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SYSTEM TO PREDICT  
CHARACTERISTICS OF SOLID  
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LOADED PARA METHOXY

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CINNAMIC ACID (PMCA)

## PHYSICAL CHARACTERIZATION OF BEESWAX AND GLYCERYL MONOSTEARAT BINARY SYSTEM TO PREDICT CHARACTERISTICS OF SOLID LIPID NANOPARTICLE (SLN) LOADED PARA METHOXY CINNAMIC ACID (PMCA)

NOORMA ROSITA\*, DWI SETYAWAN, WIDJI SOERATRI, SUWALDI MRTODIHARDJO\*\*

\*Pharmaceutics Department, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, Pharmaceutics Department, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia. Email : noorma-r@ff.unair.ac.id

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### ABSTRACT

Objective: The aim of this study was to investigate physical characteristics of beeswax (BW), Glyceryl Monostearat (GMS) and their binary mixture before and after stressing under high shear homogenisation technique on SLN preparation to predict the optimum ratio of BW-GMS produce good characteristics of solid lipid nanoparticle loaded PMCA.

Methods: Lipid characterizations were conducted by thermal analysis (DTA), Powder X-Ray Diffraction (PXRD) and FTIR Spectrophotometri. Partition of PMCA on lipid/acetic buffer pH 4,2 was determined by indirect method, and PMCA concentration was measured by spectrophotometer at 302 nm. SLN characteristics based on their morphology was determined using Transmission Electron Microscope (TEM), particle size and its polydispersity index which were measured with Delsa Nano™ Particle Size Analyser (PSA). SLN physical stability based on minimum of particle size variation during 40 days storage. Percentage of PMCA entrapped in SLN was determined by centrifugation method.

Results and Conclusion: The result showed that ratio of BW-GMS 5:5 (% w/w) produced the best blank SLN and the best characteristics of PMCA-SLN

Keywords: Para methoxy cinnamic acid (PMCA), Solid lipid nanoparticle (SLN), Beeswax, Glyceryl monostearat, Binary mixture

### INTRODUCTION

Solid lipid nanoparticles (SLN), one of colloidal system based on nanotechnology have been proposed as an alternative colloidal drug delivery. Compared to liposome and emulsion, SLN possess some advantages, such as protection of incorporated active compounds against chemical degradation and more flexibility in modulating the release of compound [1, 2]. Another advantages are biodegradable, non toxic, stable against coalescence and drug leakage [3] and none to use higher surfactant concentrations, therefore it is able to avoid potential necessity to perform tolerability experiment [1, 4]. Standard manufacturing procedure is dissolving or dispersing the drug in the molten lipid prior to high pressure or high shear homogenization [5].

Quality of SLN is determined on its particle size, size stability and percentage drug entrapment. Good SLNs have 10 - 1000 nm in size and high percentage of drug entrapment [4, 6], that influence the drug release and drug stability. Some factors that affected on quality of SLN are type of lipid and its concentration.

According to Jennings *et al*, [7], the uses of GMS as lipid SLN carrier performed larger percentage of drug entrapment than beeswax, but tend to form agglomeration. In contrast, SLN using beeswax as lipid carrier performed more physically stable SLN but low in percentage of drug entrapment performance.

The aim of this study was to explore the possibility of beeswax (BW) and glyceryl monostearate (GMS) combination as lipid core in SLN to produce good SLN characteristics through physical characterization of the lipid Para methoxy cinnamic acid (PMCA), a hydrolyzed product of ethyl-p-methoxycinnamic (EPMC), which is the highest component of *Kaempferia Galanga* extract, was used as model of antiinflammatory drug for dermal uses.

Lipid characterizations were conducted by thermal analysis (DTA), Powder X-Ray Diffraction (PXRD) and FTIR Spectrophotometry. Partition of PMCA on lipid/ acetic buffer pH 4,2 was determined by indirect method and PMCA concentration was measured by spectrophotometre. SLN characteristics based on their morphology was observed using Transmission Electron Microscope (TEM), particle size and its polydispersity index which were measured using Delsa Nano™ Particle Size Analyser (PSA). SLN physical stability was based on minimum of particle size variation during 40 days storage.

Several ratio of BW-GMS were made as blank SLNs to find the best SLN characteristics especially in particle size, its distribution and their physical stability. The blank SLN that have smallest and most stable size was loaded with PMCA. Then SLN-PMCA was determined in its percentage drug entrapment by centrifugation method. PMCA concentration was measured by spectrophotometer method.

### MATERIALS AND METHODS

#### Materials

Para methoxy cinnamic acid (PMCA), Propyleneglycol and Tween 80 (Sigma Aldrich), lipid: beeswax and glyceryl monostearate (PT. Bratako). Buffer component: acetic acid glacial and sodium citrate (E. Merck), aquadest (PT. Jawisesa).

#### Methods

##### Lipid Characterization

Single lipid of BW, GMS and their lipid binary system in several ratios (8:2, 6:4, 5:5, 4:6, 2:8) were studied in their characteristics. Several studies had been done either before and after apply stressing adjusted high shear homogenisation technique on SLN preparation (heated at 70°C and at 24.000 rpm using Ultra Turrax IKA® T25 Digital)

##### Characterization by Differential Thermal Analyzer (DTA)

Accurately weighed sample (5-8 mg) were crumped in closed 40 µl aluminium crucible pan. Samples were run at a heating rate of 10°C/min and heated from 25 - 300°C using DTA Mettler Toledo FP 85 (Switzerland), that has been calibrated with indium. The reference used for comparison were the same but empty aluminium pans. Melt temperature and thermograph profil of PMCA, BW - GMS in several ratio (10:0, 8:2, 6:4, 5:5, 4:6, 2:8 and 0:10) were studied.

##### Characterization by Powder X-ray Diffraction (PXRD)

PXRD diffraction pattern were obtained using a X ray diffractometer (Philips Xpert, Netherland). With CuKα radiation (1,54 Å) at 40kV, 30 mA, passing through a nickel filter with a divergent slit (0,5°), antiscattering slit (0,5°) and receiving slit (0,15 mm). Scanned at a rate of 2,4°/min, over the 2θ range of 5-40°.

**Characterization by Fourier Transform Infrared (FTIR) Spectroscopy:** Sample (the pure lipid BW, GMS and their binary system; and blank SLN) were dispersed with KBR (IR grade) in the ratio of 100:1 and then were compressed at 29,4 kN. FTIR were recorded from 4000 – 500 cm<sup>-1</sup>.

#### Preparation of blank SLNs

Several formulas of blank SLNs (table.1) composed by beeswax (BW) and glyceryl monostearate (GMS) as lipid core (100:0, 80:20;

60:40, 50:50, 40:60, 20:80 and 0:100) were prepared by high shear homogenization method. 12% of tween 80 was used as surfactant and 20% of propylene glycol was used as co-surfactant. Acetic buffer pH 4.2,  $\mu=0.5$  was used as aqueous phase. Lipid was melted at 70°C mixed with tween 80 and PG in aqueous phase in 70°C. They were stirred at 24,000 rpm for 8 minutes, with 30 seconds intervals every two minutes, using an Ultra Turax homogenizer T-25.

The hot dispersions were cooled keep by stirring in a reduced speed gradually.

Table 1: Formula blank SLN

Ingredients	Function	Concentration							
		BA	BB	BC	BD	BE	BF	BG	
beeswax	Lipid component of SLN	100	80	60	50	40	20	0	
Glyceryl monostearate	Lipid component of SLN	10 %	0	20	40	50	60	100	
Tween 80	surfactant	12%	12%	12%	12%	12%	12%	12%	
Propylene glycol	Co-surfactant	20%	20%	20%	20%	20%	20%	20%	
Acetic buffer pH 4,2, $\mu=0,5$	Aqueous phase	Ad 100%	Ad 100%	Ad 100%	Ad 100%	Ad 100%	Ad 100%	Ad 100%	

Table 2: Formula PMCA-SLN

Ingredients	Function	Concentration			
		FA	FD	FG	
PMCA	Active ingredient	0,88%*	0,88%	0,88%	
beeswax (BW)	Lipid component of SLN	100	50	0	
Glyceryl monostearate (GMS)	Lipid component of SLN	10 %	50	100	
Tween 80	surfactant	12%	12%	12%	
Propylene glycol	Co-surfactant	20%	20%	20%	
Acetic buffer pH4,2 $\mu=0,5$	Aqueous phase	Ad 100%	Ad 100%	Ad 100%	

Note: \* theurapeutical equivalent to Sodium Diclofenac as dermal antiinflammation drug [8]

#### Characterisation of blank SLNs

##### a. Measurement of blank SLNs Particle Size

Each sample was diluted with water (1:10) before measurement. The particle size were analyzed by Delsa Nano Particle Size Analyser at 25°C. Each measurement was performed in triplicates and the particle average diameter and polydispersity index (PI) was determined.

##### b. Measurement of blank SLNs physical stability

Physical stability of blank SLNs were determined by their changes of particle size after 40 days storage at controlled condition.

##### c. Observation of blank SLNs morphology

The morphology of SLNs were observed by Transmission Electron Microscope (TEM). Samples were stained with phosphor tungstic acid (PTA) 2% w/v and were placed on copper grids with former film for viewing at 120 kV (JEOL JEM-1400) and were analyzed using software.

#### Preparation of PMCA-SLN

SLN loaded PMCA were produced using same technique As core lipid of SLN was used the smallest and the most stables size of SLN blank. SLN with single lipid also made as comparison. PMCA was added in Tween 80 solution in PG mixed with aqueous phase.

#### Characterisation of PMCA-SLNs

All PMCA-SLNs were characterized in their viscosity, pH, morphology and their particle size. PMCA percentage entrapment efficiency was determined by centrifugation method.

#### Percentage of Drug Entrapment (Loading capacity)

Drug entrapment efficiency was determined by centrifugation method. It was calculated from the ratio of the drug amount

incorporate in SLN to total added drug amount. Centrifugation was carried out using Hettich Rotofix 32 Centrifuge.

About 1 gm of SLNs dispersion containing the drug was placed in the centrifuge tube, and sample were centrifuged at 2,500 rpm for 45 minutes. The amount of the free drug in the supernatant was estimated at 302 nm by spectrophotometry

$$\%DE = \frac{C_{total\ drug} - C_{free} \times 100}{C_{total\ drug}}$$

## RESULT AND DISCUSSION

### Lipid Characterisation

Based on DTA profile, it had showed that endothermic profile of GMS was sharper than BW. It indicated that GMS more crystalline than BW. GMS addition reduced amorphous of BW.

In ratio BW:GMS of 50:50 showed different profile among others, and its melting temperature was the lowest than others. This information is important, because according to Jenning [7] melting temperature affected particle size of SLN.

The result of X-ray diffraction of single BW and GMS before and after stress condition were shown in figure 3 and 4. Diffractogram of beeswax was sharp and had high intensity value, showed that BW have ordered lattice crystal. There was no changes of profile and intensity of BW diffractogram under stress condition. Compare to BW, Diffractogram of GMS was not sharp and had many peaks. It showed that lattice crystal of GMS was less ordered than BW and GMS which have many polymorph crystal. According to Jenning [7] the orderness of lattice crystal correspond to the capability of lipid to entrap the drug. The drug was more difficult to be inserted in the particle lipid that have ordered lattice crystal and was easier to expelled from the carrier.

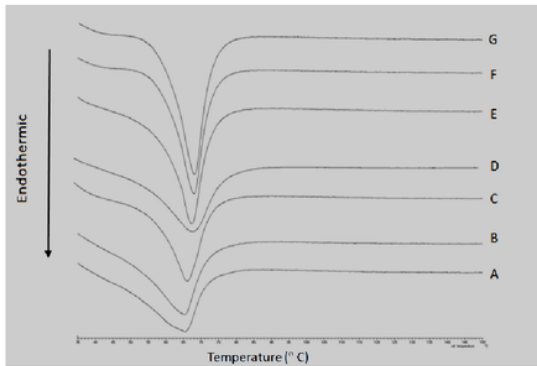


Fig. 1: DTA Thermogram of Beeswax:GMS in several composition BW:GMS, A. 10:0, B. 8:2, C.6:4, D. 5:5, E. 4:6, F. 2:8 and G.0:10 (%w/w).

Table 3: Melting point and enthalpy value of Beeswax:GMS in several ratios BW:GMS, A. 10:0, B. 8:2, C.6:4, D. 5:5, E. 4:6, F. 2:8 and GMS .0:10 (% w/w).

BW:GMS ratio (% w/w)	Melting point (°C)	Enthalpy (J/g)
0:10 (G)	65,7	110
2:8 (F)	65,5	119
4:6 (E)	65,4	131
5:5 (D)	62,3	115
6:4 (C)	64,6	103
8:2 (B)	64,1	103
10:0 (A)	64,5	103

Based on phase diagram profile, it is known that binary system in ratio BW:GMS of 50:50 was a simple eutectic mixture.

There were differences between diffractogram before and after stress applied to GMS. Before stress condition, it showed many peaks, on 2θ:19,45; 20,39; 21,61; 22,79; and 23,43 but reduced number peak was shown after treatment, on 2θ : 20,49 and 22,95. It showed that there was a change of crystal packing or there was a polymorphic transition. From figure 5 and 6, it known that diffraction peaks correspond to the ratio of BW:GMS. Increasing of ratio GMS in binary system of BW led to intensity and ordered lattice crystall disorder. GMS is capable to block the formation of the crystalline regularity of BW, thus potential energy of molecular bond becomes smaller. FTIR spectrum of single beeswax, single GMS and binary system of Beeswax:GMS (5:5 %b/b) before treatment (physically mixture) were showed in figure 8, and after treatment (heating and high shear mixing) in figure 9. Physically mixture BW in GMS showed reduced internal strength of hydrogen bonding of GMS. It impacted on reducing melting temperature of single BW or GMS either (figure 2). There was no new peak or lost of peak in that IR spectrum caused by treatment, but only change of peak intensity (super impose). That indicated that there was no chemical

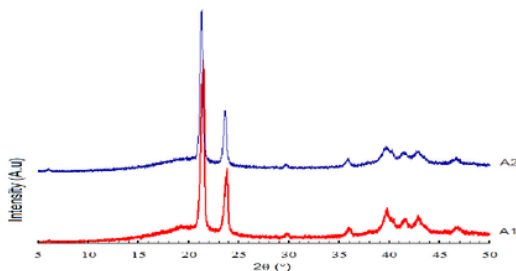


Fig. 3: X ray diffractogram of Beeswax before (A<sub>1</sub>) and after stress (A<sub>2</sub>)

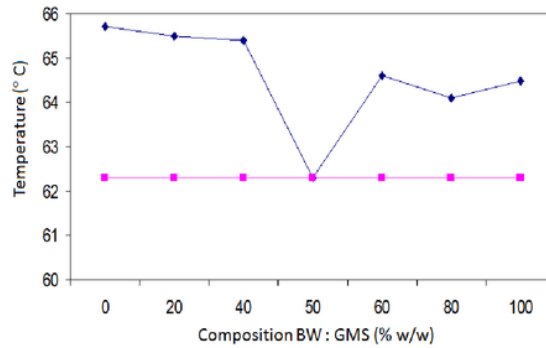


Fig. 2: Phase diagram of Beeswax:GMS in several ratios BW:GMS, A. 10:0, B. 8:2, C.6:4, D. 5:5, E. 4:6, F. 2:8 and G.0:10 (%w/w).

interaction between BW and GMS in binary system both before and after treatment. From the result of PMCA partition in lipid/acetic buffer pH 4,2 were known that increasing of ratio GMS led to increase PMCA partition in lipid (figure 10). The addition of GMS in beeswax could keep the molecule of drug inserted better in carrier. It was agreed with Jenning statement [7] that have been discussed previously.

GMS have emulsifying characteristics. Theoretically, the addition of GMS would increase PMCA solubilized in lipid. This contradiction phenomenon indicated that in this condition packing crystal was more dominant to influence PMCA entrapment in binary system BW and GMS.

#### a. Particle Size

Table 4 and figure 9 showed the particle size of all blank SLNs with several ratio of beeswax and GMS were prepared at several time storage. SLN were stored at room temperature (20-30°C) and RH 2%. Their stability was determined by their standard deviation. The particle size distribution indicated by the polydispersity index (PI) which is showed in figure 11.

The addition of GMS could decreased the particle size up to ratio 50% GMS, it may be due to the emulsifying effect of GMS. It agreed with Bunjes statement [4] that increasing emulgator decreased the particle size. In contrast, the further addition of GMS increased the particle size that observed with Delsa Nano PSA. It could be because of dilution effect as part of measurement procedure using Delsa Nano PSA.

The addition of water could swell SLN consisting lipid and emulgator.

It showed that SLN blank ratio 50:50 have the smallest particle size of  $192,8 \pm 14,6$  nm. It had the smallest polydispersity index (0,108) compare to others, that is indicated as the most homogenous system.

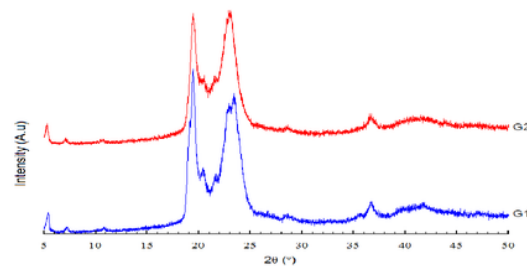


Fig. 4: X ray diffractogram GMS before (G<sub>1</sub>) and after stress (G<sub>2</sub>)



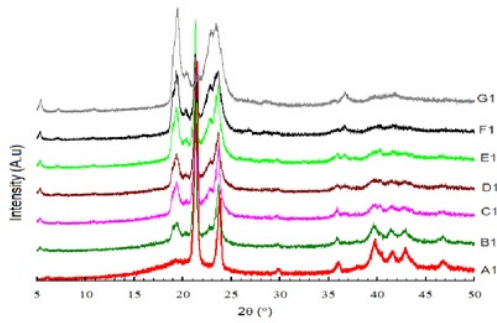


Fig. 5: X ray diffractogram of Beeswax : GMS in several ratios before stress apply. A.10:0, B. 8:2, C.6:4, D. 5:5, E. 4:6, F. 2:8 and G.0:10 (%w/w)

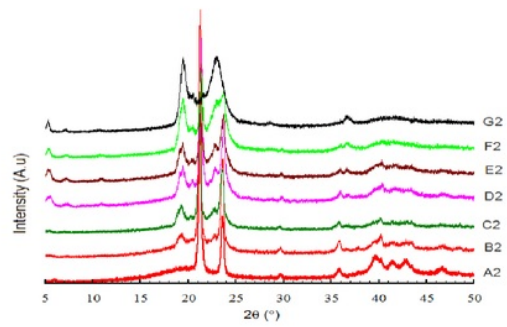


Fig. 6: X ray diffractogram of Beeswax : GMS in several ratio after stress apply. A.10:0, B. 8:2, C.6:4, D. 5:5, E. 4:6, F. 2:8 and G.0:10 (%w/w)

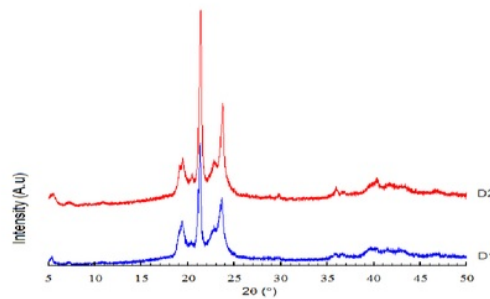


Fig. 7: X ray diffractogram of BW:GMS ratio 5:5 % w/w before (D<sub>1</sub>) and after treatment (D<sub>2</sub>)

In ratio BW: GMS 5:5 (%w/w) also looked crystal packing had been changed due to treatment (figure 7)

In further addition of GMS (60% and more) caused particles tend to agglomerate and indicated as bigger particles. GMS have several polymorph crystal of its glyceride.

It tend to change toward a stable crystal. This changes performed aggregation particles. Particle size of SLN loaded with PMCA could be seen in table 5.

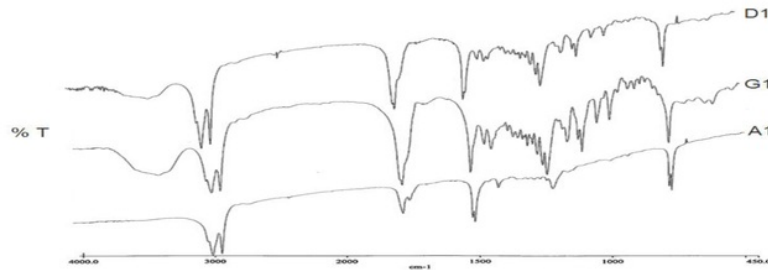


Fig. 8: Infra Red Spectra of single Beeswax (A<sub>1</sub>), single GMS (G<sub>1</sub>) and binary system Beeswax:GMS (5:5 %b/b)- D<sub>1</sub> before treatment

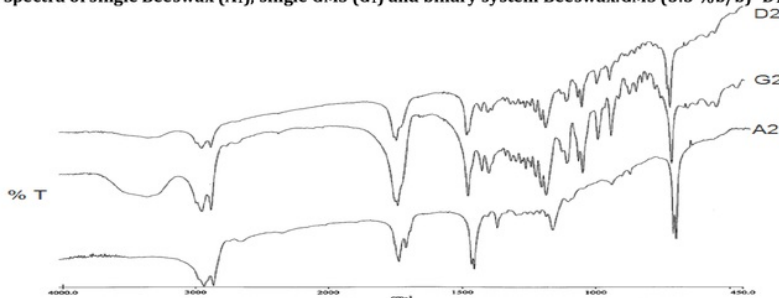


Fig. 9: Infra Red Spectra of single Beeswax (A<sub>2</sub>), single GMS (G<sub>2</sub>) and binary system Beeswax:GMS (5:5 %b/b)- D<sub>2</sub> after treatment

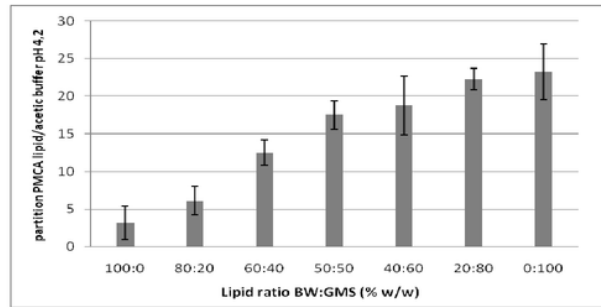


Fig. 10: Partition PMCA in lipid/actic buffer pH 4,2 μ=0,5

Table 4: Particle size and Polydispersity index of blank SLNs with several combination of beeswax and GMS, for 40 days.

Lipid ratio BW:GMS of Blank SLN	day	Mean (nm) ± SD	Mean size (nm) ± SD of particle size Blank SLN	PI
A. 100:0	1	427,3 ± 73,81	477,1 ± 60,38	0,236
	20	459,8 ± 99,17		
	40	544,3 ± 273,94		
B. 80:20	1	179,9 ± 70,43	365,4 ± 302,03	0,264
	20	202,3 ± 72,81		
	40	713,9 ± 120,15		
C. 60:40	1	247,5 ± 27,35	308,2 ± 116,27	0,192
	20	234,9 ± 19,61		
	40	442,3 ± 11,84		
D. 50:50	1	192,8 ± 14,63	220,4 ± 30,18	0,108
	20	252,7 ± 102,94		
	40	215,8 ± 59,62		
E. 40:60	1	832,6 ± 663,02	722,0 ± 237,85	0,340
	20	448,9 ± 580,31		
	40	884,3 ± 205,78		
F. 20:80	1	964,9 ± 255,91	964,9 ± 373,40	0,312
	20	1675,9 ± 1097,03		
	40	1518,1 ± 490,37		
G. 0:100	1	626,3 ± 110,22	1191,4 ± 999,45	0,546
	20	602,5 ± 383,65		
	40	2345,4 ± 1149,31		

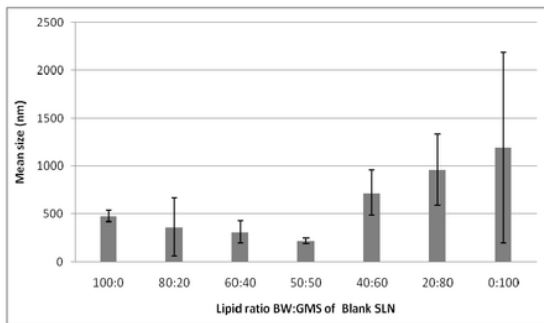


Fig. 11: Particle size of blank SLNs with several combinations of beeswax and GMS, at days 40.

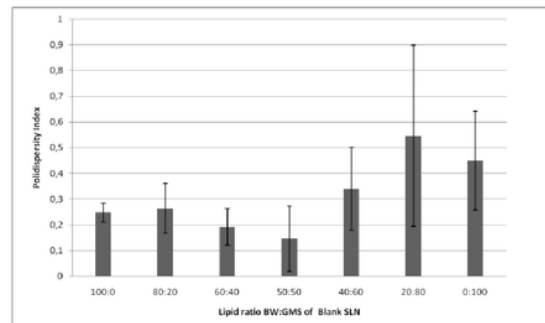


Fig. 12: Polydispersity index of blank SLNs with several combinations of beeswax and GMS, at days 40

Table 5: Particle size of PMCA-SLN with single lipid (beeswax or GMS) and its combination in 50:50

PMCA-SLN in SLN lipid ratio	day	Mean (nm)	Mean size of Formula Blank SLN BW:GMS (nm) ± SD
100:0 (single lipid: beeswax)	1	2630,8	2170,5 ± 648,9
	20	1447,8	
	40	2703,0	
50:50 Combination beeswax-GMS	1	767,3	826,5 ± 72,8
	20	804,3	
	40	907,8	
0:100 (single lipid GMS)	1	1364,9	1258,1 ± 202,7
	20	1024,3	
	40	1385,1	

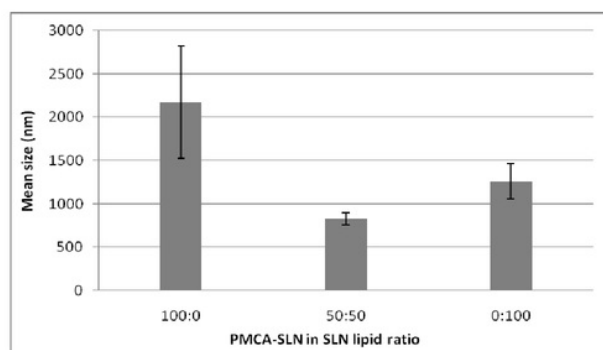


Fig. 13: Particle size of PMCA-SLN with single lipid (beeswax or GMS) and its combination in 50:50

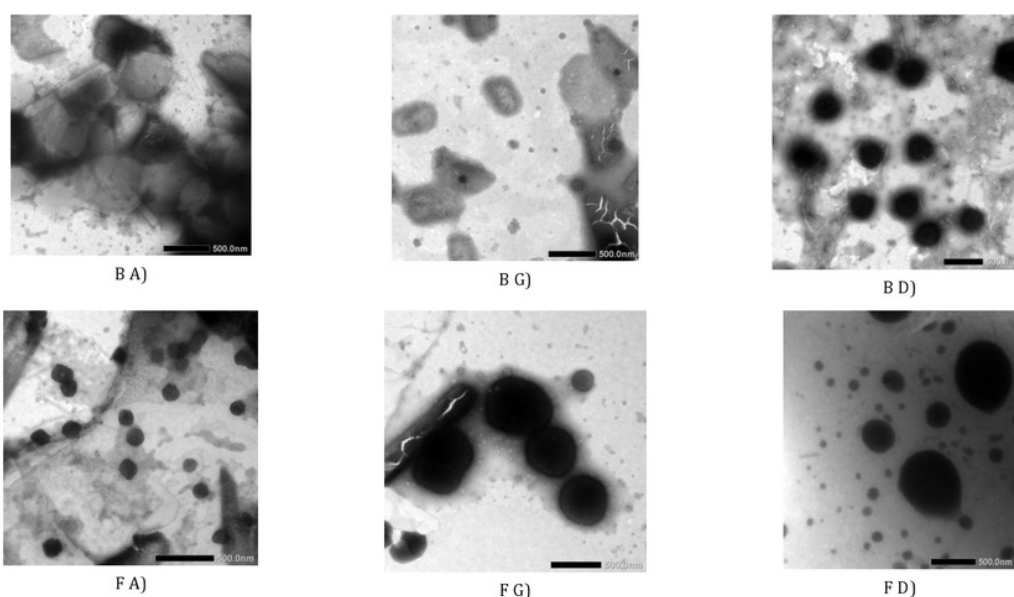


Fig. 14: Morphology of blank SLNs dan PMCA loaded SLNs

Note: B: morphology of blank SLNs A) single lipid BW, G) single lipid GMS and D) SLN with combination lipid beeswax-GMS (50:50)

F: morphology of SLN loaded PMCA A) single lipid BW, G) single lipid GMS and D) SLN with combination lipid beeswax-GMS (50:50)

SLN loaded PMCA with ratio beeswax-GMS 50:50 still had size of smaller than 1000 nm, while in single lipid SLN had size bigger than 1000 nm. The values of SLNs diameters by TEM were smaller than those measured by particle size analyser.

This may be ascribed hydration factor of SLN during sample preparation with water for particle size analyser, especially in SLN with GMS as lipid core. GMS have an emulsifying effect. PMCA loading affected size of SLN.

#### b. Morphology of SLN Using Transmission Electron Myroscope

The morphology of SLN tended to have round shapes (fig.14). *Phosphotungstic Acid* (PTA) was used as staining agent in TEM measurement. PTA is a hydrophilic substance, showed darker color in SLN which is use GMS. It was caused emulsifying effect of GMS that could absorbed PTA more than beeswax.

TEM observation showed smaller size compared to size analysis using Delsa Nano ParticleSize Analyser. It may because of the principle of Delsa Nano Particle Size Analyzer measurement is scanning, so aggregates of SLN could be scan as single particle

#### c. Viscosity and pH of blank SLNs and PMCA-SLNs

The viscosity and pH of SLNs could be seen on table 6. It seem that increasing GMS concentration increased their viscosity. All SLNs have pH in skin pH ranges.

#### 3. Percentage of Drug Entrapment (Loading capacity)

Percentage PMCA entrapped in SLN using single lipid or combination could be seen in table 7. It was known that PMCA entrapped in SLN using combination lipid beeswax-GMS in ratio 50:50 was higher than if using their single lipid as lipid core.

Table 6: Viscosity and pH value of SLNs

Lipid ratio	Viscosity (dpas) SLN-APMS (F)	pH $\pm$ SD	
		Blanko (B)	SLN-APMS (F)
A. single lipid: Beeswax	0,7 dpas	4,23 $\pm$ 0,03	4,21 $\pm$ 0,11
D. Beeswax : GMS = 50:50	15 dpas	4,22 $\pm$ 0,01	4,20 $\pm$ 0,05
G. single lipid: GMS	150 dpas	4,20 $\pm$ 0,01	4,22 $\pm$ 0,05

The particle size affected the viscosity of SLN. It agreed with Jores K statement [9].

Table 7: Percentage of PMCA entrapped in SLN

Lipid ratio	Mean % PMCA in SLN $\pm$ SD
100:0 (single lipid: beeswax)	79,52 $\pm$ 5,59
0:100 (single lipid GMS)	84,69 $\pm$ 5,42
50:50 Combination beeswax:GMS	94,08 $\pm$ 1,65

An increase of %DE in ratio BW:GMS 50:50 seemed related to the smallness that correspond to its melting temperature.

### CONCLUSION

Combination of lipid beeswax-GMS in ratio 50:50 as SLN lipid core performed the smallest, most homogenous particle size and most physically stable SLN. It also performed the highest PMCA entrapment. There was no chemical interaction between BW and GMS due to SLN process manufacturing (24.000 rpm stirring at 70°C). It was only because of polymorphic transition of GMS crystal. Lipid characteristics affected on SLN characteristics.

### ACKNOWLEDGMENT

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