

## **BAB V**

### **KESIMPULAN DAN SARAN**

#### **A. Kesimpulan**

Pertama, karakteristik *Liquid* SNEDDS pitavastatin *emulsification time* 5,30 detik, *drug loading* 108,12 mg/mL, transmittansi 97,3%, Zeta potensial -34,2 mV dan ukuran partikel sebesar 69,7 nm. kemudian pada *solid* SNEDDS Pitavastatin *emulsification time* 8,56 detik, *drug loading* 28,99 mg/g, transmittansi 63,3%, Zeta potensial -38,9 mV dan ukuran partikel sebesar 185,2 nm.

Kedua, berdasarkan parameter kecepatan obat dan jumlah obat yang terdifusi *solid* SNEDDS lebih tinggi dibandingkan *liquid* SNEDDS yaitu pada *solid* SNEDDS sebesar 132,64% dan *Liquid* SNEDDS sebesar 86,21%, sehingga bahan solidifikasi *solid* SNEDDS pitavastatin tidak mempengaruhi kemampuan obat dalam melewati membran.

#### **B. Saran**

Pertama, perlu dilakukan penelitian lebih lanjut dalam pembuatan *solid* SNEDDS pitavastatin dengan membandingkan adsorben jenis lain untuk meningkatkan kemampuan sebagai pembawa obat.

Kedua, perlu dilakukan penelitian lebih lanjut mengenai pembuatan formula sediaan obat dalam bentuk nanoemulsi serta memperhatikan karakter uji fisiknya.

Ketiga, perlu dilakukan penelitian lebih lanjut mengenai uji karakteristik meliputi: DSC, XRD, TGA dan FTIR antara *liquid* SNEDDS pitavastatin dan *solid* SNEDDS pitavastatin.

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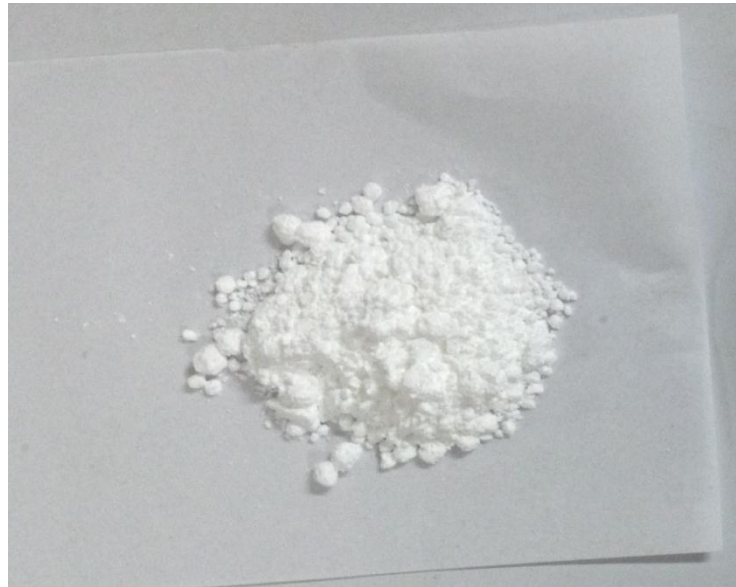
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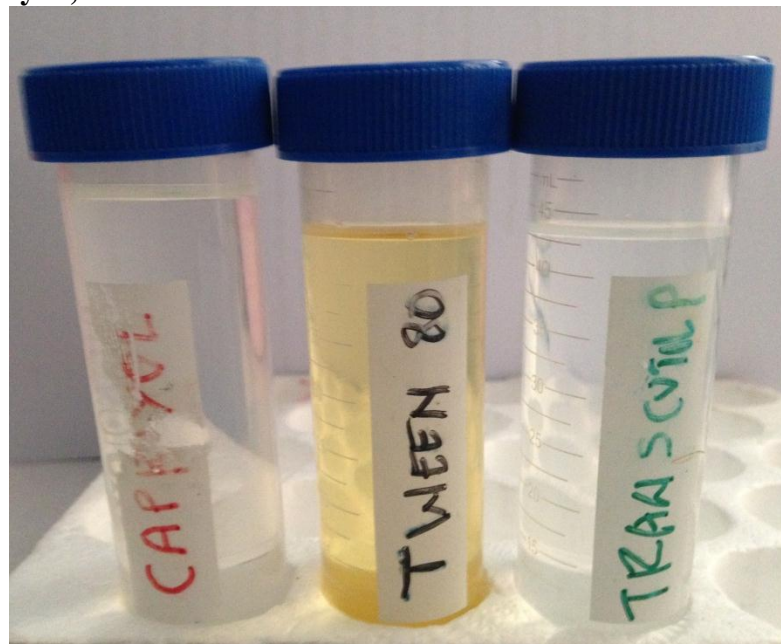
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**Lampiran 1. Bahan pitavastatin murni dan bahan minyak, surfaktan dan ko-surfaktan**

**Bahan Pitavastatin Murni**







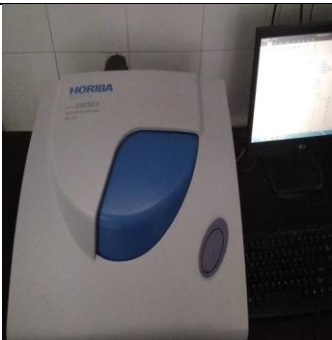



**Bahan minyak, surfaktan dan ko-surfaktan**

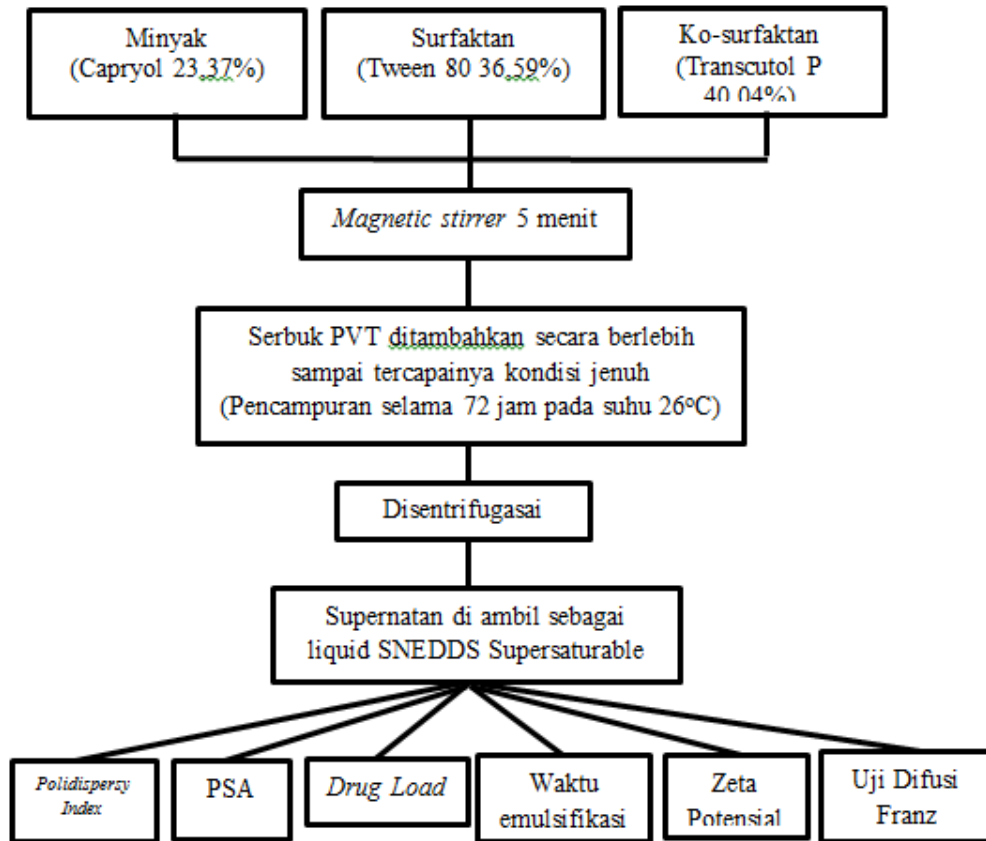


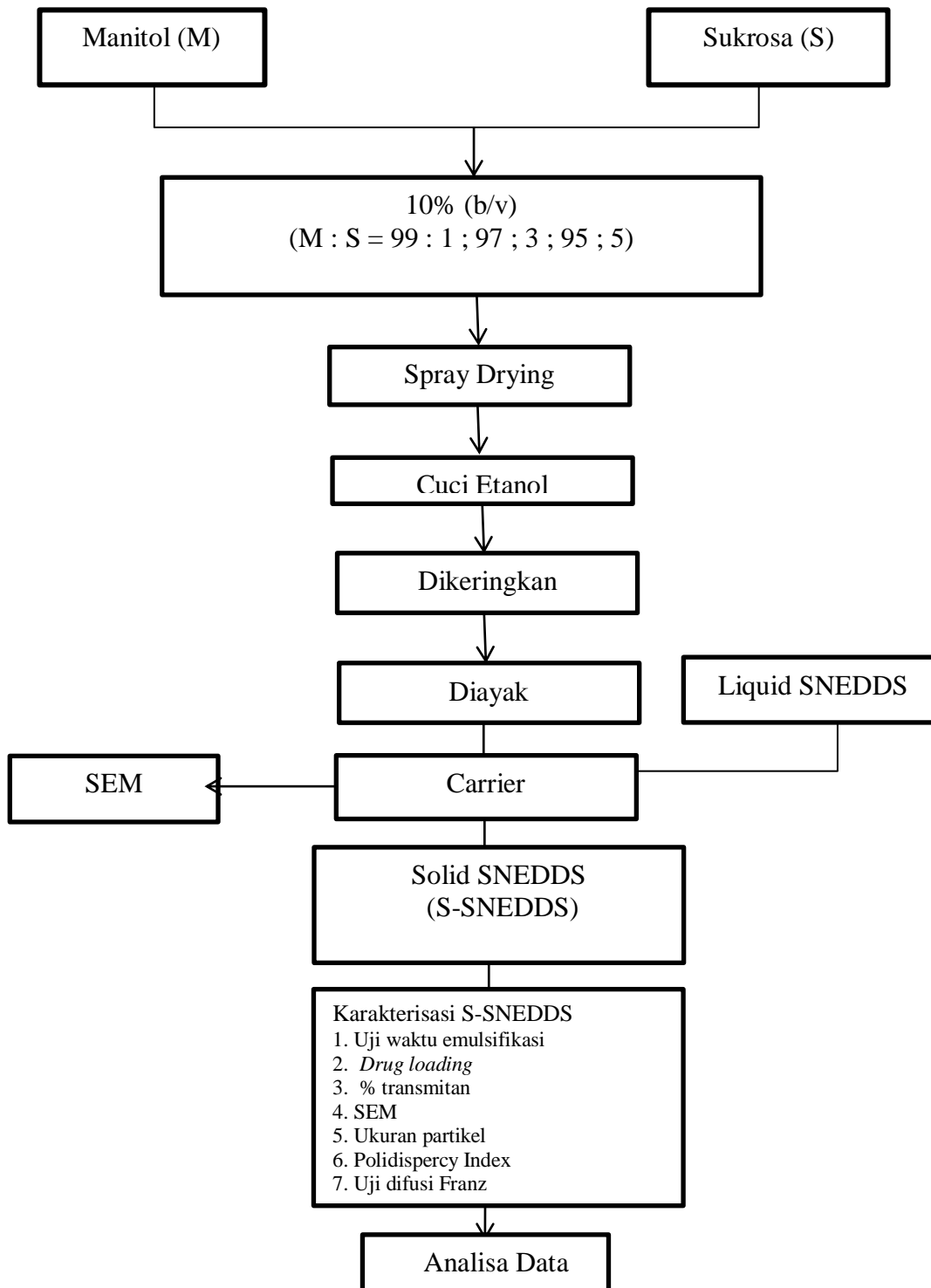


**Lampiran 2. Alat-alat yang digunakan dalam praktikum**

No	Alat	Nama Alat	Kegunaan
1		Neraca Analitik	Menimbang bahan, baik bahan baku maupun eksipien.
2		<i>Magnetic stirrer</i>	Mencampur dan menghomogenkan komponen
3		<i>Spektrofotometer Uv-Vis</i>	Membaca serapan bahan aktif, transmattan dan <i>drug loading</i> sediaan
4		Sentrifugasi	<i>Centrifuge</i> sampel

No	Alat	Nama Alat	Kegunaan
5		<i>Particel size analyzer (PSA)</i>	Mengukur ukuran partikel sampel
6		Mikro pipet	Memipet sampel yang diperlukan
7		<i>Stopwacth</i>	Menghitung waktu
8		<i>Difusion Franz Cell</i>	Alat untuk menguji difusi sediaan

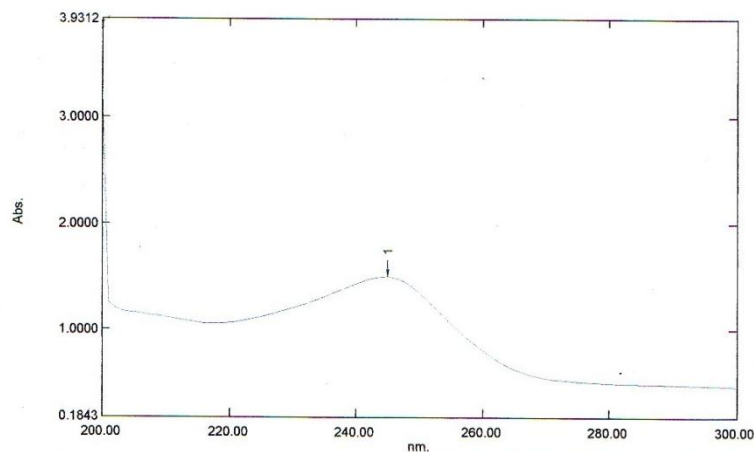
**Lampiran 3. Skema Pembuatan SNEDDS Pitavastatin**

**Lampiran 4. Skema pembuatan *solid* SNEDDS Pitavastatin**

## Lampiran 5. Pembuatan kurva kalibrasi dan validasi metode analisis

### a. Penentuan panjang gelombang maksimum

Panjang gelombang maksimum yang diperoleh dari scanning larutan pitavastatin konsentrasi 10 µg/mL yaitu panjang gelombang maksimum sebesar 245 nm, serapan 0,729 dengan pelarut metanol pro analisis.



No.	P/V	Wavelength	Abs.	Description
1	⬆️	245.00	0.7291	
2	⬇️	218.00	0.6569	

### b. Kurva kalibrasi

Kurva kalibrasi dengan pelarut metanol pa.

Konsentrasi (µg/mL)	Pembacaan 1	Pembacaan 2	Pembacaan 3	Pembacaan 4	Rata-rata
1	0.151	0.152	0.165	0.165	0.1583
2	0.215	0.215	0.251	0.251	0.2330
4	0.335	0.334	0.364	0.364	0.3493
6	0.484	0.484	0.465	0.466	0.4748
8	0.572	0.571	0.612	0.611	0.5915
10	0.792	0.792	0.757	0.757	0.7745
12	0.865	0.865	0.871	0.872	0.8683

$$a = 0,0764$$

$$b = 0,0734x$$

$$r = 0,9972$$

Persamaan

$$y = a + bx$$

$$= 0,0764 + 0,0734x$$

Keterangan

$x$  = konsentrasi ( $\mu\text{g/mL}$ )

$y$  = serapan

c. Linearitas

Konsentrasi ( $\mu\text{g/mL}$ )	Pembacaan 1	Pembacaan 2	Pembacaan 3	Pembacaan 4	Rata-rata
1	0.151	0.152	0.165	0.165	0.1583
2	0.215	0.215	0.251	0.251	0.2330
4	0.335	0.334	0.364	0.364	0.3493
6	0.484	0.484	0.465	0.466	0.4748
8	0.572	0.571	0.612	0.611	0.5915
10	0.792	0.792	0.757	0.757	0.7745
12	0.865	0.865	0.871	0.872	0.8683

$$a = 0,0764$$

$$b = 0,0734x$$

$$r = 0,9972$$

Hasil linieritas diperoleh  $R = 0,9972$ , sehingga dapat disimpulkan bahwa data linier.

d. Penentuan perolehan kembali (*Recovery*)

Konsentrasi	Replikasi	Absorbansi	Kadar ( $\mu\text{g/mL}$ )	Konsentrasi sebenarnya	%
80%	1	0.425	4.752	5.667	84%
	2	0.431	4.834	5.667	85%
	3	0.452	5.120	5.667	90%
100%	1	0.590	7.002	7.419	94%
	2	0.591	7.015	7.419	95%
	3	0.621	7.424	7.419	100%
120%	1	0.775	9.524	9.109	105%
	2	0.779	9.578	9.109	105%
	3	0.778	9.565	9.109	105%
Rata-rata %					95,9 %
Simpangan Baku (SD)					0,08

Keterangan:

$$\text{Kadar} = (\text{rata-rata serapan} - 0,0764) / 0,0734$$

$$\text{Nilai Sebenarnya} = \frac{\text{Kadar}}{1000} \times \text{volume pembuatan} \times \text{faktor pengenceran}$$

$$\% \text{ Recovery} = \frac{\text{Kadar}}{\text{Sebenarnya}} \times 100\%$$

## e. Penentuan Simpangan baku relative (RSD)

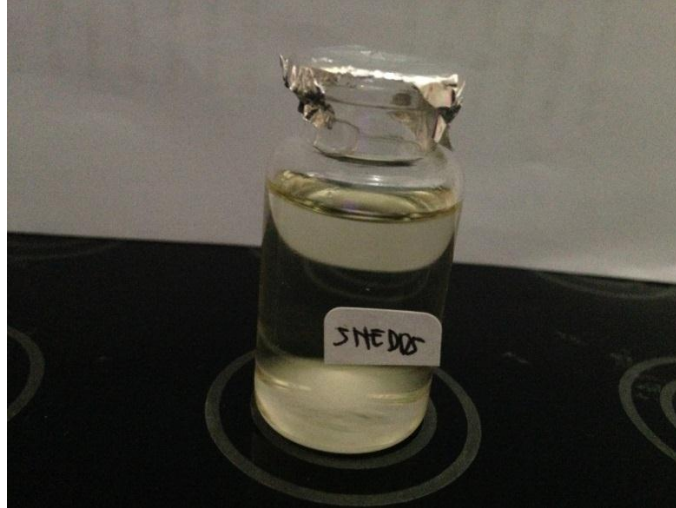
Replikasi	Absorbansi	Kadar
1	0.572	6.756
2	0.572	6.756
3	0.572	6.756
4	0.573	6.770
5	0.573	6.770
6	0.579	6.852
7	0.579	6.852
8	0.589	6.988
9	0.589	6.988
10	0.592	7.029
SD		0.11
RATA-RATA		6.852
RSD		0.016

Keterangan :

$$\text{Simpangan baku relative (RSD)} = \frac{\text{SD}}{\text{Rata-rata}} \times 100\%$$

**Lampiran 6. Bentuk sediaan SNEDDS Pitavastatin**

a. Formula SNEDDS sebelum ditambah pitavastatin



b. Formula SNEDDS setelah ditambah pitavastatin berlebih





c. Formula SNEDDS pitavastatin *supersaturable*



d. Formula SNEDDS pitavastatin *supersaturable* setelah ditambah *aquadestilata* (*emulsification*).



*Liquid* SNEDDS pitavastatin

## Lampiran 7. Pengujian Karakteristik SNEDDS pitavastatin

### 1. *Emulsification time liquid* SNEDDS pitavastatin

Formula	Waktu (detik)			Rata-Rata	SD
	Replikasi 1	Replikasi 2	Replikasi 3		
<i>Liquid</i> SNEDDS	5.12	5.49	5.29	5.30	0.19

### 2. % Transmitan *liquid* SNEDDS pitavastatin

Formula	% Transmitan			Rata-Rata (%)	SD
	Replikasi 1	Replikasi 2	Replikasi 3		
<i>Liquid</i> SNEDDS	97	97,5	97,4	97,3	0.26

### 3. *Drug loading liquid* SNEDDS pitavastatin

Absorbansi	Pengenceran 1		Pengenceran 2		Faktor Pengenceran total	Kadar	<i>Drug Load</i> (mg/mL)
	Volume	Faktor Pengenceran	Volume	Faktor Pengenceran			
0.999	20	51	20	151	7701	12.578	96.86
1.134	20	51	20	151	7701	14.418	111.03
1.127	20	51	20	151	7701	14.323	110.30
1.165	20	51	20	151	7701	14.841	114.29
Rata-Rata							108.12
SD							7.70

### Perhitungan *Drug loading liquid* SNEDDS pitavastatin

Keterangan:

$$\begin{aligned} \text{Pengenceran 1} &= \frac{\text{Volume pengambilan} + \text{volume Pelarut I}}{\text{Volume pengambilan}} \\ &= \frac{20 \mu\text{L} + 1 \text{ mL methanol}}{20 \mu\text{L}} \\ &= 51 \end{aligned}$$

$$\begin{aligned} \text{Pengenceran 2} &= \frac{\text{Volume pengambilan} + \text{volume Pelarut I}}{\text{Volume pengambilan}} \\ &= \frac{20 \mu\text{L} + 3 \text{ mL methanol}}{20 \mu\text{L}} \\ &= 151 \end{aligned}$$

Faktor pengenceran total = Faktor pengenceran 1 x Faktor pengenceran 2

Kadar :  $y = 0,0764 + 0,0734x$

$$1. \quad 0,999 = 0,0764 + 0,0734x$$

$$0,999 - 0,0764 = 0,0734x$$

$$x = 12,578$$

*Drug loading* = (kadar x total faktor pengenceran)/ 1000  $\mu\text{L}$

$$= (12,578 \times 7701)/1000 \mu\text{L}$$

$$= 96,86 \text{ mg/mL}$$

$$2. \quad 1,134 = 0,0764 + 0,0734x$$

$$1,134 - 0,0764 = 0,0734x$$

$$x = 14,418$$

*Drug loading* = (kadar x total faktor pengenceran)/ 1000  $\mu\text{L}$

$$= (14,418 \times 7701)/1000 \mu\text{L}$$

$$= 111,03 \text{ mg/mL}$$

$$3. \quad 1,127 = 0,0764 + 0,0734x$$

$$1,127 - 0,0764 = 0,0734x$$

$$x = 14,323$$

*Drug loading* = (kadar x total faktor pengenceran)/ 1000  $\mu\text{L}$

$$= (14,323 \times 7701)/1000 \mu\text{L}$$

$$= 110,30 \text{ mg/mL}$$

$$4. \quad 1,165 = 0,0764 + 0,0734x$$

$$1,165 - 0,0764 = 0,0734x$$

$$x = 14,841$$

*Drug loading* = (kadar x total faktor pengenceran)/ 1000  $\mu\text{L}$

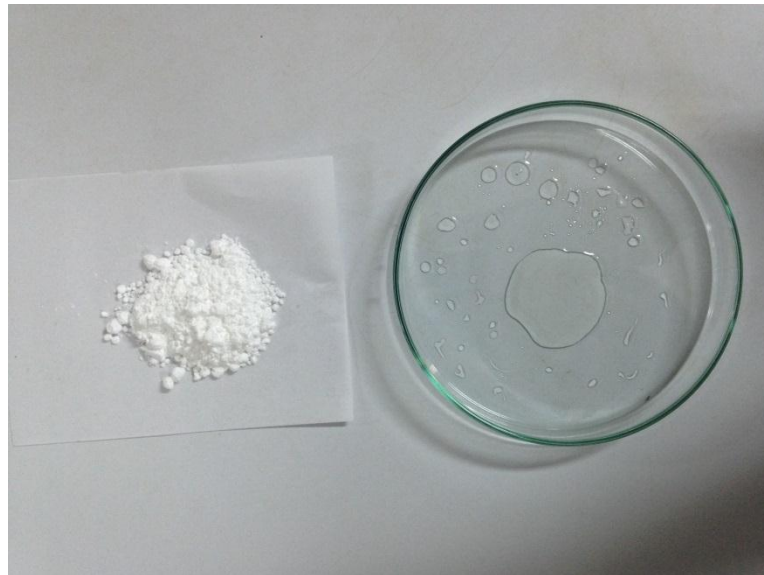
$$= (14,841 \times 7701)/1000 \mu\text{L}$$

$$= 114,29 \text{ mg/mL}$$

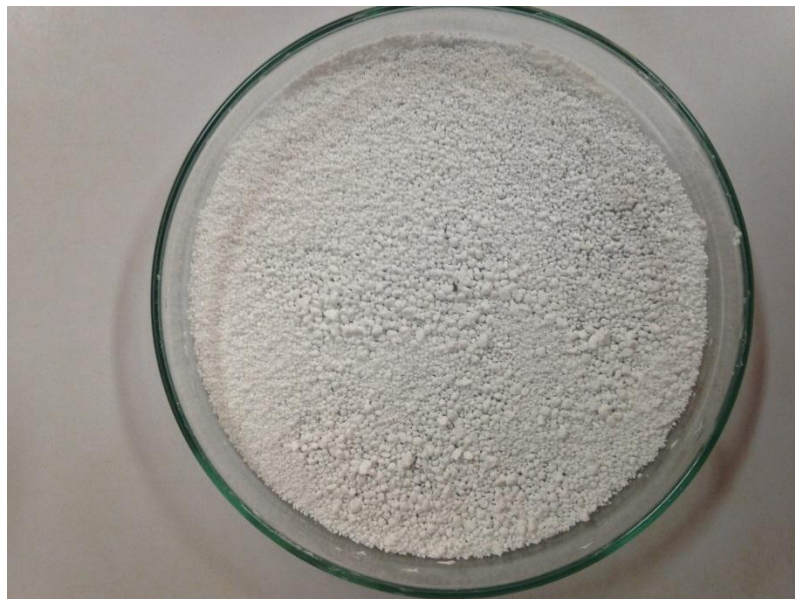
Rata-rata *Drug loading liquid* SNEDDS pitavastatin =  $(96,86 + 111,03$

$$+ 110,30 + 114,29) = 108,12 \text{ mg/mL}$$

**Lampiran 8. Solidifikasi *liquid* SNEDDS menjadi *solid* SNEDDS pitavastatin**



Solidifikasi dengan *mesoporous* manitol



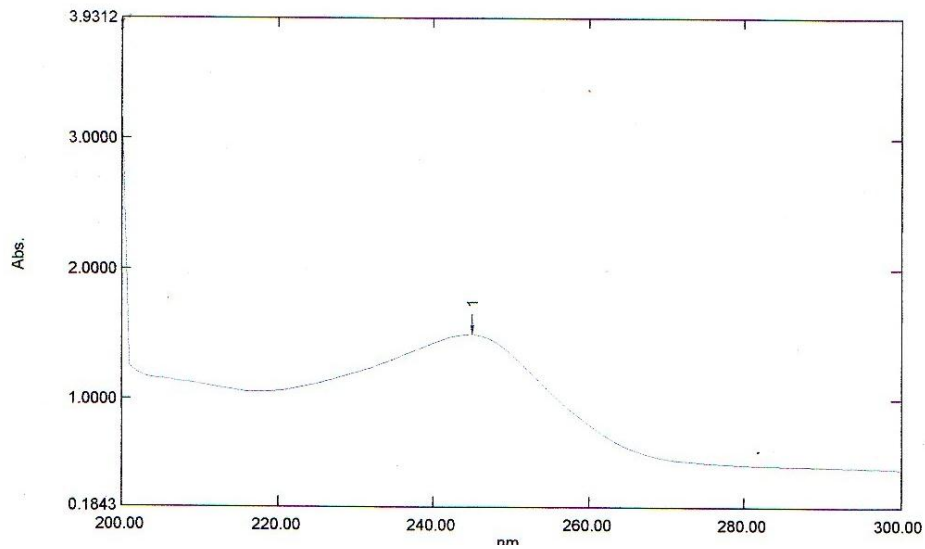
*Solid* SNEDDS pitavastatin

**Lampiran 9. Emulsifikasi solid SNEDDS pitavastatin**

**Lampiran 10. Panjang gelombang pitavastatin dalam dapar fosfat pH 7,4.**

Panjang gelombang maksimum yang diperoleh dari *scanning* larutan pitavastatin yaitu panjang gelombang maksimum sebesar 245 nm dengan serapan 0,721 nm dengan pelarut dapar fosfat pH 7,4.

Data Set: File\_181203\_123625 - RawData



**Lampiran 11. Kurva kalibrasi pitavastatin dalam dapar fosfat pH 7,4.**

Konsentrasi ( $\mu\text{L}$ )	Pembacaan 1	Pembacaan 2	Pembacaan 3	Rata-rata
1	0.147	0.147	0.108	0.127
2	0.214	0.214	0.214	0.214
4	0.337	0.336	0.338	0.338
6	0.541	0.541	0.526	0.534
8	0.68	0.679	0.681	0.680
10	0.718	0.719	0.705	0.712
12	0.859	0.858	0.844	0.851

Persamaan regresi linier kurva baku antara konsentrasi dan serapan diperoleh nilai :

$$a = 0,0707$$

$$b = 0,0745$$

$$r = 0,9917$$

$$y = 0,0707 + 0,0745x$$

## Lampiran 12. Pengujian Karakteristik *solid* SNEDDS pitavastatin

### 1. *Emulsification time solid* SNEDDS pitavastatin

Formula	Waktu (detik)			Rata-Rata	SD
	Replikasi 1	Replikasi 2	Replikasi 3		
<i>Solid</i> SNEDDS	8,31	8,62	8,76	8,56	0.23

### 2. % Transmitan *solid* SNEDDS pitavastatin

Formula	% Transmitan			Rata-Rata (%)	SD
	Replikasi 1	Replikasi 2	Replikasi 3		
<i>Solid</i> SNEDDS	62,9	63,5	63,4	63,3	0.32

### 3. *Drug loading solid* SNEDDS pitavastatin

Absorbansi	Pengenceran 1		Kadar	Jumlah	DL (mg/g)
	Vol	FP			
0.342	100	51	3.621	1.85	30.27
0.334	100	51	3.512	1.79	29.36
0.335	100	51	3.525	1.80	29.48
0.312	100	51	3.212	1.64	26.85
Rata-Rata					28.99
SD					1.48

Perhitungan *Drug load solid* SNEDD pitavastatin

Penimbangan solid 61 mg



$$\text{Kadar} : y = 0,0764 + 0,0734x$$

$$1. \quad 0,342 = 0,0764 + 0,0734x$$

$$0,342 - 0,0764 = 0,0734x$$

$$x = 3,621$$

$$\text{Jumlah} = (\text{kadar} \times \text{faktor pengenceran}) \times 10/1000$$

$$= (3,621 \times 51) \times 10/100$$

$$= 1,85$$

$$\text{Drug loading} = 1000 / \text{penimbangan solid} \times \text{jumlah}$$

$$= 1000 / 61 \text{ mg} \times 1,85$$

$$= 30,27 \text{ mg/g}$$

$$2. \quad 0,334 = 0,0764 + 0,0734x$$

$$0,334 - 0,0764 = 0,0734x$$

$$x = 3,512$$

$$\text{Jumlah} = (\text{kadar} \times \text{faktor pengenceran}) \times 10/1000$$

$$= (3,512 \times 51) \times 10/100$$

$$= 1,79$$

$$\text{Drug loading} = 1000 / \text{penimbangan solid} \times \text{jumlah}$$

$$= 1000 / 61 \text{ mg} \times 1,79$$

$$= 29,36 \text{ mg/g}$$

$$3. \quad 0,335 = 0,0764 + 0,0734x$$

$$0,335 - 0,0764 = 0,0734x$$

$$x = 3,525$$

$$\text{Jumlah} = (\text{kadar} \times \text{faktor pengenceran}) \times 10/1000$$

$$= (3,525 \times 51) \times 10/100$$

$$= 1,80$$

$$\text{Drug loading} = 1000 / \text{penimbangan solid} \times \text{jumlah}$$

$$= 1000 / 61 \text{ mg} \times 1,80$$

$$= 28,99 \text{ mg/g}$$

$$4. \quad 0,312 = 0,0764 + 0,0734x$$

$$0,312 - 0,0764 = 0,0734x$$

$$x = 3,212$$

$$\text{Jumlah} = (\text{kadar} \times \text{faktor pengenceran}) \times 10/1000$$

$$= (3,212 \times 51) \times 10/100$$

$$= 1,64$$

$$\text{Drug loading} = 1000 / \text{penimbangan solid} \times \text{jumlah}$$

$$= 1000 / 61 \text{ mg} \times 1,64$$

$$= 26,85 \text{ mg/g}$$

$$\text{Rata-rata Drug loading solid SNEDDS pitavastatin} = (30,27 + 29,36 + 29,48 + 26,85) = 28,99 \text{ mg/g}$$

### Lampiran 13. Data SPSS SNEDDS pitavastatin

Parameter	Liquid SNEDDS	Solid SNEDDS
Emulsification time*	5,30±0,19	8,56±0,23
Persen transmittan*	97,3±0,26	63,3±0,32
Drug loading**	108,12±7,70	28,99±1,48

Keterangan:

\* = *liquid* dan *solid* SNEDDS tidak memiliki perbedaan yang signifikan

\*\* = tidak bisa dibandingkan

#### 1. Waktu Emulsifikasi

##### One-Sample Kolmogorov-Smirnov Test

		Solid	liquid
N		3	3
Normal Parameters <sup>a,b</sup>	Mean	8.5633	5.3000
	Std. Deviation	.23029	.18520
	Absolute	.264	.188
Most Extreme Differences	Positive	.198	.188
	Negative	-.264	-.181
Kolmogorov-Smirnov Z		.457	.326
Asymp. Sig. (2-tailed)		.985	1.000

a. Test distribution is Normal.

b. Calculated from data.

Kesimpulan : Nilai Signifikasi pada *solid* SNEDDS pitavastatin  $0,985 > 0,05$  (H<sub>0</sub> diterima), *Liquid* SNEDDS pitavastatin dengan nilai signifikasi  $1,000 > 0,05$  (H<sub>0</sub> diterima). Data tersebut mengikuti distribusi normal sehingga dapat dilakukan analisis dengan *independent* T-Test.

##### Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Waktu	Equal variances assumed	.261	.636	-19.126	4	.000	-3.26333	.17062	-3.73705	-2.78962
	Equal variances not assumed			-19.126	3.824	.000	-3.26333	.17062	-3.74577	-2.78090

Kesimpulan: Nilai sig (2-tailed) *Equal variances not assumed* (diasumsikan kedua varian tidak sama) =  $0,000 < 0,05$  maka  $H_0$  ditolak atau waktu emulsifikasi *solid* SNEDDS pitavastatin terdapat perbedaan yang signifikan dengan waktu emulsifikasi *liquid* SNEDDS pitavastatin.

## 2. % Transmitan

**One-Sample Kolmogorov-Smirnov Test**

		Liquid	Solid
N		3	3
Normal Parameters <sup>a,b</sup>	Mean	97.3000	63.2667
	Std. Deviation	.26458	.32146
	Absolute	.314	.328
Most Extreme Differences	Positive	.225	.234
	Negative	-.314	-.328
Kolmogorov-Smirnov Z		.544	.567
Asymp. Sig. (2-tailed)		.929	.904

a. Test distribution is Normal.

b. Calculated from data.

Kesimpulan: Nilai Signifikasi pada pengujian difusi *liquid* SNEDDS pitavastatin  $0,929 > 0,05$  ( $H_0$  diterima), pengujian difusi *solid* SNEDDS pitavastatin dengan nilai signifikasi  $0,904 > 0,05$  ( $H_0$  diterima). Data tersebut mengikuti distribusi normal sehingga dapat dilakukan analisis dengan *independent* T-Test.

**Independent Samples Test**

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Jumlah obt terdifusi	Equal variances assumed	5.372	.023	-2.184	76	.032	-15.28082	6.99577	-29.21410	-1.34755
	Equal variances not assumed			-2.184	69.763	.032	-15.28082	6.99577	-29.23427	-1.32737

Kesimpulan:

- Pada *Equal variances assumed* nilai  $f = 5,372$  dengan nilai  $Sig = 0,023$ . Karena nilai  $sig < 0,05$  maka  $H_0$  ditolak atau kedua varian antara *liquid* dan *solid* SNEDDS pitavastatin tidak sama pada pengujian difusi.

- Pada *Equal variances assumed* nilai  $t = -2,184$  dengan nilai Sig. (*2-tailed*) 0,032. Karena nilai Sig. (*2-tailed*)  $< 0,05$  maka  $H_0$  ditolak atau terdapat perbedaan yang signifikan antara liquid dan solid SNEDDS pitavastatin dalam kecepatan terdifusi obat melewati membran.

**a. Liquid SNEDDS Pitavastatin**

1. Data difusi franz

- Replikasi 1:

Waktu (jam)	Absorbansi		Sampel Vol (mL)	Difusi Vol (mL)	Difusi (times)	Concentration		Conc. (mg/L)	Koreksi	koreksi kum	total diffusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.078	0.077	1	1	2	0.098	0.085	0.183	0.011	0.011	0.195	3.118	0.681
0.08	0.087	0.087	1	1	2	0.219	0.219	0.438	0.027	0.039	0.477	7.634	1.667
0.12	0.096	0.095	1	1	2	0.340	0.326	0.666	0.042	0.081	0.747	11.950	2.609
0.17	0.124	0.123	1	1	2	0.716	0.702	1.418	0.089	0.169	1.587	25.389	5.544
0.25	0.14	0.141	1	1	2	0.930	0.944	1.874	0.117	0.286	2.160	34.562	7.546
0.5	0.186	0.187	1	1	2	1.547	1.561	3.108	0.194	0.480	3.589	57.419	12.537
1	0.273	0.273	1	1	2	2.715	2.715	5.429	0.339	0.820	6.249	99.986	21.831
2	0.422	0.421	1	1	2	4.714	4.700	9.414	0.588	1.408	10.822	173.156	37.807
3	0.554	0.553	1	1	2	6.485	6.471	12.956	0.810	2.218	15.174	242.784	53.010
4	0.597	0.596	1	1	2	7.062	7.048	14.110	0.882	3.100	17.210	275.356	60.121
5	0.638	0.636	1	1	2	7.612	7.585	15.197	0.950	4.050	19.246	307.940	67.236
6	0.705	0.704	1	1	2	8.511	8.497	17.008	1.063	5.113	22.121	353.928	77.277

## - Replikasi 2 :

Waktu (jam)	Absorbansi		Sampel Vol (mL)	Difusi Vol (mL)	Difusi (times)	Concentration		Conc. (mg/L)	Koreksi	koreksi kum	total diffusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.078	0.078	1	1	2	0.098	0.098	0.197	0.012	0.012	0.209	3.346	0.730
0.08	0.082	0.082	1	1	2	0.152	0.152	0.304	0.019	0.031	0.335	5.367	1.172
0.12	0.089	0.088	1	1	2	0.246	0.233	0.479	0.030	0.061	0.540	8.636	1.886
0.17	0.091	0.09	1	1	2	0.273	0.259	0.532	0.033	0.094	0.627	10.027	2.189
0.25	0.096	0.097	1	1	2	0.340	0.353	0.693	0.043	0.138	0.831	13.296	2.903
0.5	0.147	0.146	1	1	2	1.024	1.011	2.035	0.127	0.265	2.300	36.798	8.034
1	0.172	0.173	1	1	2	1.360	1.373	2.733	0.171	0.436	3.168	50.693	11.068
2	0.32	0.321	1	1	2	3.345	3.359	6.704	0.419	0.855	7.559	120.939	26.406
3	0.397	0.396	1	1	2	4.378	4.365	8.743	0.546	1.401	10.144	162.311	35.439
4	0.453	0.457	1	1	2	5.130	5.183	10.313	0.645	2.046	12.359	197.740	43.175
5	0.535	0.55	1	1	2	6.230	6.431	12.661	0.791	2.837	15.498	247.968	54.141
6	0.632	0.626	1	1	2	7.531	7.451	14.982	0.936	3.773	18.755	300.087	65.521

- Replikasi 3 :

Waktu (jam)	Absorbansi		Sampel Vol (mL)	Difusi Vol (mL)	Difusi (times)	Concentration		Conc. (mg/L)	Koreksi	koreksi kum	total diffusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.079	0.078	1	1	2	0.112	0.098	0.210	0.013	0.013	0.223	3.574	0.780
0.08	0.081	0.082	1	1	2	0.139	0.152	0.291	0.018	0.031	0.322	5.152	1.125
0.12	0.088	0.089	1	1	2	0.233	0.246	0.479	0.030	0.061	0.540	8.636	1.886
0.17	0.092	0.091	1	1	2	0.286	0.273	0.559	0.035	0.096	0.655	10.483	2.289
0.25	0.099	0.098	1	1	2	0.380	0.367	0.747	0.047	0.143	0.890	14.236	3.108
0.5	0.185	0.183	1	1	2	1.534	1.507	3.041	0.190	0.333	3.374	53.985	11.787
1	0.214	0.215	1	1	2	1.923	1.936	3.860	0.241	0.574	4.434	70.939	15.489
2	0.32	0.31	1	1	2	3.345	3.211	6.556	0.410	0.984	7.540	120.643	26.341
3	0.497	0.496	1	1	2	5.720	5.707	11.427	0.714	1.698	13.125	209.994	45.850
4	0.553	0.554	1	1	2	6.471	6.485	12.956	0.810	2.508	15.464	247.422	54.022
5	0.625	0.624	1	1	2	7.437	7.424	14.861	0.929	3.437	18.298	292.766	63.923
6	0.717	0.716	1	1	2	8.672	8.658	17.330	1.083	4.520	21.850	349.595	76.331

Persamaan kurva baku pitavastatin dengan dapar fosfat pH 7,4 yaitu  $y = 0.0707 + 0.0745x$ , dimana  $y$  adalah serapan dan  $x$  adalah kadar pelepasan.



- Konsentrasi diperoleh dengan memasukkan serapan yang diperoleh pada persamaan kurva baku ( $y = 0.0707 + 0.0745x$ ), dimana  $y$  adalah serapan dan  $x$  adalah kadar pelepasan.

3 menit :

$$1. y = 0.0707 + 0.0745x$$

$$0,079 = 0,0707 + 0,0745x$$

$$0,079 - 0,0707 = 0,0745x$$

$$x = 0,112 \text{ mg/L}$$

$$2. y = 0.0707 + 0.0745x$$

$$0,078 = 0,0707 + 0,0745x$$

$$0,078 - 0,0707 = 0,0745x$$

$$x = 0,098 \text{ mg/L}$$

$$\text{Konsentrasi} = \frac{(x_1 + x_2)}{2} \times \text{Total volume difusi}$$

$$= \frac{(0,112 + 0,098)}{2} \times 2$$

$$= 0,21 \text{ mg/L}$$

- Pengambilan medium tiap selang waktu sebanyak 1 mL dan diganti dengan volume medium yang sama, karena pada tiap pengambilan terjadi pengurangan kadar dalam medium tersebut sehingga agar kadar dalam medium dianggap tetap maka kadar tersebut dijadikan faktor koreksi.

Faktor koreksi :

$$\begin{aligned}
 3 \text{ menit} &= \frac{\text{Vol yang diambil}}{\text{Vol medium}} \times \text{Konsentrasi} \\
 &= \frac{1 \text{ mL}}{16 \text{ mL}} \times 0,21 \text{ mg/mL} \\
 &= 0,013
 \end{aligned}$$

Faktor koreksi kumulatif <sub>2</sub> = faktor koreksi <sub>2</sub>

$$\begin{aligned}
 \text{Faktor koreksi kumulatif } 3 &= \text{faktor koreksi } 3 + \text{koreksi kumulatif } 2 \\
 &= 0,018 + 0,013 \\
 &= 0,031
 \end{aligned}$$

- Total difusi diperoleh dari Koreksi kumulatif + konsentrasi
- Jumlah obat yang terdifusi (mcg) = 16 x total difusi
- Jumlah obat terdifusi (mcg/cm<sup>2</sup>) =  $\frac{\text{Jumlah obat yang terdifusi (mcg)}}{4,58}$

- Total difusi *liquid* SNEDDS pitavastatin

Waktu	Rep 1	Rep 2	Rep 3	Mean	SD
0	0	0	0	0	0
0.05	0.681	0.730	0.780	0.730	0.05
0.08	1.667	1.172	1.125	1.321	0.30
0.12	2.609	1.886	1.886	2.127	0.42
0.17	5.544	2.189	2.289	3.341	1.91
0.25	7.546	2.903	3.108	4.519	2.62
0.5	12.537	8.034	11.787	10.786	2.41
1	21.831	11.068	15.489	16.129	5.41
2	37.807	26.406	26.341	30.185	6.60
3	53.010	35.439	45.850	44.766	8.84
4	60.121	43.175	54.022	52.439	8.58
5	67.236	54.141	63.923	61.767	6.81
6	77.277	65.521	76.331	73.043	6.53

WAKTU	AUC REP 1	AUC REP 2	AUC REP 3
0	0.017	0.018	0.020
0.05	0.039	0.032	0.032
0.08	0.071	0.051	0.050
0.12	0.204	0.102	0.104
0.17	0.545	0.212	0.225
0.25	2.510	1.367	1.862
0.5	8.592	4.776	6.819
1	29.819	18.737	20.915
2	45.408	30.922	36.096
3	56.566	39.307	49.936
4	63.679	48.658	58.973
5	72.256	59.831	70.127
6	72.256	59.831	70.127
AUC	351,964	263,845	315,285
%RELAUC	97,77%	73,29%	87,58%
RATA-RATA		86,21%	

Perhitungan AUC : (serapan total difusi ke-2 + serapan total difusi ke-1) x (waktu ke-2 – waktu ke-1)x 1/2

Replikasi 1

$$\begin{aligned} \text{Waktu 0} &= (0,681+0) \times (0,05 - 0) \times \frac{1}{2} \\ &= 0,017 \end{aligned}$$

$$\begin{aligned} \text{Waktu 0,05} &= (1,667+0,681) \times (0,08 - 0,05) \times \frac{1}{2} \\ &= 0,039 \end{aligned}$$

b. *Solid* SNEDDS Pitavastatin

- Replikasi 1

Waktu (jam)	Absorbansi		Volume Sampling	Volume Pengencer	Pengenceran	Konsentrasi		Kons. (mg/L)	Koreksi	total koreksi	total difusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.087	0.086	1	1	2	0.219	0.206	0.425	0.027	0.027	0.451	7.223	1.577
0.08	0.107	0.106	1	1	2	0.487	0.474	0.962	0.060	0.087	1.048	16.771	3.662
0.12	0.193	0.193	1	1	2	1.641	1.641	3.283	0.205	0.292	3.574	57.191	12.487
0.17	0.298	0.299	1	1	2	3.050	3.063	6.114	0.382	0.674	6.787	108.600	23.712
0.25	0.325	0.325	1	1	2	3.412	3.412	6.825	0.427	1.100	7.925	126.802	27.686
0.5	0.426	0.425	1	1	2	4.767	4.754	9.521	0.595	1.696	11.217	179.471	39.186
1	0.513	0.514	1	1	2	5.935	5.948	11.883	0.743	2.438	14.321	229.135	50.030
2	0.561	0.562	1	1	2	6.579	6.592	13.171	0.823	3.261	16.432	262.914	57.405
3	0.697	0.697	1	1	2	8.403	8.403	16.807	1.050	4.312	21.118	337.895	73.776
4	0.712	0.711	1	1	2	8.605	8.591	17.196	1.075	5.387	22.582	361.317	78.890
5	0.727	0.726	1	1	2	8.806	8.792	17.598	1.100	6.486	24.085	385.355	84.139
6	0.897	0.896	1	1	2	11.087	11.073	22.160	1.385	7.871	30.031	480.501	104.913

## - Replikasi 2

Waktu (jam)	Absorbansi		Sampel Vol (mL)	Difusi Vol (mL)	Difusi (times)	Concentration		Conc. (mg/L)	Koreksi	koreksi kum	total diffusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.078	0.079	1	1	2	0.098	0.112	0.210	0.013	0.013	0.223	3.574	0.780
0.08	0.081	0.082	1	1	2	0.139	0.152	0.291	0.018	0.031	0.322	5.152	1.125
0.12	0.096	0.095	1	1	2	0.340	0.326	0.666	0.042	0.073	0.739	11.829	2.583
0.17	0.123	0.121	1	1	2	0.702	0.675	1.377	0.086	0.159	1.537	24.584	5.368
0.25	0.226	0.225	1	1	2	2.084	2.071	4.155	0.260	0.419	4.573	73.175	15.977
0.5	0.369	0.365	1	1	2	4.003	3.949	7.952	0.497	0.916	8.867	141.878	30.978
1	0.405	0.405	1	1	2	4.486	4.486	8.971	0.561	1.476	10.448	167.164	36.499
2	0.565	0.565	1	1	2	6.632	6.632	13.265	0.829	2.305	15.570	249.122	54.393
3	0.682	0.681	1	1	2	8.202	8.189	16.391	1.024	3.330	19.721	315.530	68.893
4	0.752	0.751	1	1	2	9.141	9.128	18.269	1.142	4.472	22.741	363.852	79.444
5	0.891	0.89	1	1	2	11.006	10.993	21.999	1.375	5.847	27.846	445.529	97.277
6	0.901	0.902	1	1	2	11.140	11.154	22.294	1.393	7.240	29.534	472.545	103.176

## - Replikasi 3

Waktu (jam)	Absorbansi		Sampel Vol (mL)	Difusi Vol (mL)	Difusi (times)	Concentration		Conc. (mg/L)	Koreksi	koreksi kum	total diffusion (ppm)	difusi (mcg)	difusi (mcg/cm <sup>2</sup> )
	Read 1	Read 2				Read 1	Read 2						
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	0.077	0.078	1	1	2	0.085	0.098	0.183	0.011	0.011	0.195	3.118	0.681
0.08	0.084	0.085	1	1	2	0.179	0.192	0.371	0.023	0.035	0.406	6.494	1.418
0.12	0.093	0.092	1	1	2	0.300	0.286	0.586	0.037	0.071	0.657	10.515	2.296
0.17	0.132	0.131	1	1	2	0.823	0.809	1.632	0.102	0.173	1.806	28.891	6.308
0.25	0.216	0.216	1	1	2	1.950	1.950	3.900	0.244	0.417	4.317	69.070	15.081
0.5	0.345	0.344	1	1	2	3.681	3.667	7.348	0.459	0.876	8.224	131.587	28.731
1	0.415	0.414	1	1	2	4.620	4.606	9.226	0.577	1.453	10.679	170.867	37.307
2	0.465	0.465	1	1	2	5.291	5.291	10.581	0.661	2.114	12.696	203.129	44.351
3	0.562	0.561	1	1	2	6.592	6.579	13.171	0.823	2.937	16.108	257.731	56.273
4	0.652	0.651	1	1	2	7.800	7.786	15.586	0.974	3.912	19.497	311.957	68.113
5	0.791	0.79	1	1	2	9.665	9.651	19.316	1.207	5.119	24.434	390.950	85.360
6	0.891	0.89	1	1	2	11.006	10.993	21.999	1.375	6.494	28.493	455.882	99.538

- Konsentrasi diperoleh dengan memasukkan serapan yang diperoleh pada persamaan kurva baku ( $y = 0.0707 + 0.0745x$ ), dimana  $y$  adalah serapan dan  $x$  adalah kadar pelepasan.

3 menit :

$$1. y = 0.0707 + 0.0745x$$

$$0,077 = 0,0707 + 0,0745x$$

$$0,077 - 0,0707 = 0,0745x$$

$$x = 0,085 \text{ mg/L}$$

$$2. y = 0.0707 + 0.0745x$$

$$0,078 = 0,0707 + 0,0745x$$

$$0,078 - 0,0707 = 0,0745x$$

$$x = 0,098 \text{ mg/L}$$

$$\text{Konsentrasi} = \frac{(x_1 + x_2)}{2} \times \text{Total volume difusi}$$

$$= \frac{(0,085 + 0,098)}{2} \times 2$$

$$= 0,183 \text{ mg/L}$$

- Pengambilan medium tiap selang waktu sebanyak 1 mL dan diganti dengan volume medium yang sama, karena pada tiap pengambilan terjadi pengurangan kadar dalam medium tersebut sehingga agar kadar dalam medium dianggap tetap maka kadar tersebut dijadikan faktor koreksi.



Faktor koreksi :

$$\begin{aligned}
 3 \text{ menit} &= \frac{\text{Vol yang diambil}}{\text{Vol medium}} \times \text{Konsentrasi} \\
 &= \frac{1 \text{ mL}}{16 \text{ mL}} \times 0,183 \text{ mg/mL} \\
 &= 0,011
 \end{aligned}$$

Faktor koreksi kumulatif <sub>2</sub> = faktor koreksi <sub>2</sub>

$$\begin{aligned}
 \text{Faktor koreksi kumulatif } 3 &= \text{faktor koreksi } 3 + \text{koreksi kumulatif } 2 \\
 &= 0,023 + 0,011 \\
 &= 0,035
 \end{aligned}$$

- Total difusi diperoleh dari Koreksi kumulatif + konsentrasi
- Jumlah obat yang terdifusi (mcg) = 16 x total difusi
- Jumlah obat terdifusi (mcg/cm<sup>2</sup>) =  $\frac{\text{Jumlah obat yang terdifusi (mcg)}}{4,58}$

- Total difusi *solid* SNEDDS pitavastatin

WAKTU	REP 1	REP 2	REP 3	MEAN	SD
0	0	0	0	0	0
0.05	1.577	0.780	0.681	1.013	0.491
0.08	3.662	1.125	1.418	2.068	1.388
0.12	12.487	2.583	2.296	5.789	5.803
0.17	23.712	5.368	6.308	11.796	10.330
0.25	27.686	15.977	15.081	19.581	7.033
0.5	39.186	30.978	28.731	32.965	5.504
1	50.030	36.499	37.307	41.278	7.589
2	57.405	54.393	44.351	52.050	6.835
3	73.776	68.893	56.273	66.314	9.032
4	78.890	79.444	68.113	75.482	6.388
5	84.139	97.277	85.360	88.925	7.259
6	104.913	103.176	99.538	102.542	2.743

WAKTU	AUC REP 1	AUC REP 2	AUC REP 3
0	0.039	0.020	0.017
0.05	0.087	0.032	0.035
0.08	0.269	0.062	0.062
0.12	0.905	0.199	0.215
0.17	2.142	0.889	0.891
0.25	8.359	5.869	5.476
0.5	22.304	16.869	16.509
1	53.717	45.446	40.829
2	65.591	61.643	50.312
3	76.333	74.168	62.193
4	81.514	88.360	76.736
5	94.526	100.226	92.449
6	94.526	100.226	92.449
AUC	500.31	494.01	438.17
%RELAUC	138.98%	137.23%	121.72%
Rata-rata		132.64%	

- Penimbangan *solid* SNEDDS pitavastatin untuk uji difusi franz

$$\text{Drug loading solid SNEDDS pitavastatin} = 28,99 \text{ mg/g}$$

Setiap kompartemen difusi berisi 16 mL dapar fosfat pH 6,8 dan pH 7,4

*Solid* SNEDDS pitavastatin yang digunakan untuk pengujian difusi franz

$$= \frac{\text{Vol Kompartemen difusi franz}}{\text{Rata-rata drug loading solid SNEDDS PVT}} \times 1000$$

$$= \frac{16}{28,99 \text{ mg/g}} \times 1000$$

$$= 551,9 \text{ mg}$$

Jadi *solid* SNEDDS pitavastatin yang ditimbang untuk pengujian difusi franz sebanyak 551,9 mg.

- Perhitungan difusi

$$\text{Nilai koreksi} = \frac{\text{Volume yang diambil}}{\text{volume didalam chamber difusi}} \times \text{konsentrasi}$$

$$\text{Nilai koreksi kumulatif} = \text{Nilai koreksi ke-3} + \text{nilai koreksi kumulatif ke-2}$$

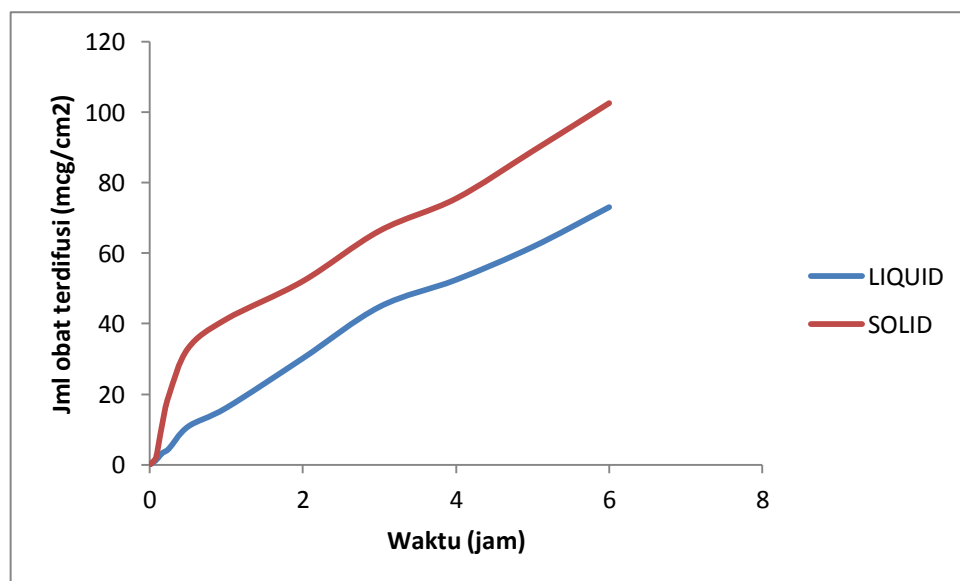
$$\text{Total difusi} = \text{Nilai koreksi} + \text{nilai koreksi kumulatif}$$

Jumlah obat yang terdifusi (mcg)

$$= \text{Volume dalam chamber difusi} \times \text{nilai total difusi}$$

$$\% \text{RELAUC} = \frac{\text{Rata-rata obat terdifusi}}{(360 \times 100)} \times 100$$

- Grafik difusi *liquid* dan *solid* SNEDDS pitavastatin



## Lampiran 15. PSA Liquid SNEDDS Pitavastatin

2019.04.11 18:34:08

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Scientific

HORIBA SZ-100 for Windows [Z Type] Ver2.10

### SZ-100

#### OPT 17.nsz Measurement Results

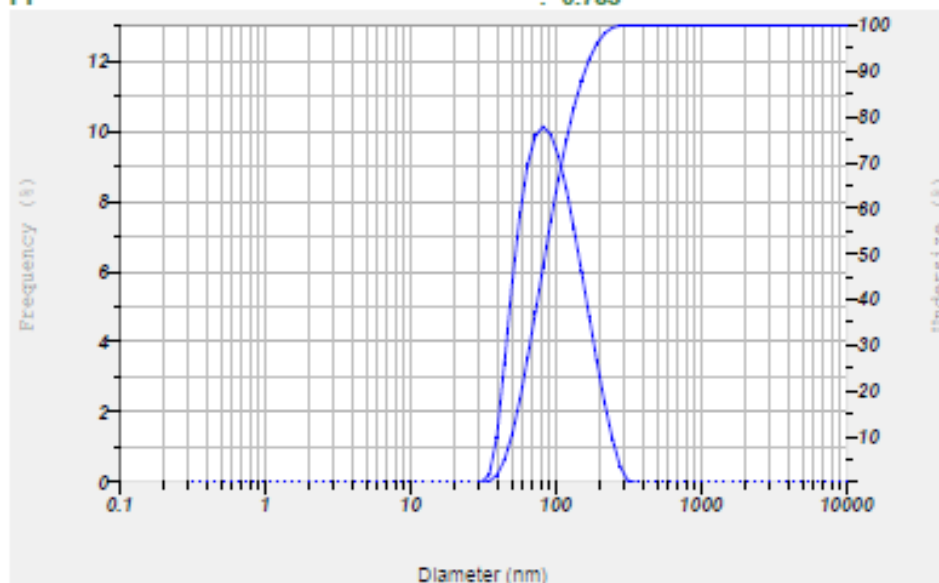
Date : Tuesday, July 17, 2018 11:44:02  
 Measurement Type : Particle Size  
 Sample Name : Formula Optimum  
 Scattering Angle : 90  
 Temperature of the Holder : 24.8 °C  
 Dispersion Medium Viscosity : 0.898 mPa·s  
 Transmission Intensity before Meas. : 31065  
 Distribution Form : Standard  
 Distribution Form(Dispersity) : Monodisperse  
 Representation of Result : Scattering Light Intensity  
 Count Rate : 1965 kCPS

#### Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	96.2 nm	44.2 nm	77.5 nm
2	—	— nm	— nm	— nm
3	—	— nm	— nm	— nm
Total	1.00	96.2 nm	44.2 nm	77.5 nm

#### Cumulant Operations

Z-Average : 69.7 nm  
 PI : 0.783



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1/1

## Lampiran 16. Zeta potensial Liquid SNEDDS Pitavastatin

2019.04.11 10:30:37

**HORIBA**  
Scientific

HORIBA SZ-100 for Windows [Z Type] Ver2.10

**SZ-100**

### Measurement Results

Zeta OPT + PVT R7.nzt

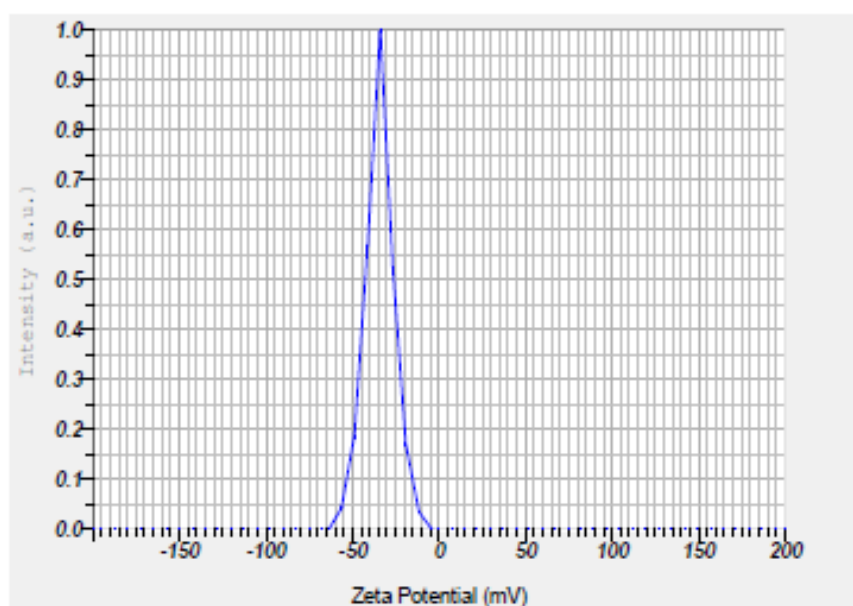
#### Measurement Results

Date : Friday, January 4, 2019 11:33:33 AM  
 Measurement Type : Zeta Potential  
 Sample Name : OPT + PVT  
 Temperature of the Holder : 24.9 °C  
 Dispersion Medium Viscosity : 0.897 mPa·s  
 Conductivity : 0.127 mS/cm  
 Electrode Voltage : 3.4 V

#### Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-34.2 mV	-0.000265 cm <sup>2</sup> /Vs
2	— mV	— cm <sup>2</sup> /Vs
3	— mV	— cm <sup>2</sup> /Vs

Zeta Potential (Mean) : -34.2 mV  
 Electrophoretic Mobility Mean : -0.000265 cm<sup>2</sup>/Vs



Explore the Future

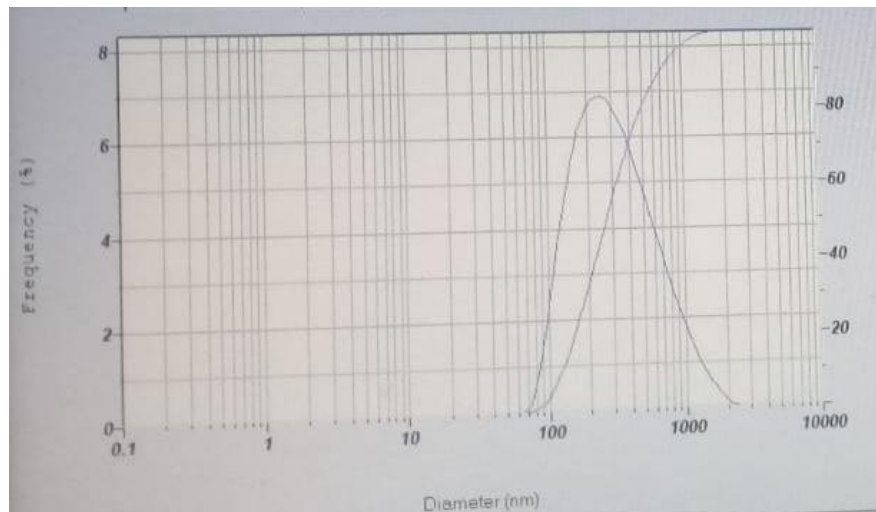
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**HORIBA**

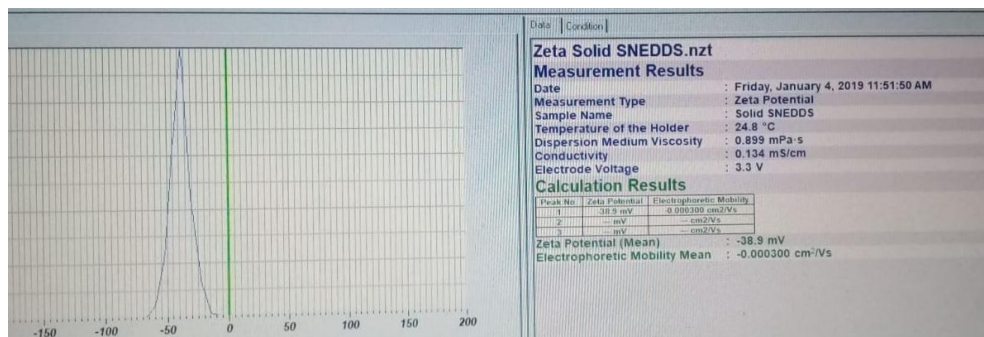
1 / 1

## Lampiran 17. PSA *solid* SNEDDS pitavastatin dan Zeta potensial *solid* SNEDDS pitavastatin

### PSA *solid* SNEDDS pitavastatin



### Zeta potensial *solid* SNEDDS pitavastatin



### Lampiran 18. Data SPSS Difusi

		Liquid	Solid
N		13	13
Normal Parameters <sup>a,b</sup>	Mean	23.1656	38.4464
	Std. Deviation	26.22641	35.78072
	Absolute	.223	.163
Most Extreme Differences	Positive	.223	.163
	Negative	-.189	-.141
Kolmogorov-Smirnov Z		.804	.586
Asymp. Sig. (2-tailed)		.538	.882

a. Test distribution is Normal.

b. Calculated from data.

Kesimpulan: Nilai Signifikasi pada pengujian difusi *liquid* SNEDDS pitavastatin  $0,538 > 0,05$  ( $H_0$  diterima), transmitan *solid* SNEDDS pitavastatin dengan nilai signifikasi  $0,904 > 0,05$  ( $H_0$  diterima). Data tersebut mengikuti distribusi normal sehingga dapat dilakukan analisis dengan *independent* T-Test.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper	
Formula	Equal variances assumed			.000	10	1.000	.00000	.31623	-.70460	.70460
	Equal variances not assumed			.000	10.000	1.000	.00000	.31623	-.70460	.70460
Jumlah obat terdifusi	Equal variances assumed	6.027	.034	-6.126	10	.000	-.87150	.14225	-1.18846	-.55454
	Equal variances not assumed			-6.126	5.000	.002	-.87150	.14225	-1.23717	-.50583

Kesimpulan:

- Pada *Equal variances assumed* nilai  $f = 6,027$  dengan nilai  $Sig = 0,034$ . Karena nilai  $sig < 0,05$  maka  $H_0$  ditolak atau hasil difusi kedua varian antara *liquid* dan *solid* SNEDDS pitavastatin tidak sama pada pengujian difusi.
- Pada *Equal variances not assumed* nilai  $t = -6,126$  dengan nilai  $Sig. (2-tailed) 0,002$ . Karena nilai  $Sig. (2-tailed) < 0,05$  maka  $H_0$  ditolak atau terdapat perbedaan yang signifikan antara *liquid* dan *solid* SNEDDS



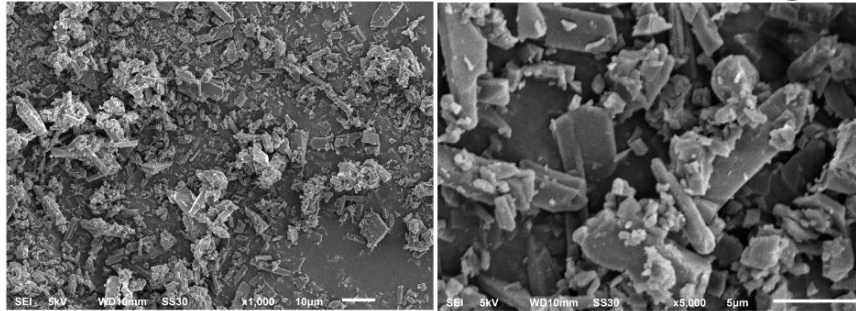
pitavastatin dalam jumlah obat terdifusi dan kecepatan terdifusi obat melewati membran.

Lampiran 19. SEM *solid* SNEDDS, adsorben *mesoporous* manitol dan Pitavastatin murni

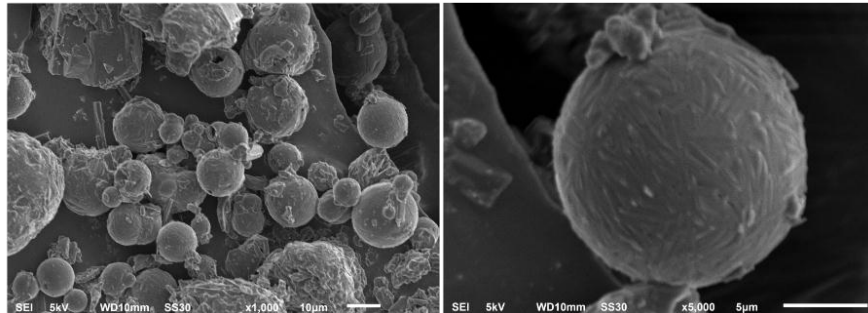
## Solidifikasi SNEDDS: SEM

1000x mag.

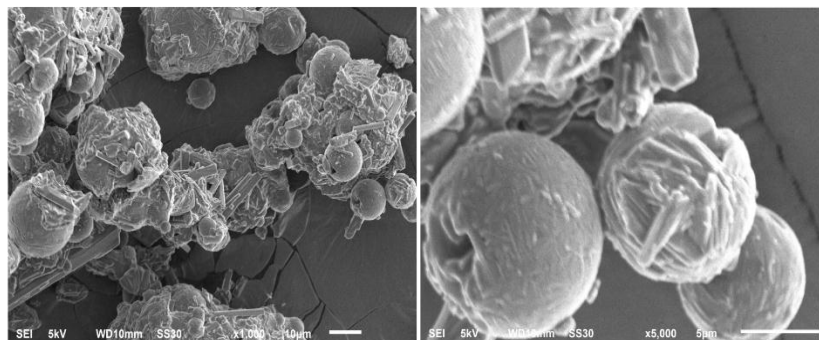
5000x mag.



Pitavastatin murni



Carrier (pembawa) mesoporous



Solid SNEDDS Pitavastatin

## Lampiran 20. CoA Pitavastatin



THANEN CHEMICALS(CHANGZHOU)CO.,LTD  
 ADDRESS: KM1707, BLDG 5, CHANGFA, 101-1# TAIHU ROAD, 213022,  
 P.R.CHINA  
 TEL: +86 519 89885717 FAX: +86 519 86801861

## Certificate of Analysis

### Pitavastatin Calcium

CHEMICAL NAME	(+)-Monocalciumbis [(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate]		
MFG.DATE	2017-08-06	TEST DATE	2017-08-06
BATCH NO.	170801	Expiry Date	2019-08-05
COUNTRY OF ORIGIN	China	CAS NO.	147526-32-7

#### RESULT OF INSPECTION

Item	Standard	Result
Appearance	A White or Pale Yellow Power	A white Power
[ $\alpha$ ] <sub>D</sub> <sup>20</sup>	+18.5° ~ -23.5°	+22.9°
UV Identification	Shows absorption Maxima at 245±2nm	$\lambda_{max}$ = 244nm
Water	≤15.0%	5.8%
Ca	4.3%~4.8%	4.6%
Heavy Metal	≤20ppm	Conforms
Related Substances	≤2.0%	0.6%
Max Single impurity%	≤0.5%	Conform
Assay	≥98% <small>For and on behalf of</small>	99.4%

  
 常州泽世化学有限公司  
 THANEN CHEMICALS(CHANGZHOU)CO.,LTD

CONCLUSION: THE PRODUCT COMPLIES WITH PRESCRIBED ENTERPRISE STANDAR