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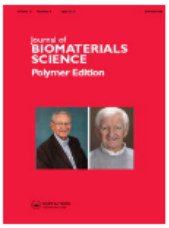
LAMPIRAN

1. Publikasi Jurnal



Journal of Biomaterials Science, Polymer Edition

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/tbsp20

Formulation and evaluation of dissolving microneedle for transdermal delivery of piperine: the effect of polymers concentration

Andi Nur Aisyah, Andi Dian Permana, Elly Wahyudin, Diany Elim, Mukarram Mujahid, Ikbal Ikbal, Nana Novriana Payung Datu & Muhammad Aswad

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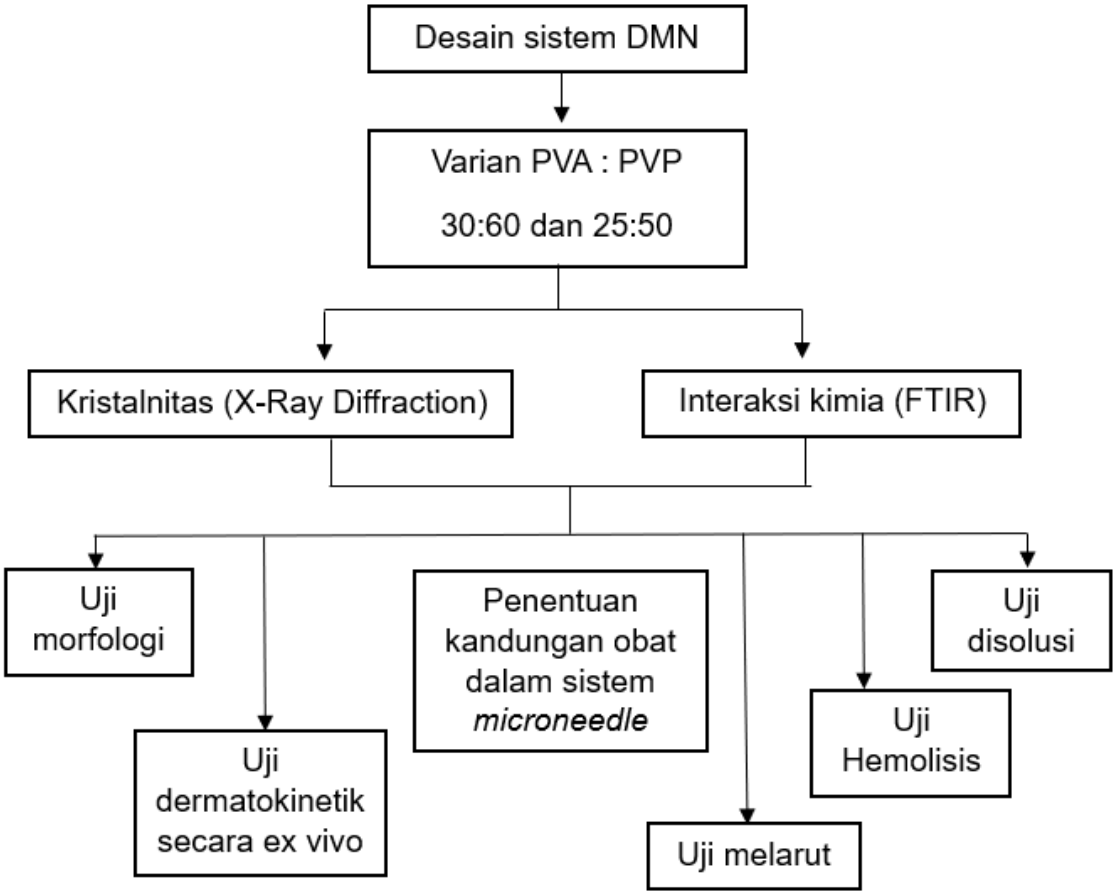
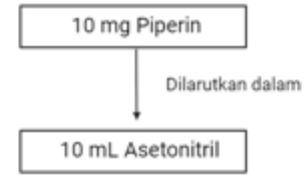
Published online: 04 Mar 2024.

2. Skema Kerja DMN PIP



3. Pembuatan Larutan Induk, Kurva Kalibrasi dan Quality Control

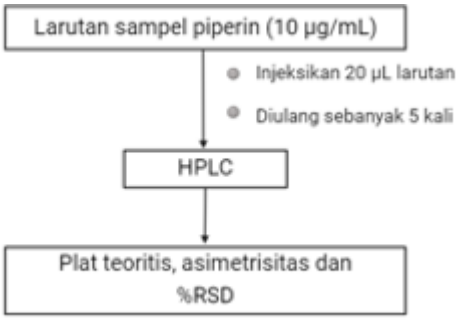
a. Larutan Induk



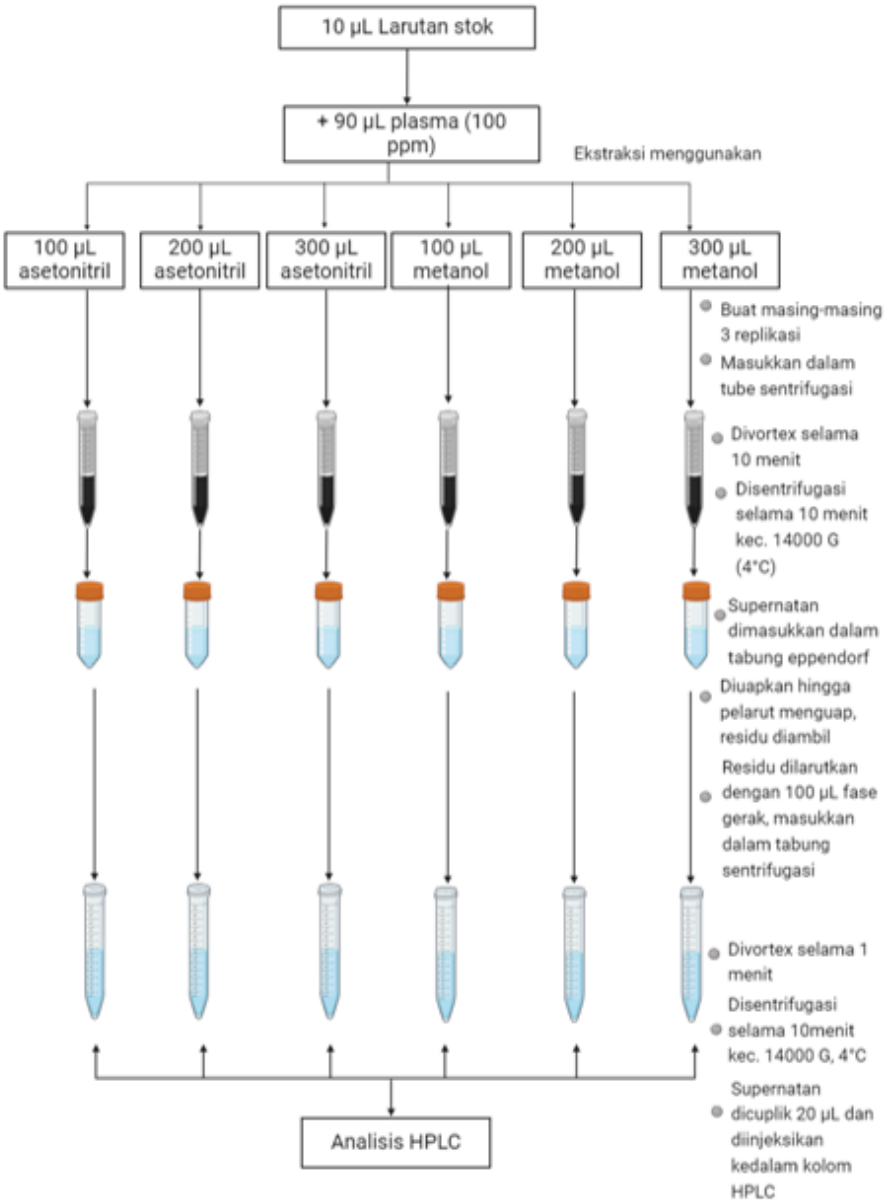
b. Kurva kalibrasi

c. Quality Control

4. Uji Kesesuaian Sistem

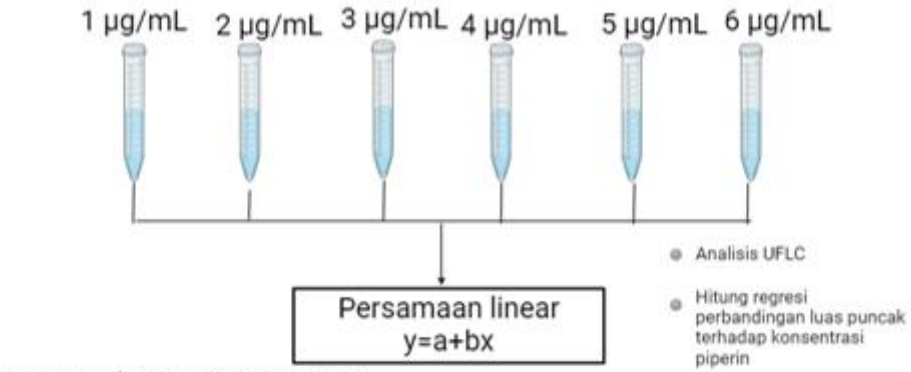


5. Penetepan Metode Ekstraksi

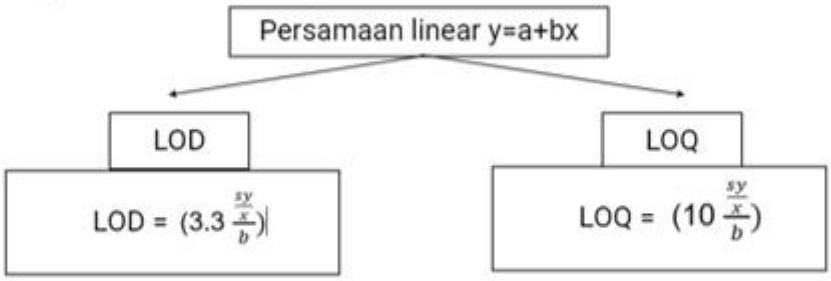


6. Validasi Metode Analisis

a. Uji Linearitas

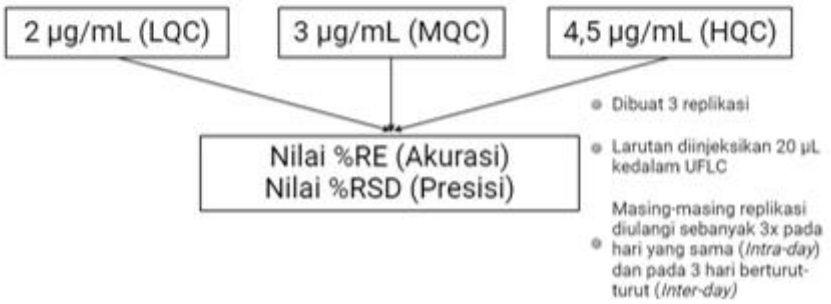


b. Pengukuran LOD dan LOQ

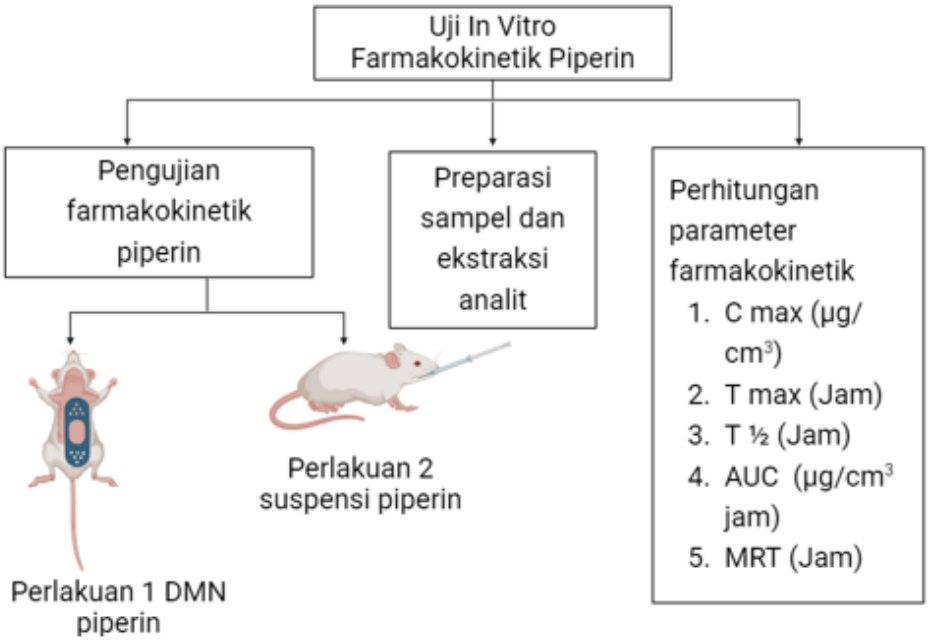


c. Uji Selektivitas

d. Uji Akurasi dan Presisi



e. Uji In Vitro Farmakokinetik Piperin



7. Kode Etik Penelitian

KOMISI ETIK PENELITIAN KESEHATAN
SEKOLAH TINGGI ILMU FARMASI MAKASSAR
THE HEALTH RESEARCH ETHICS COMMITTEE
SEKOLAH TINGGI ILMU FARMASI MAKASSAR

SURAT KETERANGAN
ETHICAL APPROVAL
Nomor: 085/EC.1.1.B/X/KEPK/2022

Komisi Etik Penelitian Kesehatan Sekolah Tinggi Ilmu Farmasi Makassar, menyatakan dengan ini bahwa penelitian dengan judul :
The Health Research Ethical Committee of Sekolah Tinggi Ilmu Farmasi Makassar states hereby that the following proposal:

"PENGEMBANGAN PIPERIN DALAM SISTEM PENGHANTARAN OBAT MICRONEEDLE SEBAGAI UPAYA OPTIMASI POTENSI SEBAGAI ANTIKANKER"

Nomor Protokol *Protocol number*	:	112210085
Lokasi Penelitian *Location*	:	LABORATORIUM BIOFARMASI UNIVERSITAS HASANUDDIN MAKASSAR; LABORATORIUM FARMAKOLOGI DAN FARMASI KLINIK SEKOLAH TINGGI ILMU FARMASI MAKASSAR
Waktu Penelitian *Time schedule*	:	24 Oktober - 24 Maret 2023 *24th October until 20th March of 2022*
Responden/Subyek Penelitian *Respondent/Research Subject*	:	Hewan Uji *Animal Experiment*
Peneliti Utama *Principal Investigator*	:	**ANDI NUR AISYAH**
NIM	:	N013202002

Telah melalui prosedur kaji etik dan dinyatakan layak untuk dilaksanakan
Has proceeded the ethical assessment procedure and been approved for the implementation

Demikianlah surat keterangan lolos kaji etik ini dibuat untuk diketahui dan dimaklumi oleh yang berkepentingan dan berlaku sejak tanggal 24 Oktober 2022 sampai dengan 24 Oktober 2023
This ethical approval is issued to be used appropriately and understood by all stakeholders and valid from the 24th October 2022 until 24th October of 2023

Makassar, 24th October 2022
Chairman

dr. Sulfian Zainur Rosyid
NIDN. 0902012103

Bersama ini menyatakan bahwa dengan dikeluarkannya surat lolos etik dari Komisi Etik Penelitian Kesehatan STIFA Makassar, maka saya **berkewajiban**:

1. Menyerahkan Laporan hasil penelitian **dan atau** Publikasi dari hasil penelitian
2. Menyerahkan laporan Serious Adverse Event (SAE) ke komisi etik dalam 27 jam dan dilengkapi dalam 7 hari serta laporan Suspected Unexpected Serious Adverse Reaction (SUSAR) dalam 72 jam setelah peneliti utama menerima laporan.
3. Melaporkan penyimpangan dari protokol yang telah disetujui (*Protocol deviation/violation*)
4. Mematuhi semua peraturan yang berlaku

8. Kerangka Teori

Inflamasi

Pemberian obat inflamasi peroral menimbulkan komplikasi

Pemberian Obat yang tidak adekuat

Piperin

Inovasi Riset

Desain Sedian dalam *dissolving microneedle* (Penetrasi obat adekuat)menembus barier kulit

- Variasi perbandingan polimer
- XRD/FTIR
- Uji Morfologi
- Penetuan Kandungan obat dalam sistem DMN
- Uji Hemolisis
- Uji Melarut
- Uji Dermatokinetik ex vivo

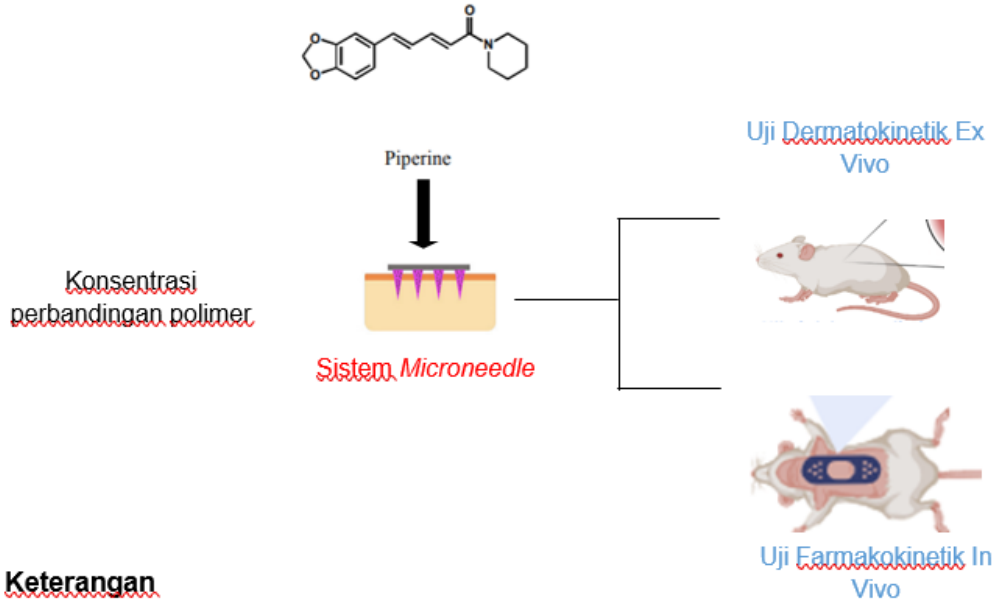
Validasi Metode Analisis senyawa piperin menggunakan HPLC

- Uji Kesesuaian sistem
- Uji Linearitas
- LOD dan LOQ
- Uji Selektivitas
- Uji Akurasi dan presisi

Uji Farmakokinetik Sediaan DMN PIP

- C_{max}
- T_{max}
- $T_{1/2}$
- AUC
- MRT

9. Kerangka Konsep



Keterangan

Variabel Bebas

Variabel Terikat

Variabel Antara

10. Analisis Statistik Blanko

Formula Blanko

A. Sebelum Uji Kekuatan Mekanik

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	721.46	180.365	111.27	0.000
Error	10	16.21	1.621		
Total	14	737.67			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
1.27318	97.80%	96.92%	95.06%

Means

Formula	N	Mean	StDev	95% CI
FB1	3	722.010	0.070	(720.372, 723.648)
FB2	3	711.093	0.943	(709.455, 712.731)
FB3	3	701.540	0.763	(699.902, 703.178)
FB4	3	708.227	0.987	(706.589, 709.865)
FB5	3	705.43	2.38	(703.79, 707.06)

Pooled StDev = 1.27318

B. Setelah Uji Kekuatan Mekanik

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	75318.5	18829.6	1805.02	0.000
Error	10	104.3	10.4		
Total	14	75422.8			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.22983	99.86%	99.81%	99.69%

Means

Formula	N	Mean	StDev	95% CI
FB1	3	672.65	3.39	(668.50, 676.80)
FB2	3	658.01	4.85	(653.85, 662.16)
FB3	3	519.63	3.27	(515.48, 523.79)
FB4	3	653.64	2.28	(649.49, 657.79)
FB5	3	515.147	1.157	(510.992, 519.302)

Pooled StDev = 3.22983

C. Penurunan Tinggi Needle (%)

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	1318.22	329.554	1299.41	0.000
Error	10	2.54	0.254		
Total	14	1320.75			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.503604	99.81%	99.73%	99.57%

Means

Formula	N	Mean	StDev	95% CI
FB1	3	6.836	0.478	(6.189, 7.484)
FB2	3	7.465	0.739	(6.817, 8.113)
FB3	3	25.929	0.495	(25.282, 26.577)
FB4	3	7.707	0.357	(7.060, 8.355)
FB5	3	26.973	0.347	(26.325, 27.621)

Pooled StDev = 0.503604

11. Analisis statistik Formula DMN PIP

A. Sebelum Uji Kekuatan Mekanik

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	697.575	174.394	437.95	0.000
Error	10	3.982	0.398		
Total	14	701.557			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.631036	99.43%	99.21%	98.72%

Means

Formula	N	Mean	StDev	95% CI
F1	3	730.797	0.040	(729.985, 731.608)
F2	3	725.087	0.080	(724.275, 725.898)
F3	3	710.777	1.087	(709.965, 711.588)
F4	3	724.147	0.095	(723.335, 724.958)
F5	3	718.090	0.890	(717.278, 718.902)

Pooled StDev = 0.631036

B. **Setelah Uji Kekuatan Mekanik**

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	73237.8	18309.5	9077.06	0.000
Error	10	20.2	2.0		
Total	14	73258.0			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
1.42025	99.97%	99.96%	99.94%

Means

Formula	N	Mean	StDev	95% CI
F1	3	669.730	0.850	(667.903, 671.557)
F2	3	653.54	1.91	(651.72, 655.37)
F3	3	517.370	0.615	(515.543, 519.197)
F4	3	651.64	2.00	(649.81, 653.47)

F5	3	515.147	1.157	(513.320, 516.974)

Pooled StDev = 1.42025

C. Penurunan Tinggi Needle (%)

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Formula	4	1215.47	303.868	6379.19	0.000
Error	10	0.48	0.048		
Total	14	1215.95			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.218253	99.96%	99.95%	99.91%

Means

Formula	N	Mean	StDev	95% CI
F1	3	8.3562	0.1188	(8.0754, 8.6369)
F2	3	9.867	0.256	(9.586, 10.148)
F3	3	27.210	0.191	(26.930, 27.491)
F4	3	10.013	0.276	(9.732, 10.293)
F5	3	28.261	0.215	(27.981, 28.542)

Pooled StDev = 0.218253

12. Analisis Statistik LOD

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
F1	.317	3	.	.889	3	.351
F2	.378	3	.	.767	3	.038
F3	.206	3	.	.993	3	.837
F4	.214	3	.	.989	3	.803
F5	.353	3	.	.823	3	.172

a. Lilliefors Significance Correction

Test Statistics[a,b]

	LOD
Kruskal-Wallis H	11.433
df	4
Asymp. Sig.	.022

a. Kruskal Wallis Test

b. Grouping Variable: Formula

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (LOD) GROUP (Formula) KRUSKAL_WALLIS(COMPARE=PAIRWISE)

/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE /CRITERIA ALPHA=0.05 CILEVEL=95.

Nonparametric Tests

Notes

Output Created		01-SEP-2024 14:44:58
Comments		
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Resources	Processor Time	00:00:00.45
	Elapsed Time	00:00:00.86

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.[a,b]	Decision
1	The distribution of LOD is the same across categories of Formula.	Independent-Samples Kruskal-Wallis Test	.022	Reject the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

Independent-Samples Kruskal-Wallis Test LOD across Formula

Independent-Samples Kruskal-Wallis Test Summary

Total N	15
Test Statistic	11.433[a]
Degree Of Freedom	4
Asymptotic Sig.(2-sided test)	.022

a. The test statistic is adjusted for ties.

Pairwise Comparisons of Formula

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
F5-F3	.333	3.651	.091	.927	1.000
F5-F2	6.000	3.651	1.643	.100	1.000
F5-F4	7.000	3.651	1.917	.055	.552
F5-F1	10.000	3.651	2.739	.006	.062
F3-F2	5.667	3.651	1.552	.121	1.000
F3-F4	-6.667	3.651	-1.826	.068	.679
F3-F1	9.667	3.651	2.647	.008	.081
F2-F4	-1.000	3.651	-.274	.784	1.000
F2-F1	4.000	3.651	1.095	.273	1.000
F4-F1	3.000	3.651	.822	.411	1.000

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.

Asymptotic significances (2-sided tests) are displayed. The significance level is .050.

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

13. Tabel 1. Persentase Penurunan Panjang Microneedle Blanko

	Formula	Sebelum Uji Kekuatan Mekanik			Setelah Uji Kekuatan Mekanik			%penurunan panjang needle	Rata-rata	SD
		Panjang (µm)	Rata-Rata	SD	Panjang (µm)	Rata-Rata	SD			
30:60	F1(10;90)	721,96	722,01	0,07	675,82	672,65	3,39	6,39	6,836	0,48
		721,98			673,05			6,77		
		722,09			669,08			7,34		
	F2(15;85)	711,18	711,093	0,94	652,71	658,007	4,85	8,22	7,465	0,74
		711,99			659,09			7,42		
		710,11			662,22			6,74		
	F3(20;80)	700,7	701,54	0,76	519,63	519,633	3,27	25,84	25,929	0,5
		701,73			522,9			25,48		
		702,19			516,37			26,46		
25:50:00	F4(15;85)	707,21	708,227	0,99	655,03	653,64	2,28	7,378	7,707	0,36
		708,29			651,01			8,087		
		709,18			654,88			7,65		
	F5(20;80)	703,31	705,427	2,38	516,34	515,147	1,16	26,58	26,973	0,35
		704,97			514,03			27,08		
		708			515,07			27,25		

14. Tabel 2. Persentase Penetrasi *Dissolving Microneedle* Blanko

	%Penetrasi				
Lapisan	FB1	FB2	FB3	FB4	FB5
1	100	100	100	100	100
2	100	100	100	100	100
3	97	88	79	86	78
4	70	35	0	33	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	0	0	0	0

a. Contoh Perhitungan Persentase Penurunan Tinggi Needle

Diketahui untuk FB1 replikasi pertama, Micronnedle berukuran 721,96 µm dan setelah uji mekanik, tingginya menjadi 675,82 µm, maka

$$\%\text{Kompressi} = \frac{\text{Tinggi sebelum uji-Tinggi sesudah uji}}{\text{Tinggi sebelum uji}} \times 100\%$$

$$= \frac{721{,}96 - 675{,}82}{721{,}96} \times 100\%$$

$$= 6{,}390\%$$

b. Perhitungan Persentase Penetrasi Lapisan Ke-n

Diketahui untuk F1 lapisan ketiga, terbentuk 70 lubang sedangkan needle berjumlah 100, maka

$$\%\text{penetrasi lapisan ke-n} = \frac{\text{Jumlah lubang pada lapisan ke-n}}{\text{Jumlah lubang total}} \times 100\%$$

$$= \frac{70}{100} \times 100\%$$

$$= 70\%$$

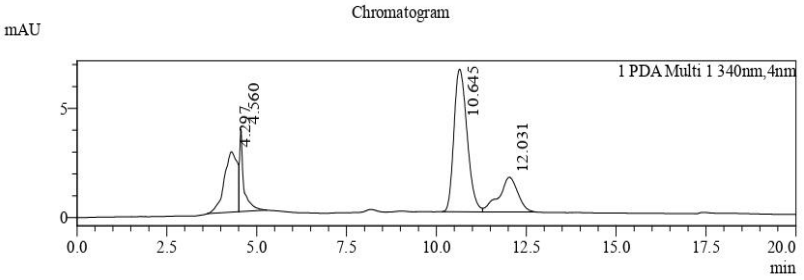
Lampiran 2. Hasil Uji Morfologi, Kekuatan Mekanik dan Kemampuan Penetrasi Dissolving Microneedle Piperin

15. Tabel 3. Persentase Penurunan Panjang Microneedle Piperin

	Formula	Sebelum Uji Kekuatan Mekanik			Setelah Uji Kekuatan Mekanik			%penurunan panjang *needle*	Rata-rata	SD
		Panjang (µm)	Rata-Rata	SD	Panjang (µm)	Rata-Rata	SD			
30:60	F1(10;90)	730,76			670,63			8,22		
		730,84	730,79	0,04	669,62	669,73	0,85	8,37	8,35	0,11
		730,79			668,94			8,46		
	F2(15;85)	725,08			651,98			10,08		
		725,17	725,08	0,08	655,67	653,54	1,9	9,58	9,86	0,25
		725,01			652,98			9,93		
	F3(20;80)	710,7			517,04			27,24		
		709,73	710,77	1,08	518,08	517,37	0,61	27	27,21	0,19
		711,9			516,99			27,37		
25:50:00	F4(15;85)	724,22			650,03			10,24		
		724,04	724,14	0,09	651,01	651,64	2	10,08	10,01	0,27
		724,18			653,88			9,7		
	F5(20;80)	718,11			516,34			28,09		
		718,97	718,09	0,89	514,03	515,14	1,15	28,5	28,26	0,21
		717,19			515,07			28,18		

16. Metode Ekstraksi Acetonitril

Metode Ekstraksi
A. Acetonitril 100 Replikasi 1

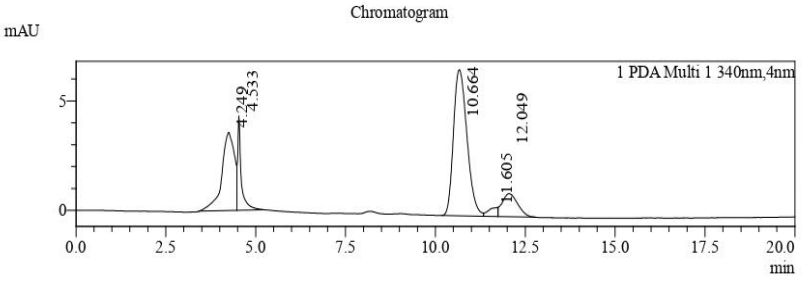


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.297	69351	2764	21.348	18.878
2	4.560	30989	3773	9.539	25.764
3	10.645	166389	6520	51.219	44.525
4	12.031	58129	1586	17.894	10.833
Total		324857	14644	100.000	100.000

B. Acetonitril 100 Replikasi 2

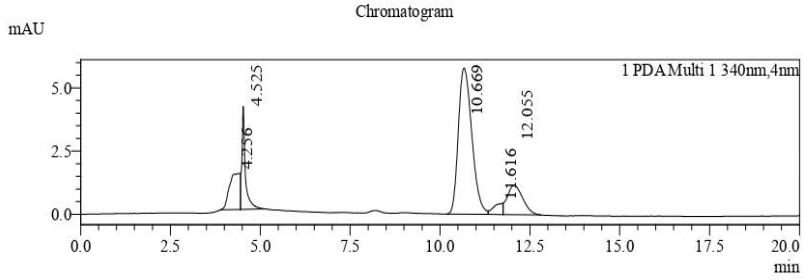


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.249	88339	3571	26.665	22.349
2	4.533	29298	4307	8.843	26.958
3	10.664	174679	6670	52.726	41.749
4	11.605	7492	379	2.261	2.371
5	12.049	31490	1050	9.505	6.573
Total		331297	15977	100.000	100.000

C. Acetonitril 100 Replikasi 3

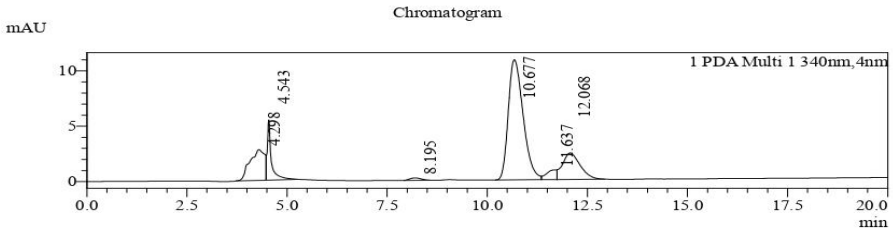


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.256	29351	1394	11.677	10.863
2	4.525	27474	4073	10.931	31.745
3	10.669	151245	5783	60.174	45.073
4	11.616	8178	414	3.254	3.226
5	12.055	35098	1166	13.964	9.092
Total		251346	12829	100.000	100.000

D. Acetonitril 200 Replikasi 1

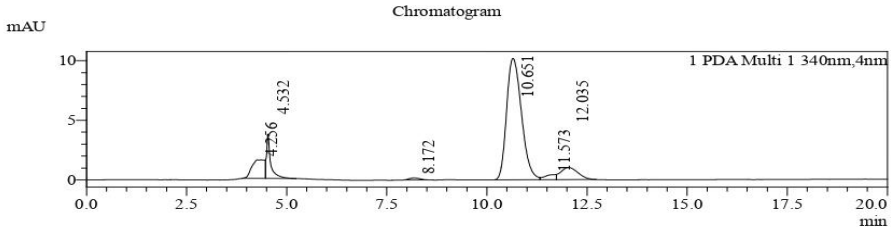


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.298	71453	2773	14.836	12.304
2	4.543	37508	5439	7.788	24.133
3	8.195	4332	219	0.899	0.971
4	10.677	280116	10858	58.160	48.177
5	11.637	15566	856	3.232	3.798
6	12.068	72654	2392	15.085	10.616
Total		481629	22537	100.000	100.000

E. Acetonitril 200 Replikasi 2

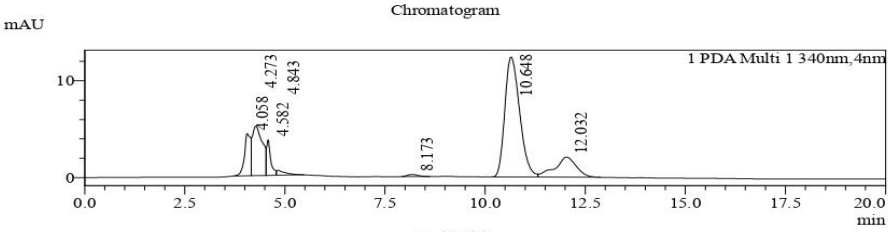


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.256	34520	1556	9.424	9.133
2	4.532	26320	3707	7.186	21.757
3	8.172	3128	170	0.854	0.998
4	10.651	263767	10188	72.012	59.787
5	11.573	8136	397	2.221	2.327
6	12.035	30413	1022	8.303	5.998
Total		366284	17041	100.000	100.000

F. Acetonitril 200 Replikasi 3

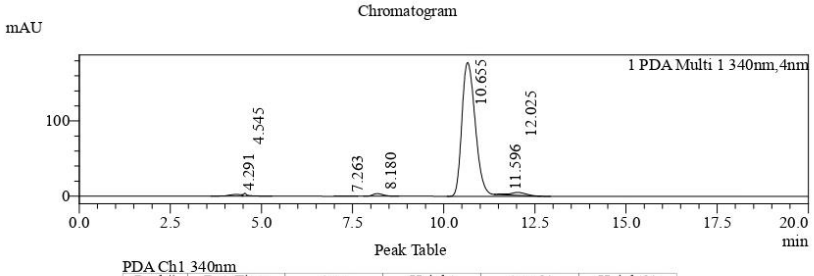


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.058	47526	4352	8.315	15.385
2	4.273	90812	5121	15.889	18.102
3	4.582	25722	3662	4.501	12.945
4	4.843	7581	506	1.326	1.790
5	8.173	4084	214	0.715	0.757
6	10.648	318850	12365	55.789	43.709
7	12.032	76956	2068	13.465	7.312
Total		571531	28289	100.000	100.000

G. Acetonitril 300 Replikasi 1

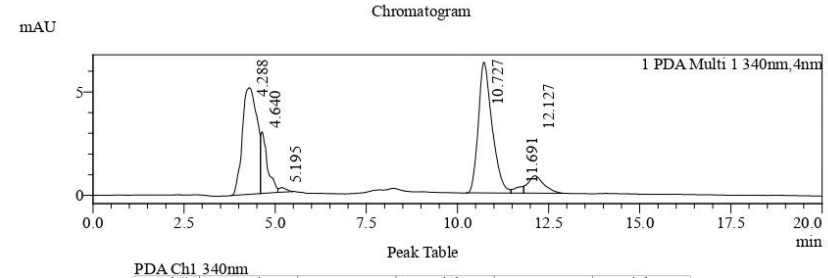


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.291	55615	2299	1.126	1.193
2	4.545	30568	3870	0.619	2.007
3	7.263	4525	260	0.092	0.135
4	8.180	69086	3426	1.399	1.777
5	10.655	4657950	177968	94.319	92.294
6	11.596	16794	1176	0.340	0.610
7	12.025	103964	3827	2.105	1.985
Total		4938502	192827	100.000	100.000

H. Acetonitril 300 Replikasi 2

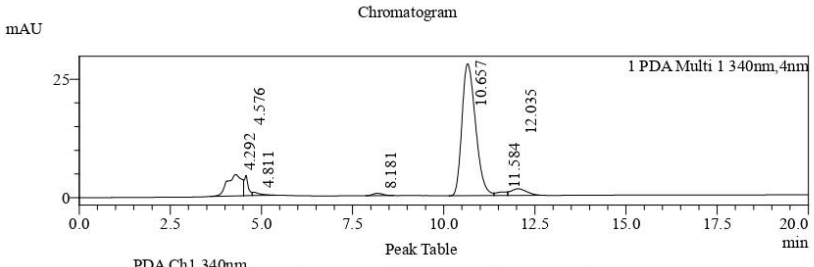


Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.288	145031	5157	37.887	32.600
2	4.640	37710	2985	9.851	18.873
3	5.195	3056	221	0.798	1.395
4	10.727	166343	6318	43.454	39.944
5	11.691	5499	295	1.437	1.866
6	12.127	25160	842	6.573	5.321
Total		382799	15817	100.000	100.000

I. Acetonitril 300 Replikasi 3



Peak Table

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Area%	Height%
1	4.292	123637	4493	12.936	11.254
2	4.576	31889	4288	3.336	10.741
3	4.811	10290	690	1.077	1.727
4	8.181	9380	478	0.981	1.198
5	10.657	722560	27807	75.600	69.656
6	11.584	15313	747	1.602	1.871
7	12.035	42697	1418	4.467	3.553
Total		955766	39921	100.000	100.000