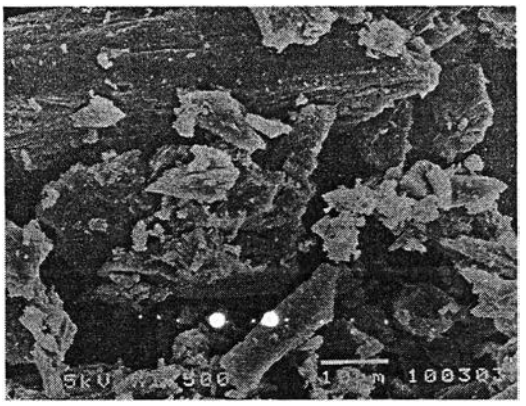


Figure 14 Scanning electron photomicrographs of diclofenac sodium in magnification x 1,500

1.2 Particle size

The geometric mean particle size of the distribution by weight of the lactose hydrate 200 mesh, dibasic calcium phosphate and diclofenac sodium determined by laser diffraction technique were found to be 42 ± 0.12, 12 ± 0.12 and 37 ± 0.12 μm, respectively.

1.3 Melting point

Melting point of diclofenac sodium, glyceryl monostearate, glyceryl palmito-stearate, glyceryl behenate, Gelucire 50/02 and glyceryl tristearate measured by using a differential scanning calorimeter were 283°C, 53°C, 57°C, 74 °C, 53 °C, and 56 °C, respectively (Table 8).

1.4 Viscosity

The viscosity of glyceryl monostearate measured by using a viscometer at 58 ± 0.5°C is 60.8 ± 0.46 mPa.s, at 68 ± 0.5°C is 42.4 ± 0.15 mPa.s and at 78 ± 0.5°C is 26.3 ± 0.17 mPa.s. The viscosity of glyceryl palmito-stearate measured by using a viscometer at 62 ± 0.5°C is 26.7 ± 0.3 mPa.s. The viscosity of glyceryl behenate measured by using a Viscometer at 79 ± 0.5°C is 22.6 ± 0.46 mPa.s. The viscosity of Gelucire 50/02 measured by using a viscometer at 58 ± 0.5°C is 21.3 ± 0.17 mPa.s. The viscosity of glyceryl tristearate measured by using a viscometer at 61 ± 0.5°C is 25.3 ± 0.42 mPa.s.

1.5 True density

The true density of lactose hydrate, dibasic calcium phosphate, diclofenac sodium, glyceryl monostearate, glyceryl palmito-stearate, gleceryl behenate, Gelucire 50/02 and glyceryl tristearate determined by using helium gas displacement were found to be 1.54 ± 0.00, 2.41 ± 0.01, 1.52 ± 0.00, 1.04 + 0.00, 1.03 ± 0.00, 1.03 ± 0.00, 1.02 ± 0.00 and 0.97 ± 0.00 g/cm^3, respectively.

Table 8 Melting point, true density and viscosity of binders

Binders	**MP (°C)**	**True density (g/cm^3)**	**Viscosity at MP + 5°C (mPa.s)**	**Viscosity at MP + 15°C (mPa.s)**	**Viscosity at MP + 25°C (mPa.s)**
GMS	53	1.04	60.8	42.4	26.3
Precirol® ATO5	57	1.03	26.7	-	-
Compritol 888 ATO®	74	1.03	22.6	-	-
Gelucire 50/02	53	1.02	21.3	-	-
Tristearin®	56	0.97	25.3	-	-

MP = melting point

2. Pelletization

2.1 Preliminary study

Melt pelletization could be made by high shear mixers in which heat was generated by the agitation of impeller, 200 – 3,000 rpm (e.g. Thomsen et al.,1993; Zhou et al.,1997; Vonk et al., 1997; Eliasen et al., 1999; Voinovich et al., 2000; Seo and Schæfer, 2001; Hamdani et al., 2002) or obtained from jacket (Thomsen et al.,1993). The meltable binder was melted, when the temperature of the product bed reach its melting point. Temperature of product bed used to produce pellets was relative to melting point of binder. In general, temperature of product bed was above 10 to 30°C of melting point of binder (Thomsen et al., 1993) and mixing time was in range 6 – 17 minutes (Schæfer et al.,1992a; 1992b; Thomsen et al.,1993).

In this study, pellets were produced by modified planetary mixer which is classified as a low shear mixer. Its paddle speeds are in the range of 100 – 200 rpm. Lactose or dibasic calcium phosphate (dbcp) and meltable materials were used to prepare blank pellets and investigate appropriate conditions of the experiment. Glycerides were selected to be binders in this study. It has been reported that glyceryl monostearate (GMS) could be an aid to make pellets by using a high shear mixer (Thomsen et al., 1993) and by process of extrusion/spheronization (Chatchawalsaisin et al., 2005). So, it was used as the main binder in this study. Other meltable materials were used to give additional information. The loading amount of each formular was 300 grams. Pelletization process relied on heat from jacket of modified planetary mixer and meltable binder which was added as powder form or molten form for different products.

First, temperature of powder bed was kept at above the melting point 5°C only for maintanced liquidized state of the binder. Pelletization process was carried out at maximum speed of the paddle, 200 rpm. The formation of pellets was observed while the process proceeded. The process was stopped when the products were stable for 3 minutes and the processing time was recorded.

Attempts were made to form blank pellets by two methods as following:

Method A *Binders were added as powdered form*

Initially, the binders were added as powdered form, method A. Pellets could be formed. The time taken to form pellets was 20 minutes. The amounts of binder that could give pellets were varying, depending on types of binder which are shown in Table 9. It was found that amounts of Tristearin® required to form pellets was more than other binders, 27 % w/w. Relatively high amount of Compritol 888 ATO®, 20%w/w, was also required to form pellets. The amounts of GMS, Precirol® ATO5 and Gelucire 50/02 required to form pellets was less, 16.5% w/w, 17.5% w/w and 17.5% w/w, respectively. This probably might be that Tristearin® and Compritol 888 ATO® possessed lipophilic nature, whereas GMS, Precirol® ATO5 and Gelucire had hydrophilic lipophilic balance. The later group of binders might like to disperse on hydrophilic surface of lactose particle, so the required amounts of the binders to form pellets were less. The amounts of GMS required to form dbcp pellets was 19% w/w

which more than those required to form lactose pellets. It could explain that the higher binder concentration had to be used for pelletization when the particle size of the filler decreased, 42μm for lactose and 12μm for dbcp, (Schæfer et al., 1992c) and thus surface area increased. It could also that GMS could not disperse onto dbcp particles so well as lactose particles. In this method, the dbcp pellets containing Precirol® ATO5, Compritol 888 ATO®, Gelucire50/02 and Tristearin® were not investigated. However, using this method, it was found that meltable binders particles, i.e. powders, beads and flakes, which were close to the wall and the bottom of the mixing bowl could melt faster and deposit onto the mixing bowl. The process was uncontrollable agglomerate growth in accordance with previous finding (Schæfer and Mathiesen, 1996b). Schæfer and Mathiesen (1996b) found that using meltable binder as flakes and high viscosity grade such as 26,500 mPa.s of PEG 20000, to form pellets the process were likely to give large balls caused by an uncontrollable agglomerate growth. In this study, although the viscosities of binders were not considerable high, uncontrollable agglomerate growth were observed for all binders studied. As the difficulty of controlling the process and reducing the size of meltable binder, the method was not chosen for further study.

Method B *Binders were added as molten form*

The use of molten binder was chosen to be the alternative method. It was found that pellets could be formed with less deposition of mass on to the wall of mixing bowl. In general, it was found that the amounts of the molten binder required to form lactose pellets were less than those required for powdered form of binders about 0.1-1.7 %, 1.3% w/w for GMS, 1.7% w/w for Precirol® ATO5, 0.9% w/w for Compritol 888 ATO® and 1.0% w/w for Tristearin®. Not much difference was observed for Gelucire 50/02 formulation as presented in Table 9. The amounts of the molten GMS required to form dbcp pellets was less than for powdered form of GMS about 0.5% w/w as presented in Table 10. The dbcp pellets containting GMS or Precirol® ATO or Gelucire 50/02 prepared by method B required binder more than the lactose pellets. It might be due to hydrophobicity of dbcp. On the other hand, the dbcp pellets containing Compritol 888 ATO® or Tristearin® prepared by method B was likely to require less binder than lactose pellets since lipophilic binders might disperse onto dbcp particle easier. Using this method of binder addition, average processing time was also shorter, and about 10

minutes. It was probably due to the fact that molten material was added, and hence did not require heating time before melting and could acted as liquid binder simultaneously.

Table 9 Amounts of binders used to form lactose pellets

Binders	HLB	MP (°C)	Viscosity at MP + 5°C (mPa.s)	Method A	Method B	Difference (A-B)
GMS	3.8	53	60.8	16.5 %	15.2 %	1.3 %
Precirol® ATO5	2	57	26.7	17.5 %	15.8 %	1.7 %
Compritol 888 ATO®	-	74	22.6	20.0 %	19.1 %	0.9 %
Gelucire 50/02	2	53	21.3	17.5 %	17.4 %	0.1 %
Tristearin®	-	56	25.3	27.0 %	26.0%	1.0 %

Method A = binders were added as powdered form

Method B = binders were added as molten form

MP = melting point

Table 10 Amounts of binders used to form dibasic calcium phosphate pellets.

Binders	HLB	MP (°C)	Viscosity at MP + 5°C (m.Pa.s)	Method A	Method B	Difference (A-B)
GMS	3.8	53	60.3	19.0 %	18.5 %	0.5 %
Precirol® ATO5	2	57	26.7	-	18.4 %	-
Compritol 888 ATO®	-	74	22.6	-	17.8 %	-
Gelucire 50/02	2	53	21.3	-	18.3 %	-
Tristearin®	-	56	25.3	-	26.0%	-

Method A = binders were added as powdered form

Method B = binders were added as molten form

MP = melting point

The appearance of the pellets obtained from two methods were found to be similar; however, the physicochemical properties of these pellets did not investigated. To facilitate the process being controlled, method B was chosen for further study.

2.2 Preparation of diclofenac sodium pellets

When GMS was used to form DS pellets by method B, it was found that the amounts of GMS required to form DS pellets was less, comparing with those required to form blank pellets, 11.8% for DS-lactose pellets (Table 11) and 15.2% for blank pellets (Table 9), 14.6% for DS-dbcp pellets (Table 11) and 18.5% for blank pellets (Table 10). It was also found that DS pellets containing dbcp as a filler required more amounts of GMS than DS pellets containing lactose as a filler did, being 14.6% for DS-dbcp pellets and 11.8% for DS-lactose pellets as presented in Table 11. This was probably due to that a higher binder concentration had to be used for pelletization when the particle size of the diluent was smaller, 42 μm for lactose and 12 μm for dbcp, providing higher surface area. Difference in surface properties between lactose and dbcp might also contribute to the different binder requirement. The dbcp was the sensitive to variations in binder concentration, which could only be varied within the range of 14.4% – 14.8% of formulation if DS pellets were to be produced. A concentration of 15% GMS gave rise to overwetting, causing uncontrollable process for dbcp formulation. The lactose pellets could be varied within the range 11.2% -12.4% of formulation. The binder concentration, therefore, could not be kept constant for lactose and dbcp in accordance with previous work (Schæfer et al., 1992c). Schæfer et al. (1992c) used four qualities of lactose, 200, 350 or 450 mesh hydrous lactose and anhydrous lactose to prepare pellets in a high shear mixer with PEG 3000. The three hydrous lactose were compared at binder concentrations, which resulted in nearly the same final size of pellets. With 200, 350 and 450 mesh lactose, higher binder concentration, i.e. 18.5%, 21% and 23% w/w, respectively and higher impeller speed, 700 rpm resulted in a larger granule size. When hydrous lactose and anhydrous lactose were compared, difference in surface properties between hydrous and anhydrous lactose might also contribute to the different binder requirement. They found that the comparisons become complicated because different binder concentrations had to be used for pelletization of different qualities. The binder concentration, therefore, could not be kept constant.

These amounts were kept constant for the formulations LA-1 – LA-9 and CA-1 – CA-9, as shown in Table 11, where the effects of process variables presented in Table 3-4 were investigated.

Formulation of DS pellets with different binders required the amounts of binders as shown in Table 12. The range of amount of binders to form DS-lactose pellets were 11.8% – 25%, depending on type of binder. Although the process parameter used were different, the amount of binders required to form blank lactose pellets (Table 9) and DS-lactose pellets (Table 11 and Table 12) were in the same rank; GMS (15.2% for blank lactose pellets and 11.8% for DS-lactose pellets) < Precirol® ATO5 (15.8% for blank lactose pellets and 15.0% for DS-lactose pellets) < Gelucire 50/02 (17.4% for blank lactose pellets and 16.7% for DS-lactose pellets) < Compritol 888 ATO® (19.1% for blank lactose pellets and 17.9% for DS-lactose pellets) < Tristearin® (26.0% for blank lactose pellet and 25.0% for DS-lactose pellets). In general, DS pellets required less amount of binders. The amount of Tristearin® and the method of adding Tristearin® used to prepare pellets were the critical factors for successful process. The TS pellets could be prepared only with one percentage amount of Tristearin® of 25% which was dividedly added, instead of poured at one time like other binders.

Table 11 Compositions of diclofenac sodium pellets (g) prepared with glyceryl monostearate, 300 g batch size

Formulation	Lactose	dbcp	DS	GMS
LA-1 – LA-9	234.6 (78.2%)	-	30 (10%)	35.4 (11.8%)
CA-1 – CA-9	-	226.2 (75.4%)	30 (10%)	43.8 (14.6%)

LA = formulation with lactose
CA = formulation with dibasic calcium phosphate
DS = diclofenac sodium
GMS = glyceryl monostearate
dbcp = dibasic calcium phosphate

Table 12 Composition of diclofenac sodium pellets (g) prepared with other binders, 300 g batch size

Formulation	Lactose	DS	Precirol	Compritol	Gelucire50/02	Tristearin
PR	225 (75%)	30 (10%)	45 (15.0%)	-	-	-
CP	216 (72.15%)	30 (10%)	-	54 (17.9%)	-	-
GL	220.5 (73.34%)	30 (10%)	-	-	49.5 (16.7%)	-
TS	195 (65.0%)	30 (10%)	-	-	-	75 (25.0%)

PR = formulation with Precirol® ATO5

CP = formulation with Compritol 888 ATO®

GL = formulation with Gelucire 50/02

TS = formulation with Tristearin®

DS = diclofenac sodium

3. Characterization of diclofenac sodium pellets

3.1 Morphology

The morphology, size, shape and surface topography, of DS pellets was investigated by image analysis and scanning electron microscopy. In general, the pellets obtained from the same compositions, LA-1 – LA-9 or CA1 - CA-9 and prepared with different mixing speed, temperature and time, LA-1 – LA-9 and CA-1 – CA-9 were shown to have similar size, shape and surface topography, as presented in Figures 15 – 25.

All LA-1 – LA-9, CA-1 – CA-9, PR, CP, GL and TS had irregular shapes and rough surfaces filled with pores. The rough surface was clearly observed for lactose formulation. The cross-section of pellets showed that there were cavities in the pellets. The effect of temperature, speed and mixing time are shown in Figures 28 - 39 with the

same process parameters. The DS pellets formed with dbcp seemed to have rounder shape and smoother surface, except for CA-2. The smaller particle of dbcp could contribute to this effect. However, it should be noted here that the amount of GMS used in dbcp formulation was higher and could give some effect. It was to be expected that the higher binder concentration gave smoother pellets. The DS-dbcp pellets might be obtained from the later state of wet massing, so they tended to be more spherical and denser than DS-lactose pellets which were formed with less molten binder. So, DS pellets formed with dbcp might be rounder shape and smoother surface than DS pellets formed with lactose.

CA-2 pellets were prepared by using the high mixing speed, 200 rpm, low mixing temperature, 5°C above GMS melting point and long mixing time, 15 min. The effect on the morphology of CA-2 pellets could not be identified here. However, high speed and long mixing time might cause breaking agglomerates, then irregular shapes were presented.

To investigate the effect of type of binders, LA-5, PR, CP, GL and TS pellets were compared. It was found that DS-lactose pellets prepared with Tristearin® possessed smoother surface than others pellets did. The amount of Tristearin® required to prepare pellets was greatest, 25.0% w/w. It might cause TS pellets rounder and smoother described for DS-dbcp pellets. However, Tristearin® pellets were sensitive to the process.

In general, with low viscosity of binder, pellets produced were smoother than those produced with high viscosity of binder. Schæfer and Mathiesen (1996c) found than low viscosity of binder, i.e. 182 mPa.s for PEG 6000 at 120°C, and high liquid saturation gave smoother pellets. In their work, it might be that high temperature gave low viscosity of binder. On the other hand, Thomsen et al. (1993) found that at low temperature, i.e. 56°C, and low speed, i.e. 500 rpm, pellets produced from the binder possessing low viscosity, i.e. 49 mPa.s for GMS at 60°C, were smoother. In this study, all of the binders used had low viscosity, i.e. 21.3 – 60.8 mPa.s at above 5°C of melting point, so the effect of viscosity was not clearly established.

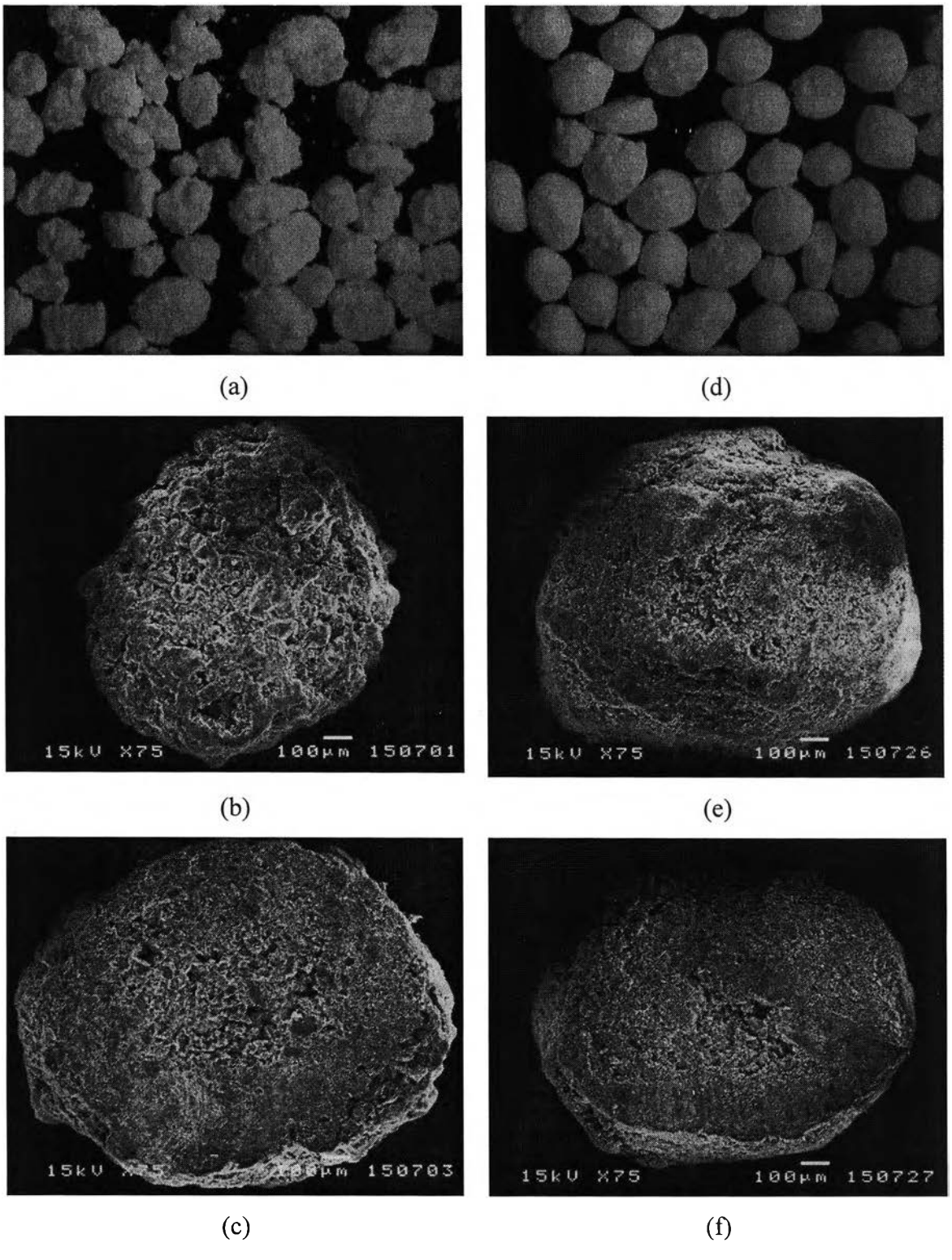
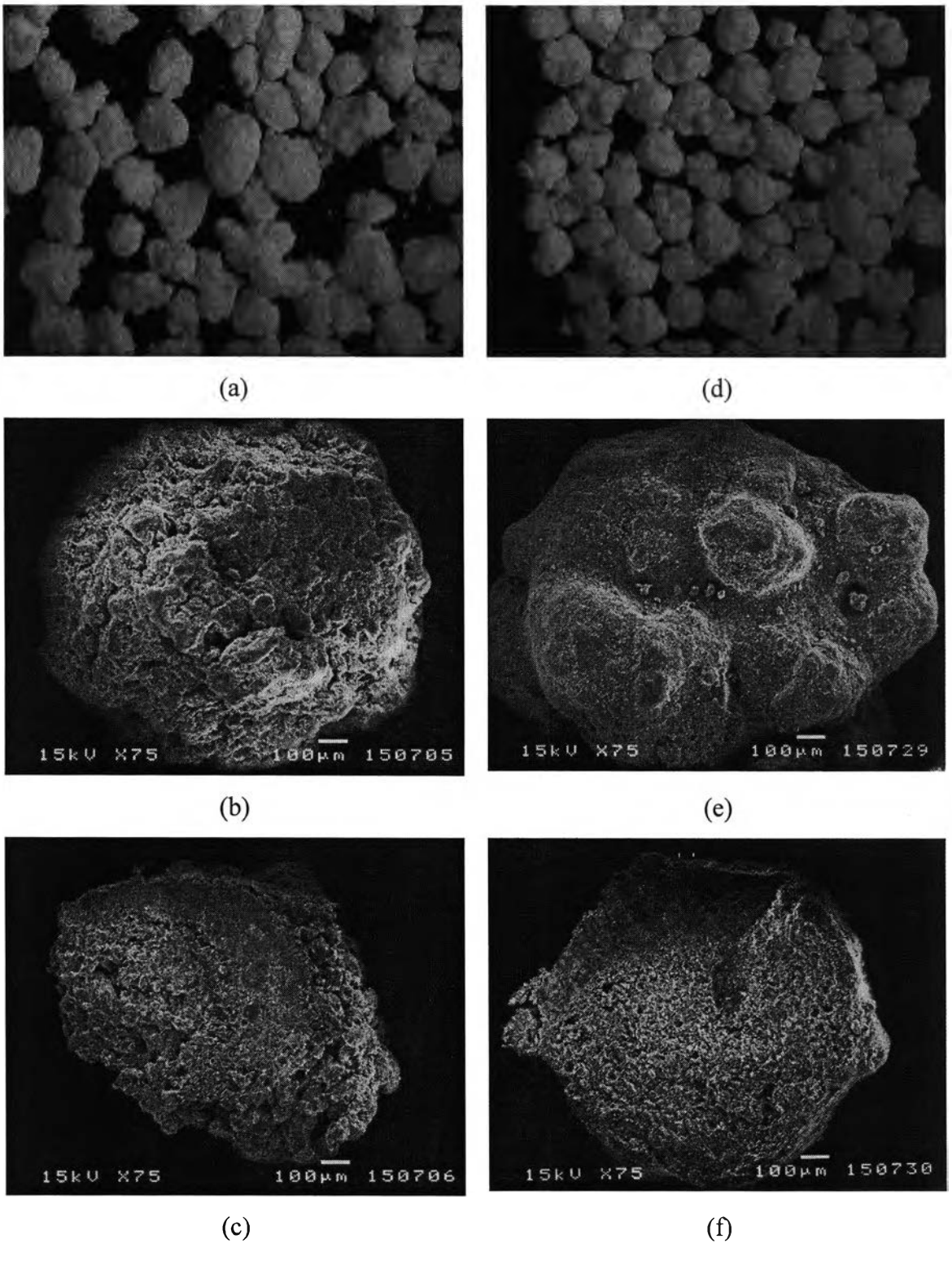


Figure 15 (a) and (d) Photomicrograph of LA-1 and CA-1

(b) and (e) Scanning electron photomicrographs of LA-1 and CA-1 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-1 and CA-1 in magnification of x 75, cross section



Figur 16 (a) and (d) Photomicrograph of LA-2 and CA-2

(b) and (e) Scanning electron photomicrographs of LA-2 and CA-2 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-2 and CA-2 in magnification of x 75, cross section

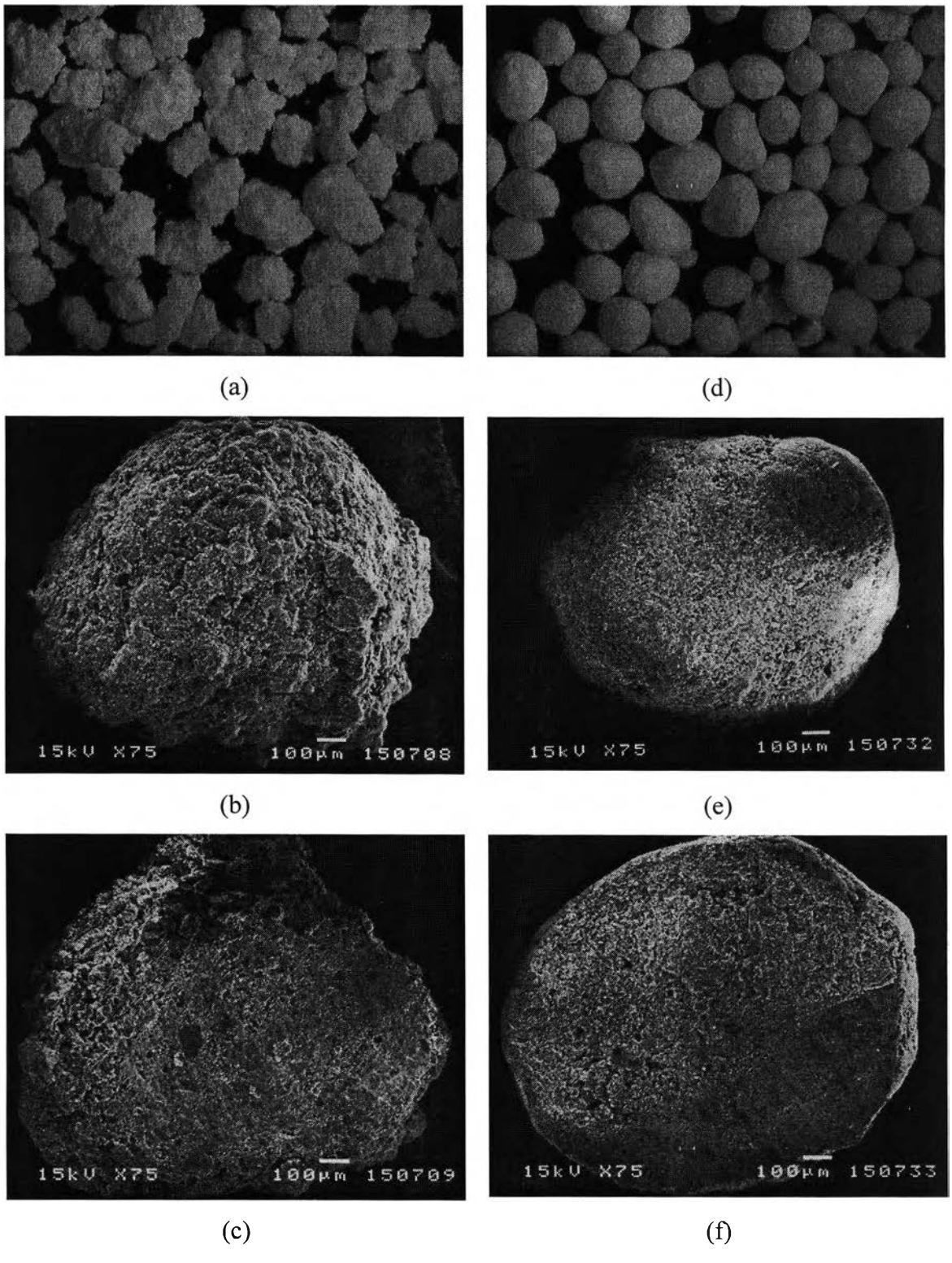


Figure 17 (a) and (d) Photomicrograph of LA-3 and CA-3

(b) and (e) Scanning electron photomicrographs of LA-3 and CA-3 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-3 and CA-3 in magnification of x 75, cross section

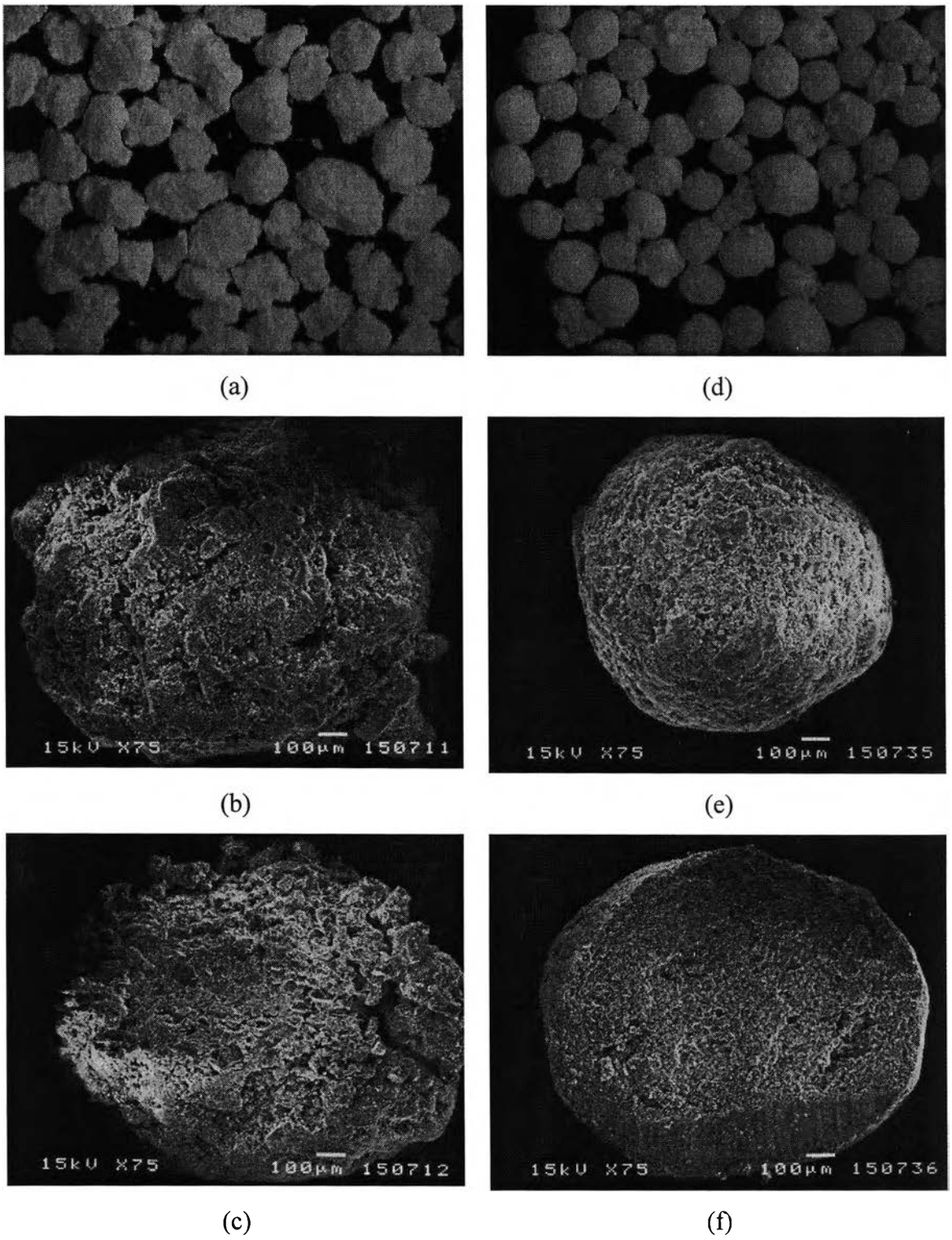


Figure18 (a) and (d) Photomicrograph of LA-4 and CA-4

(b) and (e) Scanning electron photomicrographs of LA-4 and CA-4 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-4 and CA-4 in magnification of x 75, cross section

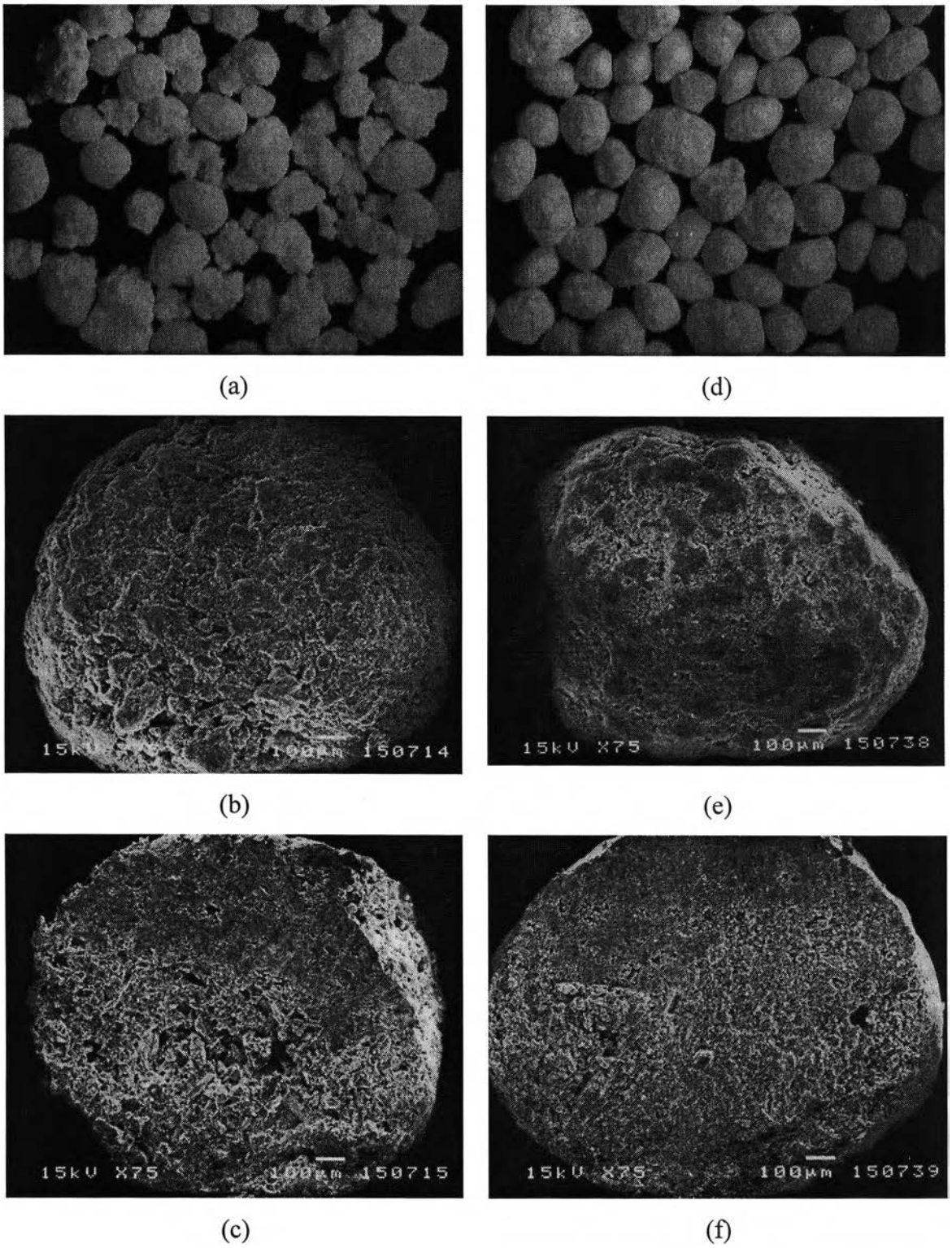


Figure 19 (a) and (d) Photomicrograph of LA-5 and CA-5

(b) and (e) Scanning electron photomicrographs of LA-5 and CA-5 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-5 and CA-5 in magnification of x 75, cross section

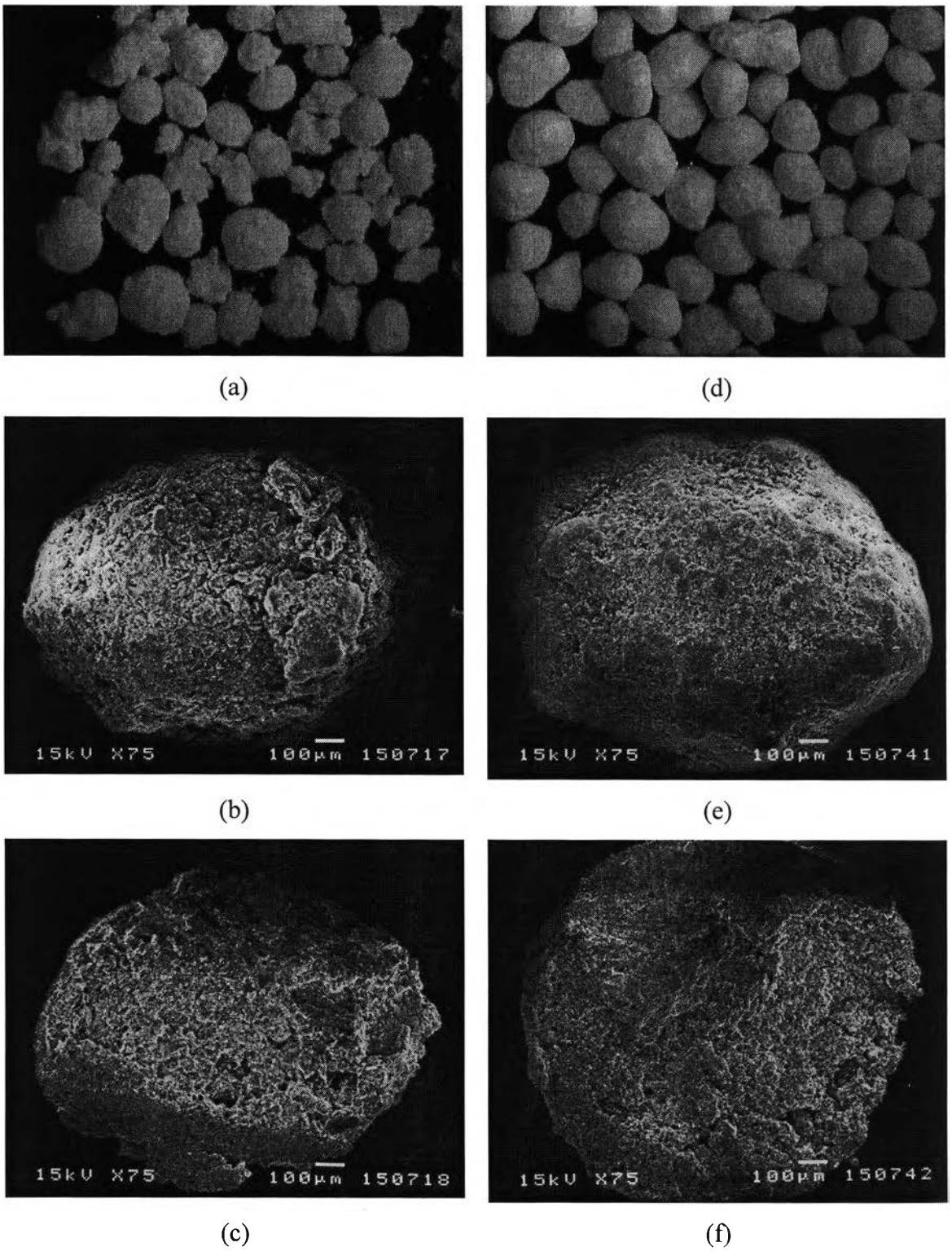


Figure 20 (a) and (d) Photomicrograph of LA-6 and CA-6

(b) and (e) Scanning electron photomicrographs of LA-6 and CA-6 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-6 and CA-6 in magnification of x 75, cross section

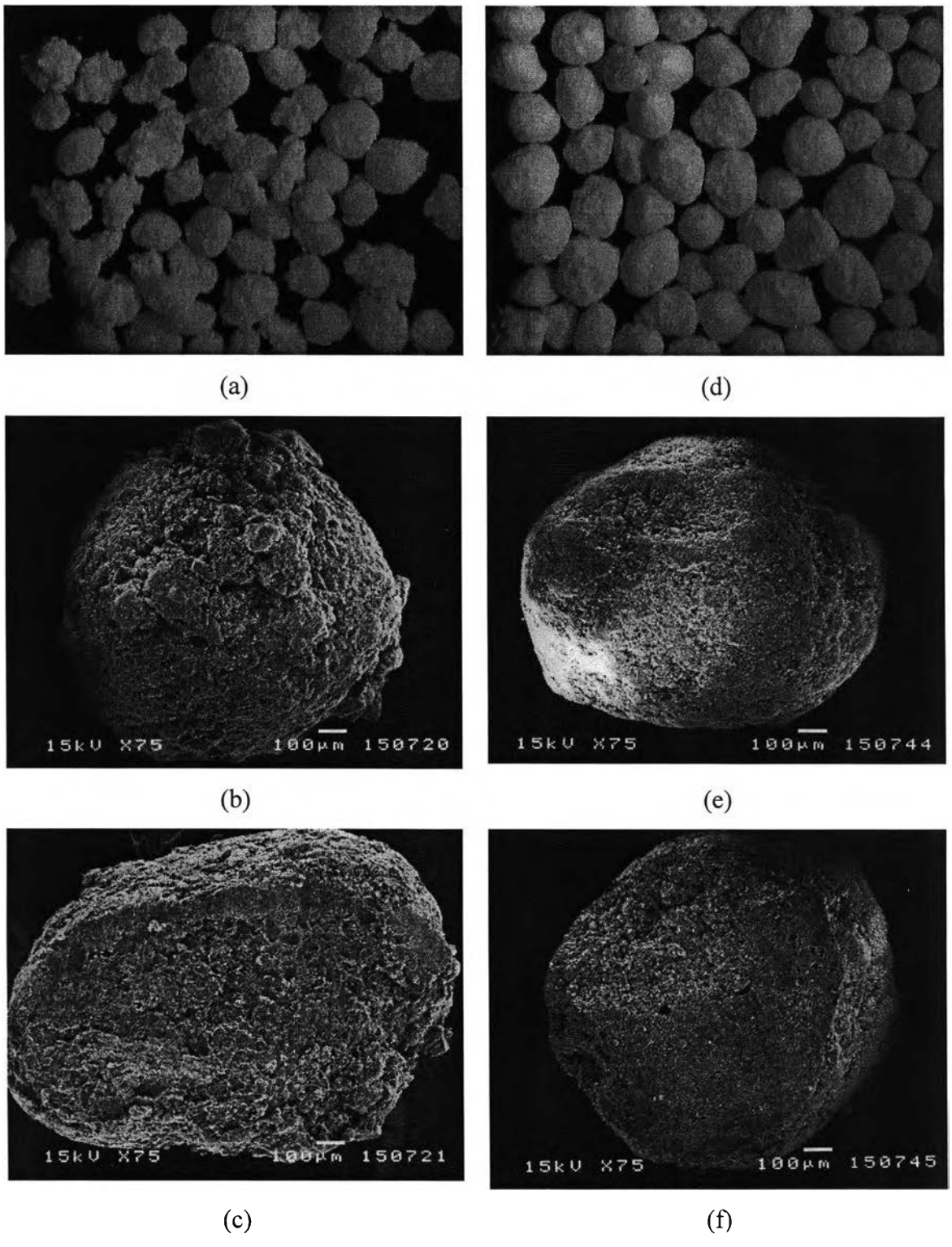


Figure 21 (a) and (d) Photomicrograph of LA-7 and CA-7

(b) and (e) Scanning electron photomicrographs of LA-7 and CA-7 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-7 and CA-7 in magnification of x 75, cross section

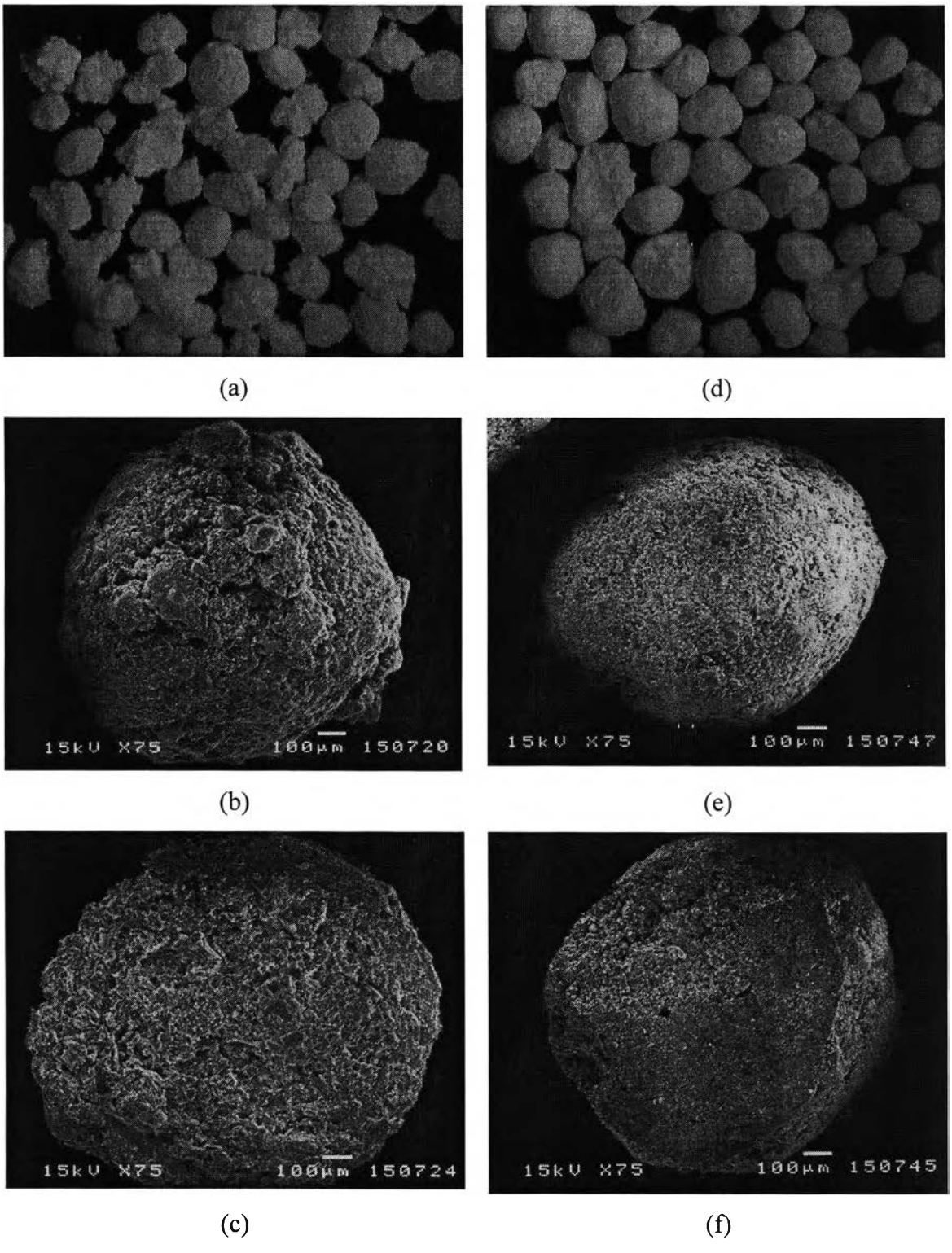


Figure 22 (a) and (d) Photomicrograph of LA-8 and CA-8

(b) and (e) Scanning electron photomicrographs of LA-8 and CA-8 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-8 and CA-8 in magnification of x 75, cross section

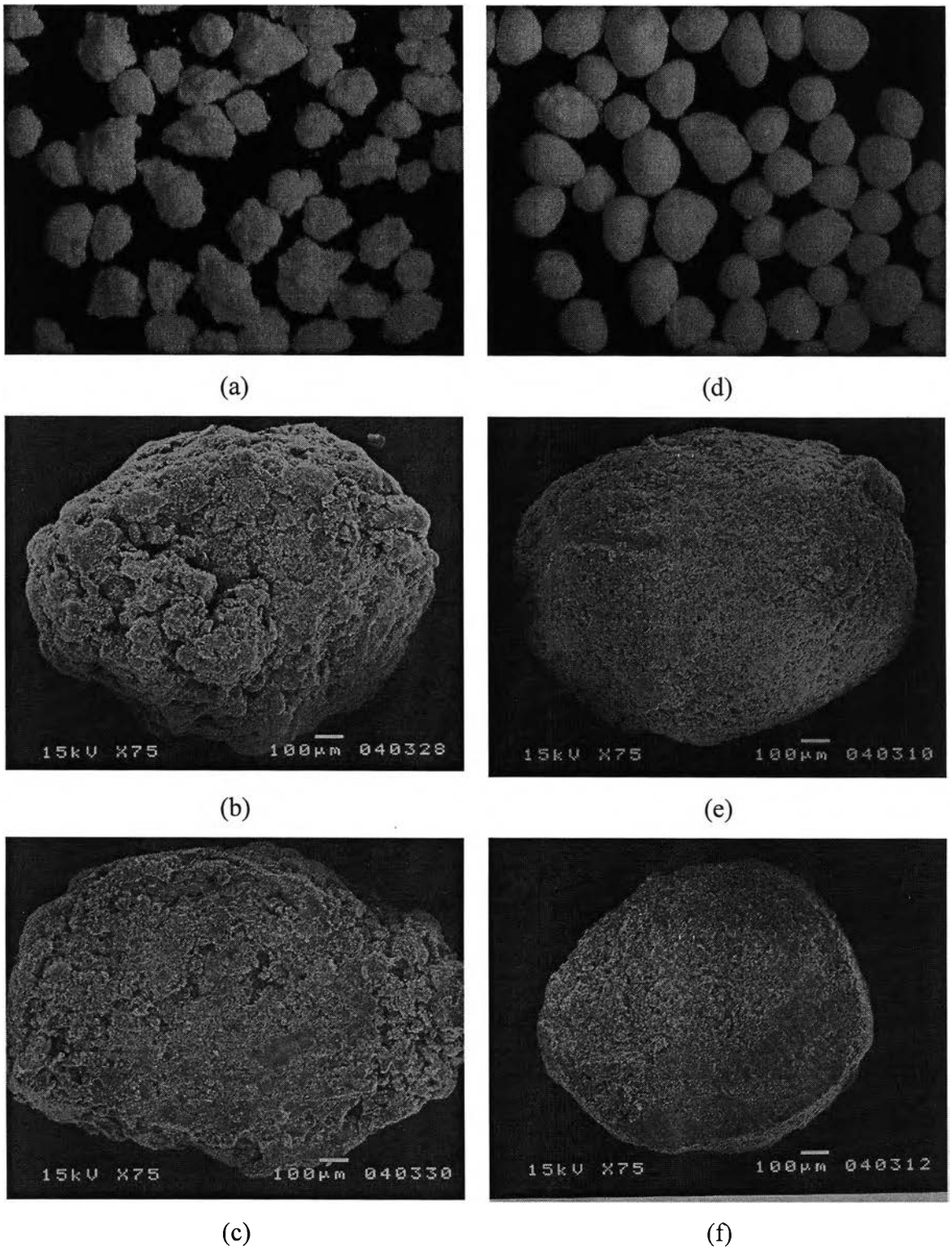


Figure 23 (a) and (d) Photomicrograph of LA-9 and CA-9

(b) and (e) Scanning electron photomicrographs of LA-9 and CA-9 in magnification of x 75

(c) and (f) Scanning electron photomicrographs of LA-9 and CA-9 in magnification of x 75, cross section

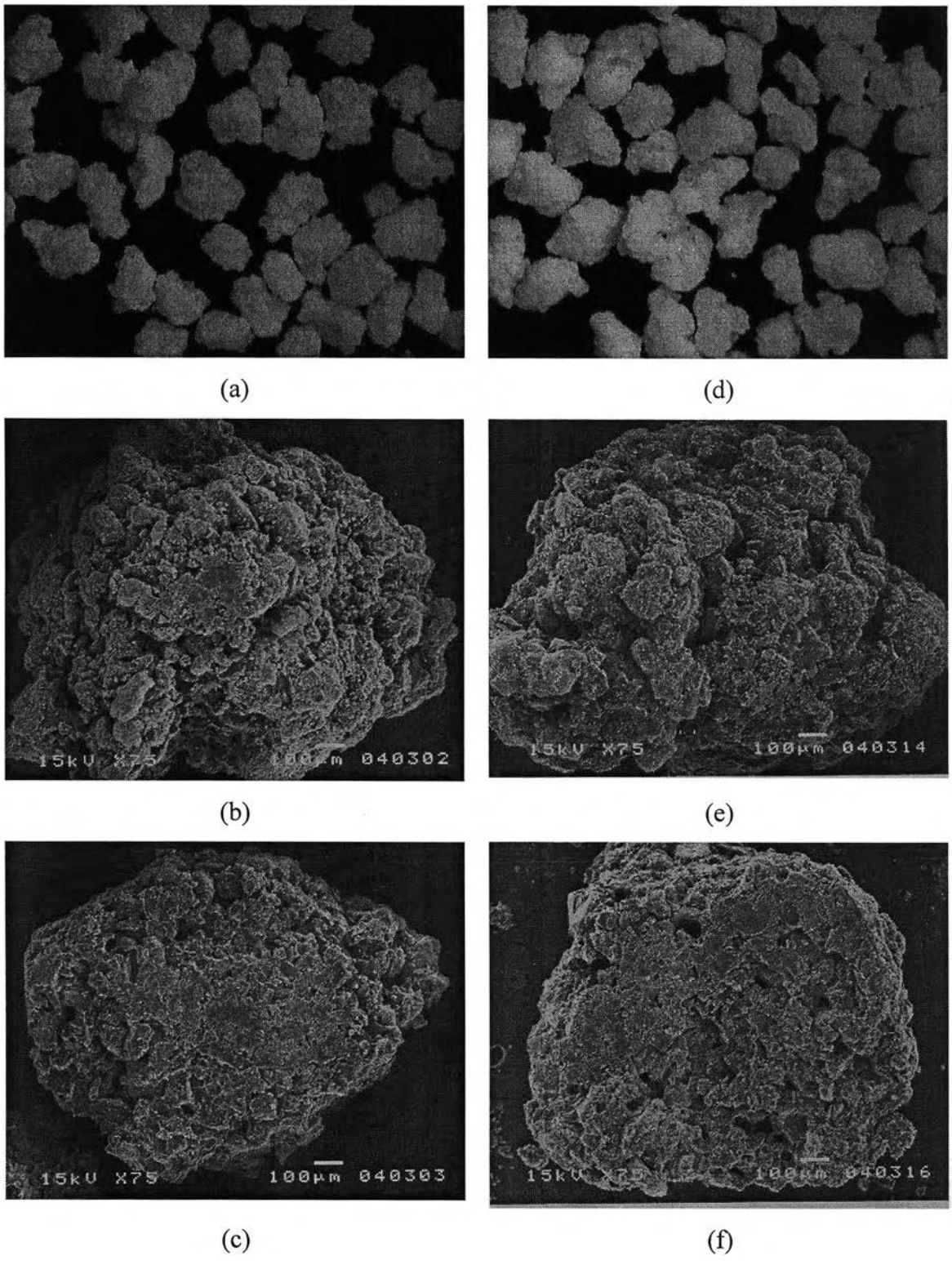


Figure 24 (a) and (d) Photomicrograph of PR and CP

(b) and (e) Scanning electron photomicrographs of PR and CP in magnification of x 75

(c) and (f) Scanning electron photomicrographs of PR and CP in magnification of x 75, cross section

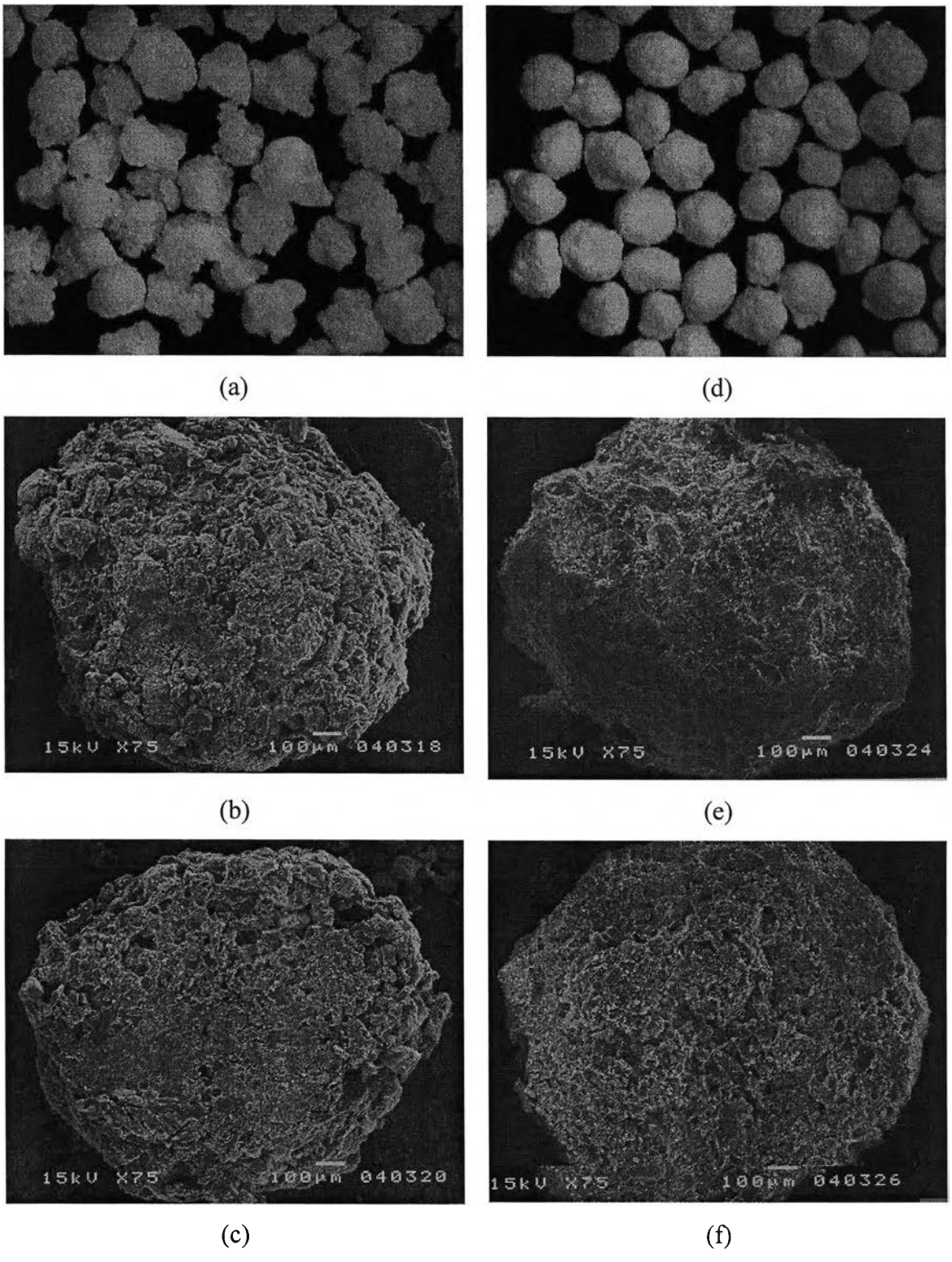


Figure 25 (a) and (d) Photomicrograph of GL and TS

(b) and (e) Scanning electron photomicrographs of GL and TS in magnification of x 75

(c) and (f) Scanning electron photomicrographs of GL and TS in magnification of x 75, cross section

3.2 Particle size distribution

3.2.1 Size distribution of pellets prepared with GMS

The size distribution of the DS-lactose-GMS (LA-1 – LA-9) and DS-dbcp-GMS (CA-1 –CA-9) pellets was determined using sieve analysis method. The percent weight of pellets retained on each sieve was calculated and plotted against sieve size as presented in Figures 26 - 27. The geometric mean diameter, d_g, and geometric standard deviation, s_g, of the pellet formulations (LA-1 – LA-9; CA-1 – CA-9) were also determined and the results were shown in Table 13.

In general, as presented in Figures 26 - 27, it was found that DS-dbcp-GMS pellets were likely to form with smaller size. On the other hand, higher percentage of lumps with greater than 2.8 mm size for DS- lactose-GMS pellets in Table 12 was evident. The size distributions of DS-lactose-GMS pellets and DS-dbcp-GMS pellets as reflected in the value of s_g were rather similar as shown in Table 13. The minimum of geometric standard deviation (s_g) of DS-lactose-GMS pellets was 1.22 for LA-2 and LA-3 and the maximum of geometric standard deviation (s_g) of DS-lactose-GMS pellets was 1.98 for LA-8. While, the minimum of geometric mean (s_g) of DS-dbcp-GMS pellets was 1.12 for CA-2 and the maximum of geometric mean (s_g) of DS-dbcp-GMS pellets was 2.19 for CA-5. In this study, the amount of GMS used for DS-lactose-GMS pellets and DS-dbcp-GMS pellets was optimized and from the mid range of 11.2% - 12.4% and the mid range of 14.4% - 14.8%, respectively. Beyond this range the pellets could not be formed. The DS-dbcp-GMS pellets were sensitive to change the amount of GMS when concentration of binder increased, large agglomerates were observed and then over wetting appeared. Schæfer et al. (1990) also found that when the PEG 3000 concentration was increased, large agglomerates were achieved. Although DS-dbcp-GMS pellets contained more amount of GMS, the ingredients seemed to hardly form agglomerate and had d_g less than DS-lactose-GMS pellets. In addition, it might be the narrow range of GMS used to form DS-dbcp-GMS pellets, which might be appropriate for particular process variables but not for all process variables studied, causing some formulation, CA-2, was high d_g ,1.66, but some formulation, CA-7, was low d_g, 0.04.

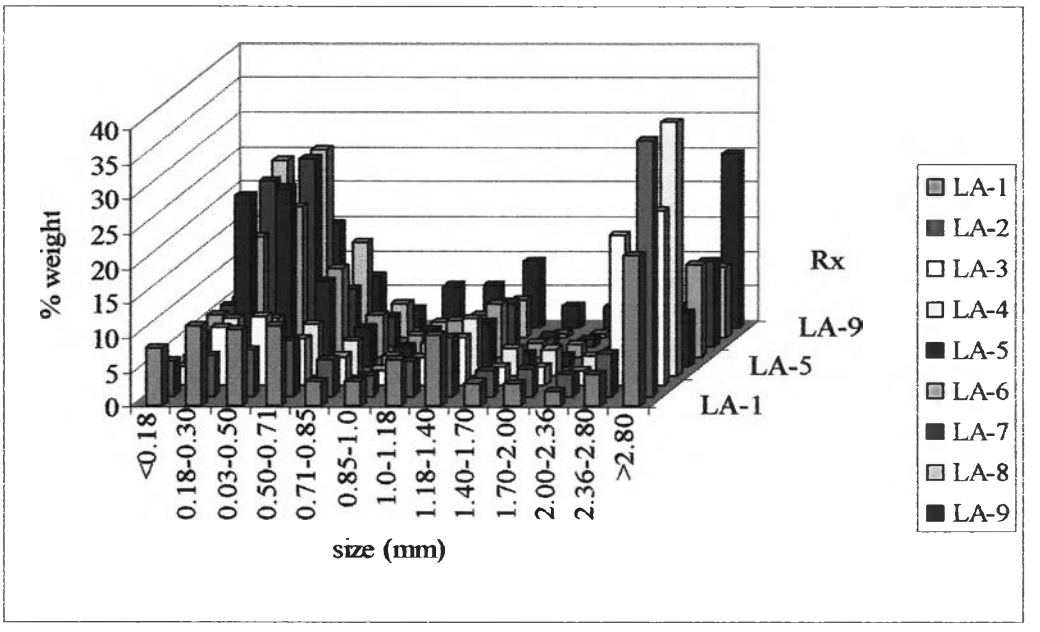


Figure 26 Size distribution of diclofenac sodium pellets prepared by lactose and GMS at the various pelletization conditions.

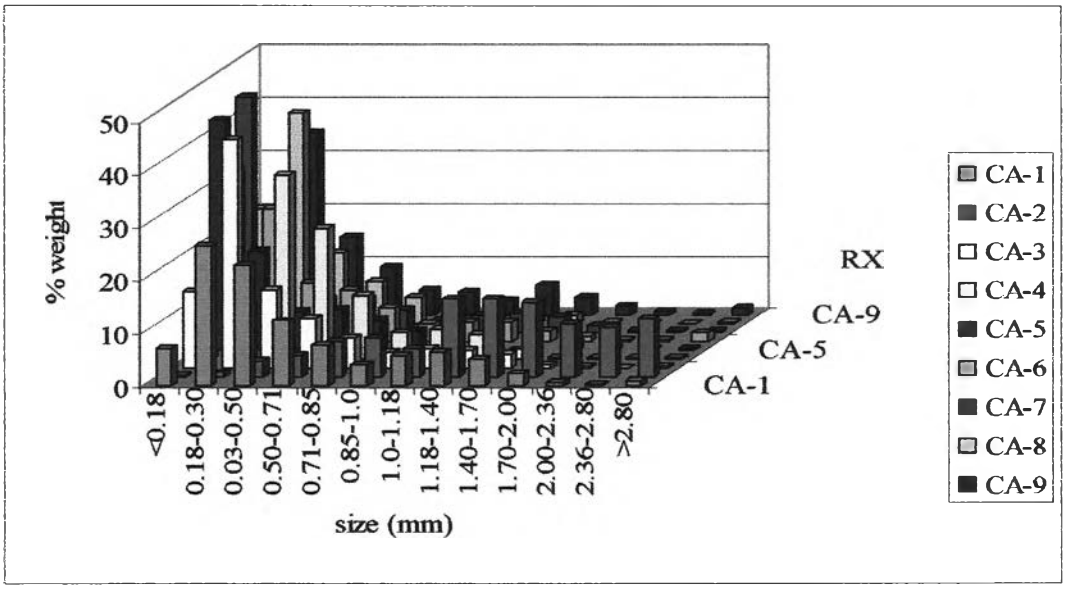


Figure 27 Size distribution of diclofenac sodium pellets prepared by dbcp and GMS at the various pelletization conditions.

Table 13 Geometric weight mean(d_g), geometric standard deviation(s_g) and lump > 2.8 mm (%) of DS pellets prepared by various conditions

Formulation	Geometric mean (d_g)	Geometric standard deviation (s_g)	Lumps > 2.8 mm (%)
LA-1	1.20	1.33	21.61
LA-2	1.75	1.22	36.79
LA-3	1.71	1.22	25.16
LA-4	1.72	1.23	36.56
LA-5	0.59	1.60	7.73
LA-6	0.78	1.50	13.13
LA-7	0.60	1.80	12.39
LA-8	0.49	1.98	10.05
LA-9	1.29	1.30	25.17
CA-1	0.56	1.32	0.72
CA-2	1.66	1.12	10.9
CA-3	0.35	1.46	0.10
CA-4	0.62	1.15	0.13
CA-5	0.14	2.19	0.33
CA-6	0.19	1.53	1.54
CA-7	0.04	1.21	0.41
CA-8	0.28	1.73	0.24
CA-9	0.34	1.82	1.23
PR	2.20	1.31	44.91
CP	2.46	1.11	55.09
GL	1.88	1.17	35.84
TS	0.89	1.22	2.11

Considering the effect of each process variable, regardless of other variables, formulations with lactose and dbcp presented different response.

At the high speed of mixing, i.e. 200 rpm, (Figures 28-29), DS-lactose-GMS pellets formulations gave large agglomerate while DS-dbcp-GMS pellets formulations tended to give fines. However, at the low speed of mixing, i.e. 100 rpm, (Figures 30-31), both DS-lactose-GMS and DS-dbcp-GMS formulations gave fines. This may be the effect of insufficient energy input of 100 rpm speed. The powders and molten binder could not mixed thoroughly, so the agglomerates could not be formed well. Many evidence (Schæfer et al., 1992a; Schæfer et al., 1993 and Zhou et al., 1997) showed that the high speed of mixing gave rise to larger granules and narrow size distribution, because the granules became more densified at a high power input. Formulation of dbcp might require higher speed than 200 rpm to produce larger granules.

Regardless of other effects, Figure 40 and Figure 46, clearly showed that increased speed of mixing gave bigger agglomerate and also provided narrower size distribution as comparing graphical results presented in Figure 43. The resultes agreed with previous works carried out with high shear mixer (Schæfer et al., 1992a; Schæfer et al., 1993 and Zhou et al., 1997). They found that increased mixing speed gave large agglomerate and narrow size distribution.

Regarding the effect of temperature, the results between Figure 32 and Figure 34 for DS-lactose-GMS pellets and between in Figure 33 and Figure 35 for DS-dbcp-GMS pellets were obtained from different temperatures, they showed similar pattern of size distribution for each filler. Size distribution (s_g) were rather wide for DS-lactose-GMS pellets, while narrower size distribution for DS-dbcp-GMS pellets obtained from different mixing temperature. Figure 41 and Figure 44 showed that increased mixing temperature did not result in clear effect on d_g and s_g of DS-lactose pellets and DS-dbcp-GMS pellets. Schæfer et al. (1993) found that at high mixing temperature, 65°C and 80°C, resulted in a marked adhesion of product to the wall of the mixer bowl, and a low jacket temperature, 40°C resulted in a large amount of lumps in the product. At a jacket temperature of 50°C no lumps were seen during the start of process, and practically no adhesion of material to the wall occurred. In this study, it was observed that the mixing temperature of 5°C above

the melting point of GMS resulted in a large amount of lumps > 2.8 mm of the product for DS-dbcp pellets formulation, which was shown in Figure 47.

The effects of mixing time are shown in Figure 36 - 39, 42, 45 and Figure 48. For DS-lactose-GMS pellets, the graphical results did not show markedly difference from those obtained when mixing speed and temperature were considered, or the size distribution were considerably wide. It was likely that increasing the mixing time yielded more lump > 2.8 mm for both DS-lactose and DS-dbcp pellets formulations, as presented in Figure 48. This results agreed with previous studies (Schæfer et al., 1990 ; 1992a ; Schæfer et al., 1993). Among DS-dbcp-GMS pellets, the formulation CA-2, which was prepared at speed of mixing of 200 rpm, temperature of mixing of 5°C above the melting point of GMS, mixing time of 15 min, possessed bigger size of pellets than other formulation, i.e. d_g = 1.66 mm. It is therefore possible that the process parameters could be further identified for preparing DS-dbcp-GMS pellets with satifactory size. It must be underlined here that process did not give smooth pellets as described earlier.

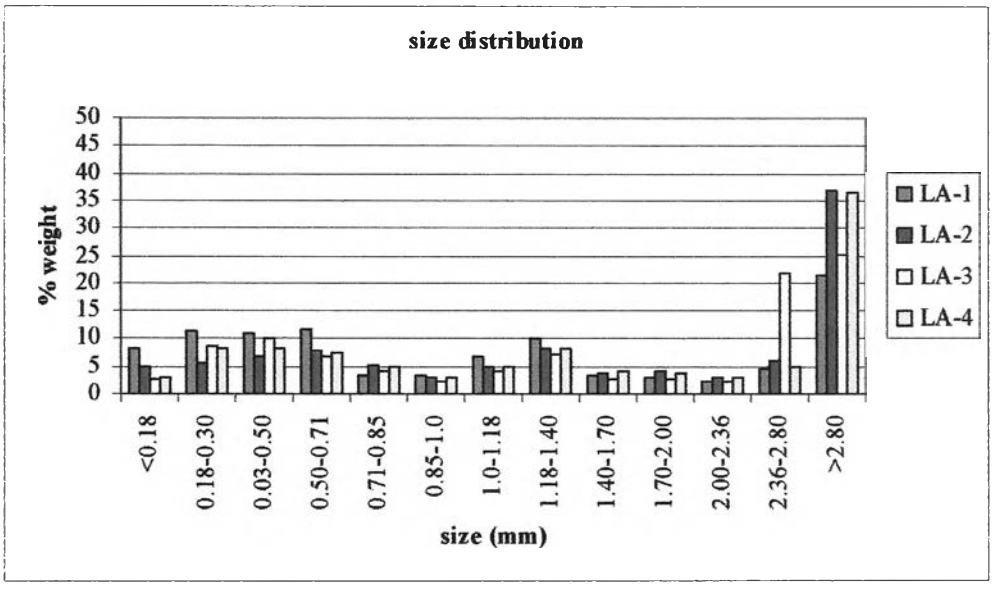


Figure 28 Size distribution of DS-lactose-GMS pellets prepared with mixing speed of 200 rpm.

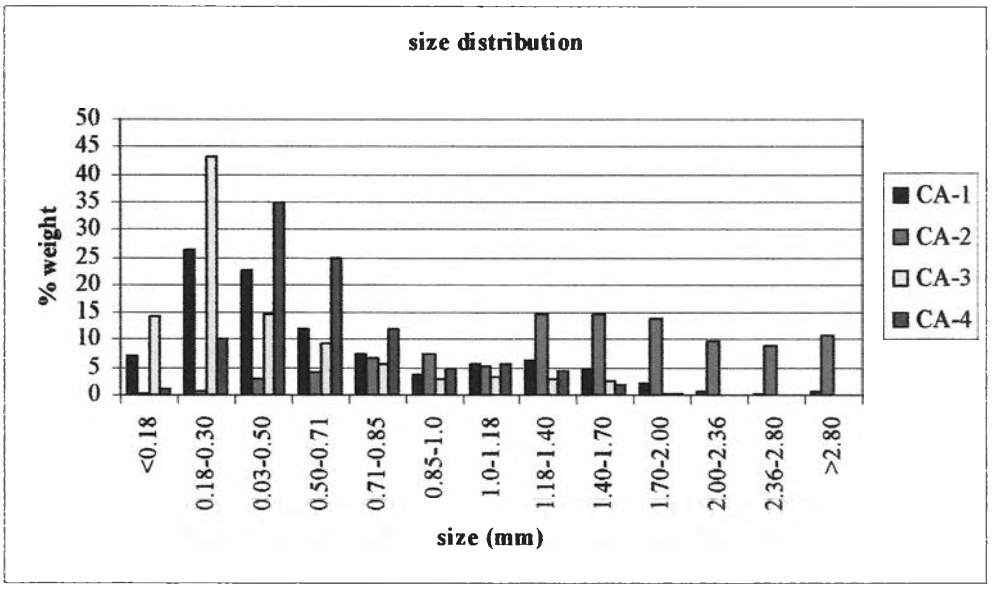


Figure 29 Size distribution of DS-dbcp-GMS pellets prepared with mixing speed of 200 rpm.

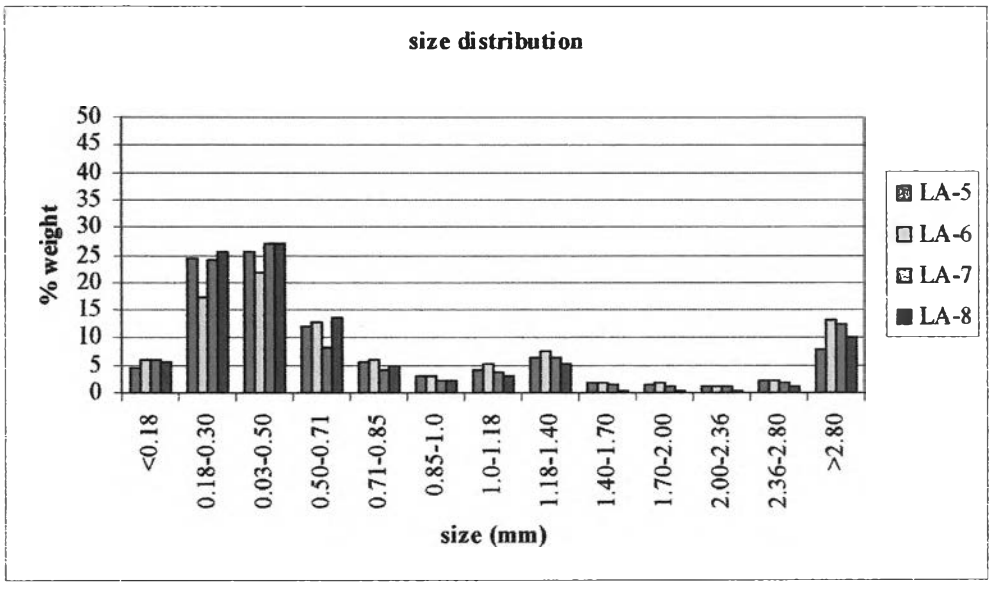


Figure 30 Size distribution of DS-lactose-GMS pellets prepared with mixing speed of 100 rpm.

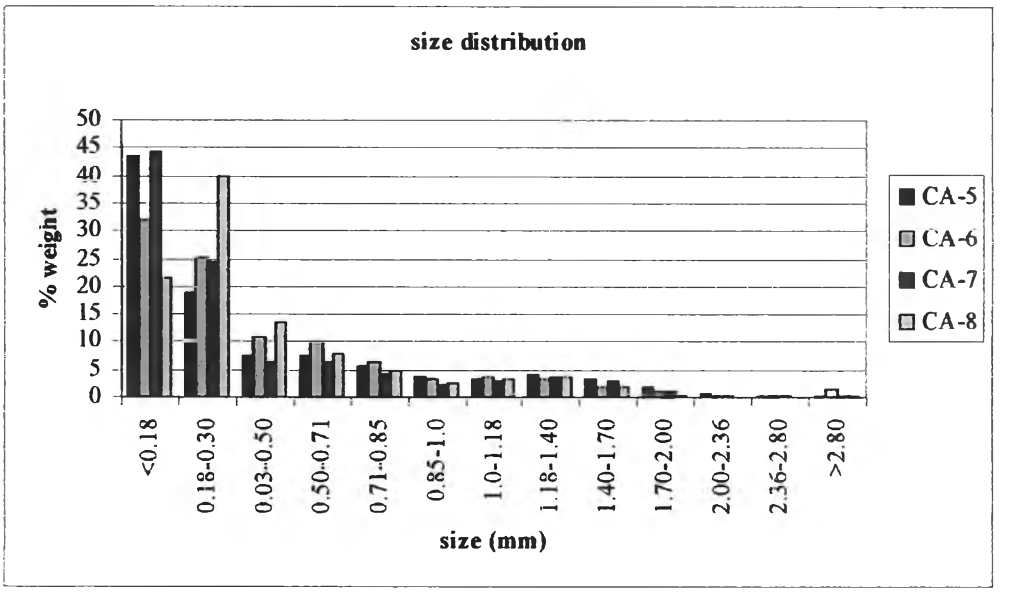


Figure 31 Size distribution of DS-dbcp-GMS pellets prepared with mixing speed of 100 rpm.

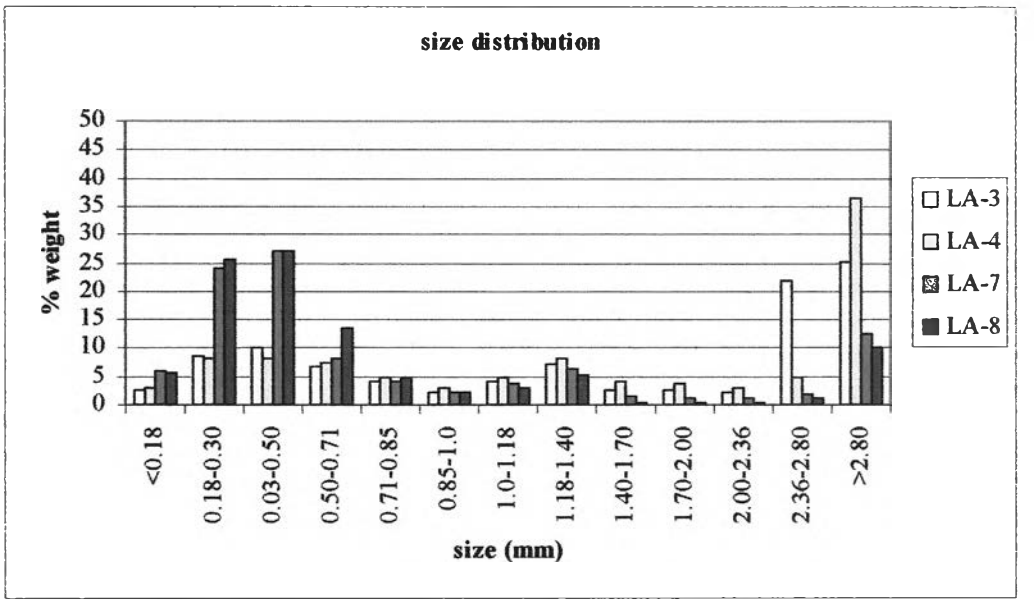


Figure 32 Size distribution of DS-lactose-GMS pellets prepared with mixing temperature of 25°C above the melting point of GMS.

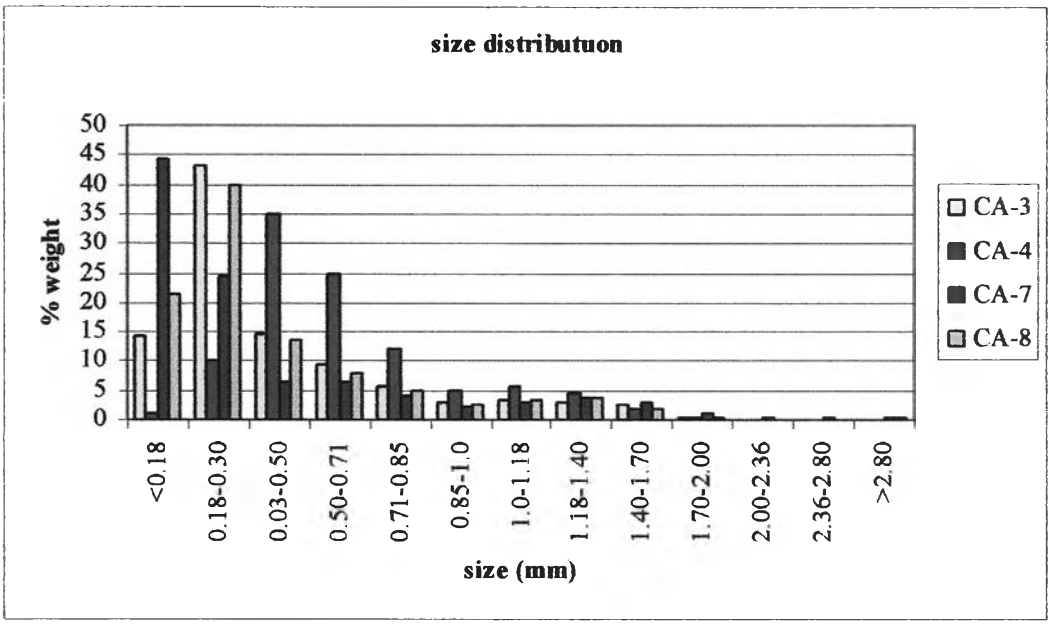


Figure 33 Size distribution of DS-dbcp-GMS pellets prepared with mixing temperature of 25°C above the melting point of GMS.

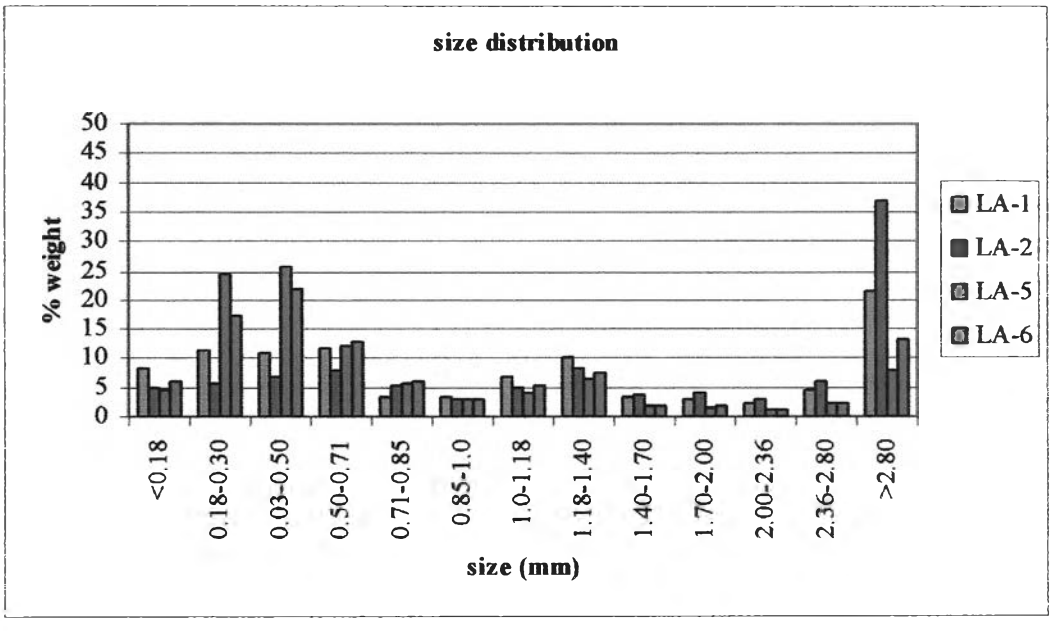


Figure 34 Size distribution of DS-lactose-GMS pellets prepared with mixing temperature of 5°C above the melting point of GMS.

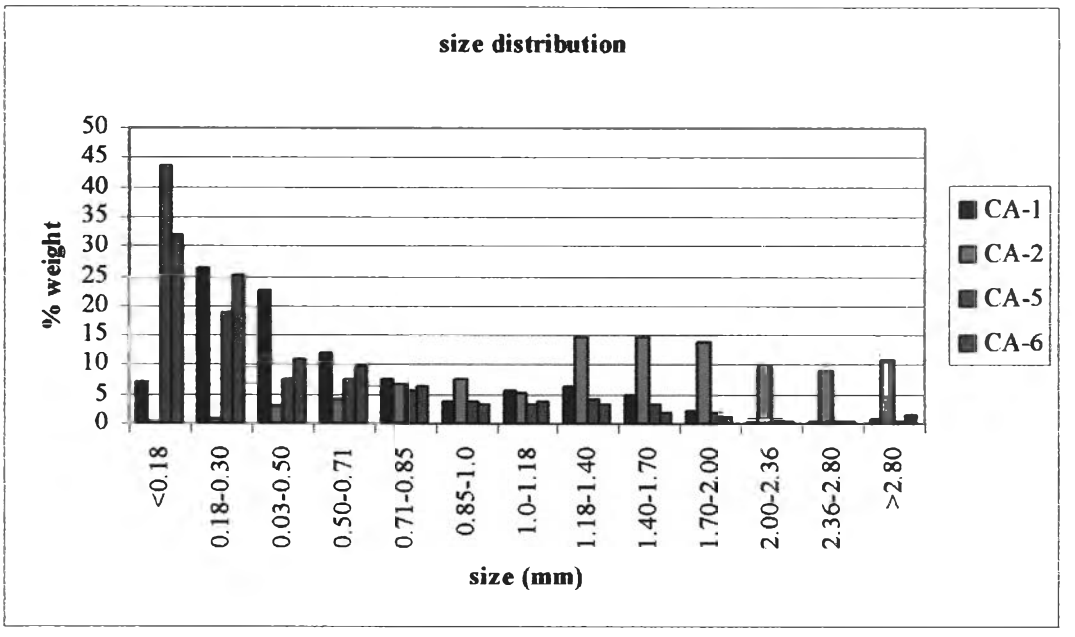


Figure 35 Size distribution of DS-dbcp-GMS pellets prepared with mixing temperature of 5°C above the melting point of GMS.

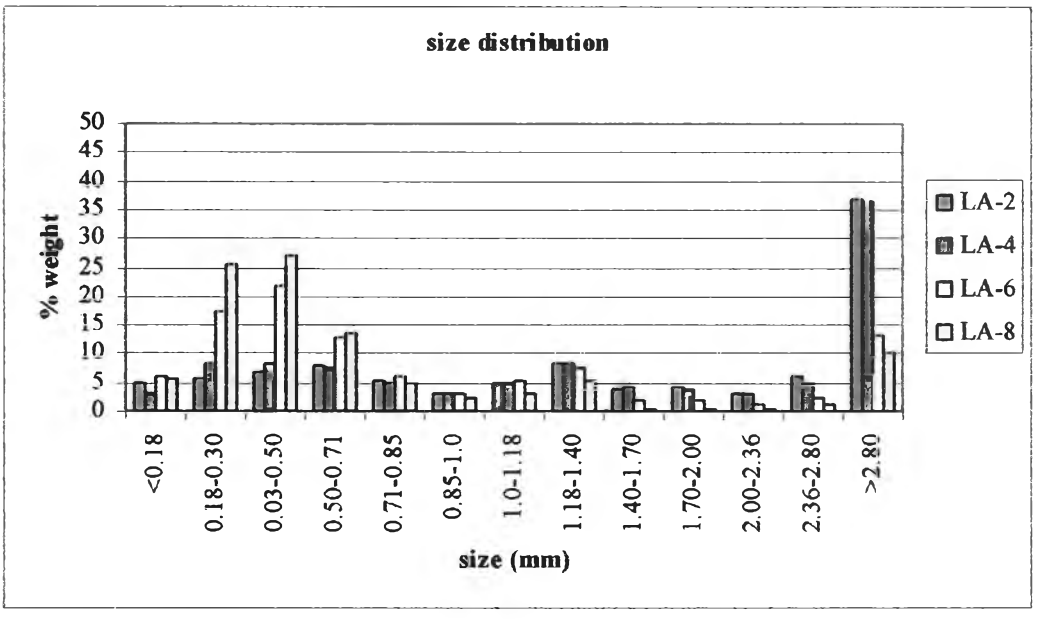


Figure 36 Size distribution of DS-lactose-GMS pellets prepared with mixing time of 15 min.

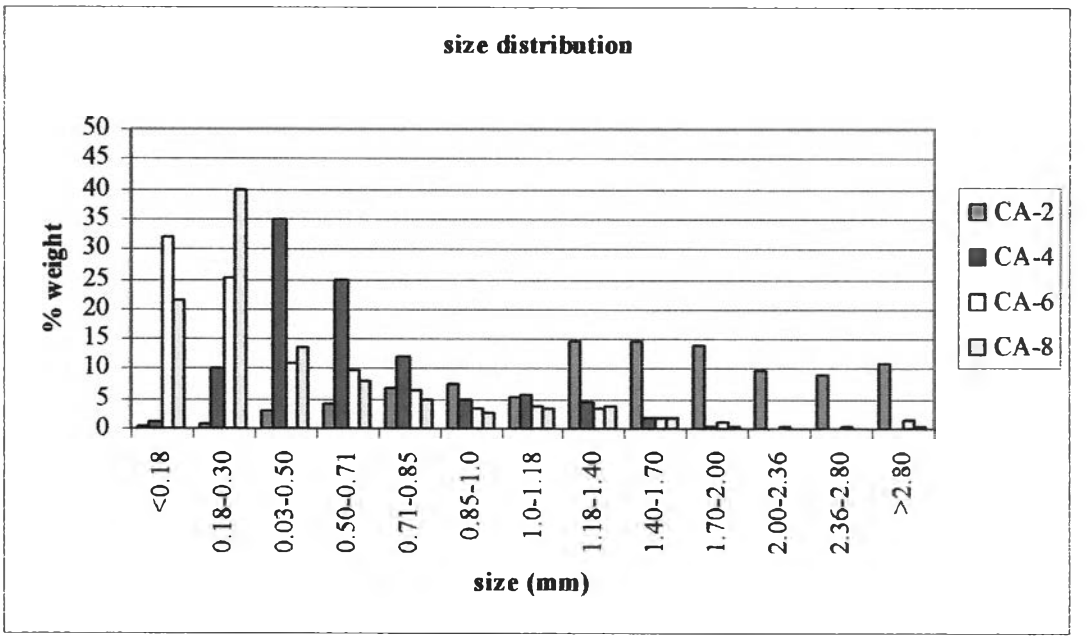


Figure 37 Size distribution of DS-dbcp-GMS pellets prepared with mixing time of 15 min.

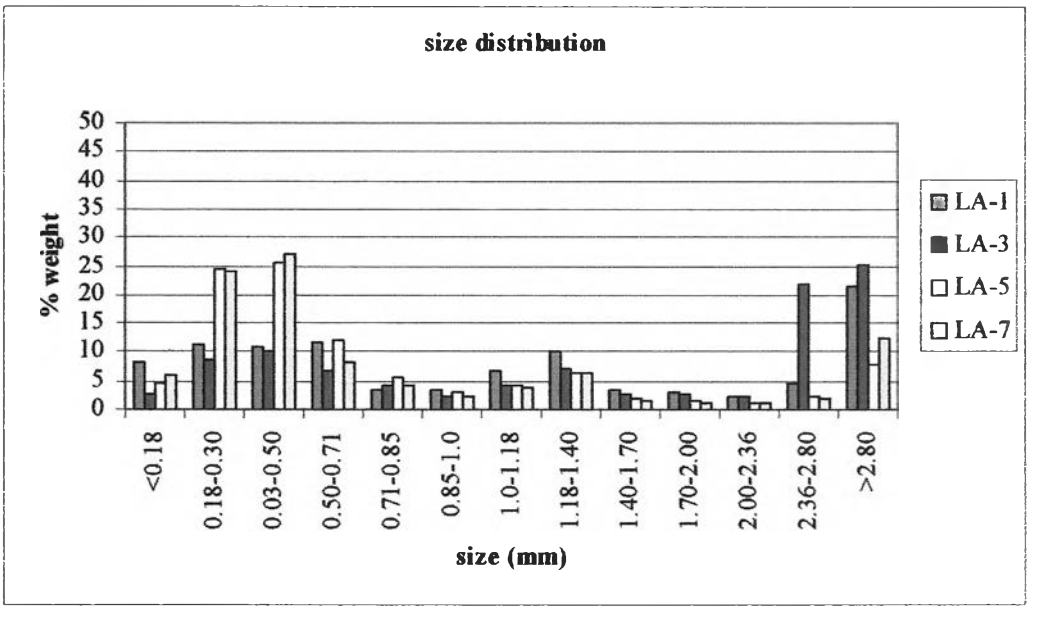


Figure 38 Size distribution of DS-lactose-GMS pellets prepared with mixing time of 10 min.

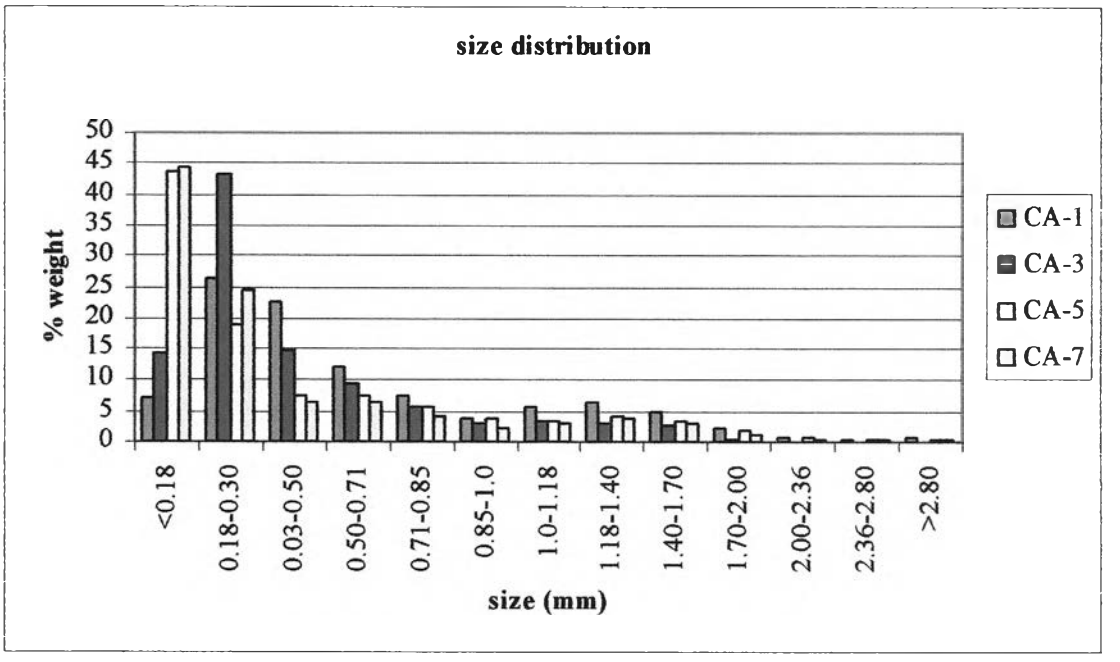


Figure 39 Size distribution of DS-dbcp-GMS pellets prepared with mixing time of 10 min.

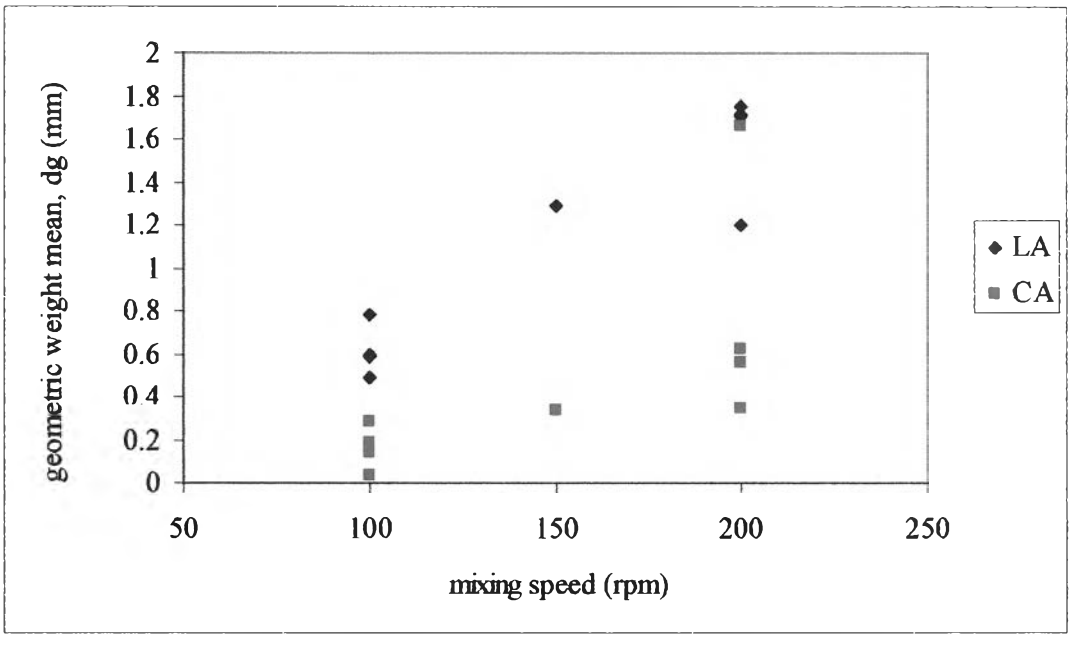


Figure 40 Effect of mixing speed on the geometric weight mean (d_g) of DS-GMS pellets

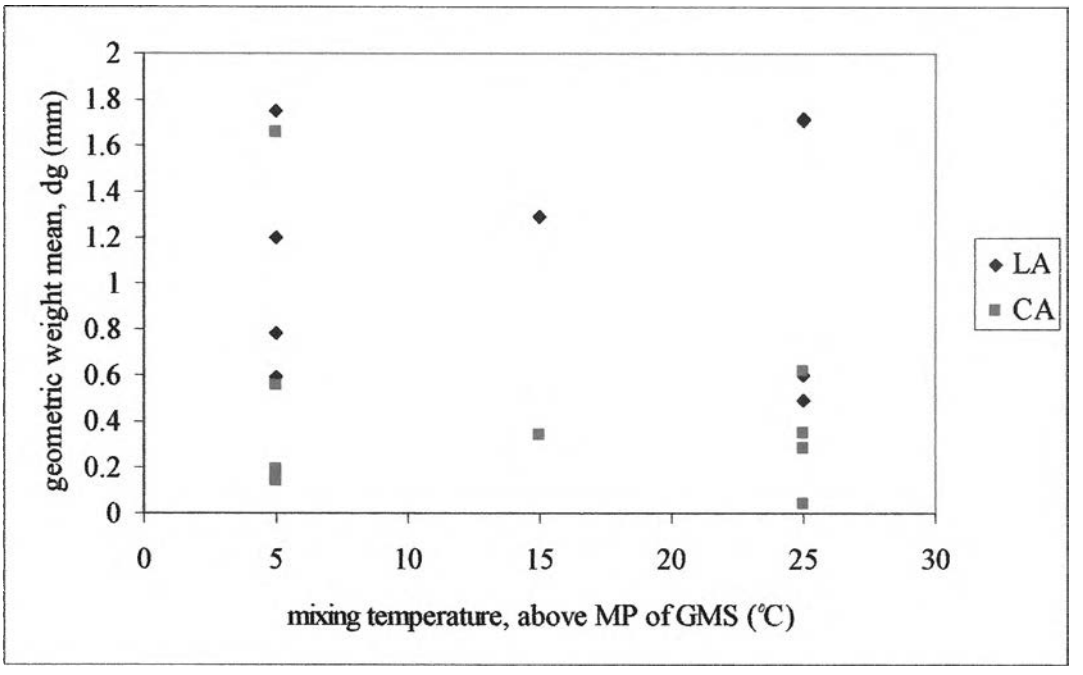


Figure 41 Effect of mixing temperature on the geometric weight mean (d_g) of DS-GMS pellets

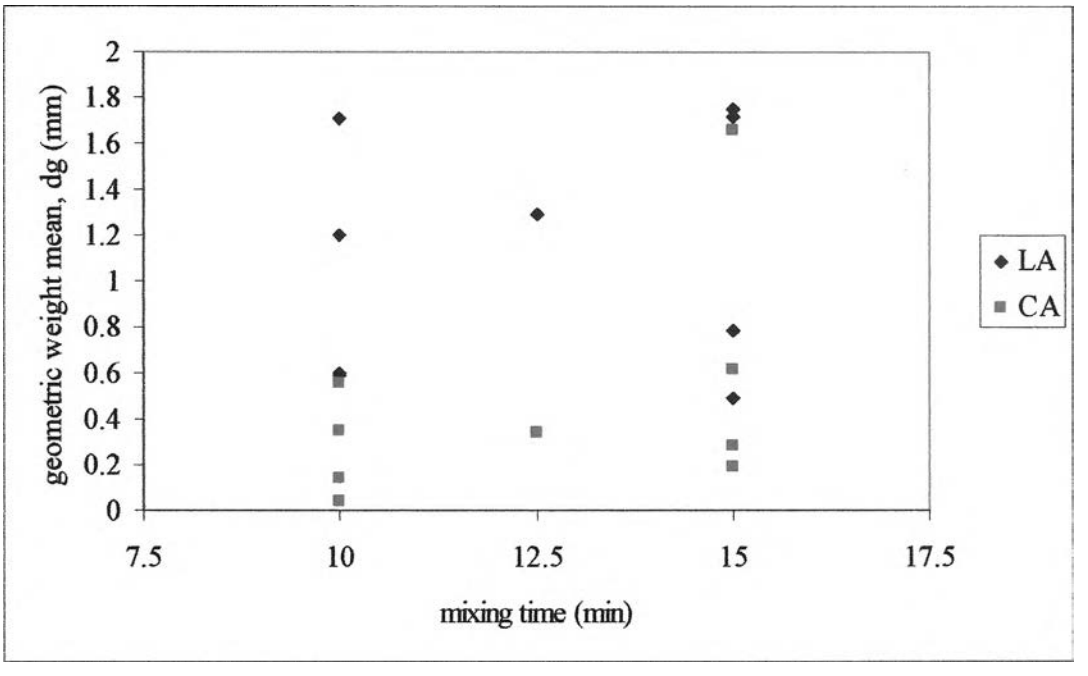


Figure 42 Effect of mixing time on the geometric weight mean (d_g) of DS-GMS pellets

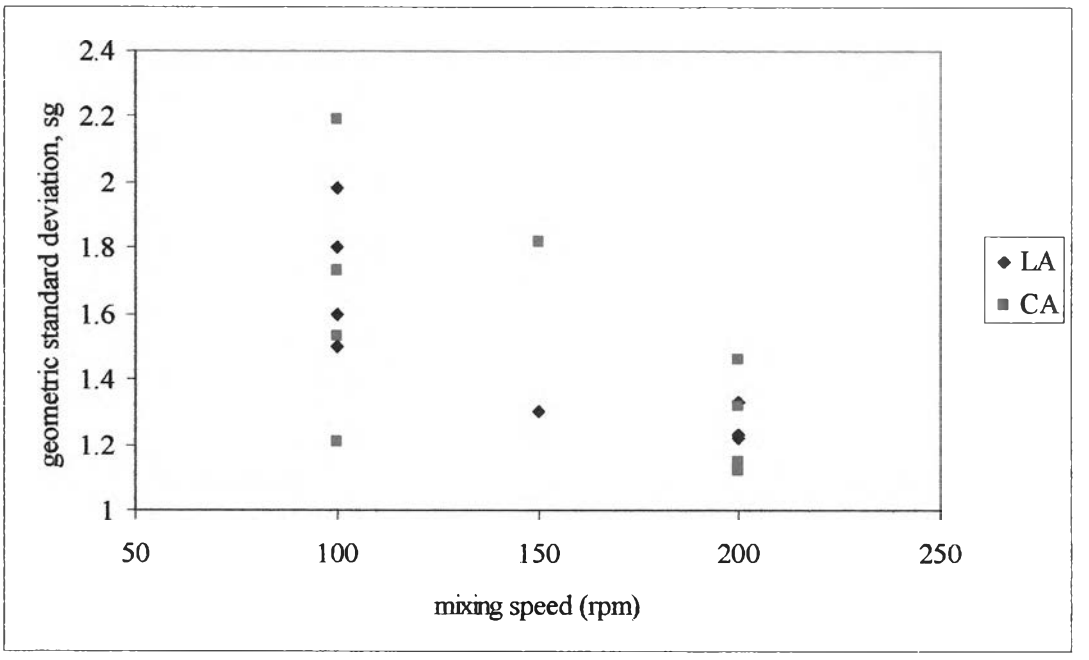


Figure 43 Effect of mixing speed on the geometric standard deviation (s_g) of DS-GMS pellets

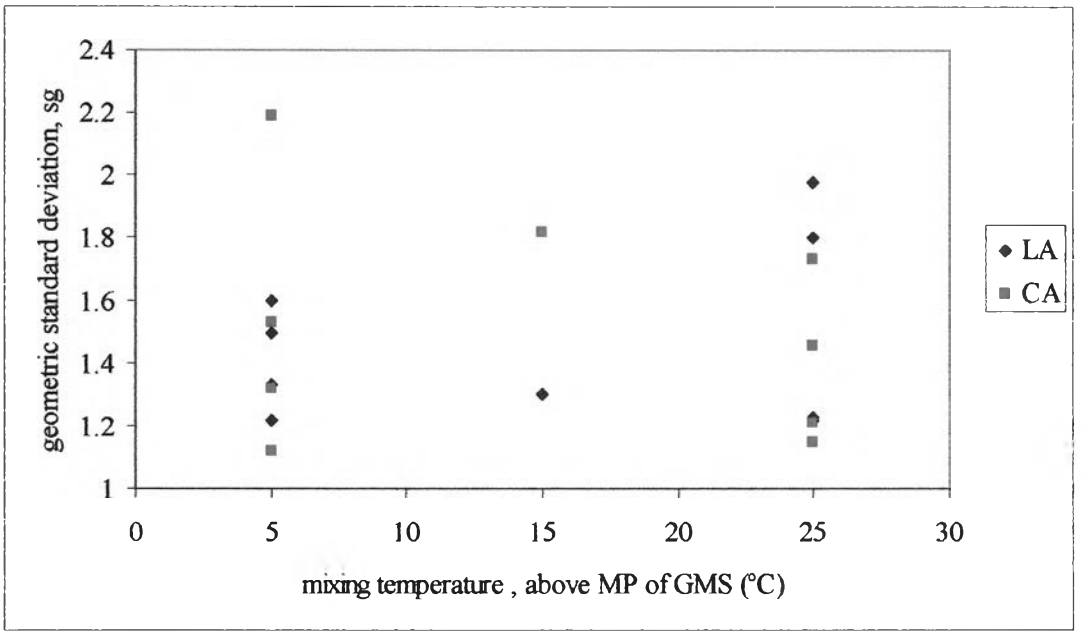


Figure 44 Effect of mixing temperature on the geometric standard deviation (s_g) of DS-GMS pellets

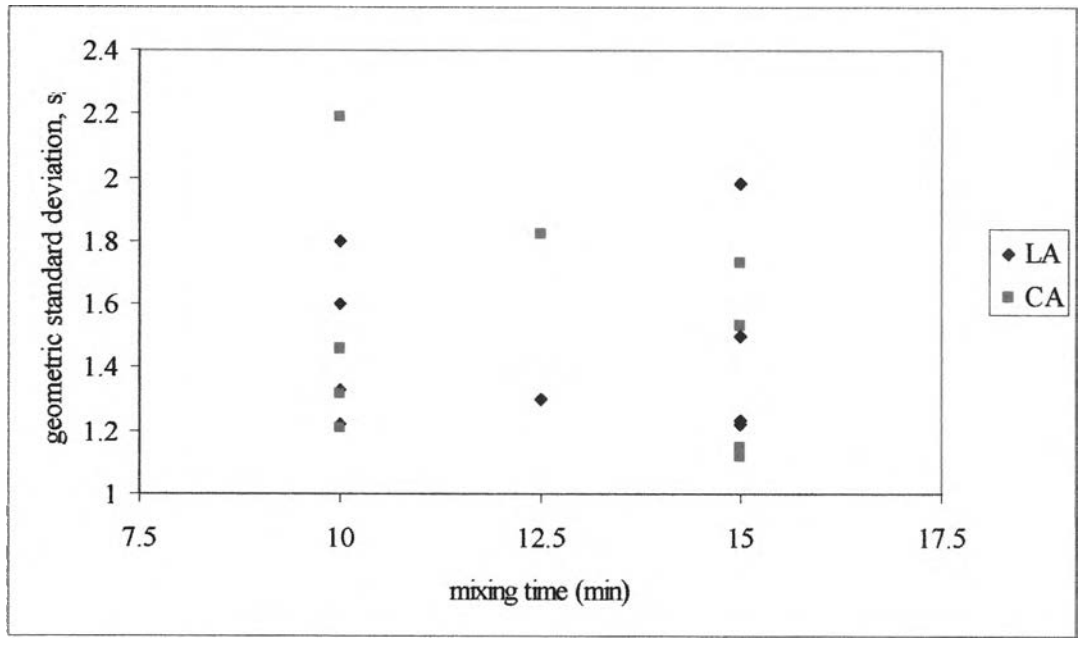


Figure 45 Effect of mixing time on the geometric standard deviation (s_g) of DS-GMS pellets

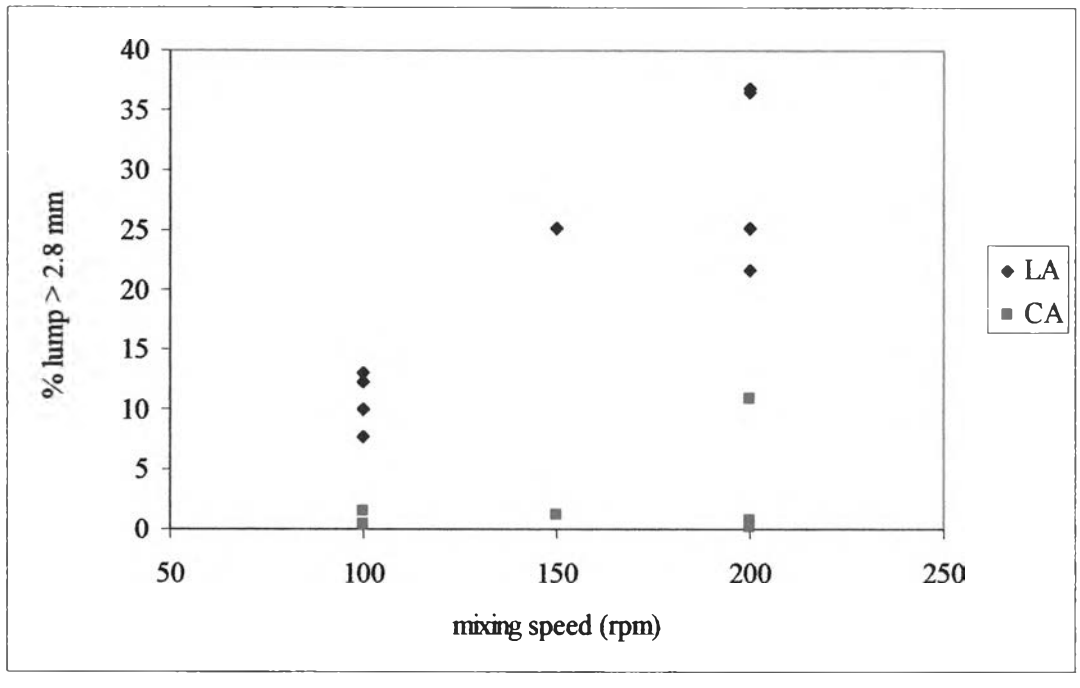


Figure 46 Effect of mixing speed on the % lump > 2.8 mm of DS-GMS pellets

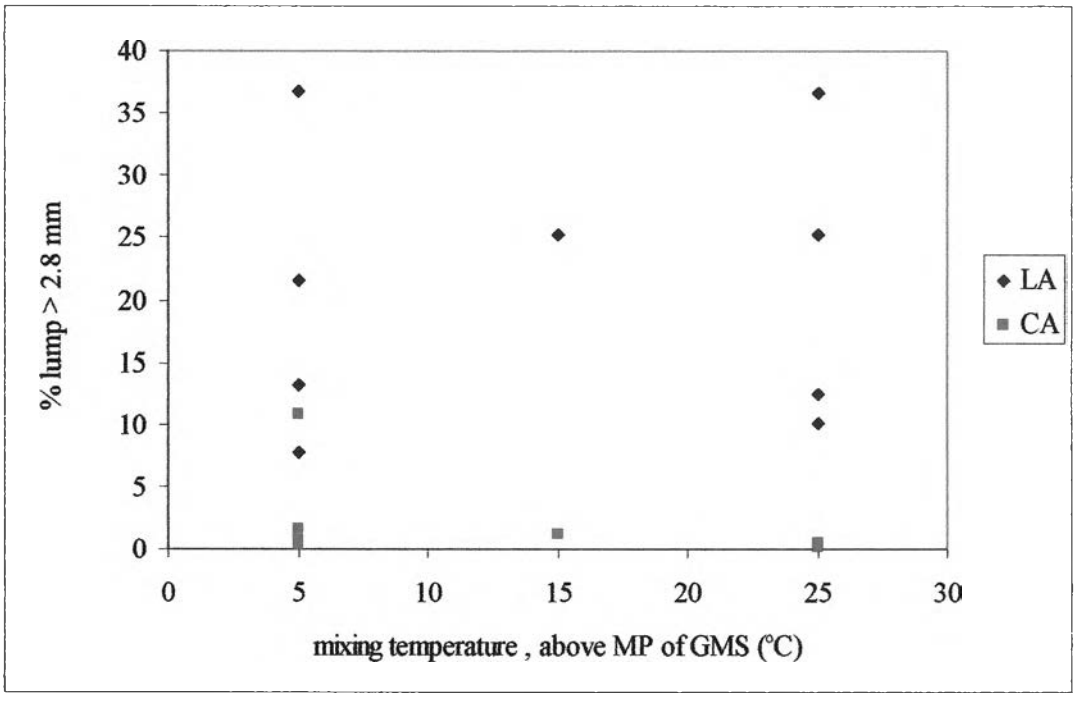


Figure 47 Effect of mixing temperature on the % lump > 2.8 mm of DS-GMS pellets

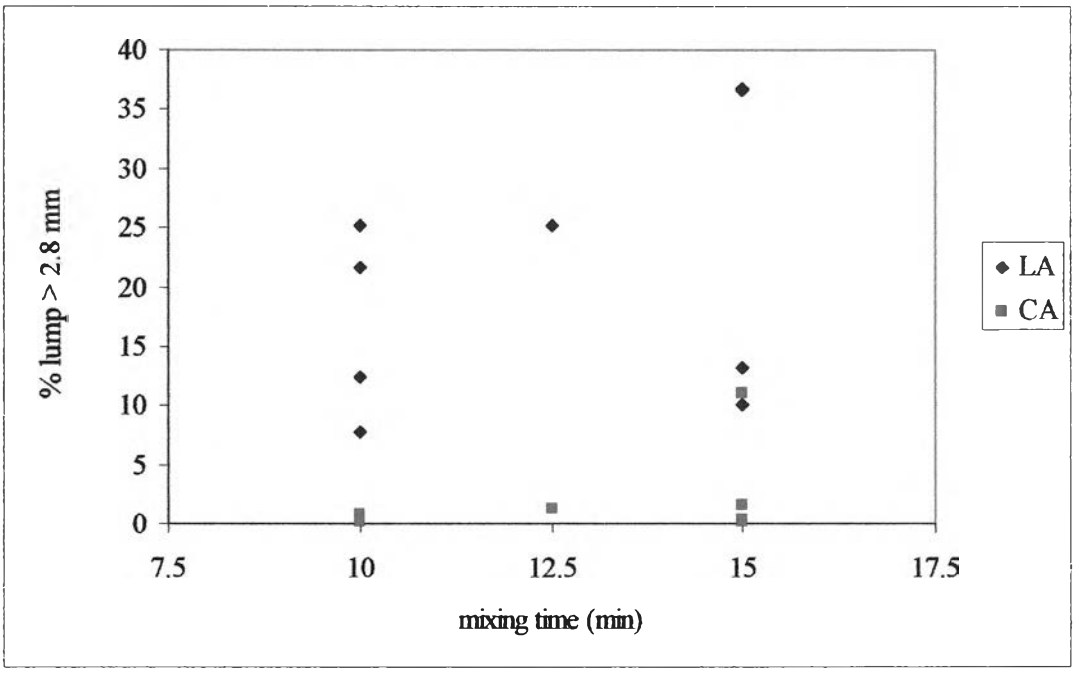


Figure 48 Effect of mixing time on the % lump > 2.8 mm of DS-GMS pellets

3.2.2 Size distribution of pellets prepared with different binders

The size distribution of the pellets prepared with different binders (LA-5, PR, CP, GL, TS) was determined using sieve analysis method. The percent weight of pellets retained on each sieve was calculated and plotted against sieve size as presented in Figure 49. The geometric mean diameter, d_g, and geometric standard deviation, s_g, of the pellet formulations (LA-5, PR, CP, GL, TS) were also determined and the results are shown in Table 13.

In general, as presented in Table 13, the size distribution of pellets prepared with different binders as reflected in the value of s_g were rather similar. The PR, CP, GL and TS pellets possessed narrow size distribution than LA-5 did, 1.31, 1.11, 1.17, 1.22 and 1.60, respectively. The narrowest size distribution was found with CP formulation, 1.11.

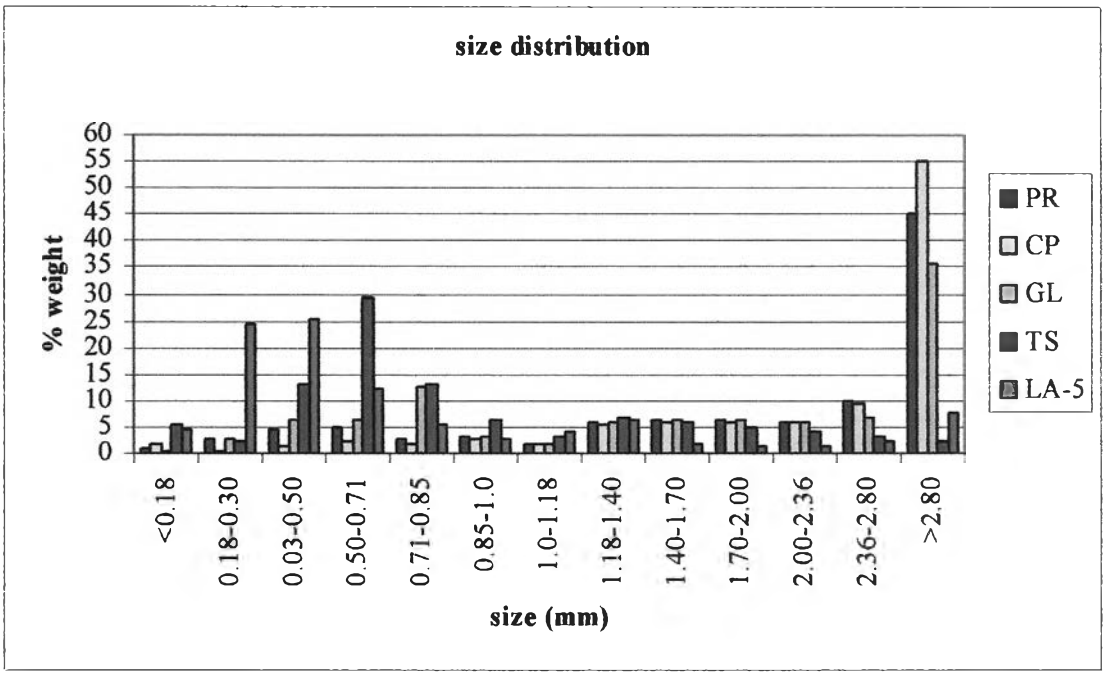


Figure 49 Size distribution of the DS-lactose-pellets prepared with different binders, using mixing speed of 100 rpm, temperature of 5°C above the melting point of binders and time of 10 min

PR = formulation with Precirol® ATO5, CP = formulation with Compritol 888 ATO®,
GL = formulation with Gelucire 50/02, TS = formulation with Tristearin®,
LA = formulation with lactose

Figures 50 - 52 show that a higher melting point of binder, i.e. 74°C for Compritol® ATO 888, gave rise to large granule but narrow size distribution. The large size and narrow size distribution which is shown in Figures 53 – 55 is also observed when using lower viscosity of binder because the distribution of a highly viscous binder is difficult, and this caused a smaller initial growth at an increasing viscosity (Schæfer and Mathiesen, 1996a).

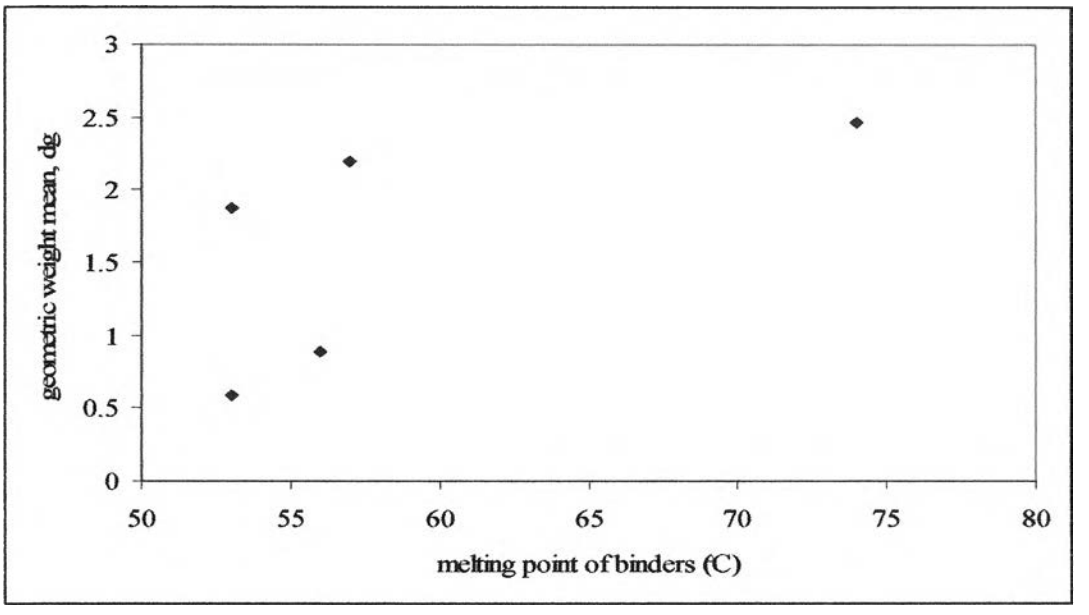


Figure 50 Effect of the melting point of binders on the geometric weight mean (d_g) of DS-lactose pellets

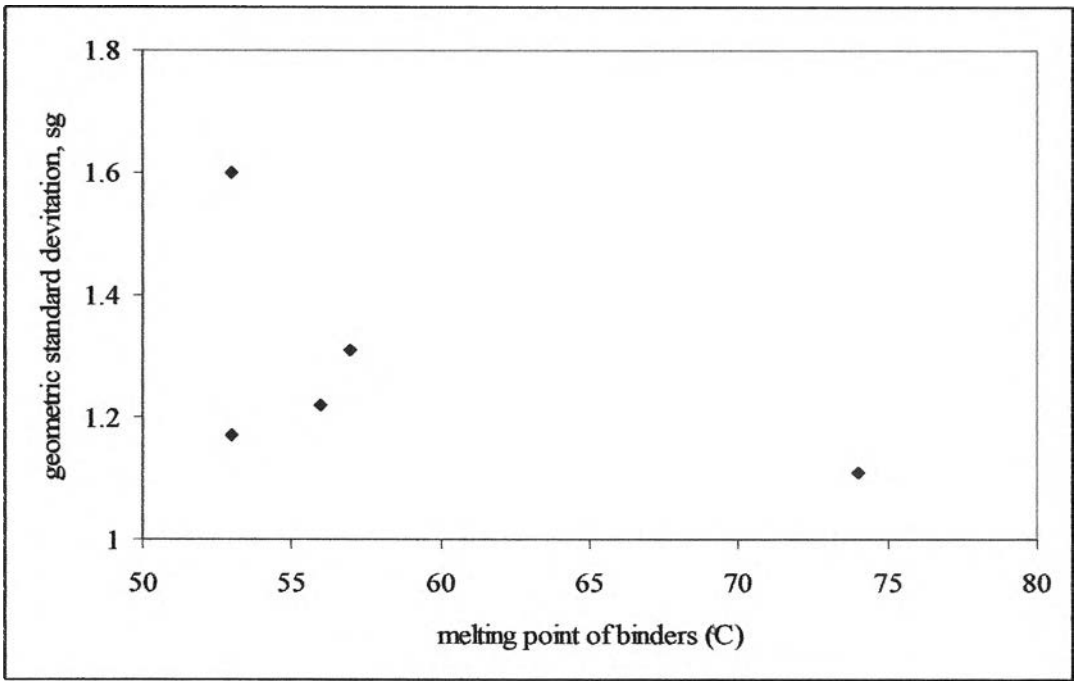


Figure 51 Effect of the melting point of binders on the geometric standard deviation (s_g) of DS-lactose pellets

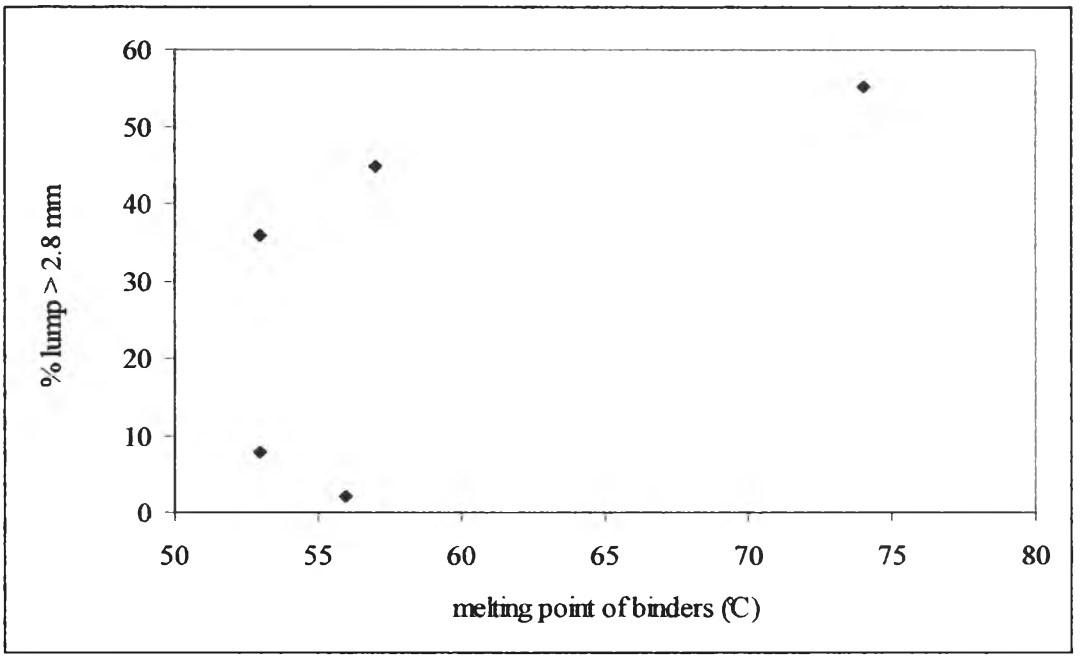


Figure 52 Effect of the melting point of binders on % lump > 2.8 mm of DS-lactose pellets

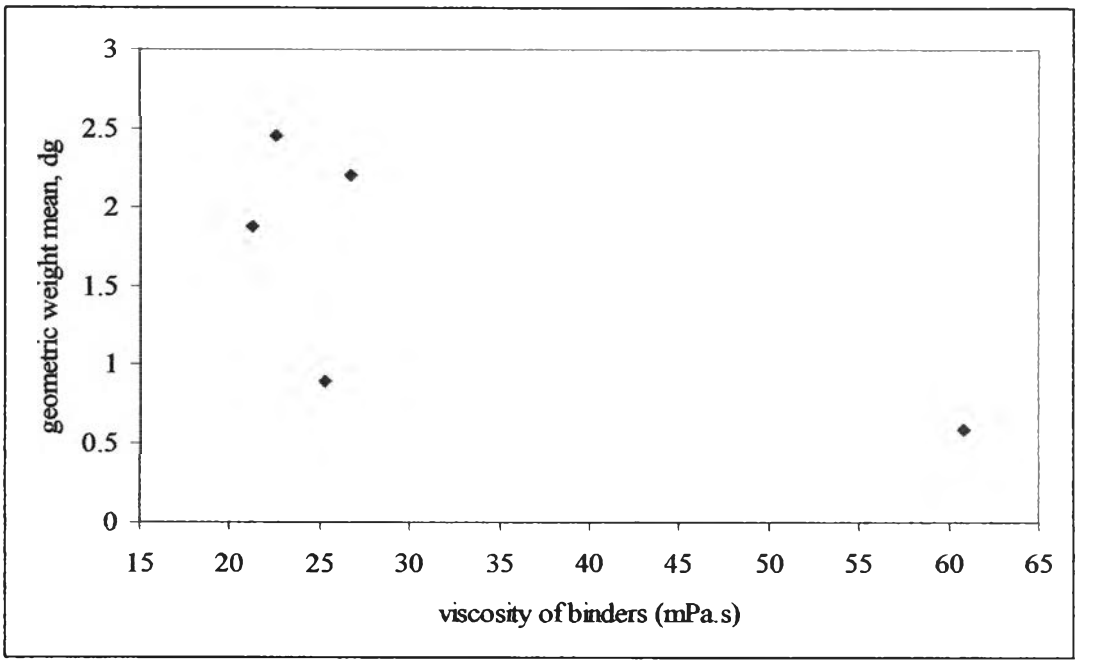


Figure 53 Effect of viscosity of binder, at 5°C above the melting point of binder on geometric weight mean (d_g) of DS-lactose pellets

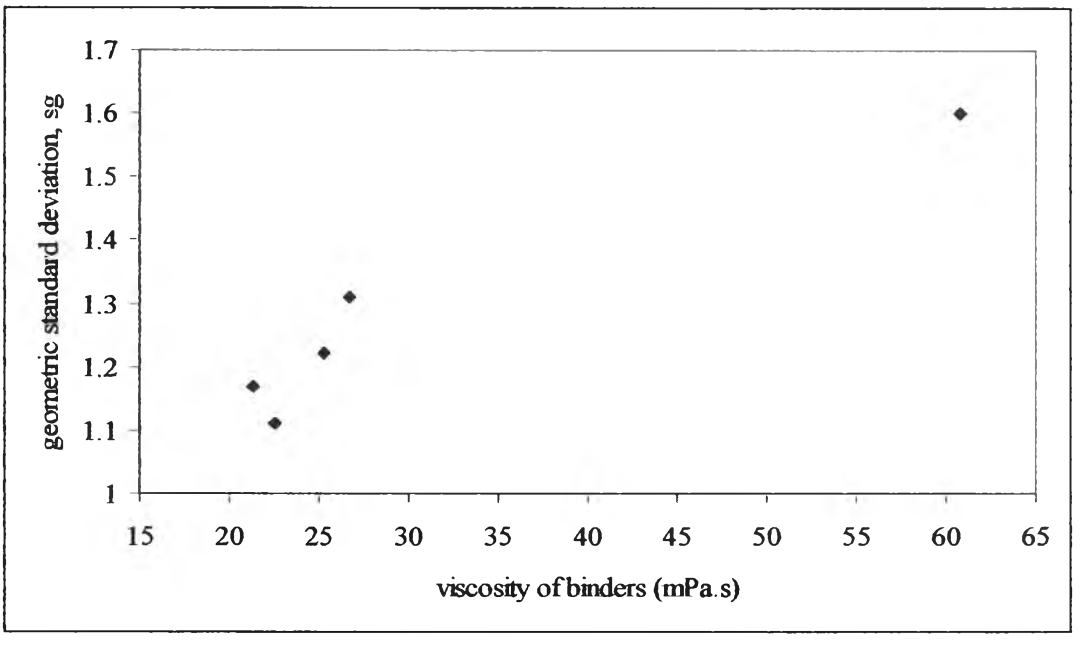


Figure 54 Effect of viscosity of binder, at 5°C above the melting point of binder on geometric standard deviation (s_g) of DS-lactose pellets

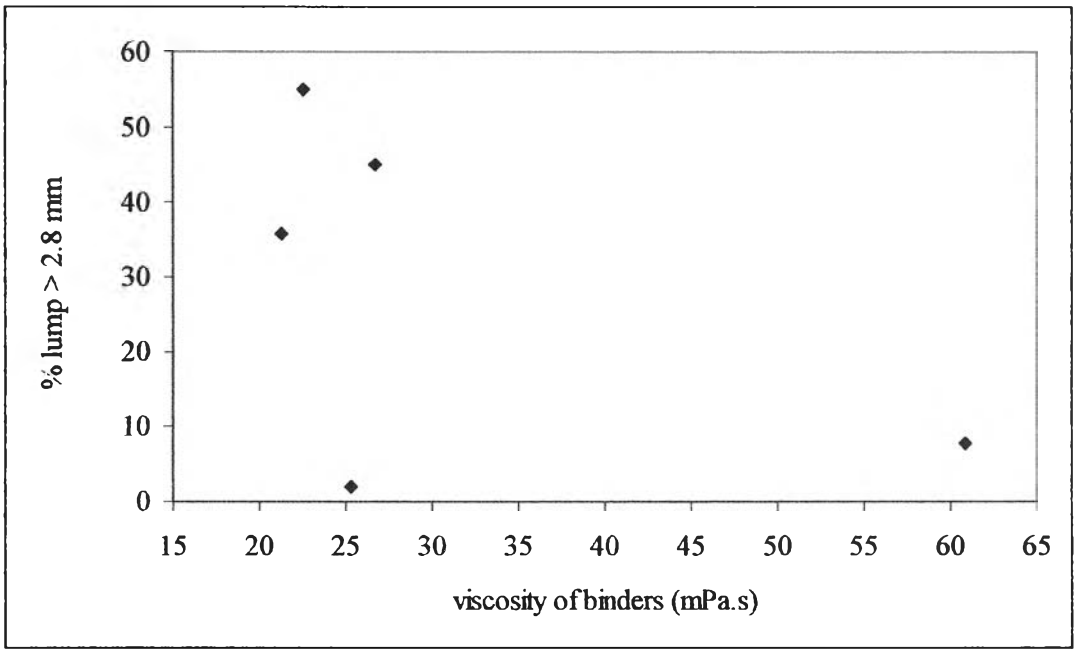


Figure 55 Effect of viscosity of binders, at 5°C above the melting point of binder on % lump > 2.8 mm of DS-lactose pellets

3.3 Determination of the angle of repose

The angle of repose of DS pellets shown in Table 14. The angle of repose of all formulations were within 22° - 32°, indicating good flowability (Nagel and Peck, 2003). If the angle of repose is low, the pellets show good flowability. Flowability of pellets depends on surface character and sphericity. If the pellet is smooth and round, it possesses good flowability. The angle of repose for DS-dbcp pellets was less than DS-lactose pellets, indicating better flowability. The maximum value of angle of repose for DS-lactose-GMS pellets was 31.31° for LA-7 which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 10 min. The minimum value of angle of repose for DS-lactose-GMS pellets was 24.29° of LA-1 which was prepared by mixing speed of 200 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 10 min. The maximum value of angle of repose for DS-dbcp-GMS pellets was 26.56° for CA-7 which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above melting point of GMS and

mixing time of 10 min. The minimum value of angle of repose for DS-dbcp-GMS pellets was 23.82° for

Table 14 The angle of repose, flow rate, bulk density, tapped density and % compressibility of DS pellets prepared from each formulation. (mean (SD))

Formulation	Angle of repose (n=3)	Flow rate (g/sec) (n=3)	Bulk density (g/ml) (n=3)	Tapped density (g/ml) (n=3)	%compressibility (n=3)
LA-1	24.29 (1.14)	7.69 (0.00)	0.55 (0.00)	0.58 (0.00)	5.17 (0.00)
LA-2	26.82 (1.15)	6.67 (0.00)	0.54 (0.00)	0.56 (0.00)	3.57 (0.00)
LA-3	29.32 (0.38)	7.14 (0.00)	0.56 (0.00)	0.59 (0.00)	5.08 (0.00)
LA-4	30.49 (0.82)	7.69 (0.00)	0.53 (0.00)	0.57 (0.00)	7.02 (0.00)
LA-5	27.10 (1.22)	9.09 (0.00)	0.60 (0.00)	0.66 (0.00)	7.69 (0.00)
LA-6	29.89 (0.25)	8.33 (0.00)	0.57 (0.00)	0.61 (0.00)	6.56 (0.00)
LA-7	31.31 (1.25)	8.58 (0.44)	0.56 (0.00)	0.60 (0.00)	6.67 (0.00)
LA-8	29.19 (0.99)	8.58 (0.44)	0.54 (0.00)	0.59 (0.00)	8.47 (0.00)
LA-9	31.09 (1.43)	8.58 (0.44)	0.56 (0.00)	0.60 (0.00)	6.67 (0.00)
CA-1	25.01 (0.55)	13.69 (1.03)	1.00 (0.00)	1.05 (0.00)	4.76 (0.00)
CA-2	26.11 (1.19)	12.04 (0.80)	0.95 (0.00)	1.02 (0.00)	6.86 (0.00)
CA-3	23.82 (1.21)	14.29 (0.00)	1.00 (0.00)	1.09 (0.00)	8.26 (0.00)
CA-4	25.77 (1.38)	13.69 (1.03)	1.04 (0.00)	1.10 (0.00)	5.45 (0.00)
CA-5	23.83 (1.56)	15.88 (1.37)	0.95 (0.00)	1.00 (0.00)	5.00 (0.00)
CA-6	24.11 (1.39)	15.08 (1.37)	0.95 (0.00)	1.02 (0.00)	6.86 (0.00)
CA-7	26.56 (1.20)	15.08 (1.37)	0.94 (0.00)	0.94 (0.00)	0.00 (0.00)
CA-8	24.24 (1.23)	16.67 (0.00)	0.99 (0.00)	1.05 (0.00)	5.71 (0.00)
CA-9	25.52 (0.94)	15.88 (1.37)	0.98 (0.00)	1.05 (0.00)	6.67 (0.00)
PR	22.48 (0.35)	8.33 (0.00)	0.51 (0.00)	0.55 (0.00)	7.27 (0.00)
CP	23.36 (1.07)	8.12 (0.37)	0.60 (0.00)	0.64 (0.00)	6.25 (0.00)
GL	32.91 (1.09)	7.69 (0.00)	0.49 (0.00)	0.53 (0.00)	7.55 (0.00)
TS	26.30 (0.46)	9.70 (0.53)	0.65 (0.00)	0.65 (0.00)	0.00 (0.00)

n = number of determinations

CA-3 which was prepared by mixing speed of 200 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 10 min. The angle of repose might be affected by both mixing speed and temperature.

In previous finding (Schæfer et al., 1992a; Schæfer et al., 1993), the pellets were found to be more rounded and smoother at a higher impeller speed and hence flew better. In this study, although the angle of repose of the pellets prepared at the high speed of mixing, i.e. 200 rpm, tended to be slightly lower (Figure 56), the effect of mixing speed could not be clearly shown.

The effect of temperature is shown in Figure 57. The result indicates that the DS-lactose-GMS pellets of lower angle of repose were prepared at low temperature, 5°C above the melting point of GMS. Increased mixing temperature, higher the angle of repose was obtained for DS-lactose-GMS pellets. However, increased mixing temperature did not result in clear effect angle of repose of DS-dbcp-GMS pellets. This results in accordance with previous works. Thomsen et al. (1993) found that pellets produced at low temperature, 56°C, was smooth, homogeneous and more spherical than pellets produced at high temperature, 86°C. Eliasen et al. (1999) also found that when prepared pellets containing lactose and stearic acid as a binder which had viscosity 10 mPa.s were prepared, a lower impeller speed, 200 rpm and low jacket temperature, 35°C, were found to give rise to smoother and more spherical agglomerates.

The effect of mixing time is shown in Figure 58. Both DS-lactose-GMS pellets and DS-dbcp-GMS pellets, the graphical results did not show markedly difference from those obtained. It might be narrow range of time in this study, so this effect was not clear.

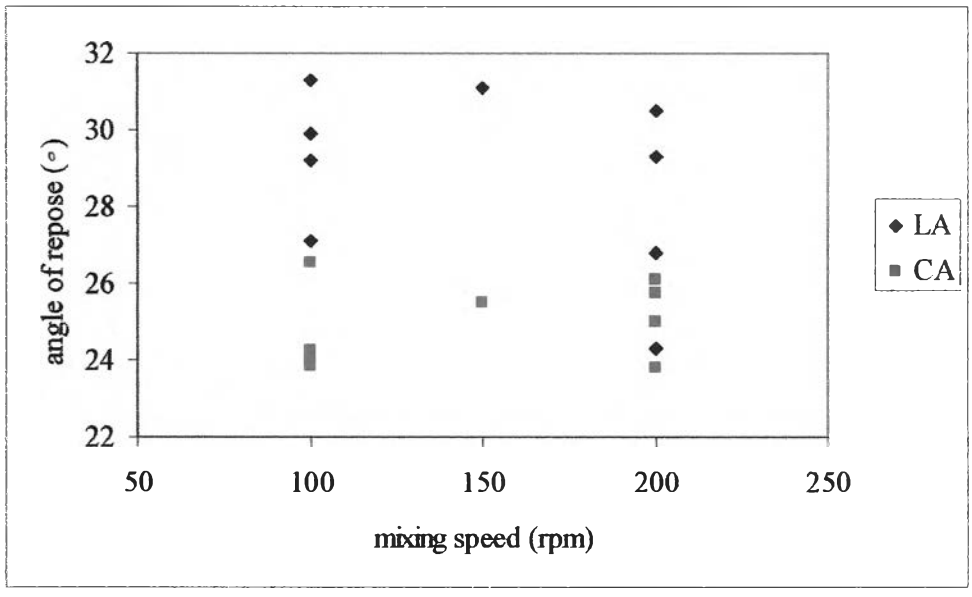


Figure 56 Effect of mixing speed on the angle of repose of DS-GMS pellets

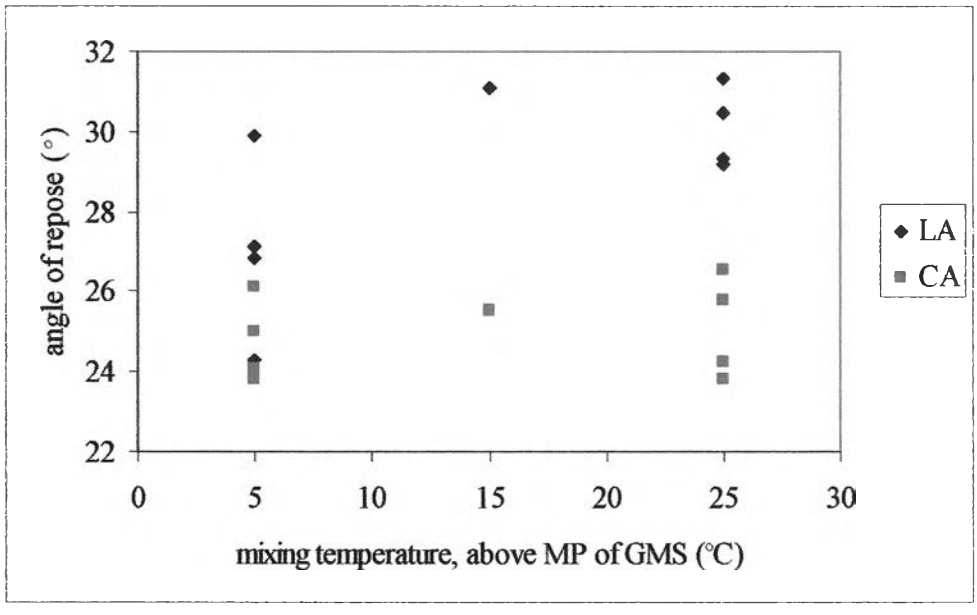


Figure 57 Effect of mixing temperature on the angle of repose of DS-GMS pellets

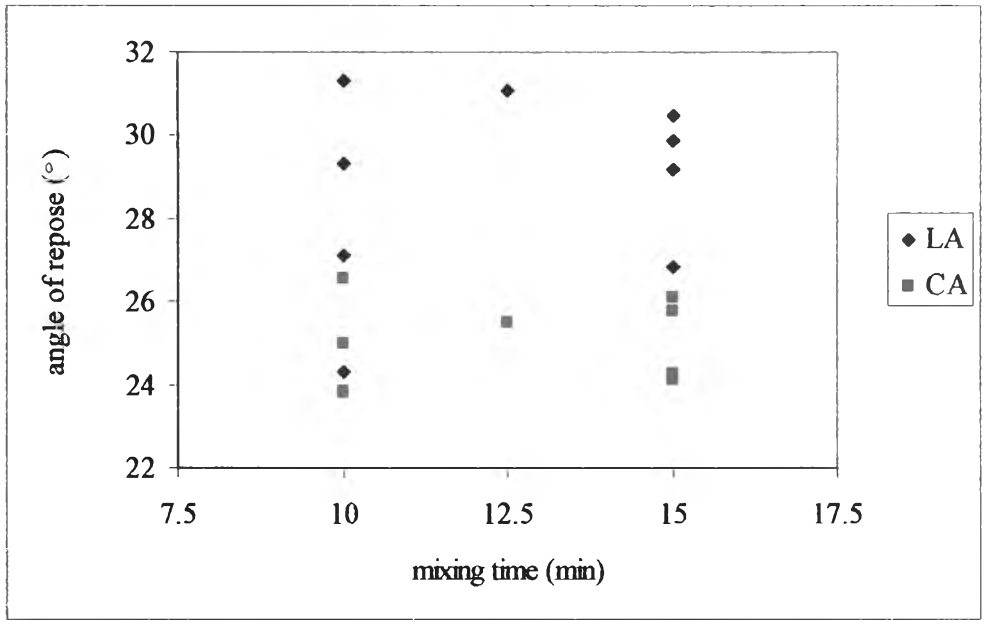


Figure 58 Effect of mixing time on the angle of repose of DS-GMS pellets

Considering the effect of binders, the angle of repose as presented in Table 13, the maximum value of angle of repose 32.91° belonged to GL pellets. The minimum value of angle of repose 22.48° belonged to PR pellets. Figure 59 showed that a higher melting point of binder, i.e. 74°C for Compritol® ATO 888 gave rise to low angle of repose. Schæfer and Mathiesen (1996a) prepared pellets containing PEG 3000 and PEG 10000 by using a high shear mixer. The results indicated that a lower binder viscosity gave more spherical pellets. However, the effect of viscosity was not clearly shown in Figure 60, possibly because the viscosity of the binder used were rather low compared with their work.

3.4 Determination of flow rate

The flow rate of DS pellets shown in Table 13. The flow rate of all formulations were within 6.67 – 16.67 g/sec, indicating good flowability. The DS-dbcp pellets flew better than DS-lactose pellets, probably because DS-dbcp pellets were rounder and had smoother surface than DS-lactose pellets.

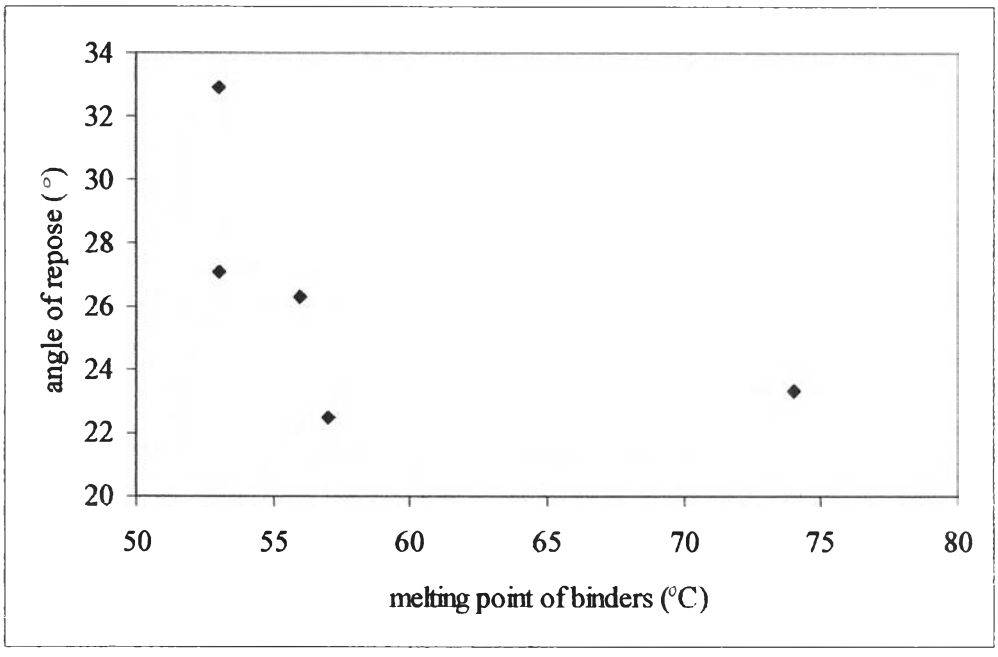


Figure 59 Effect of the melting point of binders on the angle of repose of DS-lactose pellets

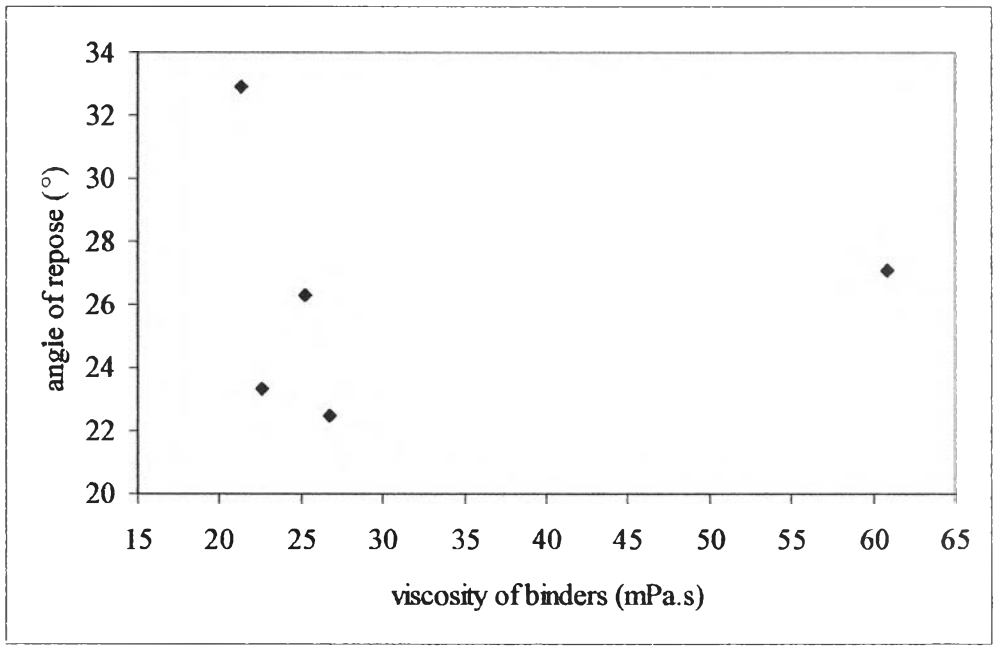


Figure 60 Effect of viscosity of binders, at 5°C above the melting point of binder on the angle of repose of DS-lactose pellets

The maximum value of flow rate for DS-lactose-GMS pellets was 9.09 g/ sec for LA-5 which was prepared by mixing speed of 100 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 10 min. The minimum value of flow rate for DS-lactose-GMS pellets was 6.67 g/sec for LA-2 which was prepared by mixing speed of 200 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 15 min. This results indicated that low mixing speed and time tended to give good flowability of pellets.

The maximum value of flow rate for DS-dbcp-GMS pellets was 16.67 g/sec for CA-8 which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 15 min. The minimum value of flow rate for DS-dbcp-GMS pellets was 12.04 g/sec for CA-2 which was prepared by mixing speed of 100 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 15 min. This results indicated that high mixing temperature tended to give good flowability of pellets.

The maximum value of the other binder pellets was 9.70 g/sec for TS pellets. The minimum value of the other binder pellets was 7.69 g/sec for GL pellets. This probably resulted from that TS pellets is rounder than the others.

3.5 Bulk density, tapped density and compressibility index

The bulk density, tapped density and compressibility index shown in Table 14. Compressibility index or Carr's compressibility was calculated by bulk density and tapped density. If the value of bulk density is close to the value of tapped density, compressibility index was close to the value of 0, indicating good flow characteristic. In general, the value of bulk density of DS-dbcp-GMS pellets were close to tapped density. So DS-dbcp-GMS pellets should possess low compressibility. Their Carr's compressibility is distributed in a narrow range 0 - 8.47 %. The maximum value of compressibility index for DS-lactose pellets was 8.47 % for LA-8 which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 15 min. The minimum value of compressibility index for DS-lactose pellets was 3.57 % for LA-2 which was prepared by mixing speed of 200 rpm, mixing

temperature of 5°C above the melting point of GMS and mixing time of 15 min. The maximum value of compressibility index for DS-dbcp-GMS pellets was 8.26 % for CA-3, which was prepared by mixing speed of 200 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 10 min. The minimum value of compressibility index for DS-dbcp-pellets was 0.00 for CA-7, which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 10 min. As a result of the low value of bulk density, tapped density and percent Carr's compressibility index, all pellets seemed to have good flow characteristics.

At the high speed of mixing, i.e. 200 rpm, low value of the compressibility index of DS-lactose-GMS pellets formulations tended to be obtained. At the low speed of mixing, i.e. 100 rpm, relatively high value of the compressibility of DS-lactose-GMS was obtained (Figure 61). On the other hand, at the high speed of mixing, i.e. 200 rpm, relatively high value of the compressibility index of DS-dbcp-GMS pellets formulations tended to be obtained.

The results shown in Figure 62 indicates that the DS-lactose-GMS pellets of lower compressibility index were likely to be obtained at low temperature, 5°C above the melting point of GMS. Increased mixing temperature, slightly higher compressibility index was obtained for DS-lactose-GMS pellets. However, increased mixing temperature did not show the effect on compressibility index of DS-dbcp-GMS pellets.

The effect of mixing time is shown in Figure 63. The graphical results did not show marked difference between the DS-lactose pellets and the DS-dbcp-GMS pellets. It might be a short range of time in this study, so this effect was not clear.

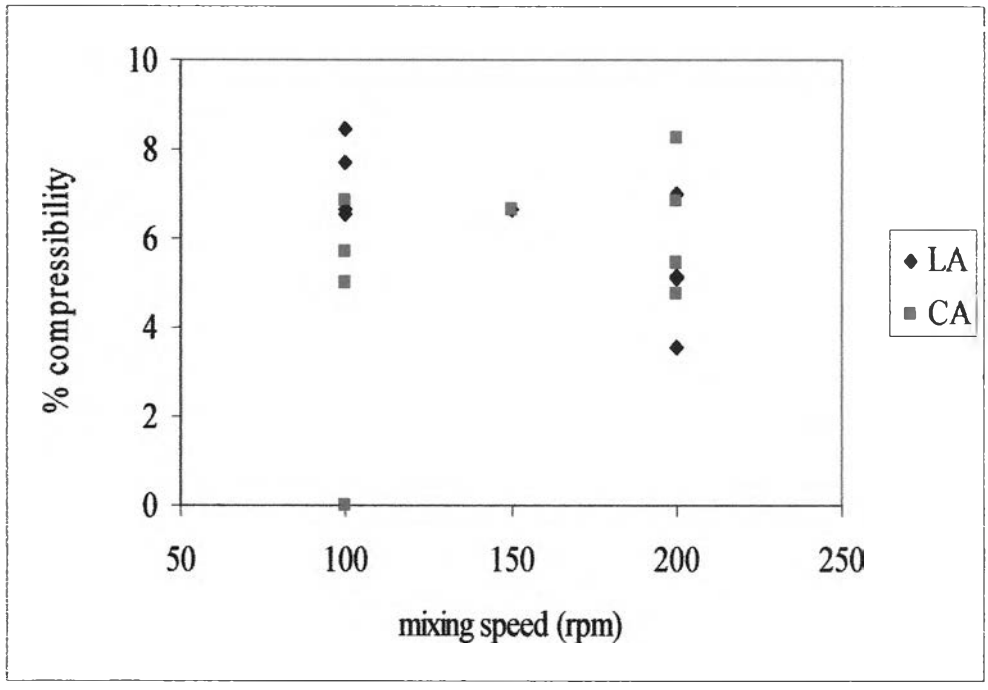


Figure 61 Effect of mixing speed on the compressibility index of DS-GMS pellets

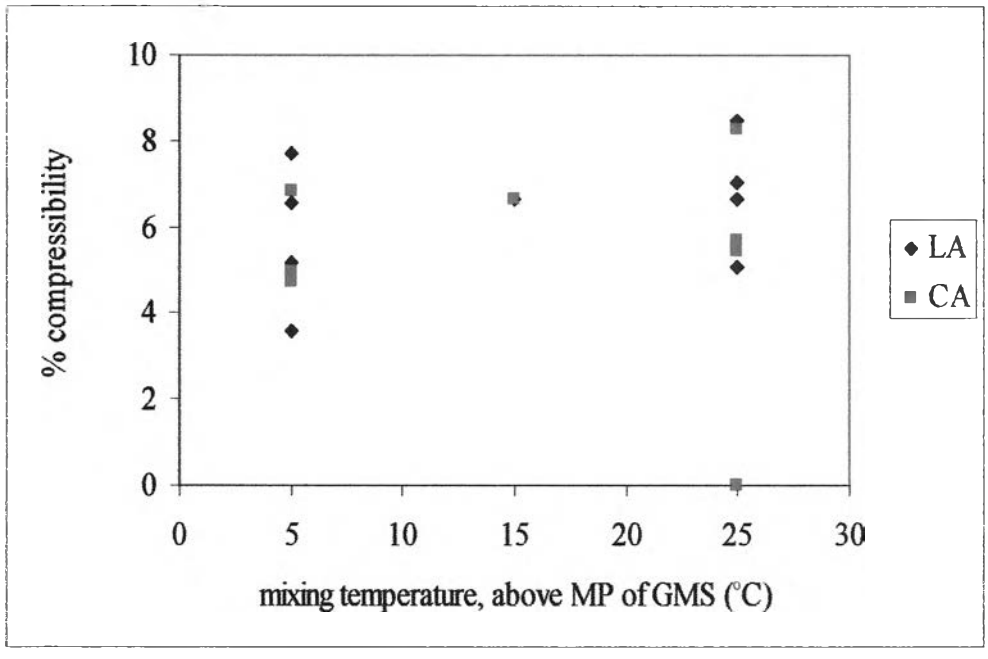


Figure 62 Effect of mixing temperature on the compressibility index of DS-GMS pellets

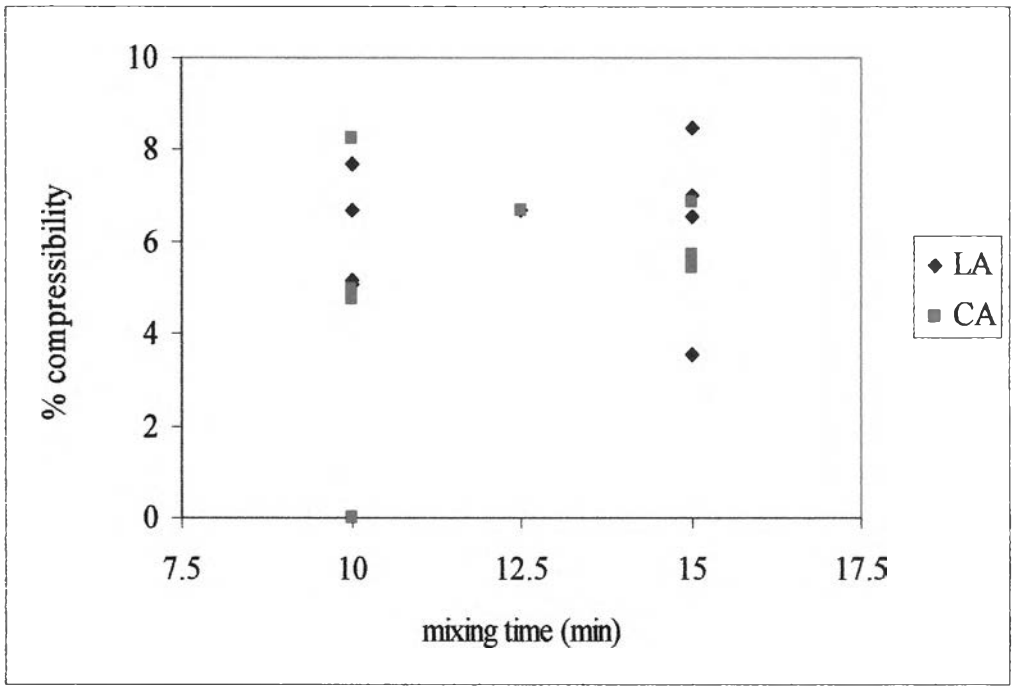


Figure 63 Effect of mixing time on the compressibility index of DS-GMS pellets

The effect of binders as presented in Figures 64 – 65, the maximum value of compressibility index of 7.55 % belonged to GL pellets. The minimum value of compressibility index 0.000 belonged to TS pellets. This result indicated TS pellets were rounder than the others. The effect of melting point and viscosity were not clearly shown.

In general, the effect of process and formulation variables on the flowability of pellets could not be established. All pellets produced in this study possessed good flowability.

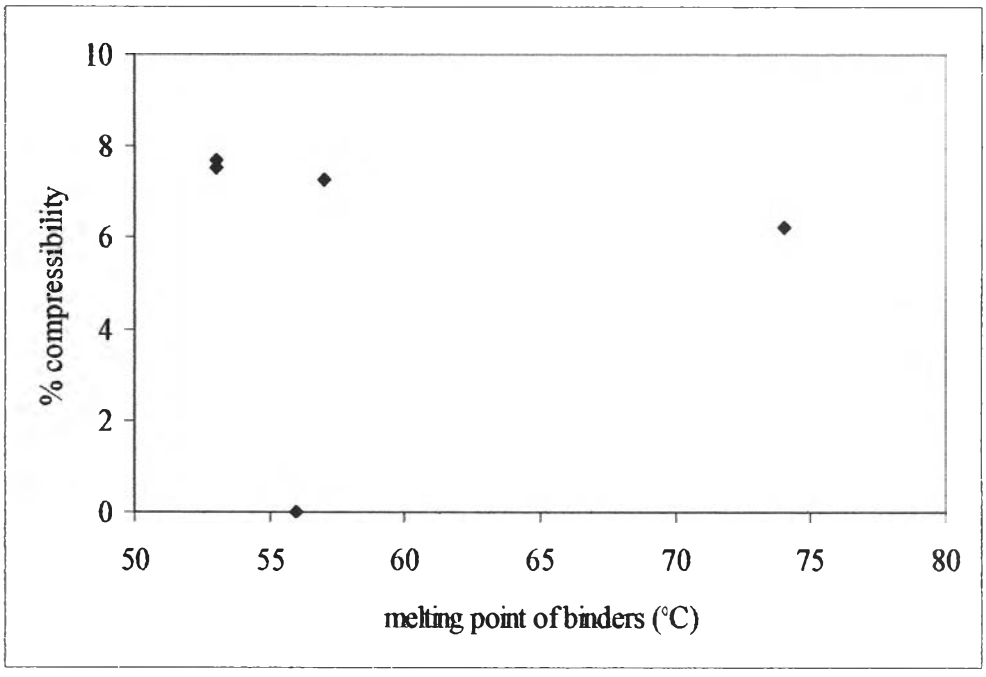


Figure 64 Effect of the melting point of binders on the compressibility index of DS-lactose pellets

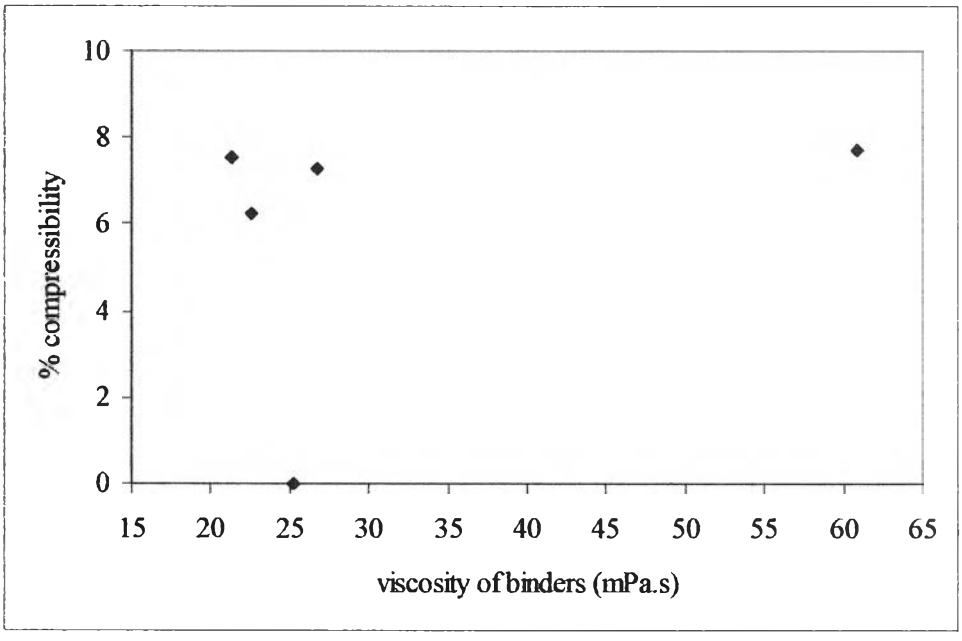


Figure 65 Effect of viscosity of binders, at 5°C above the melting point of binder on the compressibility index of DS-lactose pellets

3.6 True density

The true density of pellets produced from most of the formulation studied appeared to be in the range of 1.3695-1.8411 g/cm3 as shown in Table 15. In general, the true density of DS-dbcp pellets were higher than DS-lactose pellets, indicating that DS-dbcp pellets were denser than DS-lactose pellets. It might be dbcp has true density higher than lactose, i.e. 2.41 g/cm3 and 1.54 g/cm3, respectively, so pellets prepared with dbcp are denser than pellets prepared with lactose.

The maximum value of true density for DS-lactose-GMS pellets was 1.4473 g/cm^3 for LA-8 which was prepared by mixing speed of 100 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 15 min. The minimum value of true density for DS-lactose-GMS pellets was 1.4001 g/cm^3 for LA-5 which was prepared by mixing speed of 100 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 10 min. The maximum value of true density for DS-dbcp-GMS pellets was 1.8411 g/cm^3 for CA-4 which was prepared by mixing speed of 200 rpm, mixing temperature of 25°C above the melting point of GMS and mixing time of 15 min. The minimum value of true density for DS-dbcp-GMS pellets was 1.7458 g/cm^3 for CA-6 which was prepared by mixing speed of 100 rpm, mixing temperature of 5°C above the melting point of GMS and mixing time of 15 min.

At the high speed of mixing, i.e. 200 rpm, the true density of DS-dbcp-GMS formulations was relatively high. At the low speed of mixing, i.e. 100 rpm, the true density of DS-dbcp-GMS formulations was lower. This may be the effect of sufficient energy input of 200 rpm speed which higher power input than 100 rpm, so pellets more densification in accordance with previous work (Schæfer et al., 1992a). They found that the higher power input at a higher impeller speed gives rise to a higher densification and consequently, to a lower porosity. This effect is shown in Figure 66. However, the results for the true density of DS-lactose-GMS pellets were opposite.

Table 15 The true density, % friability, aspect ratio and roundness of DS pellets prepared from each formulation. (mean (SD))

Formulation	True density (g/ml^3) (n=5)	% friability (n=3)	Aspect ratio (n=100)	Roundness (n=100)
LA-1	1.4001 (0.0021)	0.60 (0.01)	1.316 (0.212)	2.94 (1.58)
LA-2	1.3919 (0.0020)	0.40 (0.01)	1.283 (0.153)	3.26 (2.04)
LA-3	1.4085 (0.0009)	0.60 (0.01)	1.271 (0.167)	3.01 (1.58)
LA-4	1.4012 (0.0017)	0.40 (0.01)	1.261 (0.151)	2.25 (1.01)
LA-5	1.3830 (0.0015)	0.60 (0.01)	1.288 (0.237)	2.34 (1.10)
LA-6	1.3970 (0.0027)	0.04 (0.01)	1.244 (0.146)	2.26 (1.10)
LA-7	1.4462 (0.0035)	2.00 (0.01)	1.247 (0.161)	2.35 (1.32)
LA-8	1.4473 (0.0025)	1.80 (0.01)	1.232 (0.139)	2.43 (1.30)
LA-9	1.4092 (0.0029)	2.20 (0.01)	1.226 (0.130)	2.43 (0.95)
CA-1	1.7582 (0.0033)	0.60 (0.01)	1.145 (0.053)	1.39 (0.21)
CA-2	1.7884 (0.0068)	0.60 (0.01)	1.210 (0.131)	2.13 (1.56)
CA-3	1.7809 (0.0024)	0.40 (0.01)	1.185 (1.113)	1.43 (0.24)
CA-4	1.8411 (0.0027)	0.60 (0.01)	1.153 (0.083)	1.41 (0.30)
CA-5	1.7768 (0.0022)	0.60 (0.01)	1.194 (0.098)	1.51 (0.30)
CA-6	1.7458 (0.0041)	0.00 (0.01)	1.176 (0.099)	1.47 (0.29)
CA-7	1.7882 (0.0022)	0.60 (0.01)	1.164 (0.102)	1.51 (0.34)
CA-8	1.7950 (0.0027)	0.60 (0.01)	1.175 (0.102)	1.47 (0.30)
CA-9	1.7670 (0.0014)	0.40 (0.01)	1.217 (0.547)	2.24 (0.87)
PR	1.3781 (0.0009)	0.60 (0.01)	1.314 (0.174)	3.52 (2.29)
CP	1.3595 (0.0013)	0.80 (0.01)	1.383 (0.198)	4.02 (2.69)
GL	1.4017 (0.0044)	1.00 (0.01)	1.268 (0.155)	2.60 (1.28)
TS	1.3695 (0.0022)	0.80 (0.01)	1.177 (0.085)	2.77 (1.32)

n = number of determinations

The effect of mixing temperature is shown in Figure 67. The DS-lactose-GMS pellets and DS-dbcp-GMS pellets were of lower true density at low mixing temperature, 5°C above the melting point of GMS and relatively high true density at high mixing temperature. The results indicated pellets became denser when using high mixing temperature, 25°C above the melting point of GMS. Here, molten GMS might completely surround the granule, it could be incoperated into the agglomerate and then pellets were densified.

The effect of mixing time is shown in Figure 68. Among DS-lactose-GMS pellets and DS-dbcp-GMS pellets, the graphical results did not show markedly difference. It might be narrow range of mixing time in this study, so this effect was not clear.

The results for different binders showed that the maximum value of true density was GL pellets, 1.4017 g/cm^3. The minimum value of true density was CP pellets, 1.3595 g/cm^3. Figure 69 showed that a higher melting point of binder, i.e. 74°C for Compritol® ATO 888 gave rise to low true density. The viscosity was not clearly shown in Figure 70, possibly because the viscosities of the binders used were in the same range and none of markedly high viscosity of binder was used in this study.

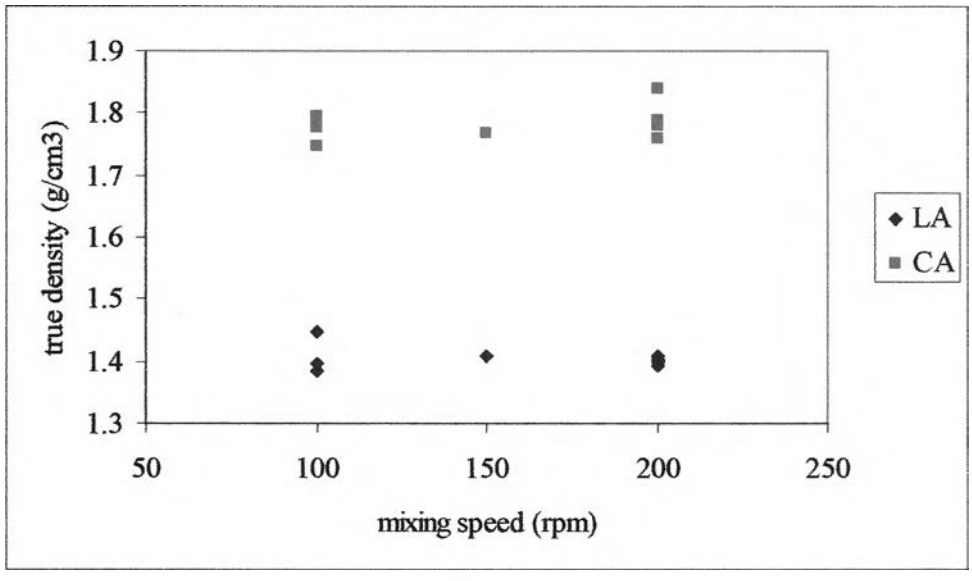


Figure 66 Effect of mixing speed on the true density of DS-GMS pellets

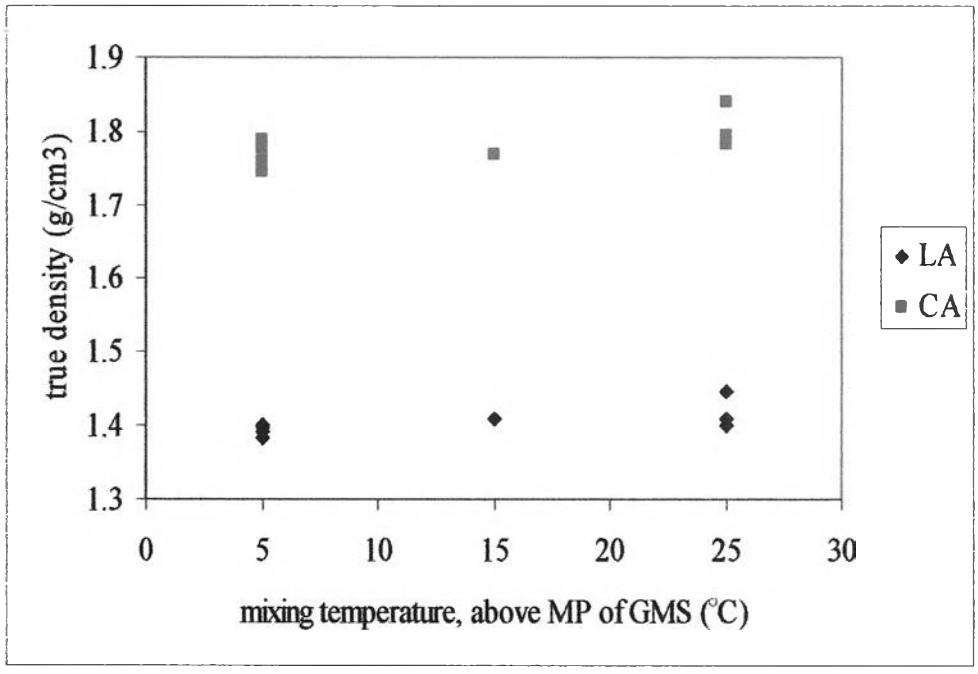


Figure 67 Effect of mixing temperature on the true density of DS-GMS pellets

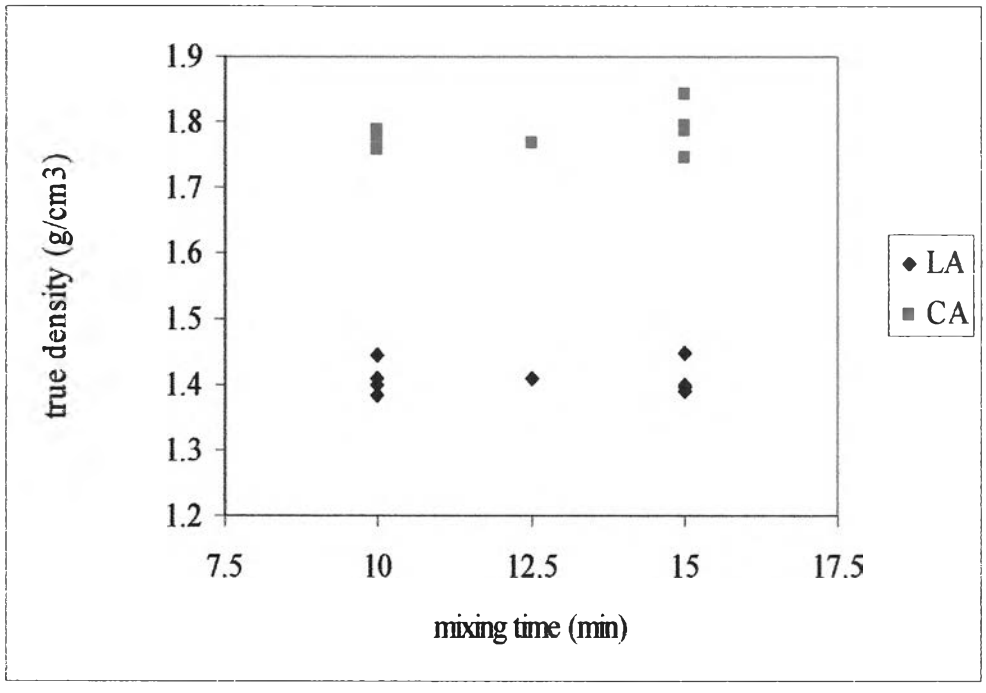


Figure 68 Effect of mixing time on the true density of DS-GMS pellets

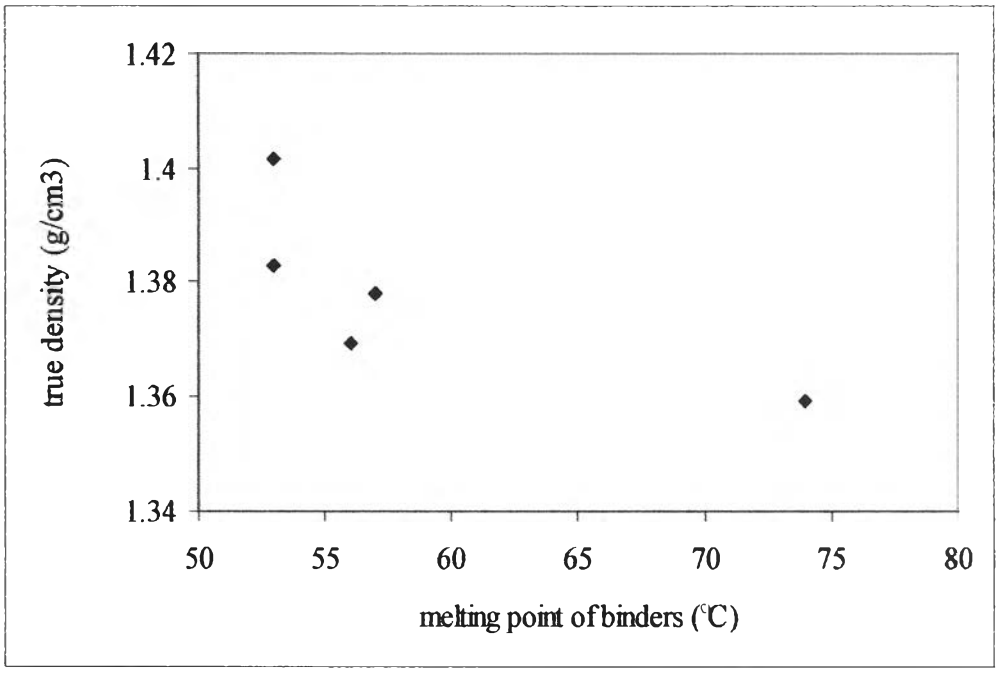


Figure 69 Effect of the melting point of binders on the true density of DS-lactose pellets

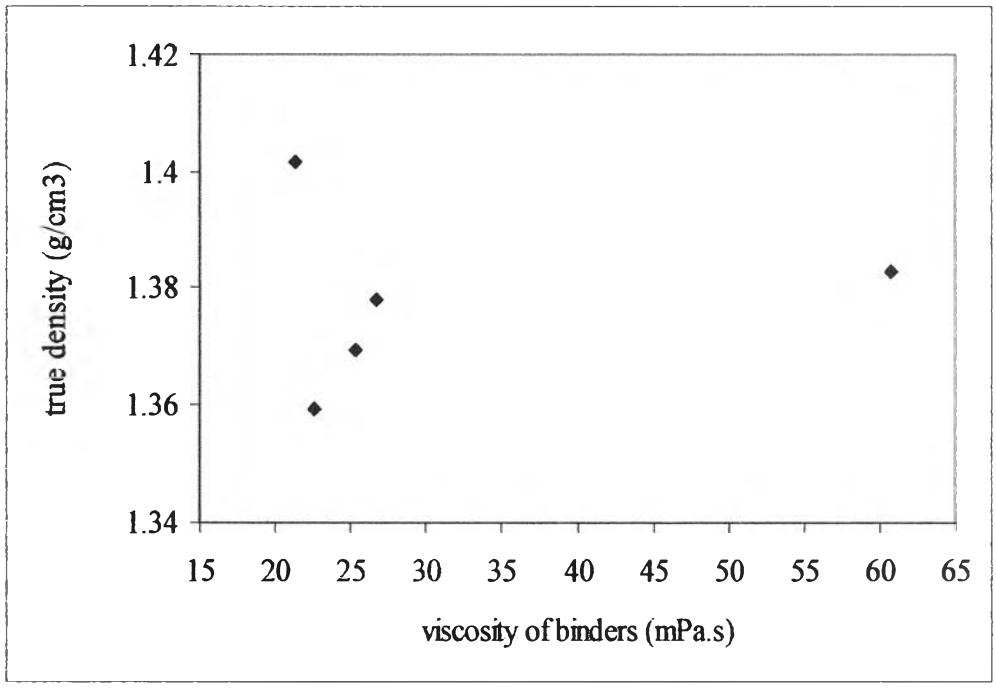


Figure 70 Effect of viscosity of binders, at 5°C above the melting point of binder on the true density of DS-lactose pellets

3.7 Percent Friability

Percent friability of DS pellets with various condition is shown in Table 15. In general, percent friability varied between 0 - 2.2%. The maximum value of percent friability for DS-lactose-GMS lactose was 2.20 for LA-9 which was prepared by mixing speed of 150 rpm, mixing temperature of 15°C above the melting point of GMS and mixing time of 12.5 min. The minimum value of percent friability for DS-lactose-GMS pellets was 0.4 for LA-2, LA-4 and LA-6 which were prepared by mixing time of 15 min. It was likely that longer mixing time gave denser DS-lactose-GMS pellets. However, this effect was not clear for DS-dbcp-GMS pellet because the maximum value of 0.06 percent friability was obtained for CA-1, CA-2, CA-4, CA-5, CA-7 and CA-8 formulations which were prepared with both long and short mixing time. The minimum value of percent friability was 0.00 for CA-6 which was prepared by mixing speed of 100 rpm, mixing temperature of 5°C above melting point of GMS and mixing time of 15 min. The result indicated DS-lactose pellets exhibited friable. It could be observed that there was no noticeable effect from types of filler. Furthermore, the percent friability was unclearly related to the types of binder.

3.8 Sphericity of pellets

In this study, degree of sphericity was derived from two parameters, i.e. aspect ratio and roundness, which based on two dimensional image of the particle. Image analysis was used to obtain these parameters and the results from various formulations were presented in Table 15. The data showed that degree of sphericity in terms of aspect ratio and roundness. The values of aspect ratio and roundness closer to 1 means the more sphericity. The aspect ratio and roundness values of DS-dbcp pellets were lower than DS-lactose pellets, so DS-dbcp pellets possessed more sphericity than DS-lactose pellets. Among DS-lactose-GMS pellets and DS-lactose-other binders pellets, different rank of sphericity parameters were found. The rank of the value of aspect ratio of pellets were as : CP > PR > LA-5 > GL > TS. The rank of the value of roundness of pellets were as : CP > PR > TS > GL > LA-5. However, this reflects that CP and PR pellets were of less sphericity.

At the high speed of mixing, i.e. 200 rpm, the aspect ratio and roundness of DS-lactose-GMS formulations was relatively high. At the low speed of mixing, i.e. 100 rpm, the aspect ratio of DS-lactose-GMS formulations was lower. In contrast to previous experiments (Schæfer et al.,1992a ; Schæfer et al., 1993), they found that the pellets were found to be more rounded and smoother at a higher impeller speed. However, the effect of mixing speed on the aspect ratio of DS-dbcp-GMS pellets could not be established as shown in Figures 71 - 72.

The effect of mixing temperature is shown in Figures 73 – 74. The DS-lactose-GMS pellets and DS-dbcp-GMS pellets were of lower aspect ratio at high mixing temperature, 25°C above the melting point of GMS and hence lower viscosity. Schæfer and Mathiesen (1996a) found that the surface plasticity of the agglomerates becomes lower at a higher viscosity of binder, and this results in agglomerates of an irregular shape. If the binder viscosity is too low, however, the deformability of the agglomerates becomes so high. However, the value of roundness of DS-lactose-GMS pellets and DS-dbcp-GMS lactose were not clearly corresponding to the above mentioned.

The effect of mixing time is shown in Figures 75 - 76. The DS-lactose-GMS pellets formulation was of lower aspect ratio at high mixing time, 15 min, and high aspect ratio at low mixing time, 10 min. This result in accordance with Schæfer et al. (1992b), they found that an increased mixing time gave rise to agglomerates which were rounder and smoother. However, the results for the aspect ratio of DS-dbcp-GMS pellets were opposite. The effect of mixing time on the value of roundness of DS-lactose-GMS pellets and DS-dbcp-GMS lactose were not clearly shown.

Regarding the effect of binders, as shown in Figures 77 – 80, Figures 77 - 78 showed that a higher melting point of binder, i.e. 74°C for Compritol® ATO 888 gave rise to low sphericity, i.e. high values of aspect ratio and roundness. However, Figures 79 - 80 showed that viscosity did not have significant effect on aspect ratio, probably the range of viscosity of binders used in this study was not varied widely and considerably low for all binder as compared with viscosity of binders used by other works (Schæfer and Mathisen, 1996a).

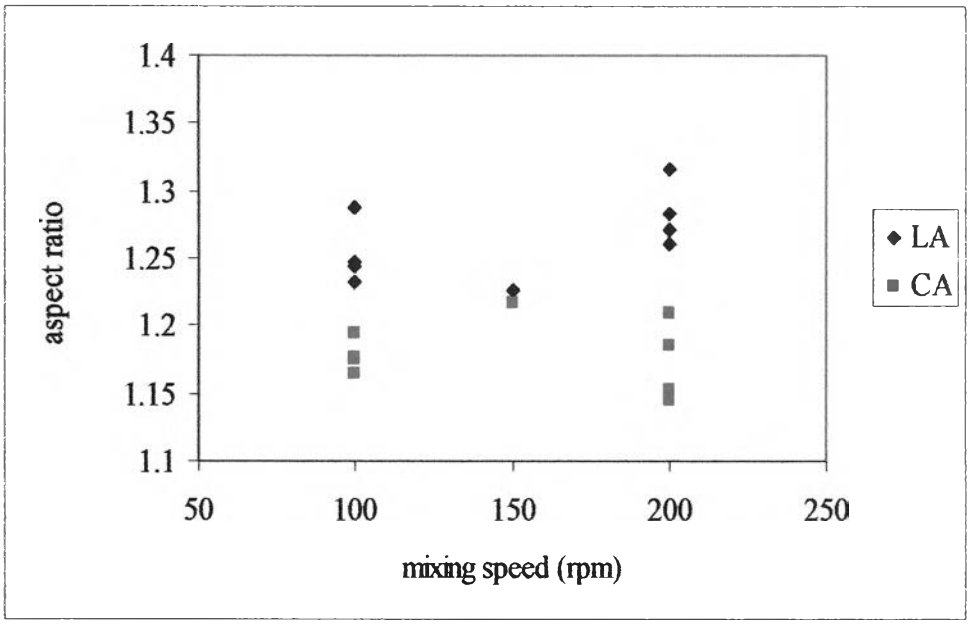


Figure 71 Effect of mixing speed on the aspect ratio of DS-GMS pellets

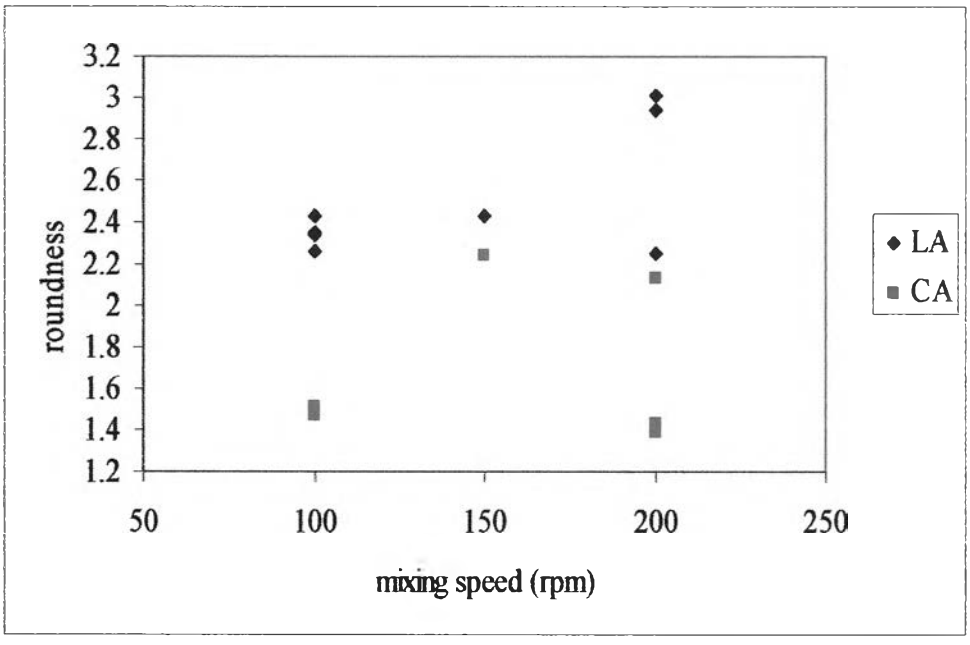


Figure 72 Effect of mixing speed on the roundness of DS-GMS pellets

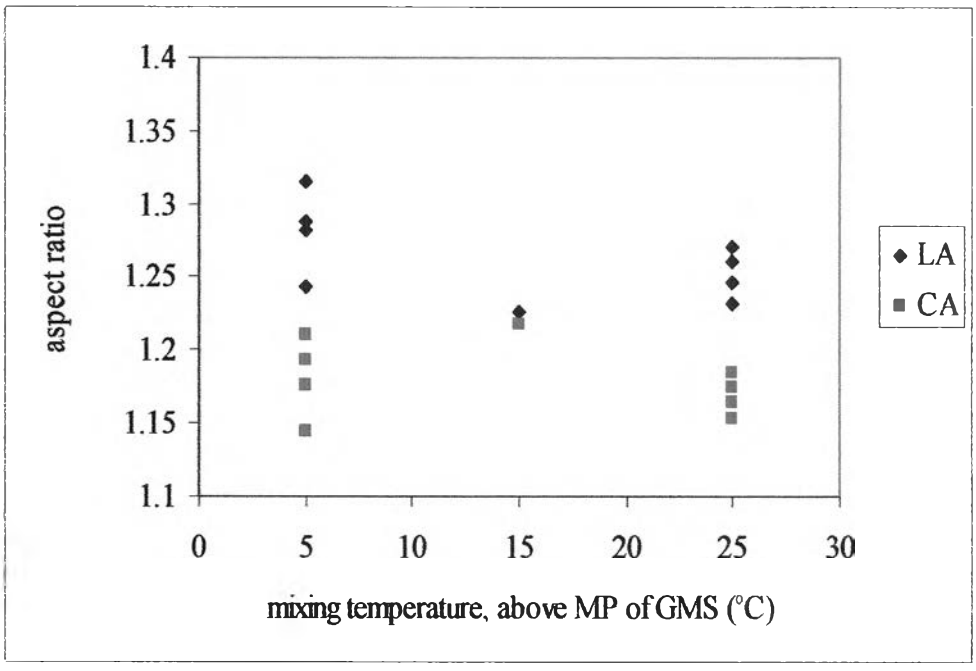


Figure 73 Effect of mixing temperature on the aspect ratio of DS-GMS pellets

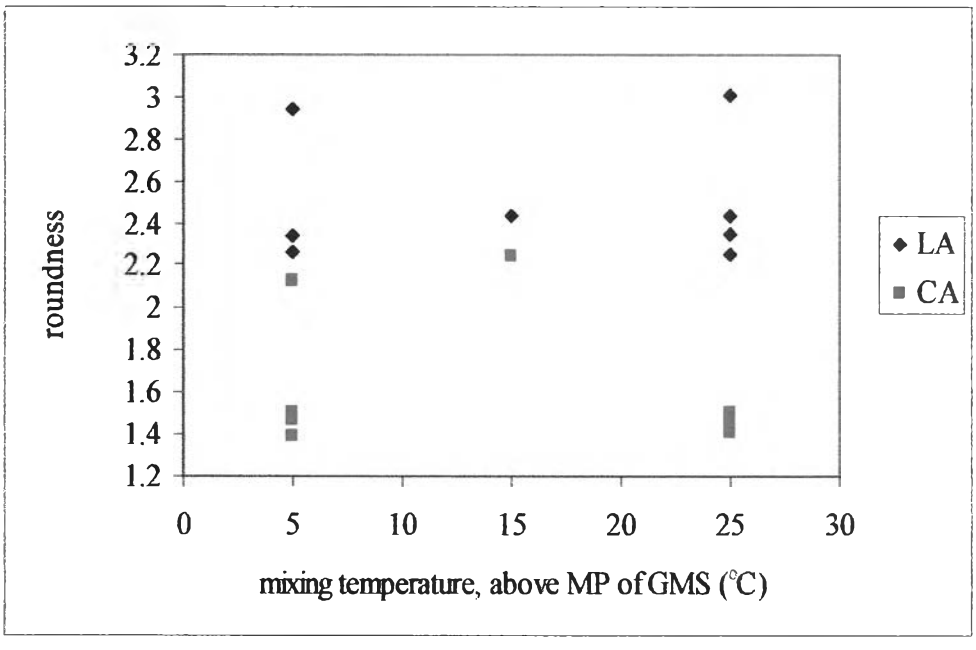


Figure 74 Effect of mixing temperature on the roundness of DS-GMS pellets

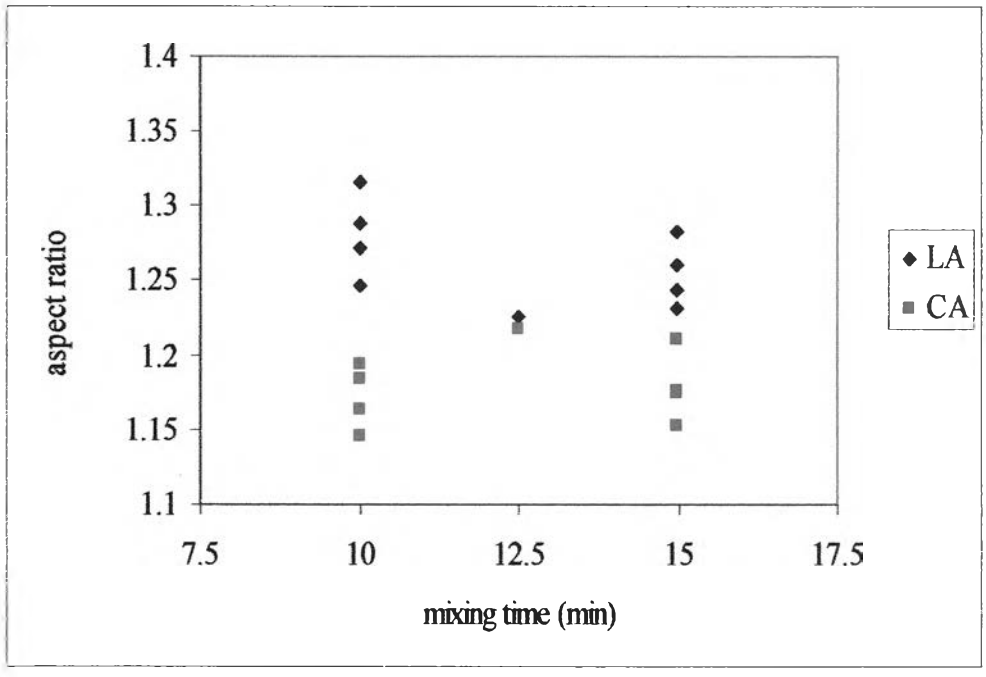


Figure 75 Effect of mixing time on the aspect ratio of DS-GMS pellets

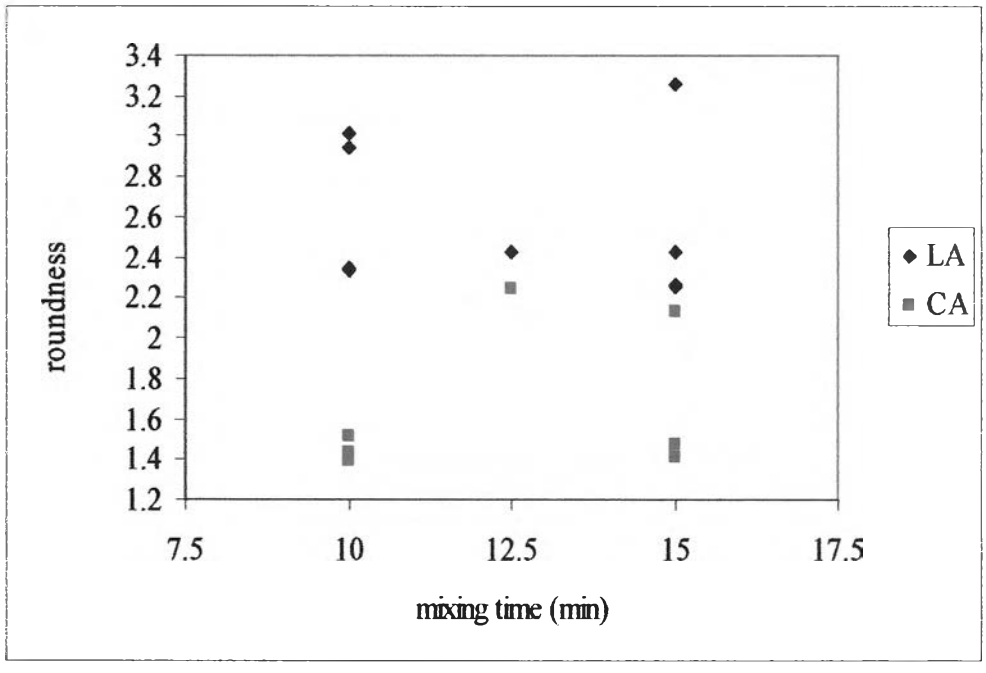


Figure 76 Effect of mixing time on the roundness of DS-GMS pellets

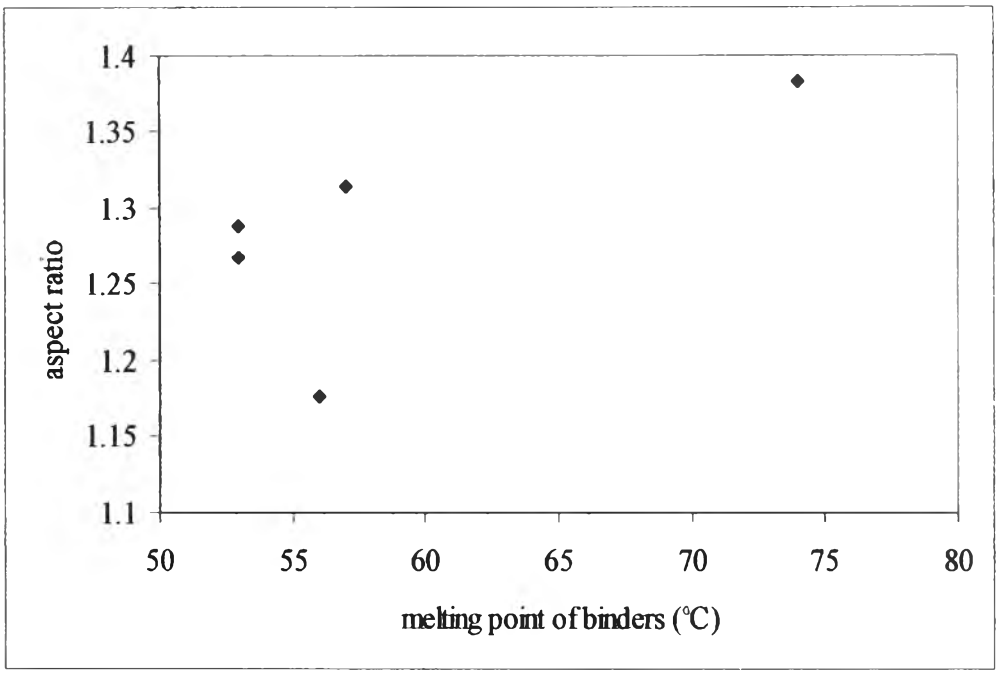


Figure 77 Effect of the melting point of binders on the aspect ratio of DS-lactose pellets

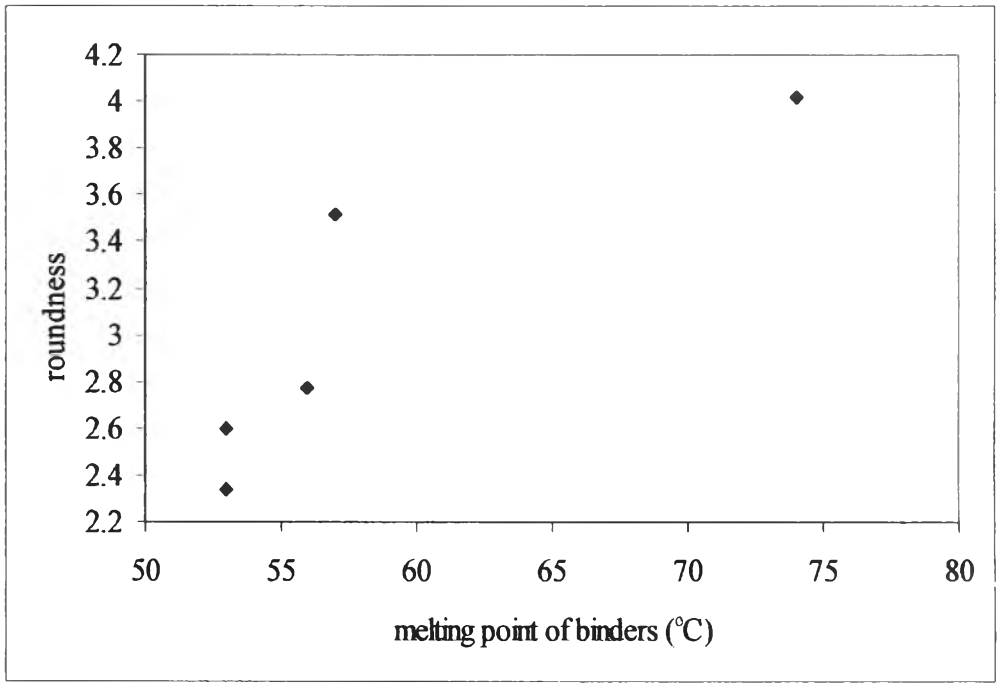


Figure 78 Effect of the melting point of binders on the roundness of DS-lactose pellets

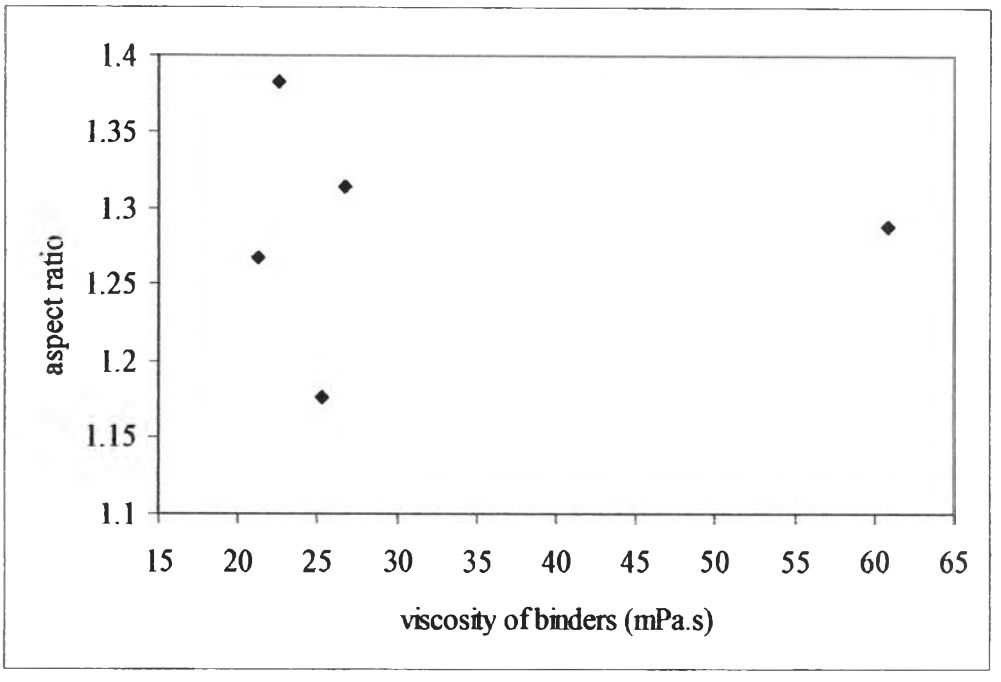


Figure 79 Effect of viscosity of binders, at 5°C above the melting point of binder on the aspect ratio of DS-lactose pellets

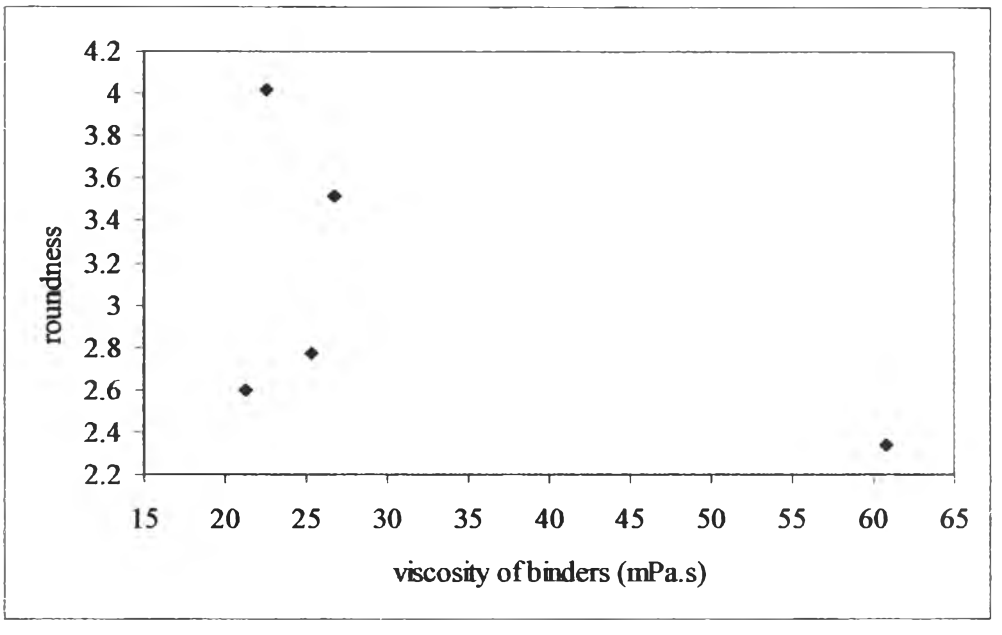


Figure 80 Effect of viscosity of binders, at 5°C above the melting point of binder on the roundness of DS-lactose pellets

3.9 The X-ray diffraction

The X- ray diffraction pattern of DS, diclofenac related compound A and DS pellets, which were produced from various conditions, are illustrated in Figures 81 – 83. The X-ray diffraction patterns of DS alone showed characteristic peaks at 6.7°, 8.6°, 15.3°, 17.3°, 20.0°, 23°, 28.0° and small peaks at the diffraction angle between 15-30°. The X-ray diffraction patterns of diclofenac related compound A showed characteristic peaks at 13.7°, 24.6°, 25.6°, 26.4°.

The eminent diffraction peaks of lactose were shown at 12.5°, 16.4°, 19.1°, 19.5°, 19.9°, 20.9°, 21.2°, 22.8°, 23.8°, 25.7° and 26.2° as presented in Figure 81. The eminent diffraction peaks of dbcp were shown at 11.7°, 21.1°, 29.4° as presented in Figure 82. The eminent diffraction peaks of GMS were shown at 19.5°, 22.9° and 23.6° as presented in Figures 81 – 82. The eminent diffraction peaks of Precirol® ATO5, Compritol 888 ATO®, Gelucire50/02 and Tristearin® were shown at 21.6° ; 21.4°, 23.4° ; 19.3°, 20.6°, 21.2°, 23.5° and 19.3°, 21.3°, respectively as presented in Figure 83.

From Figures 81 – 83, the eminent diffraction peaks of all formulations did not show peaks for DS. It might be that the amount of diclofenac sodium in all formulation was little compared with the amounts of lactose or dbcp, so the eminent diffraction peaks of lactose or dbcp dominated DS's. In addition, peaks of diclofenac related compound A did not appear in all X-ray diffraction patterns for all DS pellets.

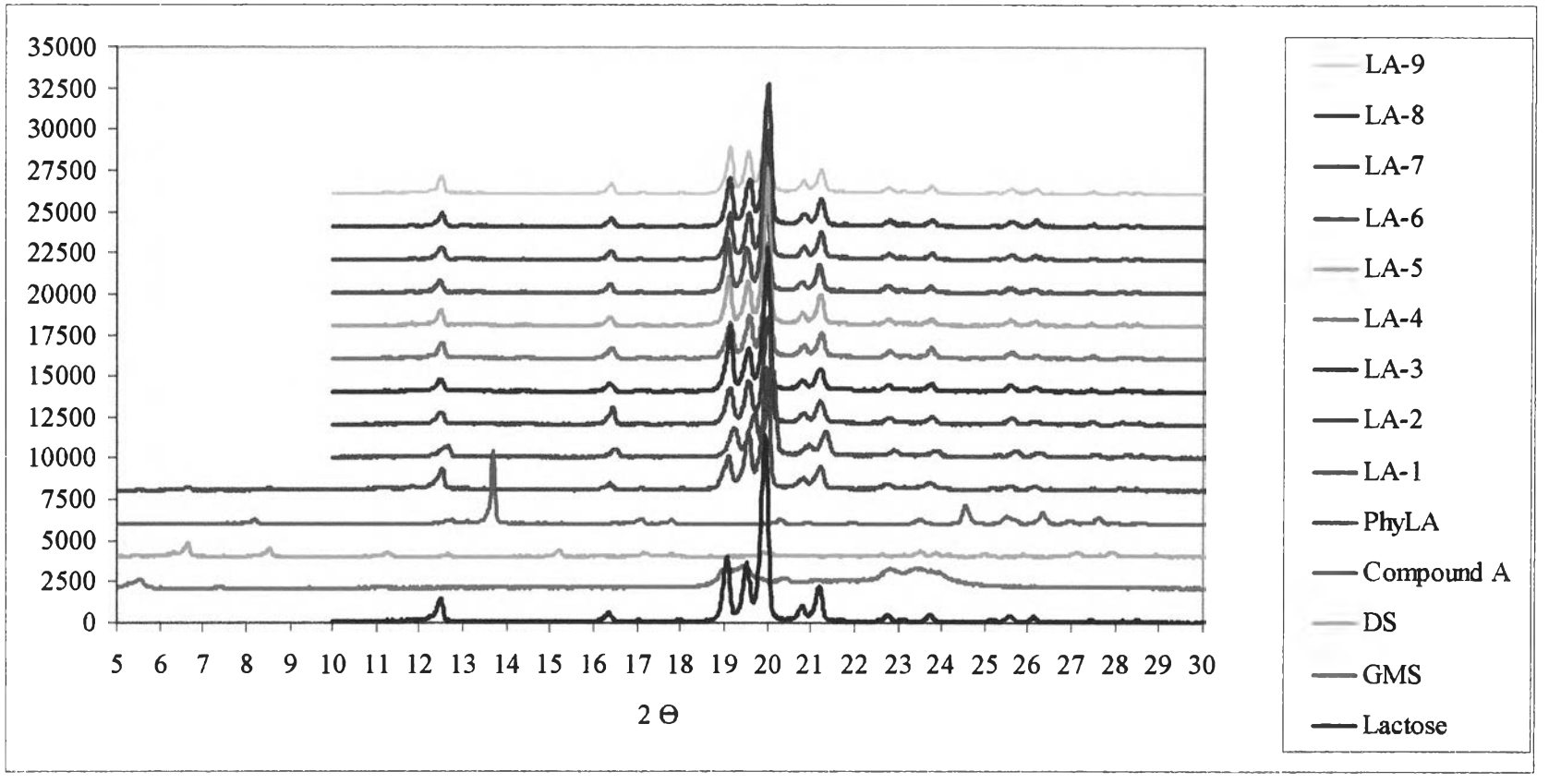


Figure 81 The X-ray diffraction pattern of DS-lactose-GMS pellets

GMS = glyceryl monostearate, DS = diclofenac sodium, Compound A = diclofenac related compound A

phyLA = physical mixture of lactose formulation, LA = lactose formulation studied

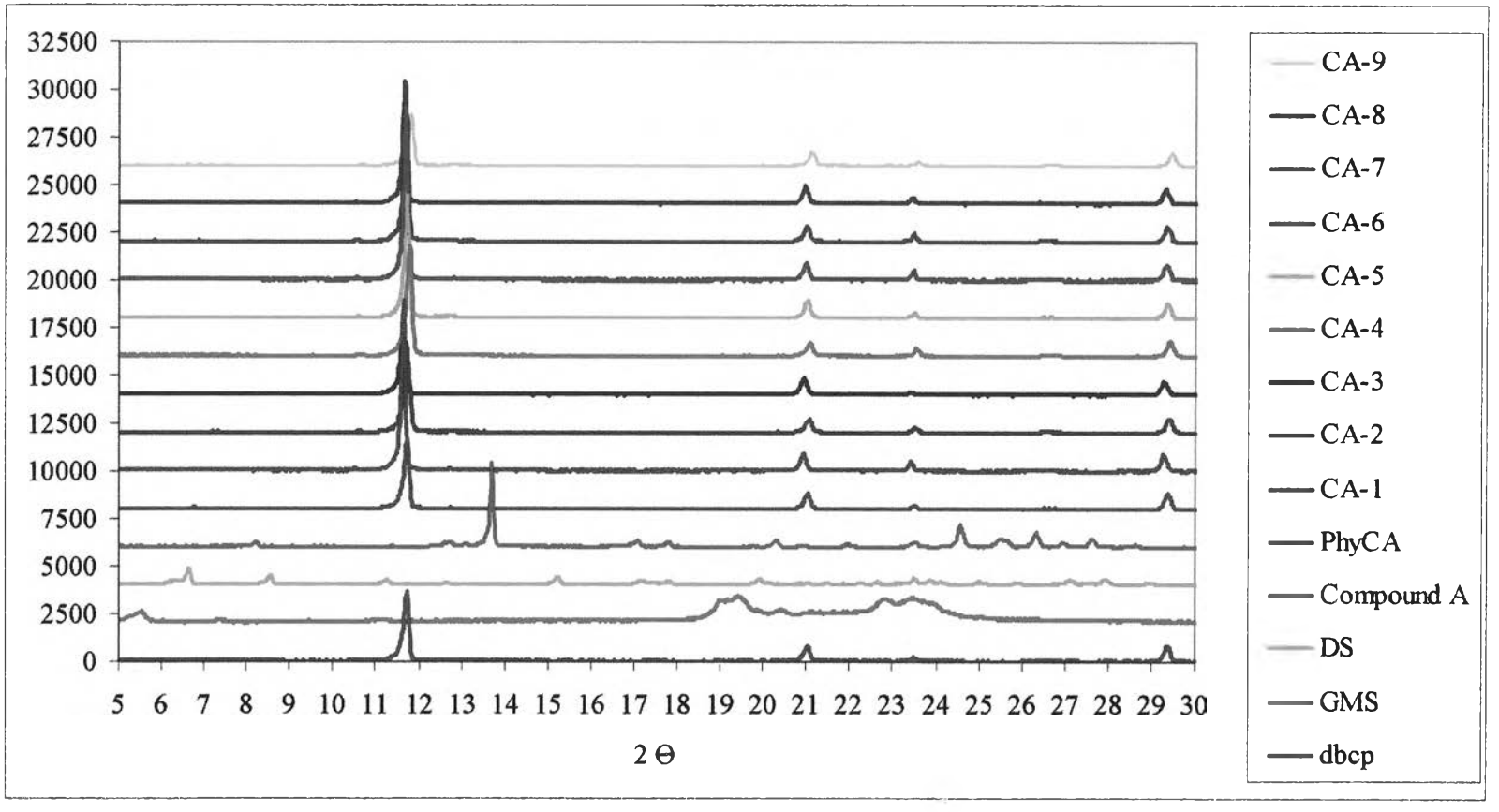
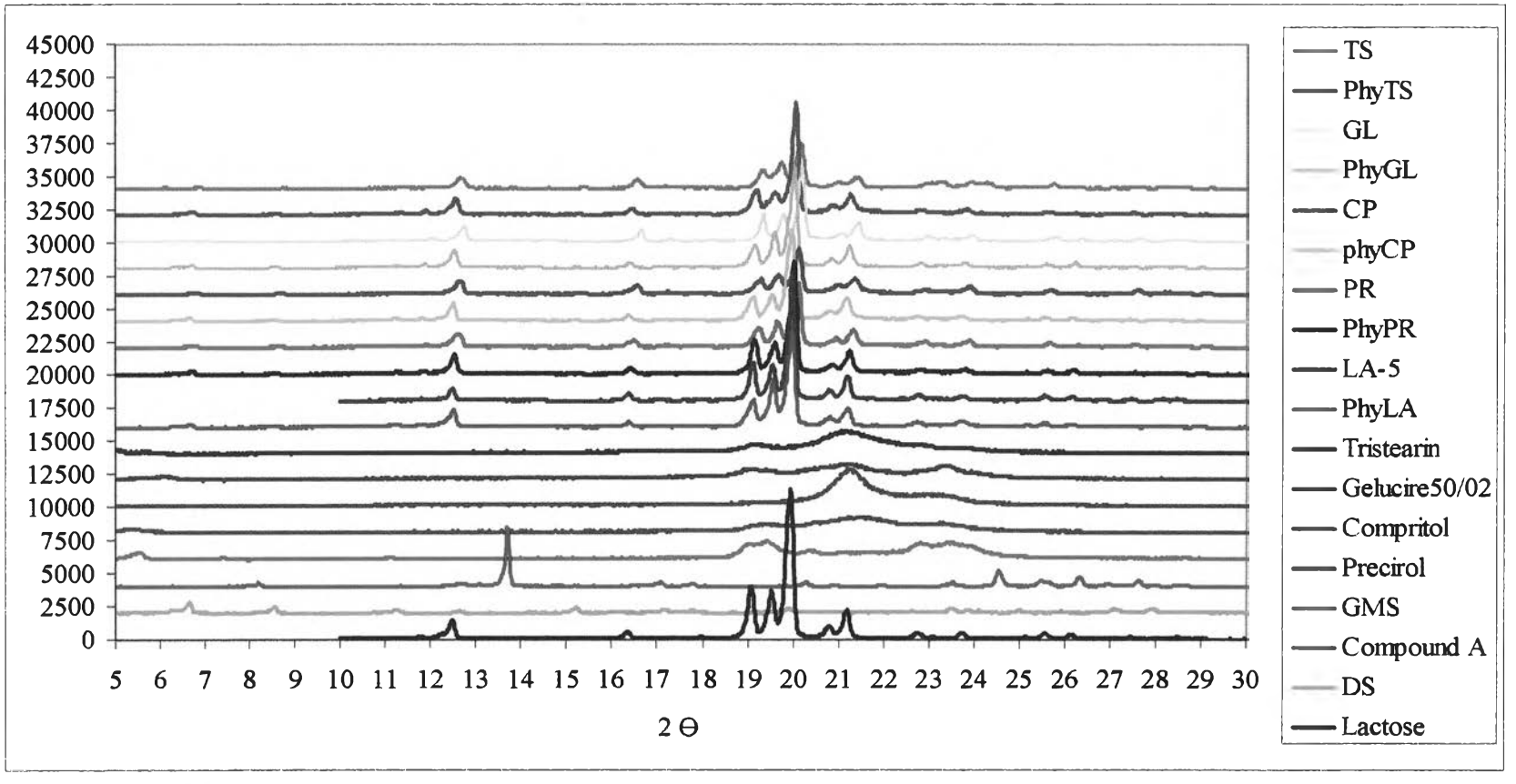


Figure 82 The X-ray diffraction pattern of DS-dbcp-GMS pellets

dbcp = dibasic calcium phosphate, GMS = glyceryl monostearate, DS = diclofenac sodium, Compound A = diclofenac related compound A, phyCA = physical mixture of dibasic calcium phosphate formulation, CA = dibasic calcium phosphate formulation studied



Figur 83 The X-ray diffraction pattern of DS pellet containing other binders

DS = diclofenac sodium, Compound A = diclofenac related compound A, GMS = glyceryl monostearate

phy = physical mixture of binder formulation, LA = lactose formulation studied, PR = Precirol formulation studied

CP = Compritol formulation studied, GL = Gelucire 50/02 formulation studied, TS = Tristearin formulation studied

3.10 The IR spectroscopy

The IR spectrum of DS is illustrated in Figure 84. The principle peaks were observed at wave numbers of 746, 1280, 1398, 1452, 1572, 3244 and 3378 cm^{-1}. The peak at 746 cm^{-1} was resulted from C-Cl. The IR absorption band at 1280 and 1398 cm^{-1} were resulted from C-N stretching. The peaks at 1452 and 1572 cm^{-1} were resulted from C=C stretching. The peak at 3244 and 3378 cm^{-1} were resulted from N-H. (Mofflat et.al, 1986)

The IR spectrum of diclofenac related compound A is illustrated in Figure 84. The principle peaks were observed at wave number of 748, 1236, 1454, 1708 and 3396 cm^{-1}. The peak at 748 cm^{-1} was resulted from C-Cl. The IR absorption band at 1236 cm^{-1} was resulted from C-N stretching. The peak at 1454 cm^{-1} was resulted from C=C stretching. The peak at 1708 was resulted indol cyclic amide. The peak at 3396 cm^{-1} was resulted from N-H. (Mofflat et.al. 1986)

The IR spectrum of lactose is illustrated in Figure 84. The principle peaks were observed at wave number of 754, 1030, 1340, 1624, 2898, 3352 and 3522 cm^{-1}. The peak at 1030 and 1340 cm-1 were resulted from C-O. The peak at 2898 cm^{-1} was resulted from C-H. The peak at 3352 cm^{-1} was resulted from O-H.

The IR spectrum of dbcp is illustrated in Figure 84. The principle peaks were observed at wave numbers of 1644, 2338, 3250 and 3474 cm^{-1}. The peak at 3474 cm^{-1} was resulted from O-H.

The IR spectrum of glycerides (GMS, Precirol® ATO5, Compritol 888 ATO®, Gelucire50/02 and Tristearin®) are shown in Figure 85. They showed the same characteristics of IR spectra because of having the same structure bone. The C=O stretching peak was presented at 1730 cm^{-1} - 1740 cm^{-1}. The IR peaks at 2848 and 2916 cm^{-1} were resulted from aliphatic C-H stretching. There was a little difference in the position of peaks.

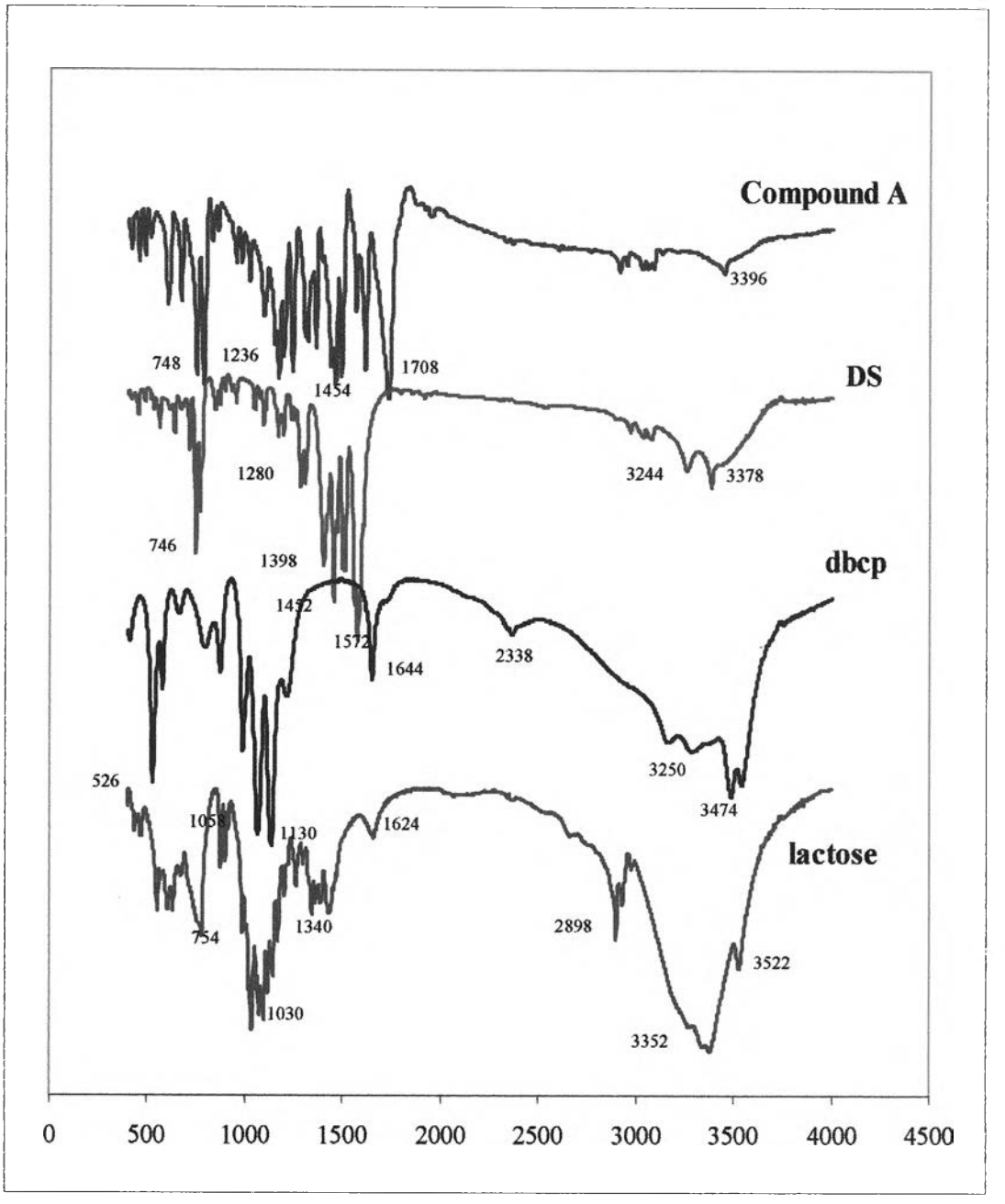


Figure 84 The IR spectrum of lactose, dbcp, diclofenac sodium and diclofenac related compound A

The principle peak of Compritol 888 ATO were observed at wave numbers of 1166, 1466, 1736, 2848 and 2918 cm^{-1}. The C-O stretching peak was presented at 1166 cm^{-1}. The aliphatic CH_2 bending is represented at 1466 cm^{-1}. The C=O stretching is represented at 1736 cm^{-1}. The IR peaks at 2848 and 2918 cm^{-1} are resulted from aliphatic CH stretching (Figure 85).

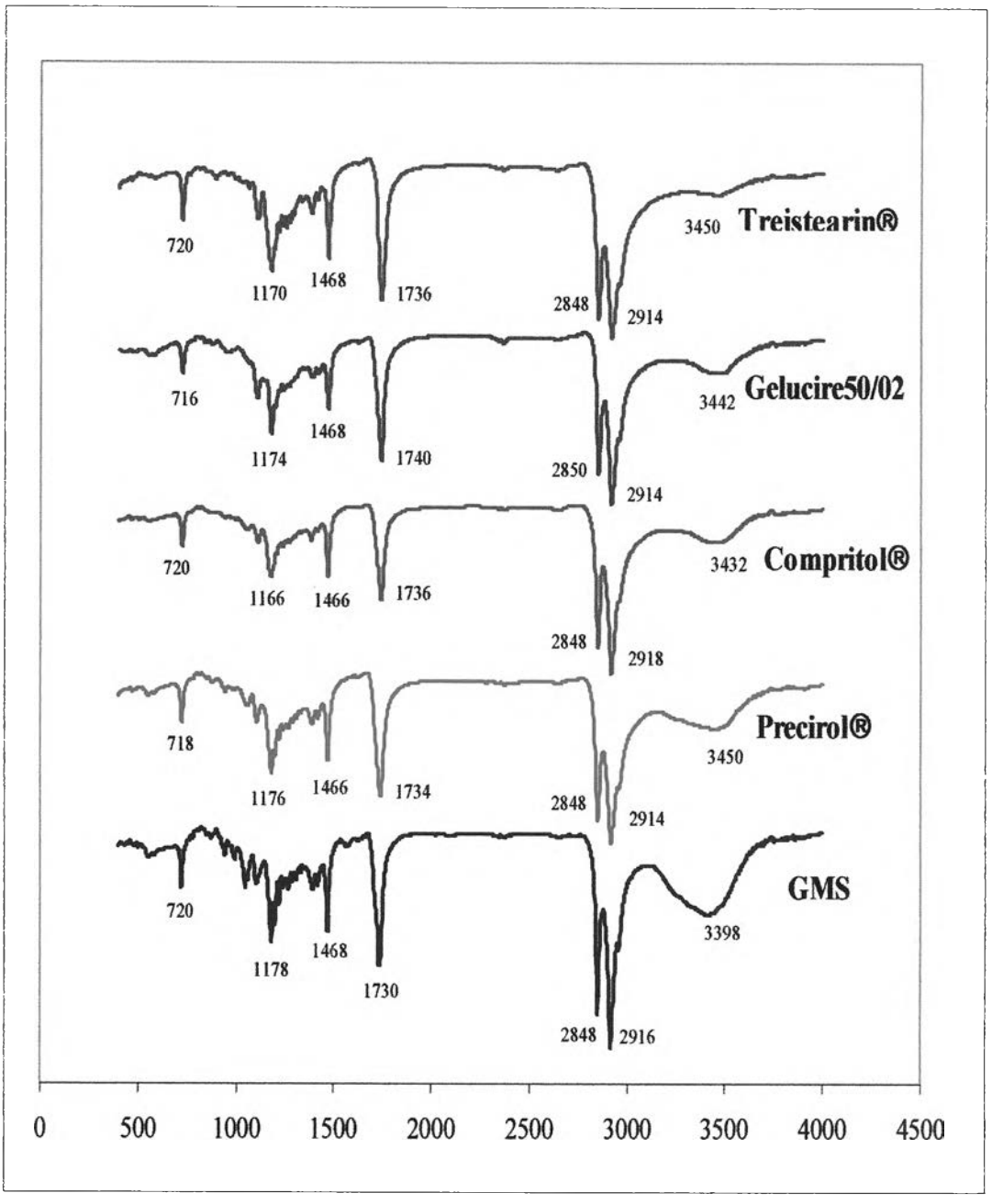


Figure 85 The IR spectrum of glyceryl monosterate (GMS), Precirol® ATO5, Compritol 888 ATO®, Gelucire50/02 and Tristearin®

The IR spectrum of DS pellets containing lactose and GMS (LA-1 to LA-9) are illustrated in Figures 86 - 87. The IR spectrum of DS-lactose-GMS pellets showed the combination of drug peak, GMS and lactose, while the principle peaks of drug, GMS and lactose were also still presented. Some position of peaks were very slightly shifted from original material. It could be concluded that interaction between drug and the melting binders were unlikely to occur and type of melting binder had no effect on the IR spectrum. If the maillard reaction is occur, the peak at 2500 cm^{-1} of N-H, aliphatic amine is found. In this result, the peak of N-H, aliphatic amine, at 2500 cm^{-1} was not presented indicating that the miallard reaction did not occur.

The IR spectrum of DS pellets contained dbcp and GMS (CA-1 to CA-9) are illustrated in Figures 88 – 89. The IR spectrum of DS pellets shown the combination of drug peak, GMS and dbcp, while the principle peaks of drug, GMS and dbcp were also still presented. Some positions of peaks were very slightly shifted from original materials too. Although, the acid-base reaction of diclofenac sodium and dibasic calcium phosphate might occur, but the peak of O-H carboxylic acid was found at 3474 cm^{-1}.

The IR spectrum of DS-other binders pellets (PR, CP, GL and TS) as illustrated in Figures 90 – 93. The IR spectrum of DS pellets prepared with different binders showed the combination of DS peaks with those of binder, whereas the characteristic peaks of both DS and binder were also still revealed. Some positions of the peaks were shifted from single material. But they had no noticeable difference.

The interaction between drug, diluents and binders was not shown in the IR characteristic bands of the physical mixture of powders. In addition, all formulations did not have the peak of diclofenac related compound A at 1078 cm^{-1}. However, it was possible that the peak of GMS and the binders found at 1730 cm^{-1} could hide its peak.

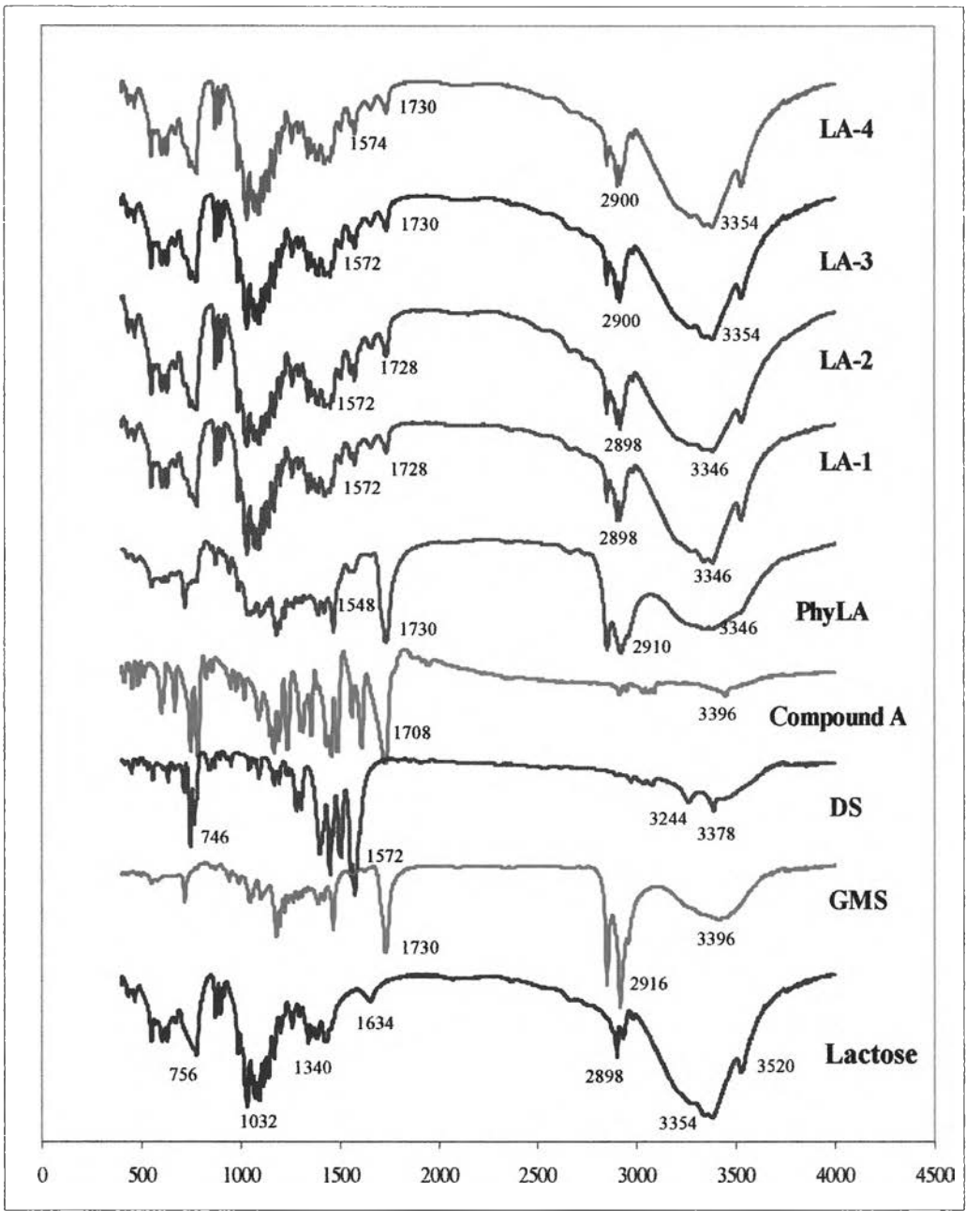


Figure 86 The IR spectrum of DS-lactose-GMS pellets for LA-1 – LA-4

GMS = glyceryl monostearate

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyLA = physical mixture of lactose formulation

LA = lactose formulations studied

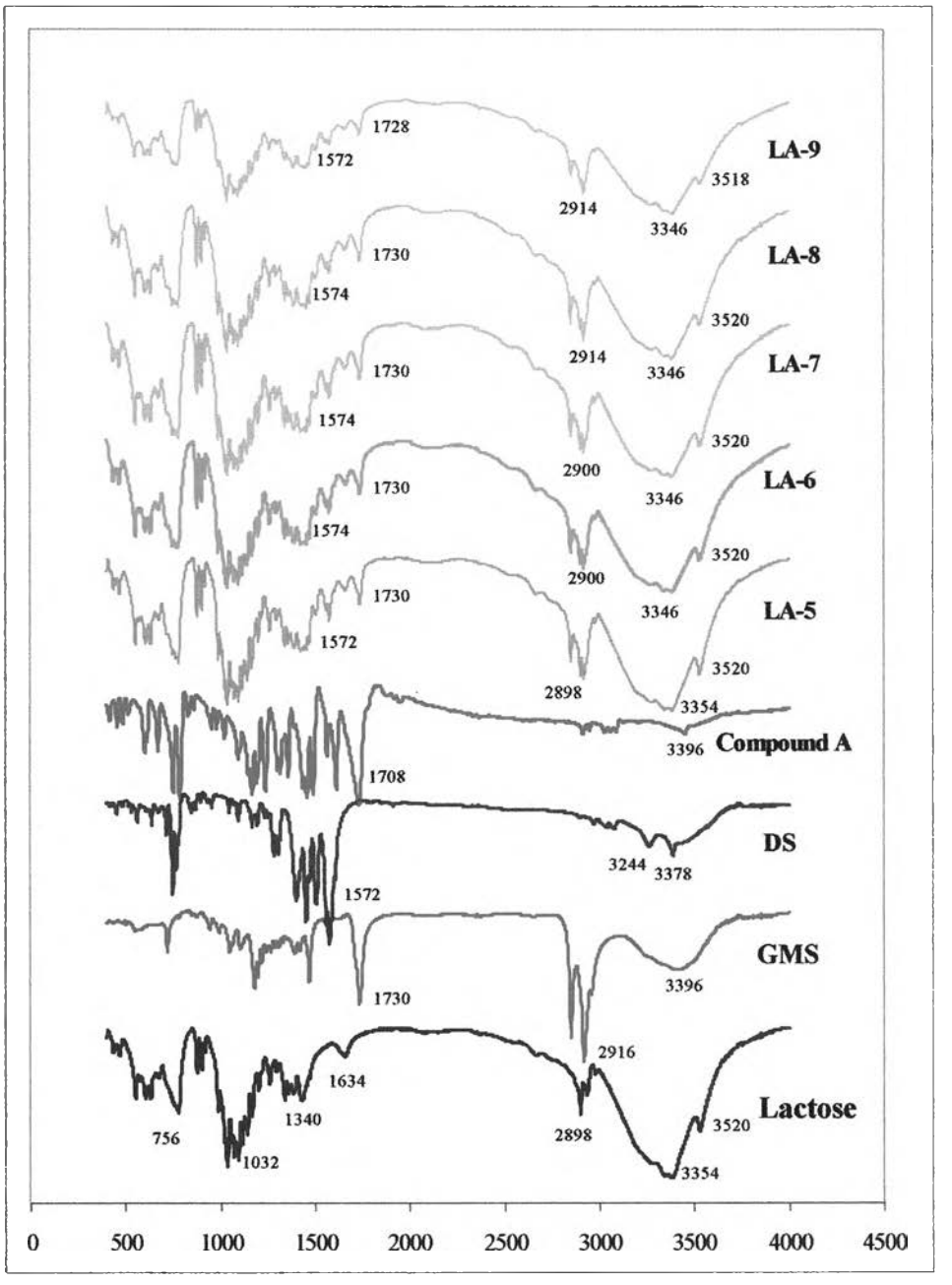


Figure 87 The IR spectrum of DS-lactose-GMS pellets for LA-5 – LA-9

GMS = glyceryl monostearate

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyLA = physical mixture of lactose formulation

LA = lactose formulations studied

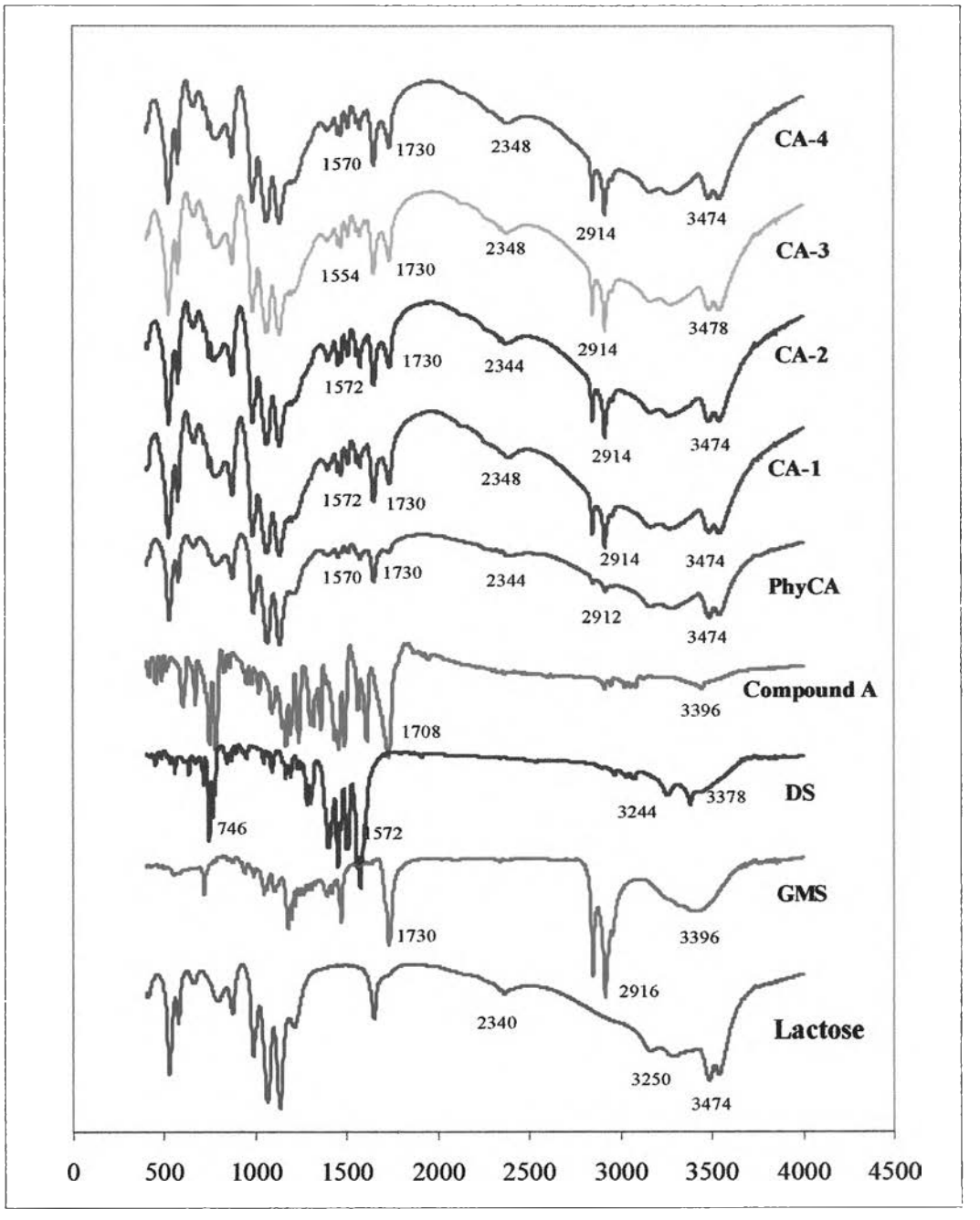


Figure 88 The IR spectrum of DS-dbcp-GMS pellets for CA-1 – CA-4

dbcp = dibasic calcium phosphate

GMS = glyceryl monostearate

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyCA = physical mixture of dibasic calcium phosphate formulation

CA = dibasic calcium phosphate formulations studied

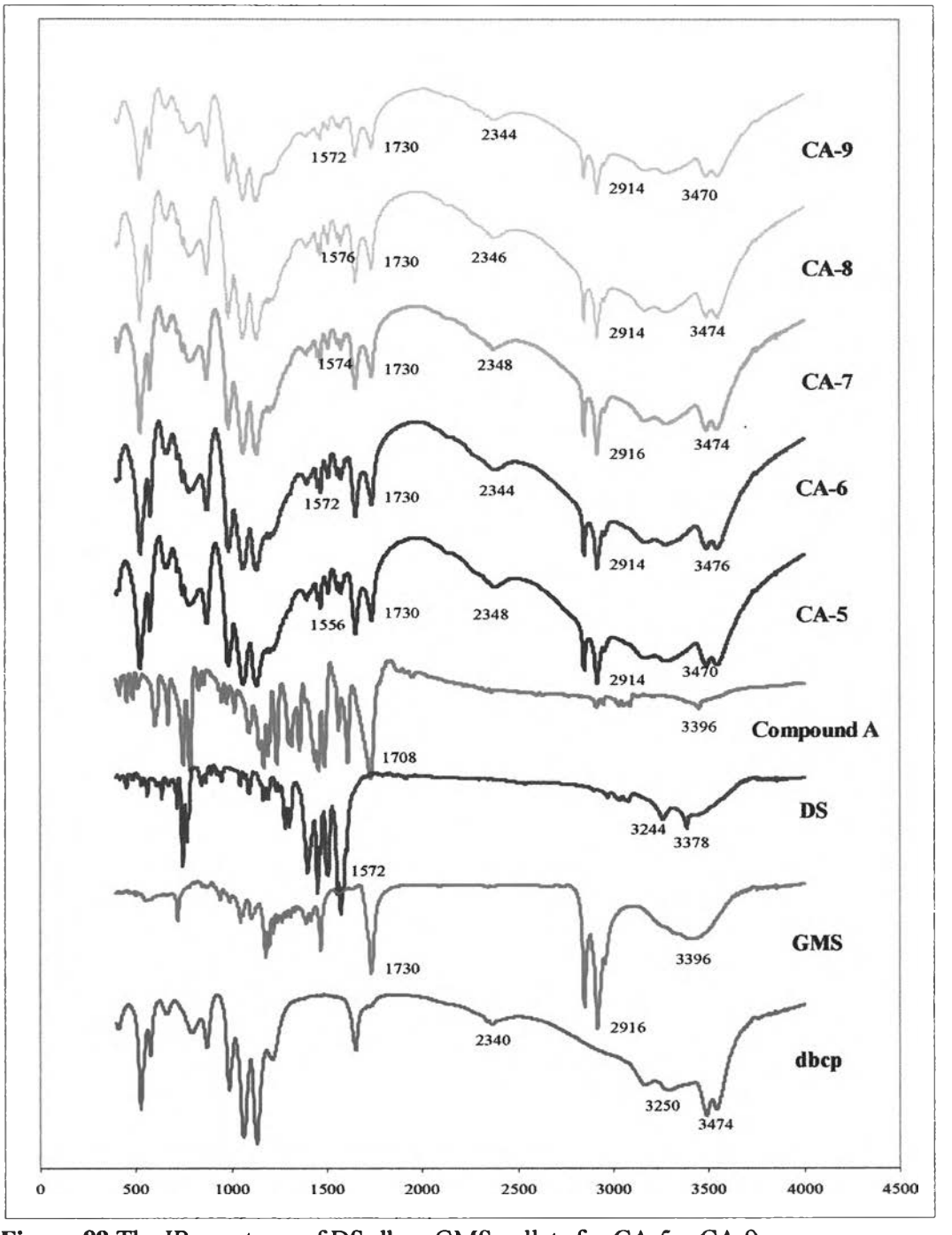


Figure 89 The IR spectrum of DS-dbcp-GMS pellets for CA-5 – CA-9

dbcp = dibasic calcium phosphate

GMS = glyceryl monostearate

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyCA = physical mixture of dibasic calcium phosphate formulation

CA = dibasic calcium phosphate formulations studied

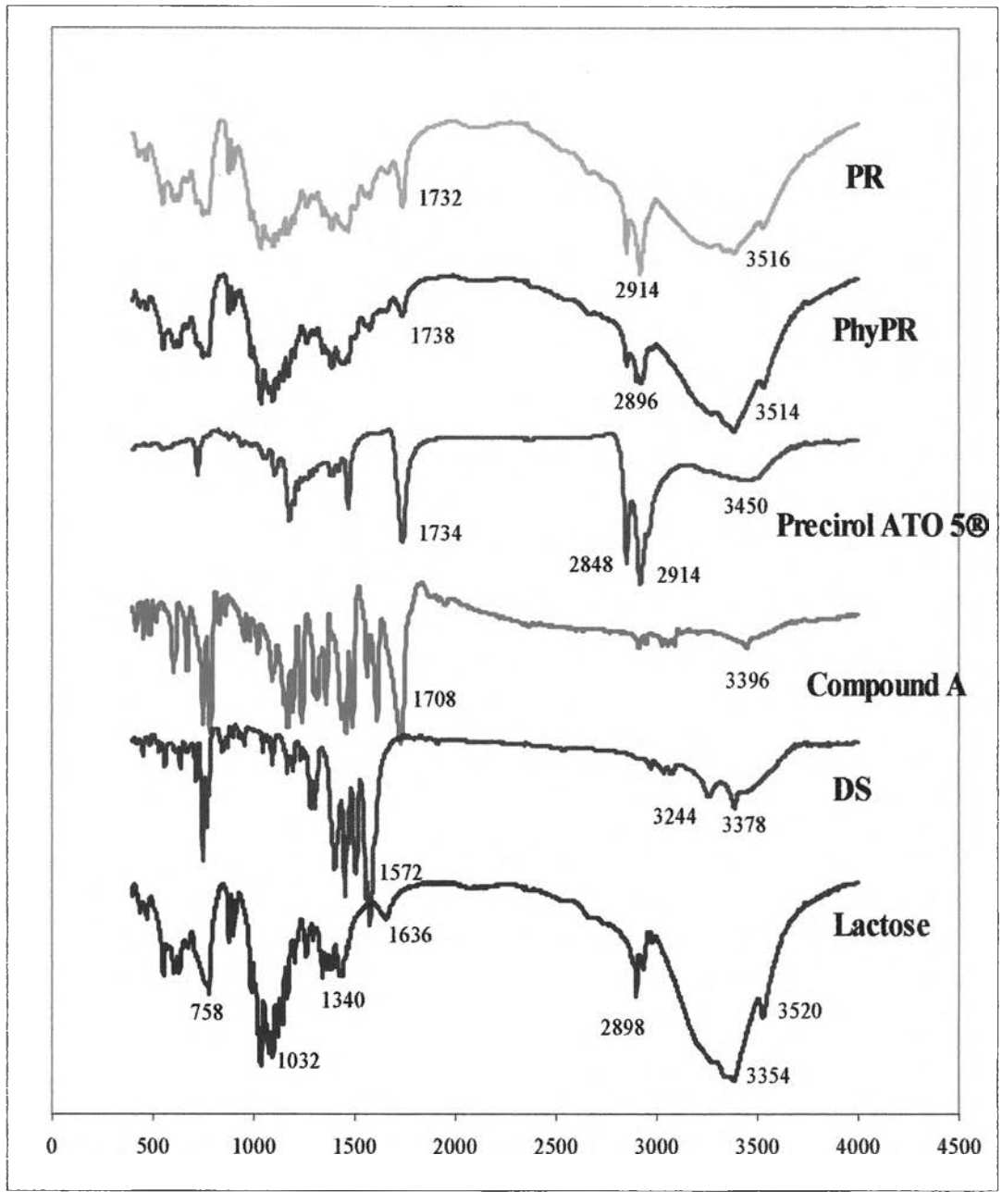


Figure 90 The IR spectrum of PR pellets

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyPR = physical mixture of Precirol® ATO5 formulation

PR = Precirol® ATO5 formulation studied

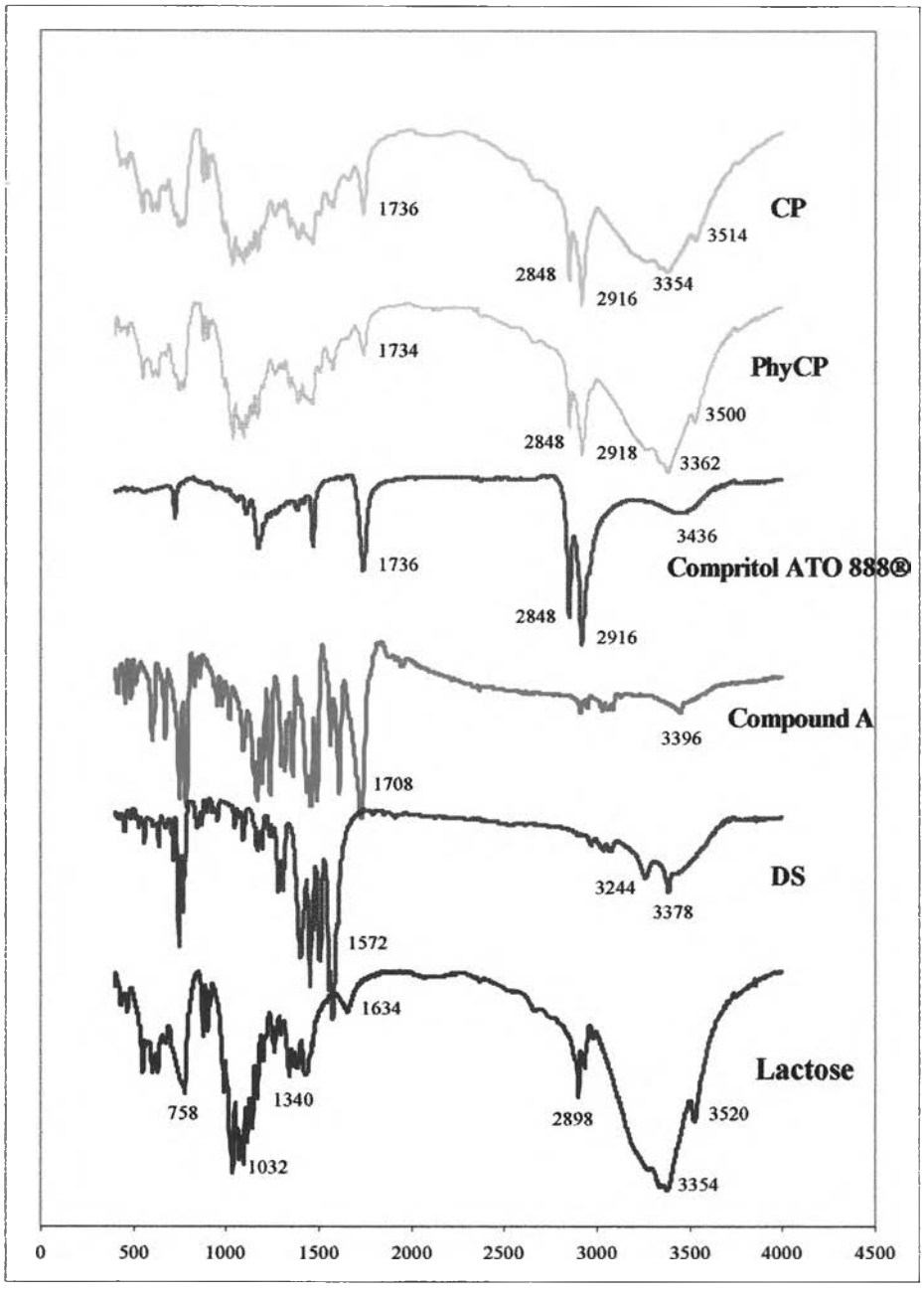


Figure 91 The IR spectrum of CP pellets

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyCP = physical mixture of Compritol ATO 888® formulation

CP = Compritol ATO 888® formulation studied

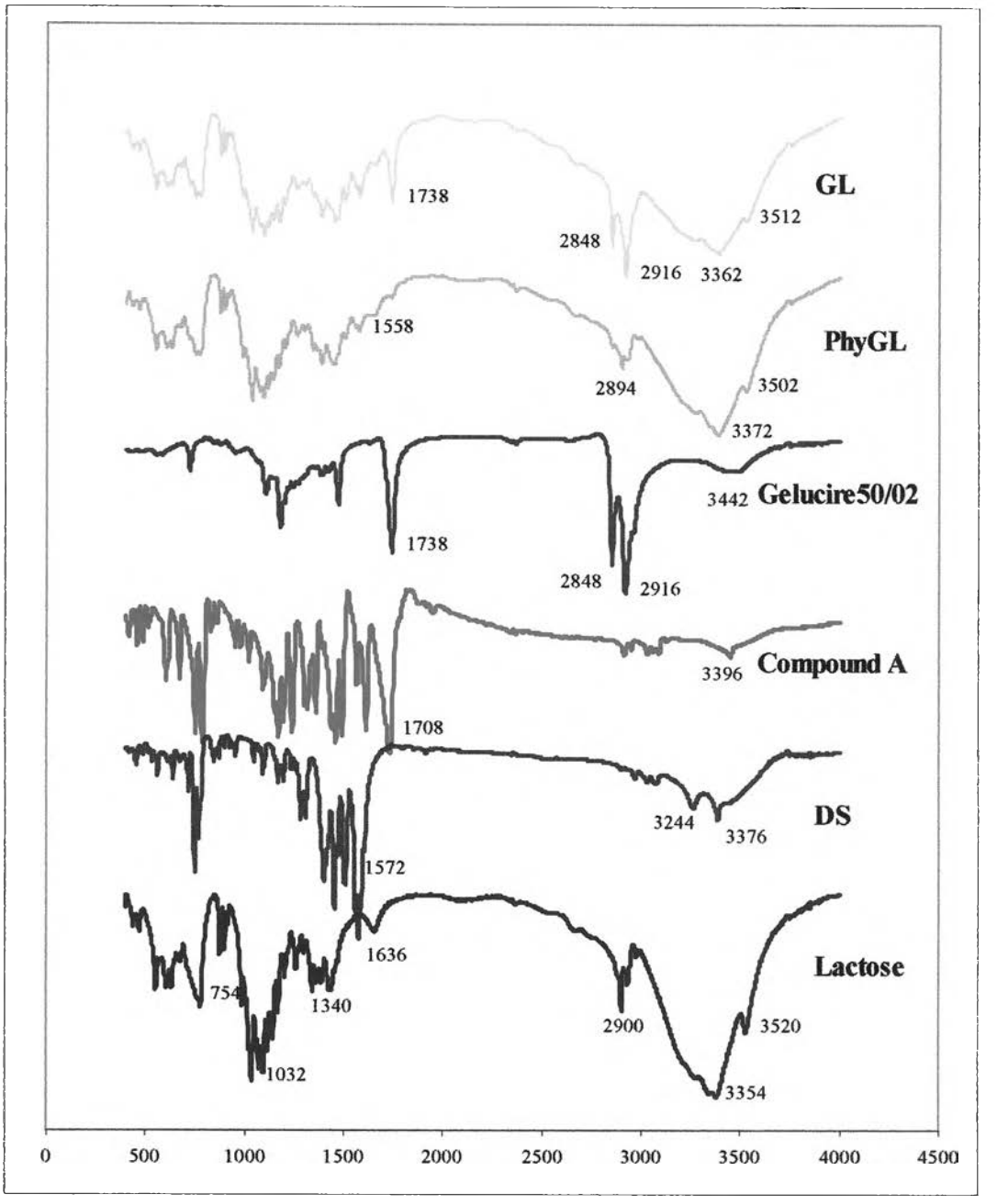


Figure 92 The IR spectrum of GL pellets

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyGL = physical mixture of Gelucire 50/02 formulation

GL = Gelucire 50/02 formulation studied

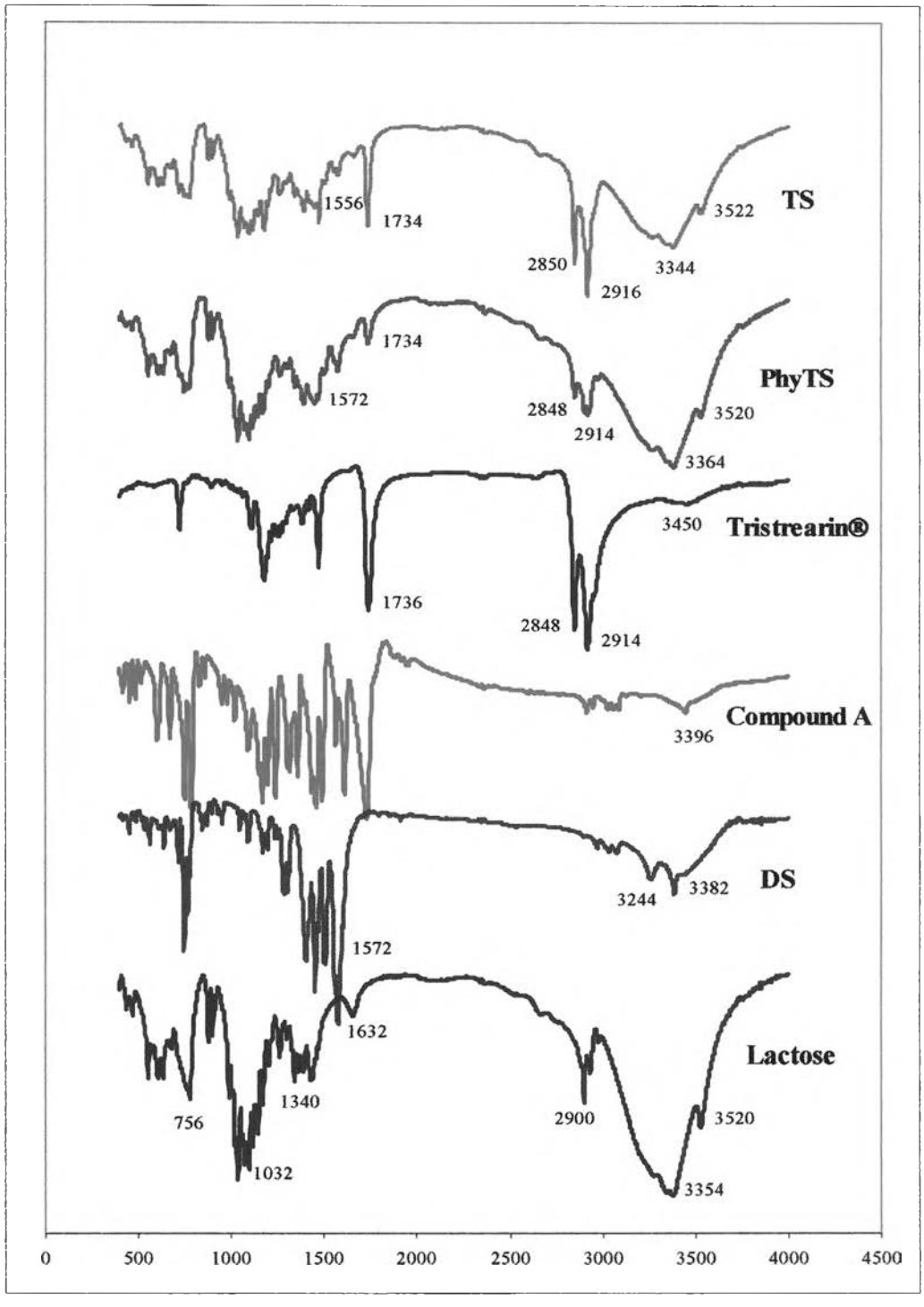


Figure 93 The IR spectrum of TS pellets

DS = diclofenac sodium

Compound A = diclofenac related compound A

phyTS = physical mixture of Tristearin® formulation

TS = Tristearin® formulation studied

3.11 The differential scanning calorimetry

The DSC thermograms of DS, GMS and lactose are shown in Figure 94. The DSC thermograms of pure DS gave an endothermic at 285°c. The DSC thermograms of GMS revealed only endothermic at 53°c, whereas lactose showed two endotherm peaks at 144°c and 221°c.

The DSC thermograms of DS pellets containing GMS and lactose (LA-1 to LA-9) are shown in Figure 94. From thermograms of DS-lactose-GMS pellets, all formulation did not show major peaks of DS. These might be results of the peaks of component in formulations.

There was no difference between the DSC thermogram patterns of DS-lactose-GMS formulation (LA-1 to LA-9), except for LA-4 which was prepared by mixing speed of 200 rpm, mixing temperature of 25°C above melting point of GMS and mixing time of 15 min. The DSC thermograms of LA-4 gave boarder endothermic peak, compared with those found for others, around 130°C. It might be that the process variables, high mixing speed, high mixing temperature and high mixing time, affected the formulation of pellets.

An endothermic peak around 190°C was observed for dbcp while that around 130°C was observed for diclofenac related compound A.

The DS-dbcp-GMS formulations (CA-1 to CA-9) exhibited similar patterns in the DSC thermograms. It was found that shape endothermic peaks were shown around 120°C - 130°C. However, it could be that the peaks of dbcp were shifted to the lower temperature rather than the peak for diclofenac related compound A. The dbcp might be change to other compound during the preparation process. Besides, the dbcp could interacted with GMS or DS because there was small endothermic peaks around 120°C - 140°C for the physical mixture of dbcp and GMS and that of dbcp, GMS and DS.

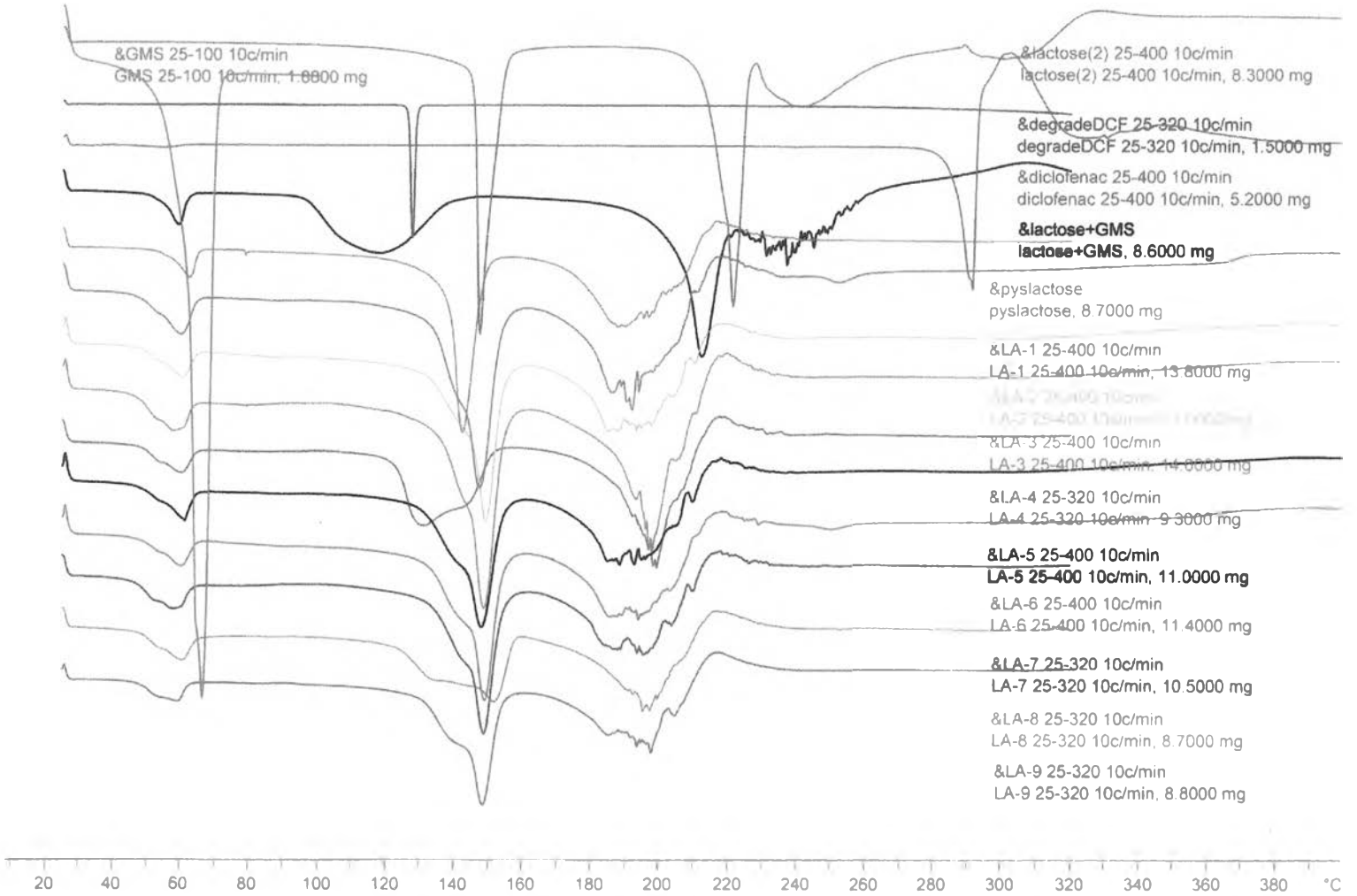


Figure 94 The DSC thermograms of DS-lactose-GMS pellets

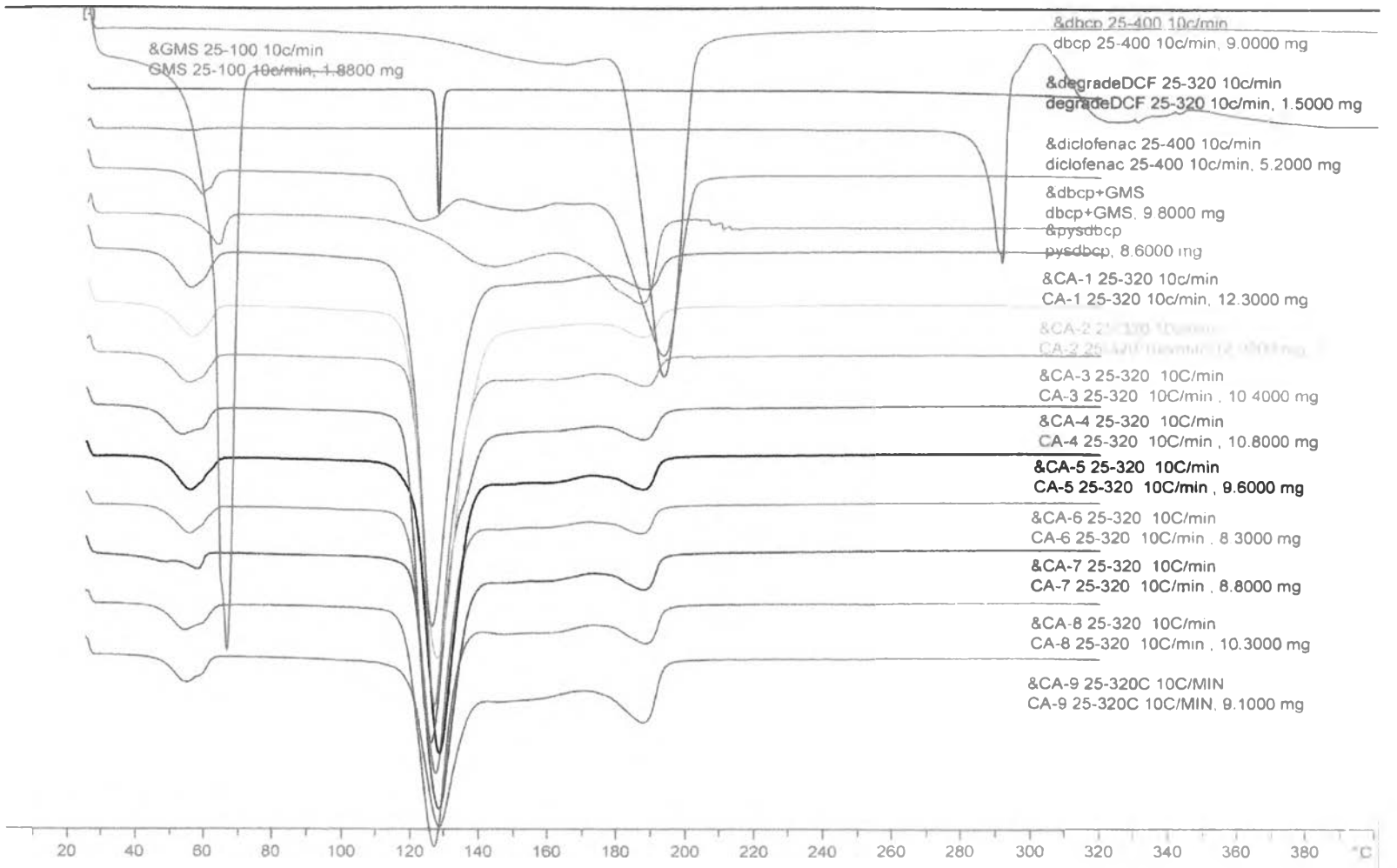


Figure 95 The DSC thermograms of DS-dbcp-GMS and pellets

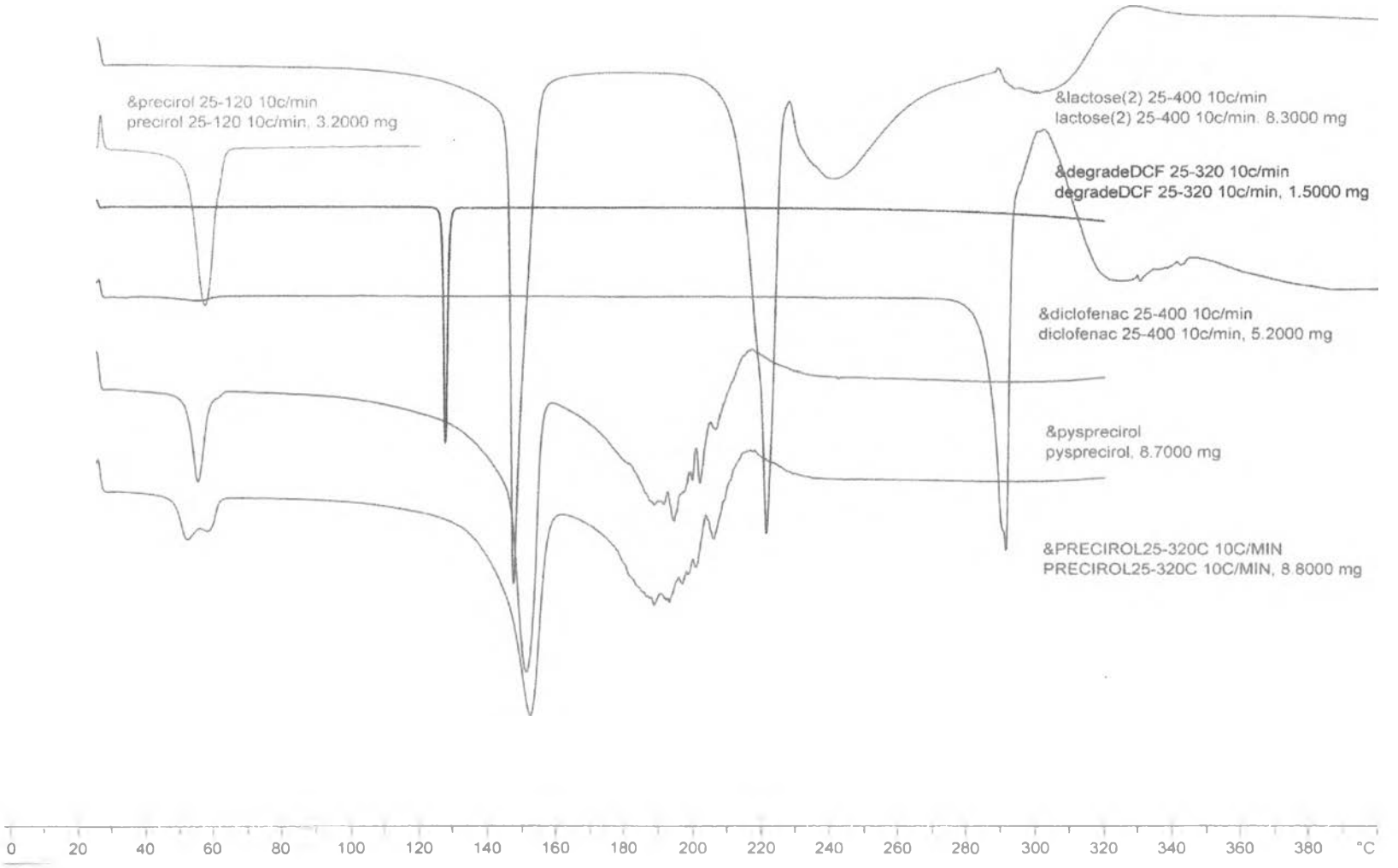


Figure 96 The DSC thermograms of PR pellets

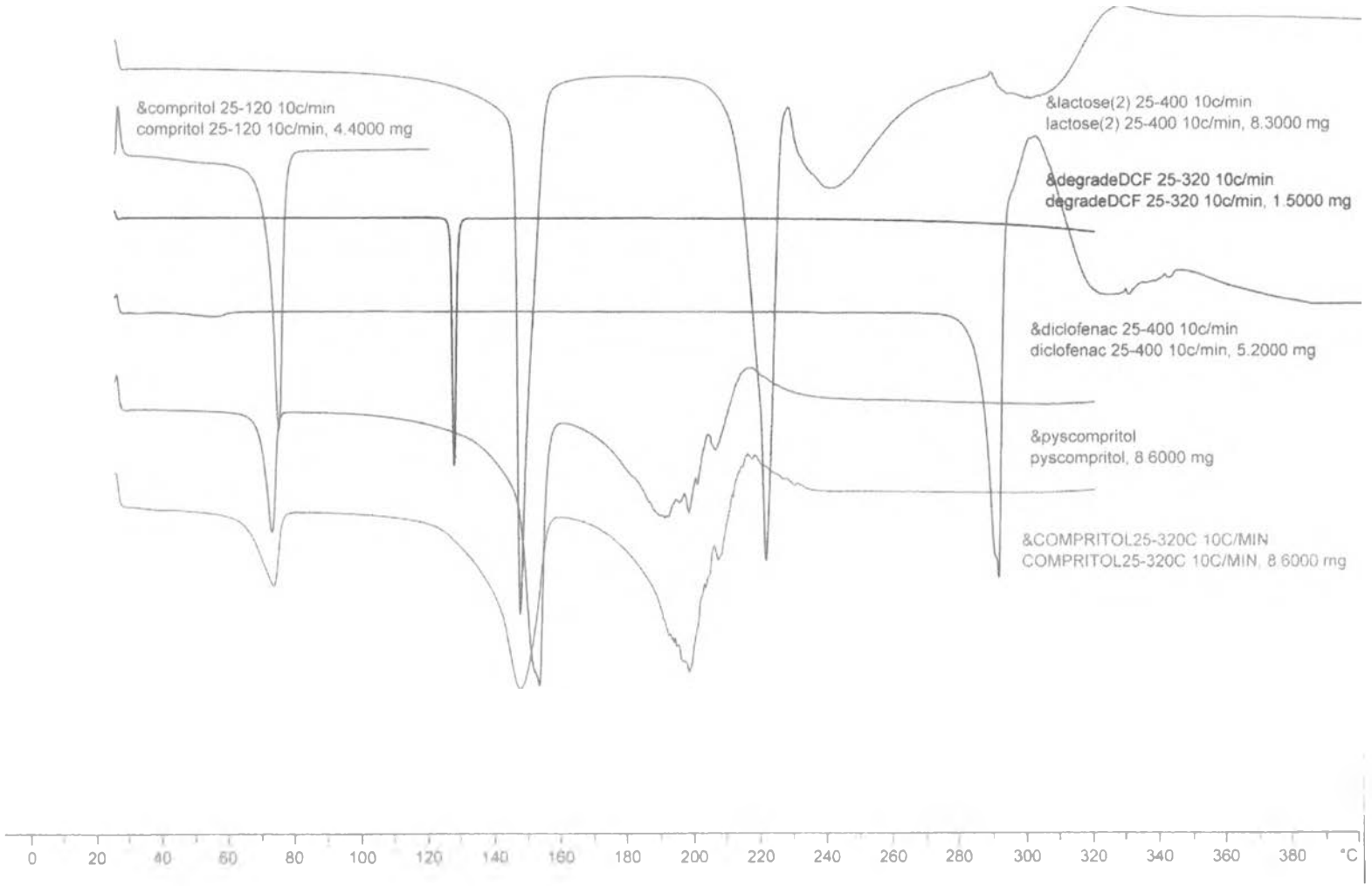


Figure 97 The DSC thermograms of CP pellets

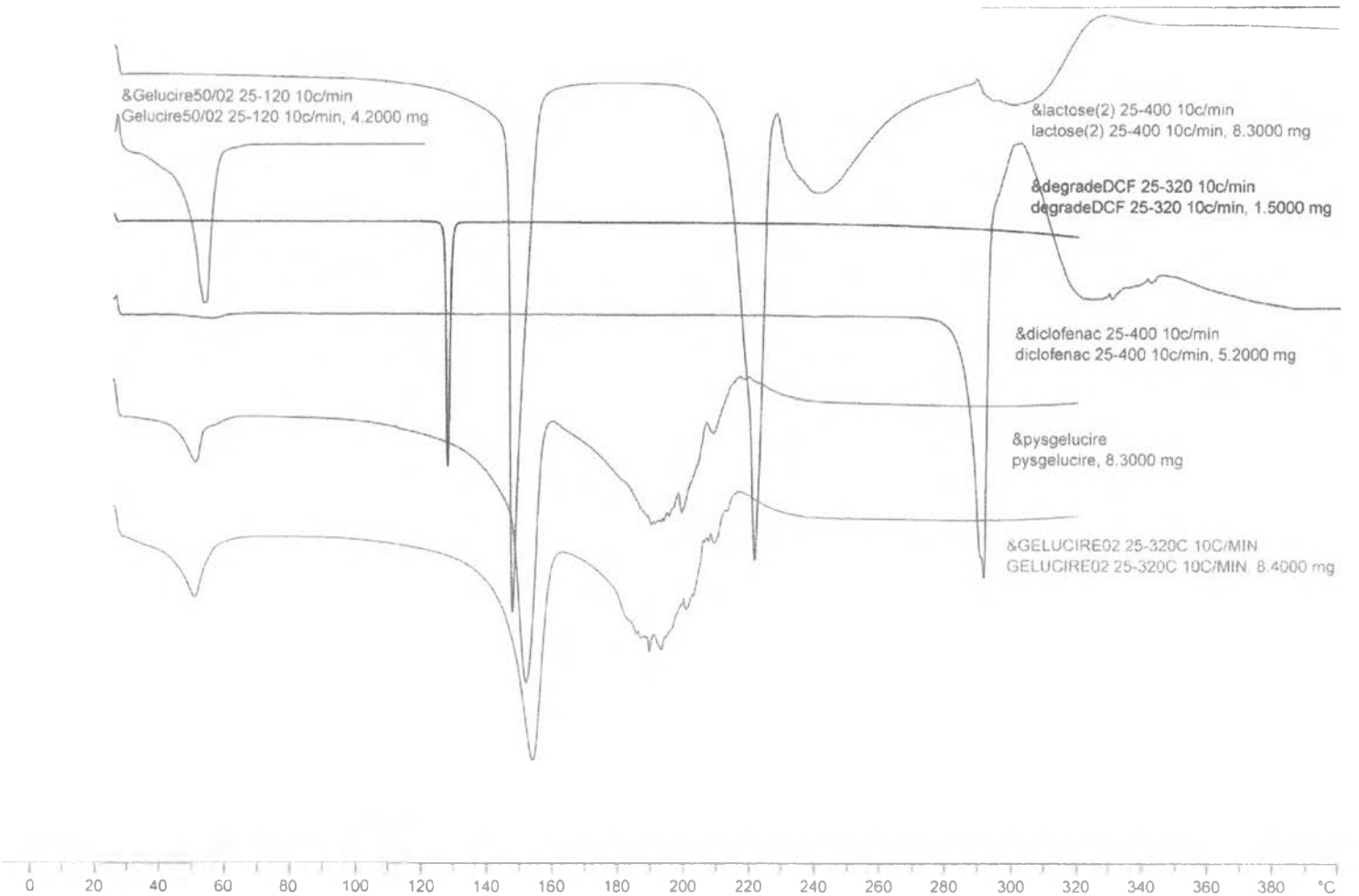


Figure 98 The DSC thermograms of GL pellets

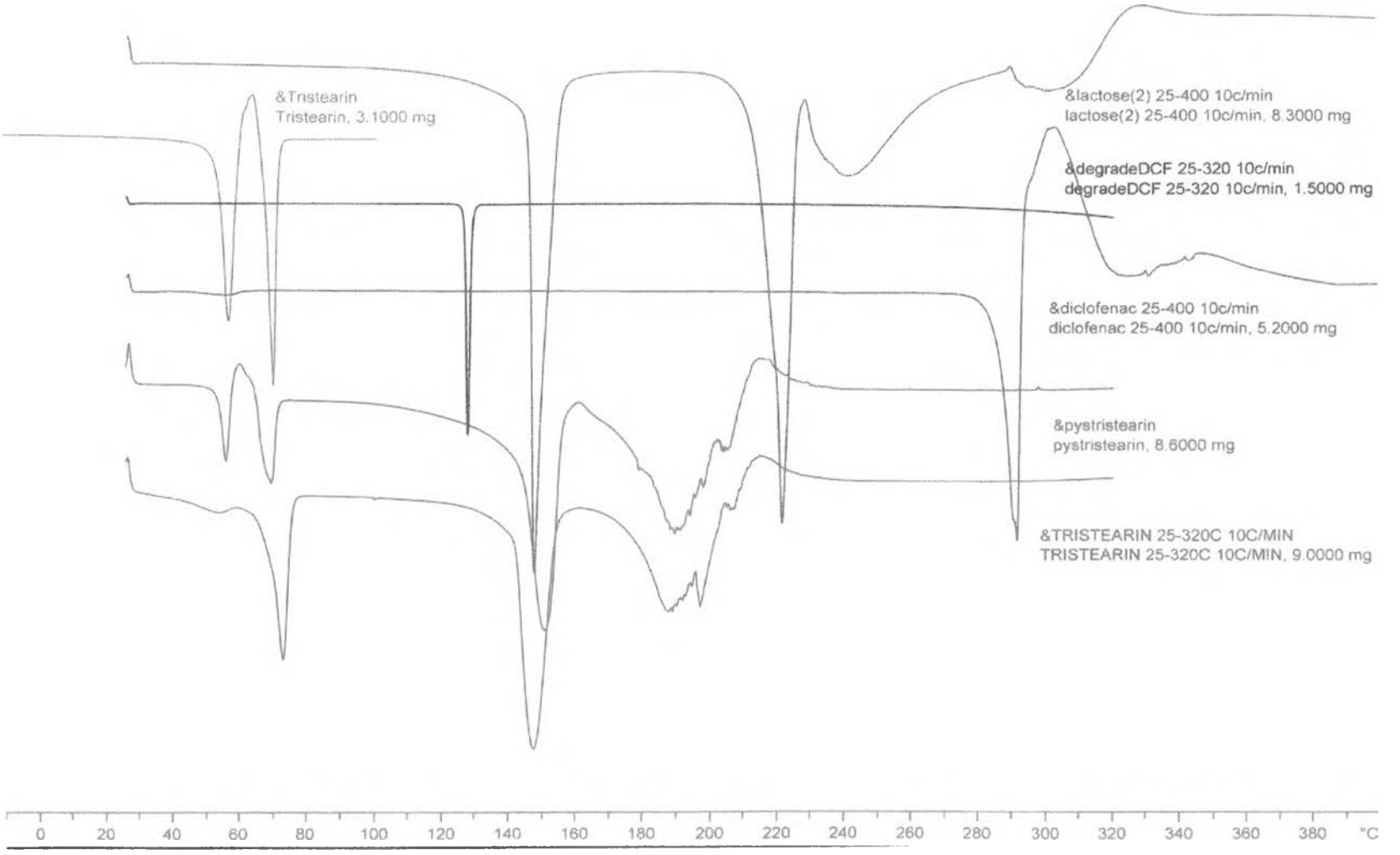


Figure 99 The DSC thermograms of TS pellet

The DSC thermograms of DS pellets containing other binders (PR, CP, GL and TS) shown in Figures 96 – 99. From thermograms of their, all formulation exhibited similar pattern in the thermograms of lactose and binder. The endotherm of lactose were shifted to the lower temperature. In general, there was no difference between peaks of pellets and those of raw materials, lactose and binders.

3.12 Drug content and uniformity of drug content of DS in pellets.

Drug content of DS pellets shown in Table 16. Drug content of DS-lactose pellets were in the range of 96.01 – 100.50%, which were in range of pharmacopoeia, being 90.0 – 110.0% for USP 27 and 95.0 – 105.0% for BP 1993. On the other hand, drug content of DS-dbcp pellets were in the range 60.61 – 92.54%, which did not comply to the pharmacopoeia standard. It might be due to that diclofenac sodium, acidic drug, was interacted with dibasic calcium phosphate, basic compound. The interaction between dbcp, basic ingredient, and DS, acidic drug, caused the loss of drug content. Although peak of diclofenac related compound A was not found in HPLC analysis, it might be other degradation products which could not be detected in this study.

A planetary mixer, a low shear mixer, was expected to give non-uniformity of drug content if the time of mixing was less (Chirkot and Propst, 1997). Nothing has been publish so far on content uniformity, may be most of their prepared pellets in high shear mixer which no this problem. Uniformity of DS content in pellets of size range 850μm, 1,000μm and 1,180μm shown in Table 17 – 19. The range of %RSD of uniformity of drug in range of pharmacopoeia, USP 27 is not more than 2. The range of % RSD of DS-lactose-GMS pellets were less than 2, except for LA-7, which was prepared with low speed of impeller, high temperature and low mixing time. The range of %RSD of DS-dbcp pellets were less than 2, except CA-1, which was prepared with high speed of impeller, low temperature and low mixing time, CA-3 which was prepared with high speed of impeller, high temperature and low mixing time, CA-4, which was prepared with high speed of impeller high temperature and high mixing time and CA-8, which was prepared with low speed of impeller, high temperature and high mixing time. The non-uniformity of content in DS-dbcp-GMS pellets might result from the degradation of drug in pellets.

At the mixing speed of 200 rpm, the relatively low value of the %RSD of DS-lactose-GMS pellets formulation tended to be obtained. This effect was shown in Figure 100. It might be due to that mixing speed of 100 rpm was too low to obtain uniformity of mixing. However, the effect of mixing speed on the value of the % RSD of DS-dbcp-GMS pellets was not clearly.

The effect of mixing temperature and mixing time is shown in Figures 101 – 102, respectively. Both DS-lactose-GMS pellets and DS-dbcp-GMS pellets, the graphical results did not have marked difference.

The effect of binders as shown in Figure 103 - 104, the results indicated that there was no relationship between %RSD and melting point or viscosity of binder.

In addition, drug content of DS pellets in different fractions of LA-9 was investigated. Drug contents of pellets from the sieve size of 7 mesh (2,800μm), 8 mesh (2,360μm), 10 mesh (2,000μm), 12 mesh (1,700μm), 14 mesh (1,400μm), 20 mesh (850μm), 25 mesh (710μm), 35 mesh (500μm), 50 mesh (300μm) and 80 mesh (180μm) sieves (n=10) were averaged to 99.96 ± 1.94% and %RSD was 1.94. This results showed that DS was dispersed homogeneously in the formulation.

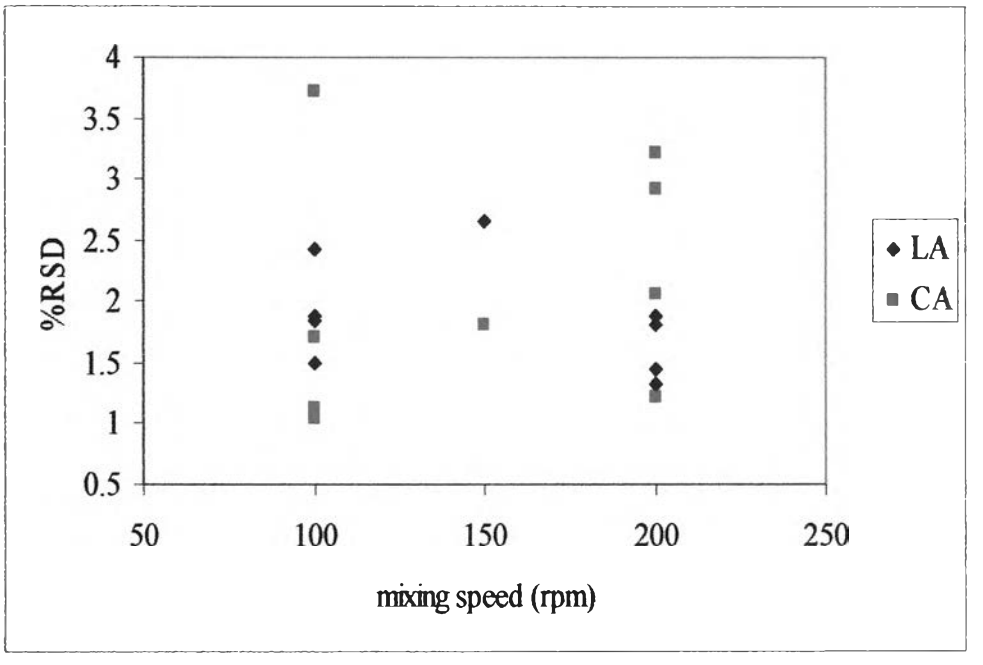


Figure 100 Effect of mixing speed on the %RSD of DS-GMS pellets

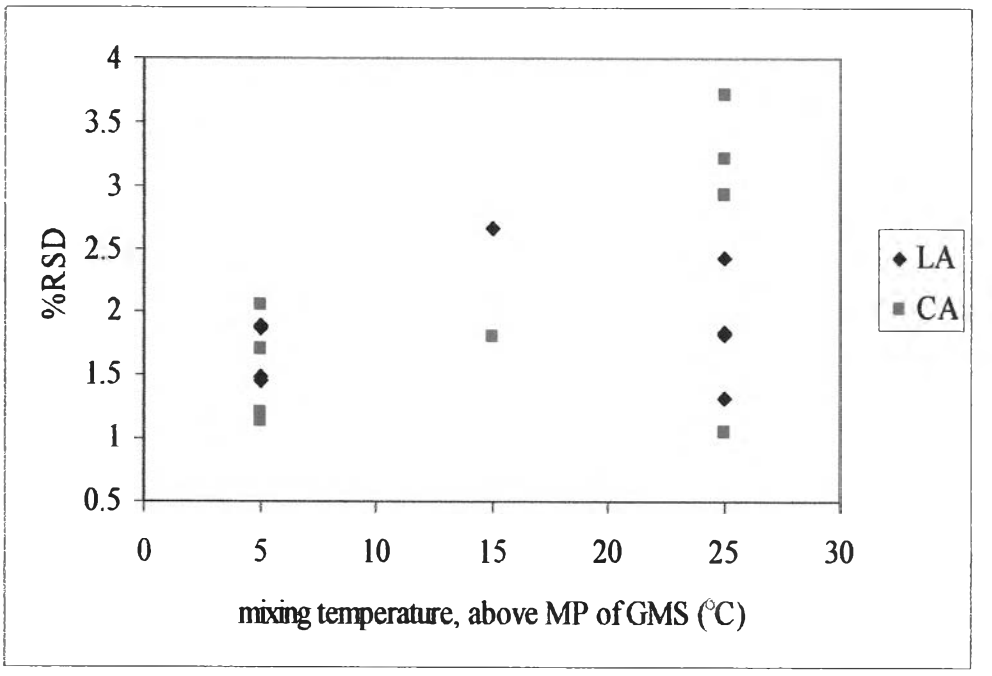


Figure 101 Effect of mixing temperature on the %RSD of DS-GMS pellets

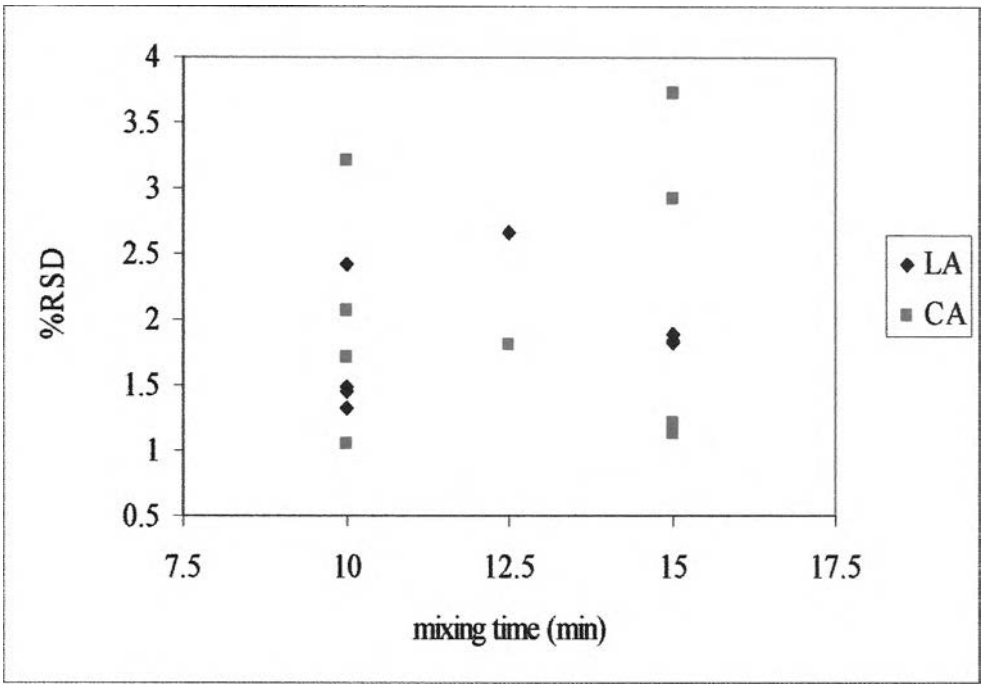


Figure 102 Effect of mixing time on the %RSD of DS-GMS pellets

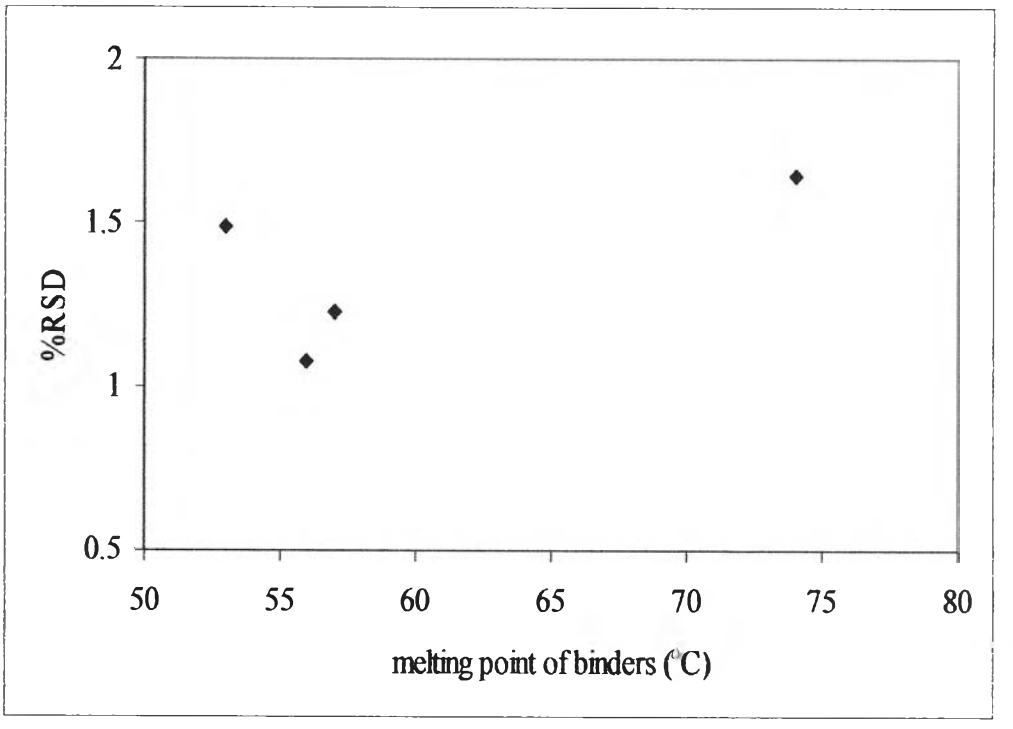


Figure 103 Effect of the melting point on the %RSD of DS-lactose pellets

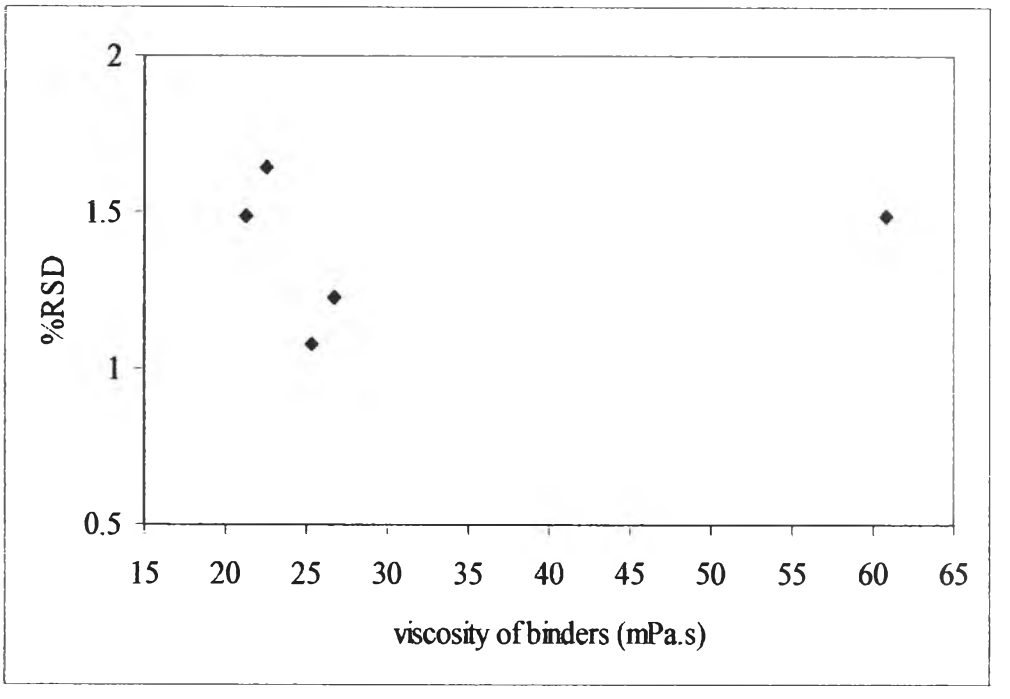


Figure 104 Effect of viscosity, at 5°C above the melting point of binder on the %RSD of DS-lactose pellets

Table 16 Percentage of diclofenac sodium content in pellets

Rx.	Sample 1	Sample 2	Average	SD
LA-1	98.94	97.38	98.16	0.11
LA-2	95.95	100.83	98.39	0.03
LA-3	95.31	99.79	97.55	0.03
LA-4	98.96	99.30	99.13	0.00
LA-5	97.08	97.69	97.39	0.00
LA-6	97.39	95.63	96.51	0.01
LA-7	96.19	97.98	97.09	0.01
LA-8	96.23	95.86	97.05	0.00
LA-9	100.91	100.08	100.50	0.01
CA-1	72.08	71.08	71.58	0.01
CA-2	90.55	94.47	92.54	0.03
CA-3	60.78	60.44	60.61	0.00
CA-4	68.75	71.02	69.89	0.02
CA-5	71.43	70.22	70.83	0.01
CA-6	74.95	71.02	72.99	0.03
CA-7	68.91	67.18	68.05	0.01
CA-8	67.42	67.04	67.23	0.00
CA-9	76.43	72.16	74.30	0.03
PR	99.14	98.99	99.07	0.31
CP	100.06	97.75	98.91	1.63
GL	98.94	95.32	97.13	2.55
TS	95.44	96.58	96.01	0.80

LA = formulation with lactose

CA = formulation with dibasic calcium phosphate

PR = formulation with Precirol® ATO5

CP = formulation with Compritol 888 ATO®

GL = formulation with Gelucire 50/02

TS = formulation with Tristearin®

DS = diclofenac sodium

Table 17 Content uniformity of diclofenac sodium pellets prepared with lactose and glyceryl monostearate

Rx.	LA-1	LA-2	LA-3	LA-4	LA-5	LA-6	LA-7	LA-8	LA-9
Sample No.	%total amount								
1	99.73	100.73	99.37	99.25	96.72	93.59	97.40	97.55	98.09
2	97.11	99.38	97.88	94.01	96.23	95.14	94.81	96.91	99.50
3	97.73	100.10	97.19	96.36	96.33	91.72	95.70	101.15	98.20
4	96.77	98.83	98.98	96.57	92.69	89.88	96.50	101.33	94.91
5	98.42	95.43	96.67	97.61	95.62	90.84	91.42	98.54	100.33
6	97.45	96.31	98.06	99.83	94.57	94.88	94.31	96.49	93.95
7	96.68	96.68	99.61	99.35	93.80	92.33	95.75	100.16	96.61
8	97.61	97.91	96.85	97.12	96.22	94.12	92.16	99.28	96.01
9	95.19	96.08	100.21	96.80	94.63	94.18	93.32	99.09	92.67
10	95.58	96.69	96.82	97.70	97.11	92.98	90.52	96.53	94.04
Average	97.12	97.81	98.16	97.56	95.39	92.97	94.19	98.70	96.43
SD	1.41	1.85	1.30	1.77	1.42	1.72	2.28	1.82	2.56
%RSD	1.45	1.89	1.32	1.82	1.49	1.88	2.42	1.84	2.66

Table 18 Content uniformity of diclofenac sodium pellets prepared with dibasic calcium phosphate and glyceryl monostearate

Rx.	CA-1	CA-2	CA-3	CA-4	CA-5	CA-6	CA-7	CA-8	CA-9
Sample No.	%total amount								
1	67.97	89.22	63.74	76.65	70.06	74.15	65.72	65.22	70.70
2	68.12	89.55	60.71	74.92	68.39	74.29	66.11	70.11	71.95
3	67.76	89.63	60.56	74.86	71.13	74.69	64.77	69.55	73.41
4	64.50	91.78	62.52	74.72	68.34	75.19	64.81	71.43	75.02
5	67.36	89.14	62.68	80.97	69.94	72.73	64.96	70.74	71.73
6	65.31	89.82	58.97	74.08	68.93	75.04	65.08	68.98	71.13
7	66.05	88.27	59.01	76.60	69.78	73.02	66.73	64.03	72.08
8	66.36	88.81	57.93	79.17	69.40	73.27	64.46	65.34	71.26
9	64.45	87.74	59.98	75.55	68.19	73.70	65.36	67.61	71.60
10	66.53	89.64	58.71	78.14	71.71	73.82	65.35	67.80	73.24
Average	66.44	89.36	60.48	76.57	69.89	73.99	65.34	68.08	72.21
SD	1.37	1.08	1.94	2.23	1.19	0.84	0.67	2.53	1.31
%RSD	2.06	1.21	3.21	2.92	1.71	1.13	1.05	3.72	1.81

Table 19 Content uniformity of diclofenac sodium pellets prepared with lactose and other binders

Rx.	PR	CP	GL	TS
Sample No.		%total amount		
1	102.16	98.86	100.18	95.85
2	102.55	98.54	101.70	98.95
3	101.90	101.71	102.35	96.65
4	101.96	99.17	101.14	96.50
5	103.98	99.87	100.07	96.49
6	101.13	99.41	98.11	98.19
7	101.03	97.40	98.97	95.81
8	101.08	97.02	98.22	96.86
9	101.06	101.30	98.57	97.37
10	99.16	97.17	99.21	95.85
Average	101.60	99.05	99.85	96.85
SD	1.25	1.62	1.49	1.05
%RSD	1.23	1.64	1.49	1.08

3.13 Dissolution study

Dissolution of DS-GMS pellets are shown in Figures 105 - 112. In general, the rate of diclofenac sodium release from DS-dbcp-GMS pellets was lower than that from DS-lactose-GMS pellets. However, most formulations showed the 80% release in 8 hour, except CA-8 and CA-9. The main effect of process variables was not clearly shown for drug release. Formulation with significant fast or delayed release was not observe.

In Figures 105 – 106, diclofenac sodium released from the formulation LA-2, LA-3, LA-6, CA-2, CA-3, CA-6 were faster than others, whereas the drug released from the formulation LA-1, LA-5, LA-7, CA-1, CA-4 and CA-8 were relatively slow.

Most formulations did not achieve 100% release. For some formulations, attempts were made to investigate if there was drug remained in residues of pellets after 8 h. After the dissolution time of 8 h, the paddle speed for pellets LA-7 was increased, rotating at 200 rpm for about 1 h. The sample was then taken and measured for the absorbance. In addition, the residues of pellets LA-5 were taken. The remaining DS in

Both methods showed that drug remained in residues were little. For LA-7, final drug concentration in medium were 82.61 ± 1.11% (n=6) which slightly more than drug concentration of 8 h, 80.18 ± 1.93% (n=6). For LA-5, drug remained in residues were 0.62 ± 0.16 % based on assayed content (n=6).

The results confirmed that the main effect of process variable could not be identified, although increased mixing speed tended to give higher area under the curve (Figure 114).

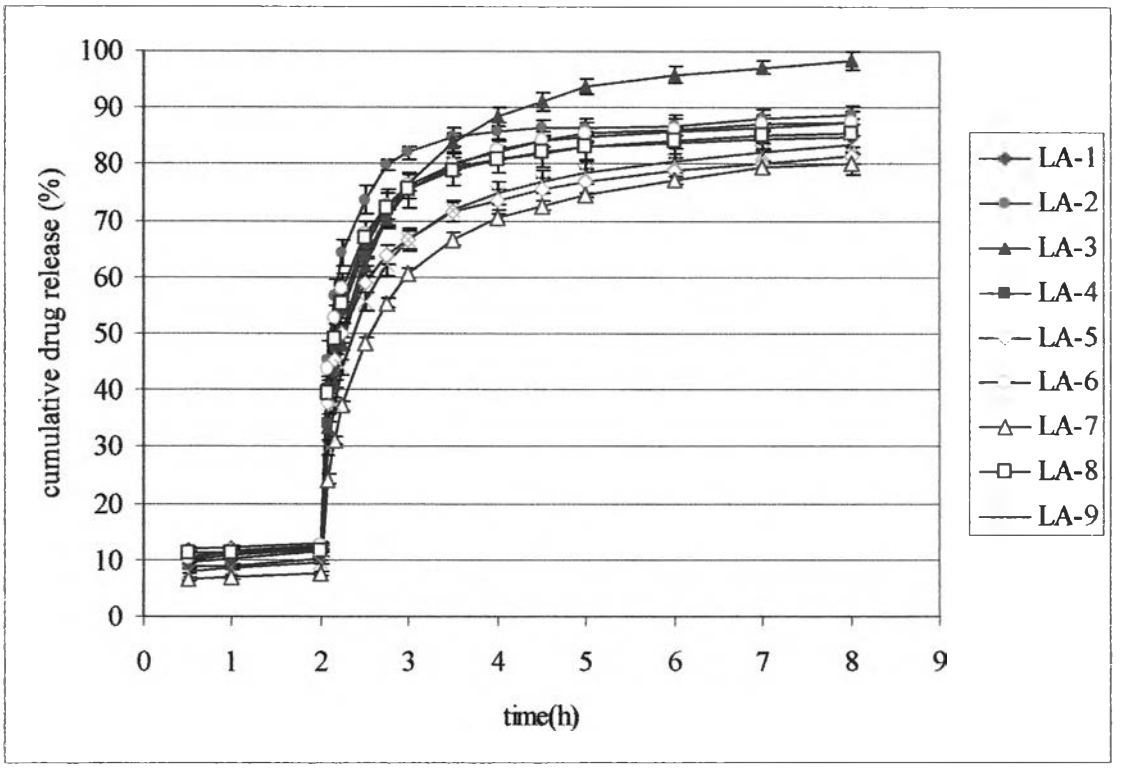


Figure 105 Dissolution profiles of DS-lactose-GMS

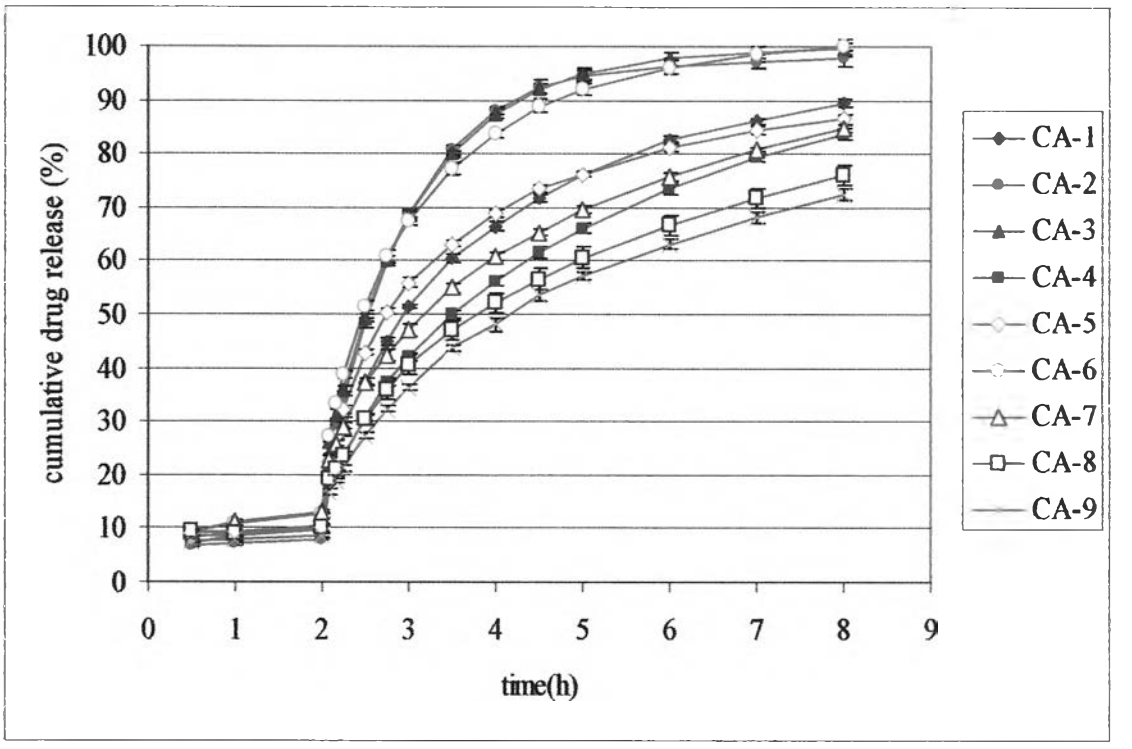


Figure 106 Dissolution profiles of DS-dbcp-GMS pellets

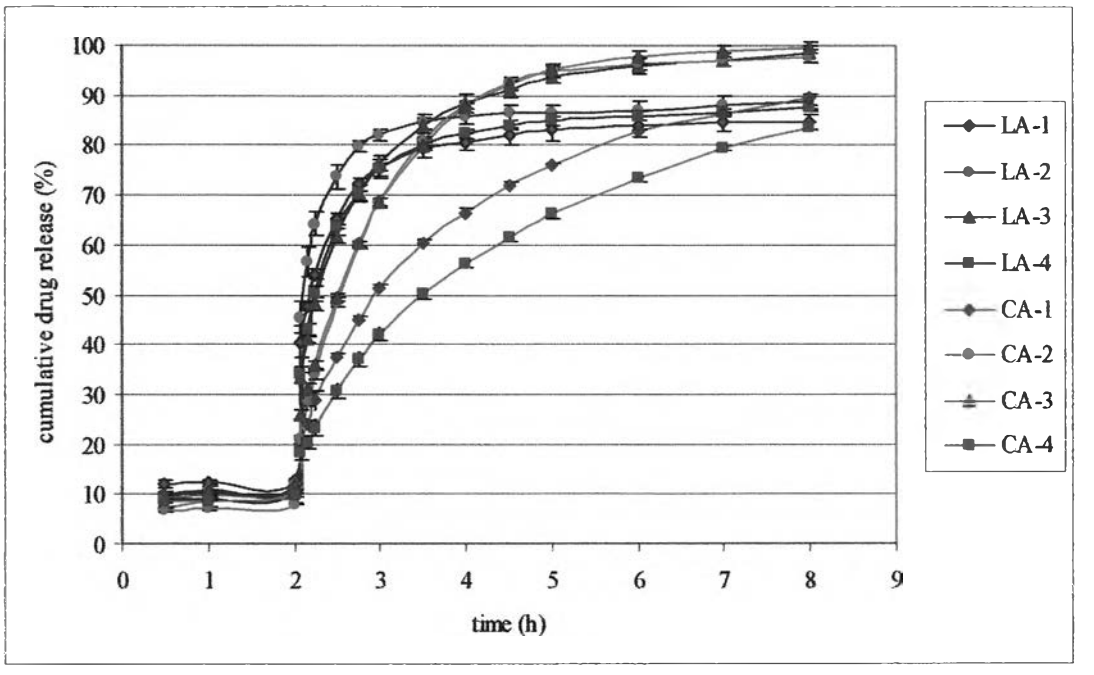


Figure 107 Dissolution profiles of DS-lactose-GMS and DS-dbcp-GMS pellets prepared with mixing speed of 200 rpm.

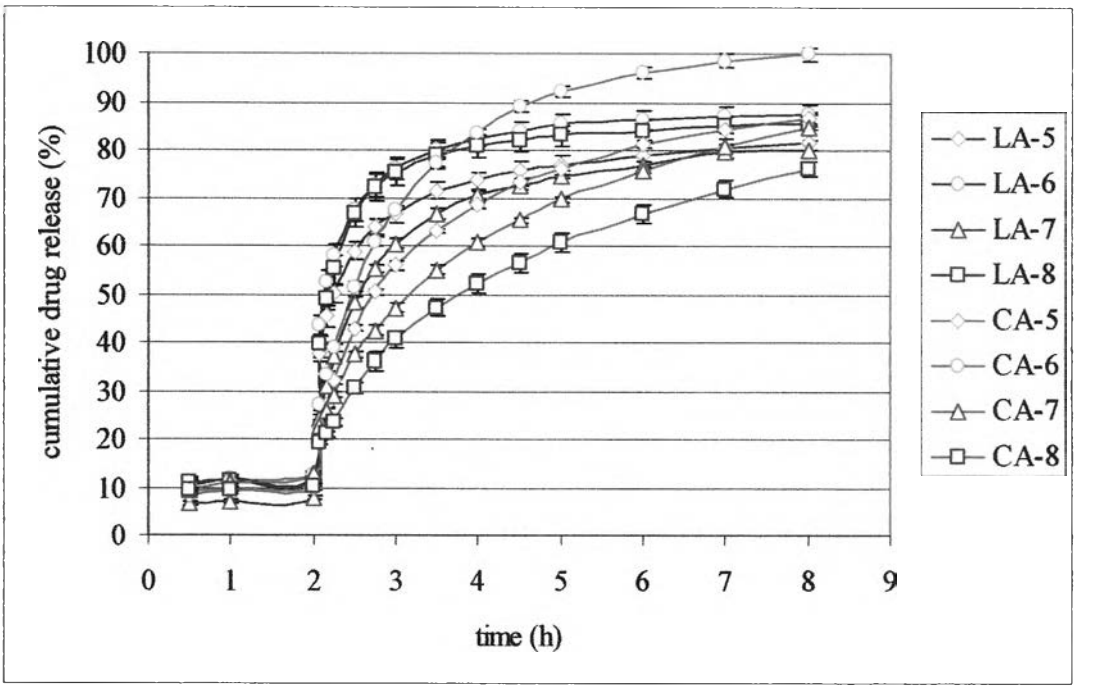


Figure 108 Dissolution profiles of DS-lactose-GMS and DS-dbcp-GMS pellets prepared with mixing speed of 100 rpm.

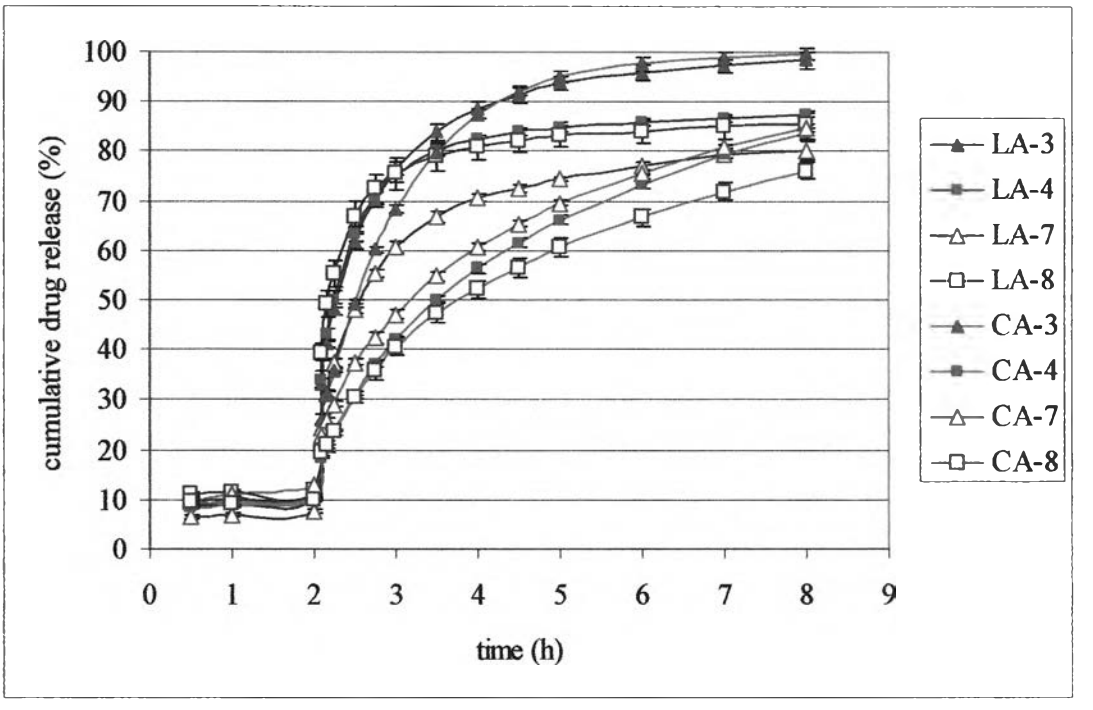


Figure 109 Dissolution profiles of DS-lactose-GMS and DS-dbcp-GMS pellets prepared with mixing temperature of 25°C above the melting point of GMS.

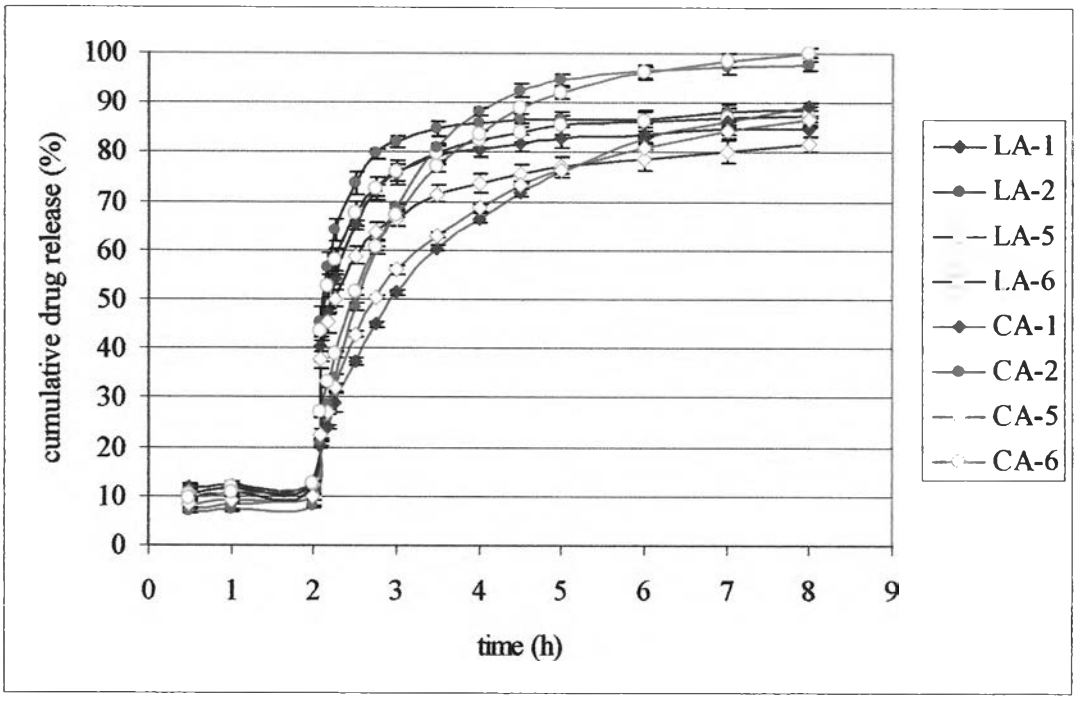


Figure 110 Dissolution profiles of DS-lactose-GMS and DS-dbcp-GMS pellets prepared with mixing temperature of 5°C above the melting point of GMS.

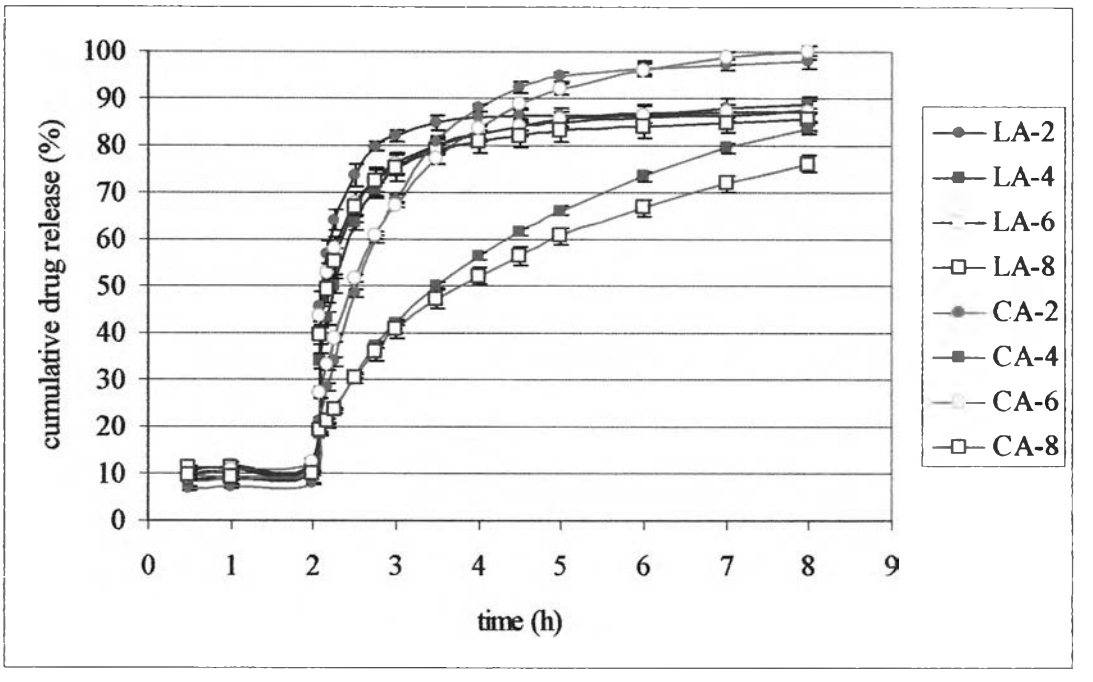


Figure 111 Dissolution profiles of DS-lactose-GMS and DS-dbcp-GMS pellets prepared with mixing time of 15 min.

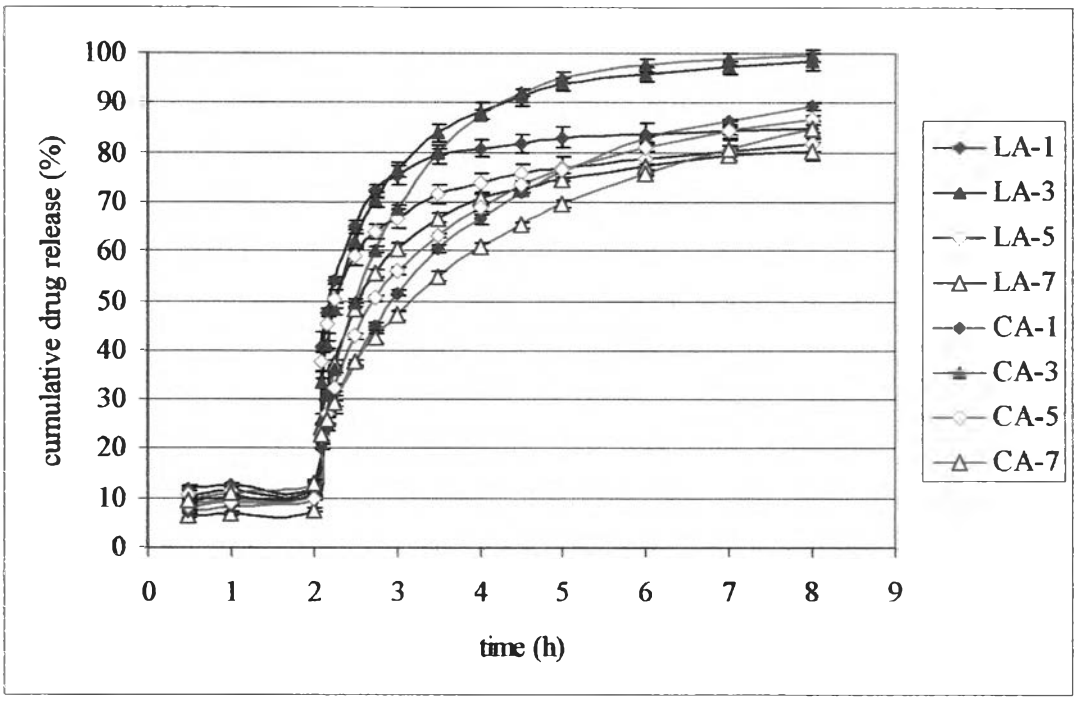


Figure 112 Dissolution profiles of DS-lactose-GMS and DS-lactose-GMS pellets prepared with mixing time of 10 min

From Figure 113, the highest drug release was found from the formulation containing Tristearin® whereas the lower drug release was found from the formulation containing GMS. The cause could not be identified by melting point and viscosity of binder as shown in Figures 117 – 118. It could be expected that the denser pellets; GL (1.4017 g/cm^3) > LA (1.3830 g/cm^3) > PR (1.3781 g/cm^3) > TS (1.3695 g/cm^3) > CP (1.3595 g/cm^3) and more lipophilicity of binder, i.e. Compritol 888 ATO® and Tristearin® would give slower drug release. However, the result was not shown as expected. It could be caused by several reasons. The amount of binder which were different could contribute some effect. It might be also that high amounts of lactose which was freely soluble in water could be dissolved and allow the medium to prenetate and dissolve the drug easily and that diclofenac sodium is also freely soluble at pH 6.8 of medium, so the effect of binder was not clearly shown.

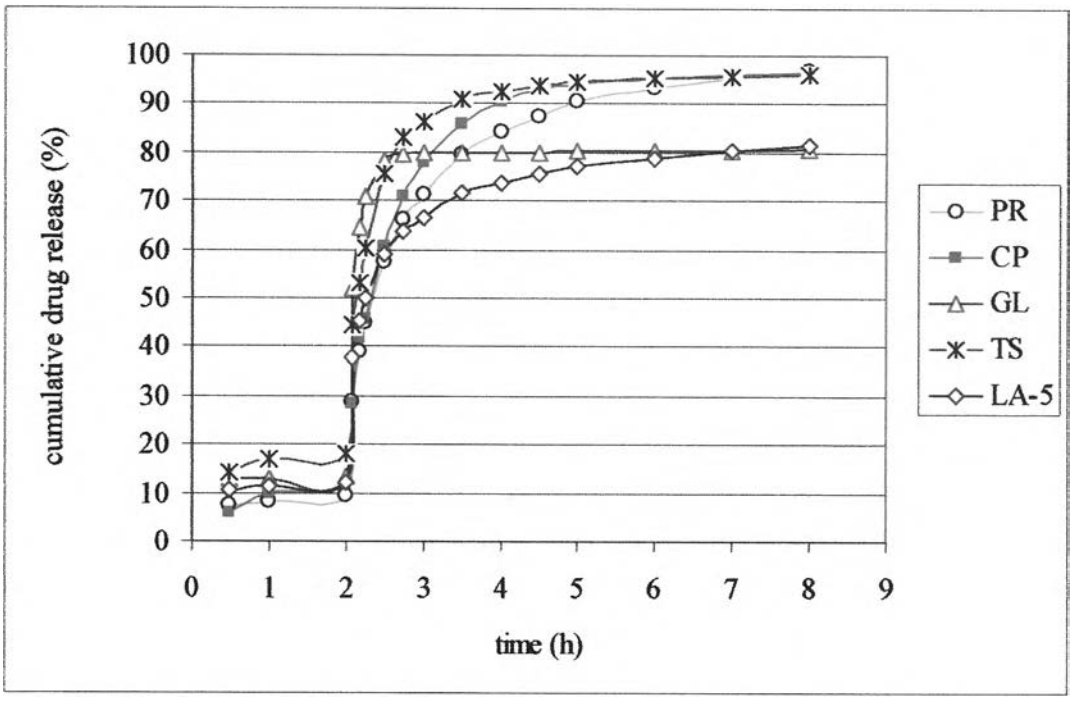


Figure 113 Dissolution profiles of the DS-lactose-pellets prepared with other binders, using mixing speed of 100 rpm, temperature of 5°C and time of 10 min

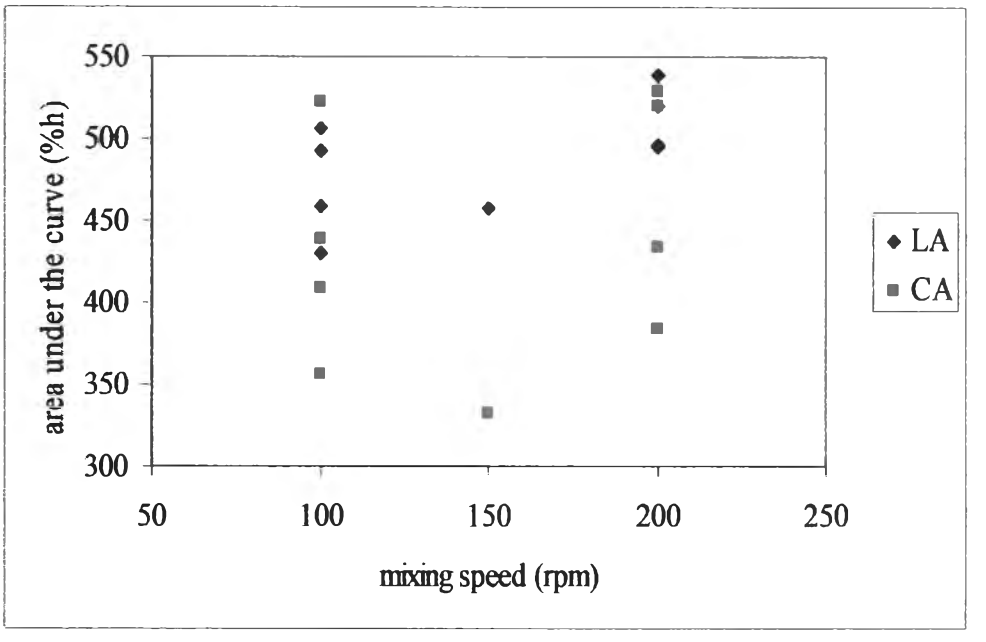


Figure 114 Effect of mixing speed on the area under the curve of DS-GMS pellets

Table 20 The area under the curve (AUC) of diclofenac sodium pellets in 0.1 N HCl solution and pH 6.8 phosphate buffer, based on assayed content

Rx	The area under the curve (AUC) (%h)							
	1	2	3	4	5	6	Mean	SD
LA-1	486.88	485.71	487.49	499.79	503.99	506.19	495.01	9.36
LA-2	515.00	512.21	518.59	523.50	525.20	528.64	520.52	6.32
LA-3	529.24	538.94	532.76	550.26	543.61	539.09	538.92	7.51
LA-4	494.69	492.51	495.01	507.62	495.42	492.73	496.33	5.66
LA-5	445.08	458.72	467.72	471.29	461.43	450.84	459.18	9.93
LA-6	496.64	504.89	487.80	516.01	516.03	515.40	506.13	11.91
LA-7	430.18	425.45	433.73	426.81	433.22	428.58	429.66	3.36
LA-8	497.66	472.72	508.56	509.13	474.72	495.14	492.99	15.96
LA-9	439.96	469.69	462.79	458.49	464.22	452.93	458.01	10.48
CA-1	435.15	436.86	433.87	433.05	431.92	431.37	433.70	2.06
CA-2	518.36	522.55	512.02	528.70	520.44	516.50	519.76	5.67
CA-3	525.91	538.47	527.86	529.90	527.47	522.26	528.65	5.45
CA-4	379.99	377.76	388.82	388.49	384.00	386.67	384.29	4.58
CA-5	440.63	436.02	435.26	437.57	441.63	441.72	438.81	2.89
CA-6	518.99	514.83	531.02	527.34	518.71	527.30	523.03	6.37
CA-7	405.03	413.44	406.47	410.53	408.33	405.35	408.19	3.29
CA-8	342.58	360.98	346.19	356.71	360.28	370.26	356.17	10.23
CA-9	333.73	339.66	326.50	332.84	327.87	335.11	332.62	4.84
PR	521.07	512.76	513.70	510.85	521.05	517.08	516.09	4.35
CP	540.06	533.81	543.90	540.89	539.17	525.21	537.17	6.72
GL	488.15	487.61	481.90	495.66	515.16	505.71	495.70	12.58
TS	584.43	565.39	567.81	571.44	556.77	563.73	538.26	9.30

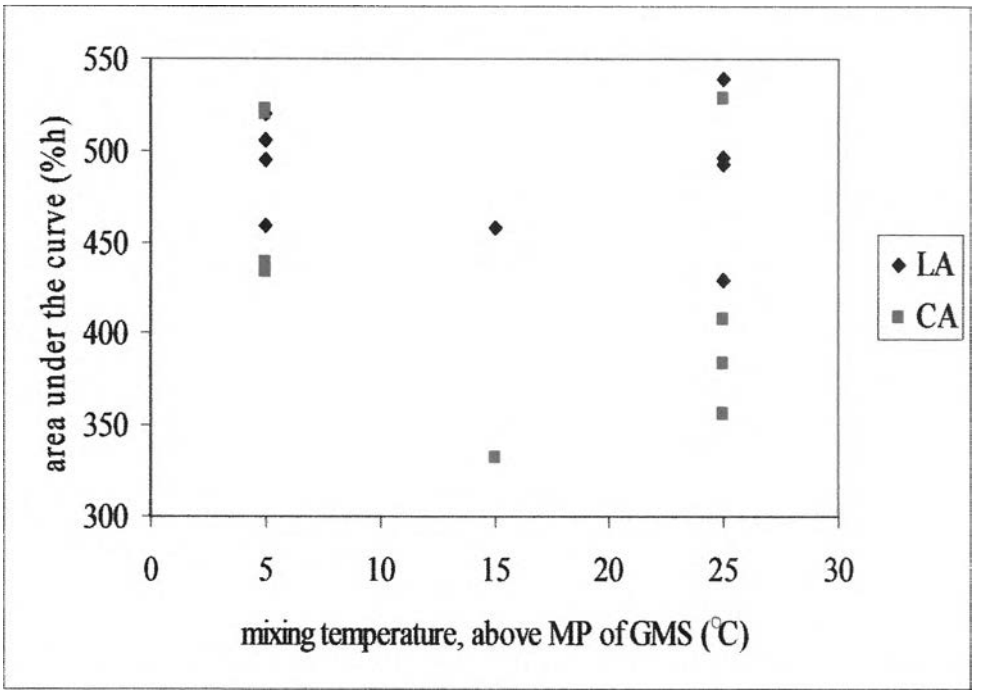


Figure 115 Effect of mixing temperature on the area under the curve of DS-GMS pellets

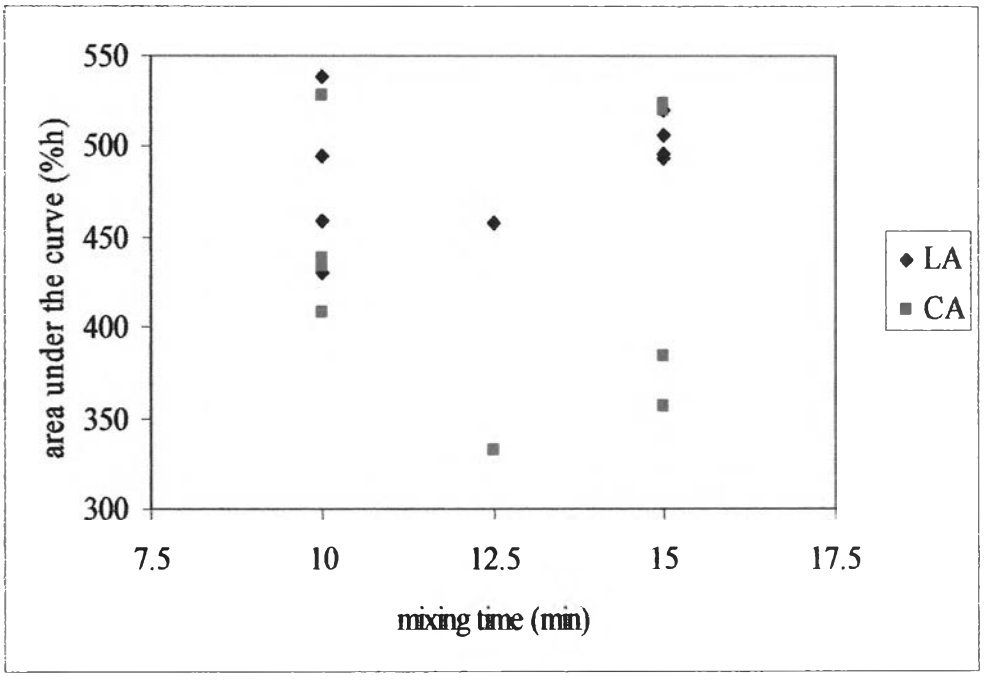


Figure 116 Effect of mixing time on the area under the curve of DS-GMS pellets

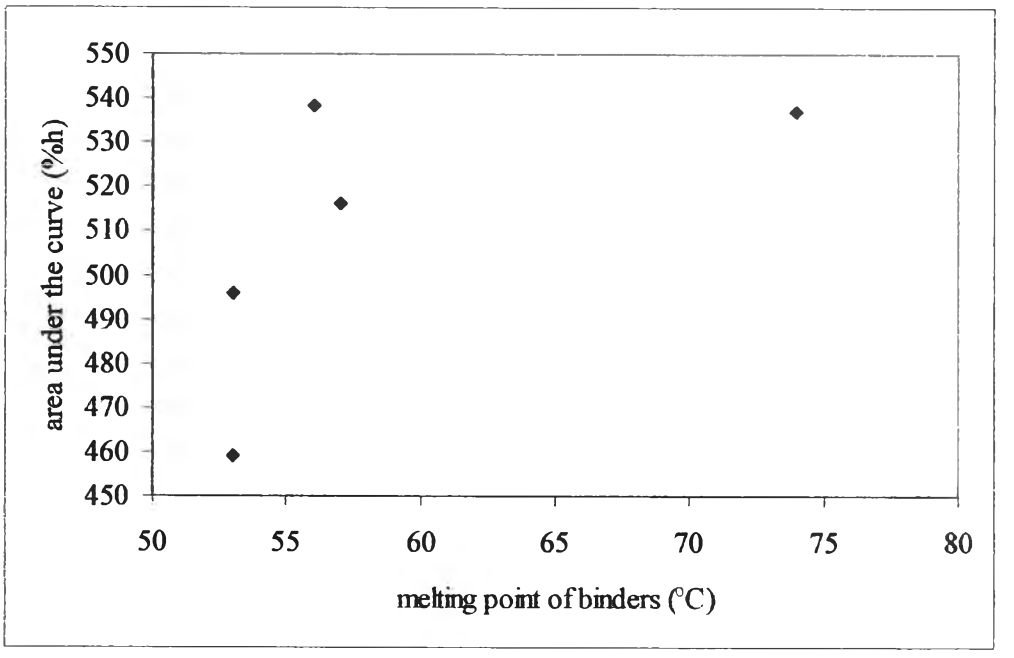


Figure 117 Effect of the melting point of binders on the area under the curve of DS-lactose pellet

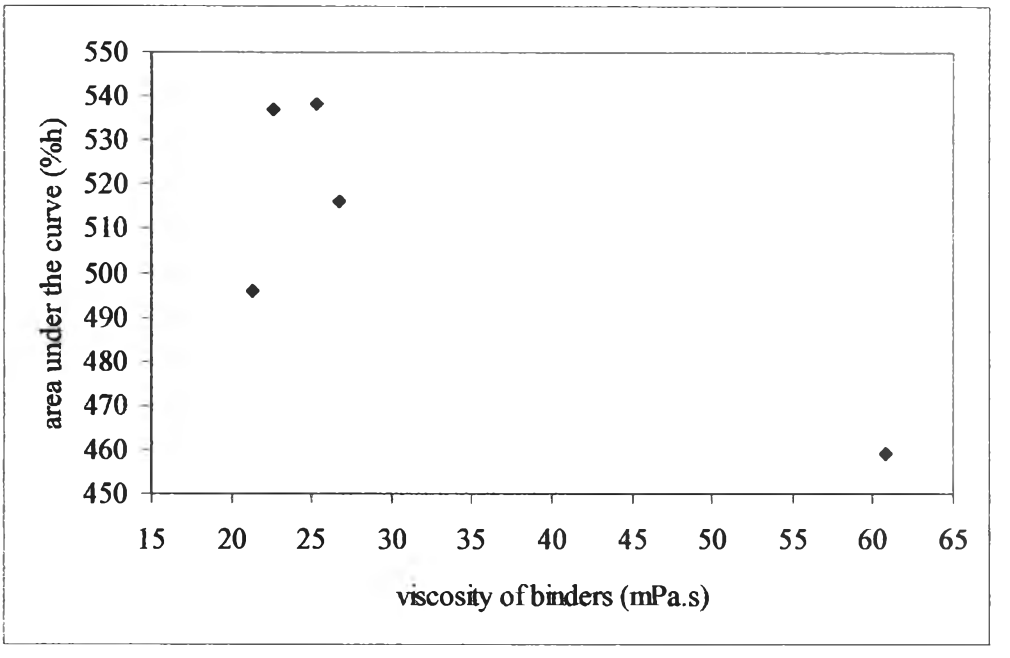


Figure 118 Effect of viscosity of binder, at 5°C above the melting point of binder, on the area under the curve of DS-lactose pellets

3.14 Stability of pellets

Due to the glycerides's chemical and physical complexity, the lipophilic binders may exhibit a complex behaviour, i.e. melting and crystallization, physical modification on storage (Hamdani et al., 2003). So the stability of formulation should be studied. In this study stability of drug content and degradation of DS was investigated, but the physicochemical properties of these pellets was not investigated.

The percentage total amount of diclofenac sodium in pellets prepared with different other binders shown in Figure 119 and Table 21 the percentage total amount of all formulations, except CA-9, were in the range of 97.13 – 102.52 %, complied to pharmacopoeia, being 90.0 – 110.0% for USP 27 and 95.0 – 105.0% for BP 1993. The percent total amount of CA-9 was in the range of 73.20 – 77.73%, which did not comply to the pharmacopoeia standard. When prepared pellets by melt technique, which using heat, DS might be decomposed to diclofenac related compound A. However, degradation of DS, diclofenac related compound A was not found in all formulation as comfimed by HPLC analysis.

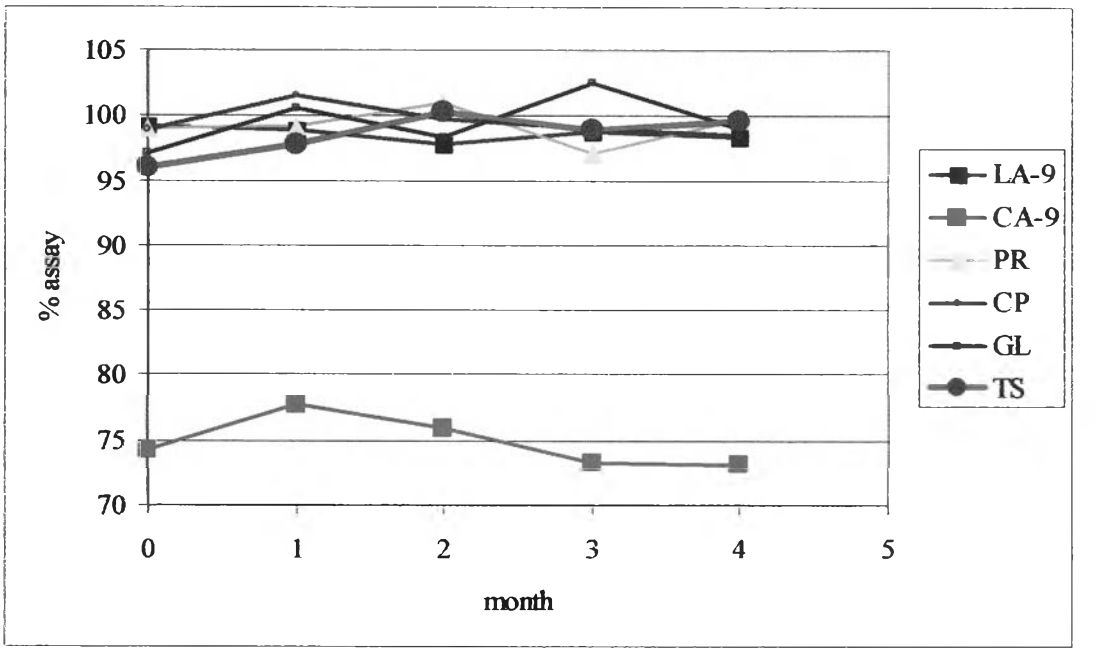


Figure 119 Relationship between % assay and time

LA = formulation with lactose, CA = formulation with dibasic calcium phosphate, PR = formulation with Precirol® ATO5, CP = formulation with Compritol 888 ATO®, GL = formulation with Gelucire 50/02, TS = formulation with Tristearin®

Table 21 %Total amount of diclofenac sodium pellets from other binders about 4 mouth

Rx.	Sample 1	Sample 2	Average	SD
Month 0				
LA-9	100.34	98.06	99.20	1.61
CA-9	76.43	72.16	74.30	3.02
PR	99.14	98.99	99.07	0.11
CP	100.06	97.75	98.91	1.63
GL	98.94	95.32	97.13	2.55
TS	95.44	96.58	96.01	0.80
Month 1				
LA-9	97.33	100.48	98.91	2.23
CA-9	79.02	76.43	77.73	1.83
PR	96.97	101.49	99.23	3.20
CP	101.69	101.44	101.57	0.18
GL	99.56	101.57	100.57	1.42
TS	97.13	98.41	97.77	0.91
Month 2				
LA-9	98.17	97.55	97.86	0.44
CA-9	76.6	75.25	75.92	0.95
PR	100.02	102.03	101.03	1.42
CP	100.20	99.24	99.72	0.68
GL	97.90	98.93	98.42	0.73
TS	101.66	98.94	100.30	1.92
Month 3				
LA-9	99.47	98.16	98.82	0.93
CA-9	74.30	72.39	73.35	1.35
PR	96.51	97.91	97.21	0.99
CP	99.21	99.01	99.11	0.14
GL	102.42	102.62	102.52	0.14
TS	97.77	100.12	98.95	1.66
Month 4				
LA-9	99.45	97.28	98.37	1.53
CA-9	74.48	71.91	73.20	1.82
PR	99.90	99.76	99.83	0.10
CP	98.47	98.64	98.56	0.12
GL	98.49	99.64	99.07	0.81
TS	98.79	100.32	99.56	1.08

LA = formulation with lactose, CA = formulation with dibasic calcium phosphate,

PR = formulation with Precirol® ATO5, CP = formulation with Compritol 888 ATO®,

GL = formulation with Gelucire 50/02, TS = formulation with Tristearin®

3.15 Statistical analysis

In general, process and formulation variables studied, i.e. mixing speed, mixing temperature and mixing time as well as types of filler (Table 22) influenced on properties, angle of repose, flow rate, bulk density, tapped density, % compressibility, true density, friability, aspect ratio, roundness, content uniformity and area under the curve of DS-GMS pellets.

The important variables were mixing speed and types of filler. Mixing speed and types of filler significantly affected on angle of repose, flow rate, bulk density, tapped density, % compressibility, true density, friability, aspect ratio, roundness, content uniformity and area under the curve. There was also interaction effect of mixing speed and types of filler on the properties of DS-GMS pellets, except for area under the curve. The interaction effect of mixing speed and temperature or mixing speed and time was also found for some properties of DS-GMS pellets, except for aspect ratio of DS-GMS pellets (Table 23).

The influence of types of filler was also interacted with mixing temperature, except for shape of DS-GMS pellets, and mixing time, except for area under the curve.

Mixing temperature and mixing time were less important variables compared with mixing speed and types of filler. Mixing temperature significantly affected on angle of repose, true density, friability, aspect ratio, roundness, content uniformity and area under the curve, whereas mixing time significantly affected only on true density and content uniformity. The interaction of both effects was found on angle of repose and true density (Table 23).

As presented in Table 24, it was clearly shown that types of binder significantly affected the properties of DS pellets studied.

Table 22 The results of the analysis of variance with full model

Response / Variables	Angle of repose	Flow rate	Bulk density	Tapped density	% compressi-bility	True density	Friability	Aspect ratio	Roundness	Content	AUC
Speed	S	S	S	S	S	S	S	S	S	S	S
Temp	S	NS	NS	NS	NS	S	S	S	S	S	S
Time	NS	NS	NS	NS	NS	S	NS	NS	NS	S	NS
Rx	S	S	S	S	S	S	S	S	S	S	S
Speed * Temp	S	S	S	S	S	S	S	NS	S	S	S
Speed * Time	S	S	S	S	S	S	S	NS	NS	S	S
Speed * Rx	S	S	S	S	S	S	S	S	S	S	NS
Temp * Time	S	NS	NS	NS	NS	S	NS	NS	S	NS	S
Temp * Rx	S	S	S	S	S	S	S	NS	NS	S	S
Time * Rx	S	S	S	S	S	S	S	S	S	S	NS
R Squared	0.709	0.892	0.992	0.978	0.302	0.990	0.432	0.114	0.243	0.987	0.802

Temp = Temperature

Rx = Formulation with different fillers, lactose and dibasic calcium phosphate

Content = Content uniformity

AUC = Area under the curve

S = Significant diffirence at a significant level ($P \leq 0.05$)

NS = No significant diffirence at a significant level ($P \leq 0.05$)

Table 23 The results of the analysis of variance with reduced model

Response / Variables	Angle of repose	Flow rate	Bulk density	Tapped density	% compressi-bility	True density	Friability	Aspect ratio	Roundness	Content	AUC
Speed	S	S	S	S	S	S	S	S	S	S	S
Temp	S	-	-	-	-	S	S	S	S	S	S
Time	-	-	-	-	-	S	-	-	-	S	-
Rx	S	S	S	S	S	S	S	S	S	S	S
Speed * Temp	S	-	-	-	-	S	S	NS	S	S	S
Speed * Time	-	-	-	-	-	S	-	-	-	S	-
Speed * Rx	S	S	S	S	S	S	S	S	S	S	NS
Temp * Time	-	-	-	-	-	S	-	-	-	NS	-
Temp * Rx	S	-	-	S	S	S	S	NS	NS	S	S
Time * Rx	-	-	-	-	-	S	-	-	-	S	-
R squared	0.639	0.873	0.983	0.970	0.053	0.990	0.387	0.099	0.218	0.987	0.391

Temp = Temperature

Rx = Formulation with different fillers, lactose and dibasic calcium phosphate

Content = Content uniformity

AUC = Area under the curve

S = Significant diffirence at a significant level ($P \leq 0.05$)

NS = No significant diffirence at a significant level ($P \leq 0.05$)

Table 24 The results of the analysis of variance comparing the sample mean of data for formulation studied

Response	Angle of repose	Flow rate	Bulk density	Tapped density	% compressi-bility	True density	Friability	Aspect ratio	Roundness	Content	AUC
Binders	S	S	S	S	S	S	S	S	S	S	S
R squared	0.961	0.904	1.000	1.000	1.000	0.978	0.999	0.126	0.103	0.738	0.904

Binders = Glyceryl monostearate, Precirol® ATO5, Compritol 888 ATO®, Gelucire 50/02 and Tristearin®

Content = Content uniformity

AUC = Area under the curve

S = Significant diffirence at a significant level ($P \leq 0.05$)

NS = No significant diffirence at a significant level ($P \leq 0.05$)