

DAFTAR PUSTAKA

- Ahmed, I. S., Elnahas, O. S., Assar, N. H., Gad, A. M., & Hosary, R. El. (2020). Nanocrystals of fusidic acid for dual enhancement of dermal delivery and antibacterial activity: In vitro, ex vivo and in vivo evaluation. *Pharmaceutics*, 12(3). <https://doi.org/10.3390/pharmaceutics12030199>
- Bakheit, A. H. H., Abd-Elgalil, A. A., Mustafa, B., Haque, A., & Wani, T. A. (2015). Telmisartan. In *Profiles of Drug Substances, Excipients and Related Methodology* (Vol. 40, pp. 371–429). Academic Press Inc. <https://doi.org/10.1016/bs.podrm.2015.01.003>
- Chin, L. Y., Tan, J. Y. P., Choudhury, H., Pandey, M., Sisinth, S. P., & Gorain, B. (2021). Development and optimization of chitosan coated nanoemulgel of telmisartan for intranasal delivery: A comparative study. *Journal of Drug Delivery Science and Technology*, 62. <https://doi.org/10.1016/j.jddst.2021.102341>
- Datu, N. N. P., Rahman, L., Marzaman, A. N. F., Roska, T. P., Sam, A., & Permana, A. D. (2023). Hydrogel-Forming Microarray Patches–Mediated Transdermal Delivery of Telmisartan from Polyethylene Glycol Reservoir. *Journal of Pharmaceutical Innovation*, 18(3), 1533–1545. <https://doi.org/10.1007/s12247-022-09699-x>
- Ernawati, I., Hidayati, H. B., & Sumarno, S. (2020). THE EFFECTS NEUROPROTECTION OF TELMISARTAN ON STROKE WITH HYPERTENSION. *MNJ (Malang Neurology Journal)*, 6(1), 41–46. <https://doi.org/10.21776/ub.mnj.2020.006.01.9>
- Gaaz, T. S., Sulong, A. B., Akhtar, M. N., Kadhum, A. A. H., Mohamad, A. B., Al-Amiry, A. A., & McPhee, D. J. (2015). Properties and applications of polyvinyl alcohol, halloysite nanotubes and their nanocomposites. In *Molecules* (Vol. 20, Issue 12, pp. 22833–22847). MDPI AG. <https://doi.org/10.3390/molecules201219884>
- International, A. D., & University, M. (2021). *World Alzheimer Report 2021*.
- Kamoun, E. A., Loutfy, S. A., Hussein, Y., & Kenawy, E. R. S. (2021). Recent advances in PVA-polysaccharide based hydrogels and electrospun nanofibers in biomedical applications: A review. In *International Journal of Biological Macromolecules* (Vol. 187, pp. 755–768). Elsevier B.V. <https://doi.org/10.1016/j.ijbiomac.2021.08.002>
- M., Safar, M. M., Abdelsalam, R. M., & Zaki, H. F. (2020a). Telmisartan Protects Against Aluminum-Induced Alzheimer-like



- Pathological Changes in Rats. *Neurotoxicity Research*, 37(2), 275–285.
<https://doi.org/10.1007/s12640-019-00085-z>
- Khalifa, M., Safar, M. M., Abdelsalam, R. M., & Zaki, H. F. (2020b). Telmisartan Protects Against Aluminum-Induced Alzheimer-like Pathological Changes in Rats. *Neurotoxicity Research*, 37(2), 275–285.
<https://doi.org/10.1007/s12640-019-00085-z>
- Kumar, A., & Han, S. S. (2017). PVA-based hydrogels for tissue engineering: A review. In *International Journal of Polymeric Materials and Polymeric Biomaterials* (Vol. 66, Issue 4, pp. 159–182). Taylor and Francis Inc.
<https://doi.org/10.1080/00914037.2016.1190930>
- Lalitha, N., Sanjay, P. P., Vyshak, M., & Kadri, U. (2010). Stability-Indicating Reverse Phase HPLC Method for the Determination of Cefazolin. In *Tropical Journal of Pharmaceutical Research* (Vol. 9, Issue 1).
<http://www.tjpr.org>
- Lee, J. W., Park, J. H., & Prausnitz, M. R. (2008). Dissolving microneedles for transdermal drug delivery. *Biomaterials*, 29(13), 2113–2124.
<https://doi.org/10.1016/j.biomaterials.2007.12.048>
- Mangang, K. N., Thakran, P., Halder, J., Yadav, K. S., Ghosh, G., Pradhan, D., Rath, G., & Rai, V. K. (2023). PVP-microneedle array for drug delivery: mechanical insight, biodegradation, and recent advances. In *Journal of Biomaterials Science, Polymer Edition* (Vol. 34, Issue 7, pp. 986–1017). Taylor and Francis Ltd.
<https://doi.org/10.1080/09205063.2022.2155778>
- Mitić, M., & Lazarević-Pašti, T. (2021). Does the application of acetylcholinesterase inhibitors in the treatment of Alzheimer's disease lead to depression? In *Expert Opinion on Drug Metabolism and Toxicology* (Vol. 17, Issue 7, pp. 841–856). Taylor and Francis Ltd.
<https://doi.org/10.1080/17425255.2021.1931681>
- Parmar, P. K., Wadhawan, J., & Bansal, A. K. (2021). Pharmaceutical nanocrystals: A promising approach for improved topical drug delivery. In *Drug Discovery Today* (Vol. 26, Issue 10, pp. 2329–2349). Elsevier Ltd.
<https://doi.org/10.1016/j.drudis.2021.07.010>
- Permana, A. D., McCrudden, M. T. C., & Donnelly, R. F. (2019). Enhanced intradermal delivery of nanosuspensions of antifilariasis drugs using dissolving microneedles: A proof of concept study. *Pharmaceutics*, 11(7). <https://doi.org/10.3390/pharmaceutics11070346>
- Permana, A. D., Paredes, A. J., Volpe-Zanutto, F., Anjani, Q. K., Utomo, E., & Donnelly, R. F. (2020). Dissolving microneedle-mediated dermal



- delivery of itraconazole nanocrystals for improved treatment of cutaneous candidiasis. *European Journal of Pharmaceutics and Biopharmaceutics*, 154, 50–61. <https://doi.org/10.1016/j.ejpb.2020.06.025>
- Permana, A. D., Paredes, A. J., Zanutto, F. V., Amir, M. N., Ismail, I., Bahar, M. A., Sumarheni, Palma, S. D., & Donnelly, R. F. (2021). Albendazole Nanocrystal-Based Dissolving Microneedles with Improved Pharmacokinetic Performance for Enhanced Treatment of Cystic Echinococcosis. *ACS Applied Materials and Interfaces*, 13(32), 38745–38760. <https://doi.org/10.1021/acsami.1c11179>
- Permana, A. D., Tekko, I. A., McCrudden, M. T. C., Anjani, Q. K., Ramadon, D., McCarthy, H. O., & Donnelly, R. F. (2019). Solid lipid nanoparticle-based dissolving microneedles: A promising intradermal lymph targeting drug delivery system with potential for enhanced treatment of lymphatic filariasis. *Journal of Controlled Release*, 316, 34–52. <https://doi.org/10.1016/j.jconrel.2019.10.004>
- Permana, A. D., Utomo, E., Pratama, M. R., Amir, M. N., Anjani, Q. K., Mardikasari, S. A., Sumarheni, S., Himawan, A., Arjuna, A., Usmanengsi, U., & Donnelly, R. F. (2021). Bioadhesive-Thermosensitive In Situ Vaginal Gel of the Gel Flake-Solid Dispersion of Itraconazole for Enhanced Antifungal Activity in the Treatment of Vaginal Candidiasis. *ACS Applied Materials and Interfaces*, 13(15), 18128–18141. <https://doi.org/10.1021/acsami.1c03422>
- Proksch, E. (2018). pH in nature, humans and skin. In *Journal of Dermatology* (Vol. 45, Issue 9, pp. 1044–1052). Blackwell Publishing Ltd. <https://doi.org/10.1111/1346-8138.14489>
- Ran, Q., Wang, M., Kuang, W., Ouyang, J., Han, D., Gao, Z., & Gong, J. (2022). Advances of Combinative Nanocrystal Preparation Technology for Improving the Insoluble Drug Solubility and Bioavailability. In *Crystals* (Vol. 12, Issue 9). MDPI. <https://doi.org/10.3390/crust12091200>
- Rivera-Hernández, G., Antunes-Ricardo, M., Martínez-Morales, P., & Sánchez, M. L. (2021). Polyvinyl alcohol based-drug delivery systems for cancer treatment. In *International Journal of Pharmaceutics* (Vol. 600). Elsevier B.V. <https://doi.org/10.1016/j.ijpharm.2021.120478>

Rowe, B.C., Sheskey, , & M. E. Q. (2009). *Handbook of pharmaceuticalipients, sixth edition* (Vol. 6). Pharmaceutical Press.

R. A., Agustina, C., Puspitasari, D., Ramanda, R., Warjiyono, adi, D., Lisnawaty, & Indriani, K. (2020). Detecting Alzheimer's



- Disease by the Decision Tree Methods Based on Particle Swarm Optimization. *Journal of Physics: Conference Series*, 1641(1). <https://doi.org/10.1088/1742-6596/1641/1/012025>
- Sartawi, Z., Blackshields, C., & Faisal, W. (2022). Dissolving microneedles: Applications and growing therapeutic potential. In *Journal of Controlled Release* (Vol. 348, pp. 186–205). Elsevier B.V. <https://doi.org/10.1016/j.jconrel.2022.05.045>
- Şen, S., & Hacıosmanoğlu, E. (2022). Comparing the Neuroprotective Effects of Telmisartan, Perindopril, and Nebivolol Against Lipopolysaccharide-Induced Injury in Neuron-Like Cells. *Cureus*. <https://doi.org/10.7759/cureus.27429>
- Sinha, B., Müller, R. H., & Möschwitzer, J. P. (2013). Bottom-up approaches for preparing drug nanocrystals: Formulations and factors affecting particle size. In *International Journal of Pharmaceutics* (Vol. 453, Issue 1, pp. 126–141). Elsevier B.V. <https://doi.org/10.1016/j.ijpharm.2013.01.019>
- Syafika, N., Azis, S. B. A., Enggi, C. K., Qonita, H. A., Mahmud, T. R. A., Abizart, A., Asri, R. M., & Permana, A. D. (2023). Glucose-Responsive Microparticle-Loaded Dissolving Microneedles for Selective Delivery of Metformin: A Proof-of-Concept Study. *Molecular Pharmaceutics*, 20(2), 1269–1284. <https://doi.org/10.1021/acs.molpharmaceut.2c00936>
- Teodorescu, M., & Bercea, M. (2015). Poly(vinylpyrrolidone) – A Versatile Polymer for Biomedical and Beyond Medical Applications. *Polymer - Plastics Technology and Engineering*, 54(9), 923–943. <https://doi.org/10.1080/03602559.2014.979506>
- Teodorescu, M., Bercea, M., & Morariu, S. (2019a). Biomaterials of PVA and PVP in medical and pharmaceutical applications: Perspectives and challenges. In *Biotechnology Advances* (Vol. 37, Issue 1, pp. 109–131). Elsevier Inc. <https://doi.org/10.1016/j.biotechadv.2018.11.008>
- Teodorescu, M., Bercea, M., & Morariu, S. (2019b). Biomaterials of PVA and PVP in medical and pharmaceutical applications: Perspectives and challenges. In *Biotechnology Advances* (Vol. 37, Issue 1, pp. 109–131). Elsevier Inc. <https://doi.org/10.1016/j.biotechadv.2018.11.008>
- Usman, J. T., Aliyah, A., Nur, J. F., Nirmayanti, N., & Permania, A. D. (2023). Combinatorial Approach of Polymeric Patches and Solid Microneedles for Improved Transdermal Delivery of Valsartan: A Proof-of-Concept Study. *Biointerface Research in Applied Chemistry*, 13(4). <https://doi.org/10.33263/BRIAC134.314>



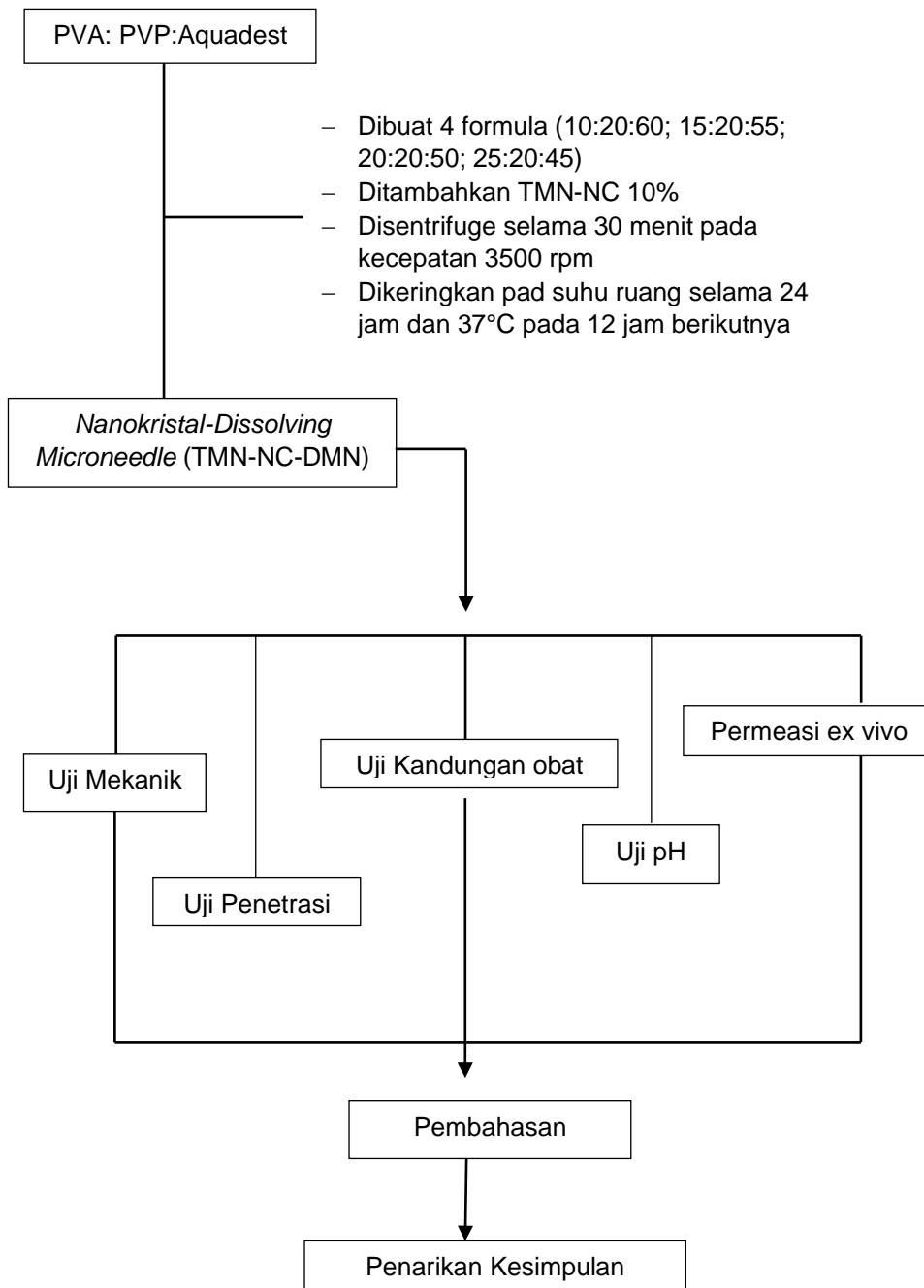
- Uthumansha, U., Prabahar, K., Gajapathy, D. B., El-Sherbiny, M., Elsherbiny, N., & Qushawy, M. (2023). Optimization and In Vitro Characterization of Telmisartan Loaded Sodium Alginate Beads and Its In Vivo Efficacy Investigation in Hypertensive Induced Animal Model. *Pharmaceutics*, 15(2). <https://doi.org/10.3390/pharmaceutics15020709>
- Xiang, H., Xu, S., Zhang, W., Li, Y., Zhou, Y., & Miao, X. (2023). Skin permeation of curcumin nanocrystals: Effect of particle size, delivery vehicles, and permeation enhancer. *Colloids and Surfaces B: Biointerfaces*, 224. <https://doi.org/10.1016/j.colsurfb.2023.113203>
- Xi, X., Gao, G., Liu, Y., & Ma, F. (2022). Drug delivery with dissolving microneedles: skin puncture, its influencing factors and improvement strategies. In *Journal of Drug Delivery Science and Technology* (Vol. 76). Editions de Sante. <https://doi.org/10.1016/j.jddst.2022.103653>
- Yamashita, S., Fukunishi, A., Higashino, H., Kataoka, M., & Wada, K. (2017). Design of supersaturable formulation of telmisartan with pH modifier: in vitro study on dissolution and precipitation. *Journal of Pharmaceutical Investigation*, 47(2), 163–171. <https://doi.org/10.1007/s40005-017-0310-3>
- Zhang, P., Hou, Y., Tu, W., Campbell, N., Pieper, A. A., Leverenz, J. B., Gao, S., Cummings, J., & Cheng, F. (2023). Population-based discovery and Mendelian randomization analysis identify telmisartan as a candidate medicine for Alzheimer's disease in African Americans. *Alzheimer's and Dementia*, 19(5), 1876–1887. <https://doi.org/10.1002/alz.12819>



Optimization Software:
www.balesio.com

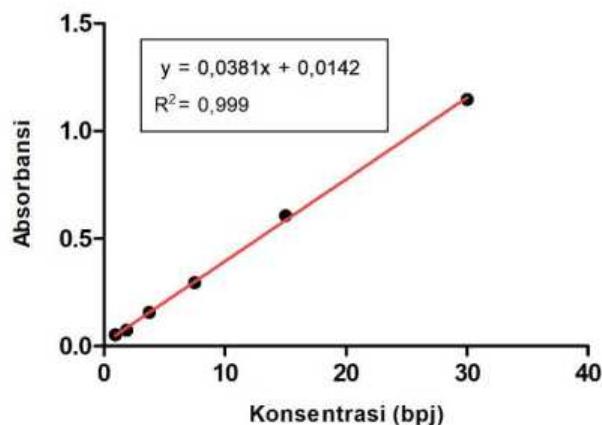
LAMPIRAN

Lampiran 1. Skema kerja umum



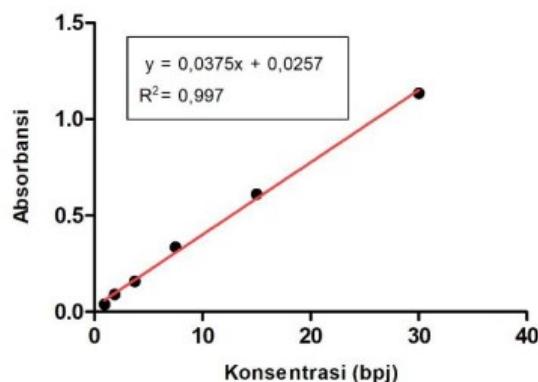
Lampiran 2. Kurva Baku

Lampiran 2.1 Kurva Baku TMN dalam etanol



Gambar 13. Kurva baku TMN dalam etanol

Lampiran 2.2 Kurva Baku TMN dalam PBS-etanol 20%



Gambar 14. Kurva baku TMN dalam PBS-etanol 20%



Lampiran 3 Perhitungan

Lampiran 3.1 Uji permeasi *ex vivo*

Persamaan: $y = 0,0375x + 0,0257$

Keterangan:

x = konsentrasi

y = absorbansi

- F1 replikasi 1 jam ke-8 diperoleh absorbansi = 0,632, sehingga untuk memperoleh konsentrasi:

$$y = 0,0375x + 0,0257$$

$$0,632 = 0,0375x + 0,0257$$

$$x = \frac{0,632 - 0,0257}{0,0375}$$

$$x = 16,168$$

$$\text{Konsentrasi dalam } 1 \text{ mL} = 16,168 \text{ } \mu\text{g/mL} \times 1 \text{ mL}$$

$$= 16,168 \text{ } \mu\text{g} = 0,016168 \text{ mg}$$

$$\text{Konsentrasi dalam } 28 \text{ mL} = 16,168 \text{ } \mu\text{g/mL} \times 28 \text{ mL}$$

$$= 452,704 \text{ } \mu\text{g} = 0,452704 \text{ mg}$$

$$\begin{aligned} \text{Faktor koreksi} &= \frac{\text{konsentrasi jam sebelumnya}}{1000} + \text{Faktor koreksi jam sebelumnya} \\ &= \frac{10,67 \text{ } \mu\text{g}}{1000} + 0,03560 \\ &= 0,04627 \text{ mg} \end{aligned}$$

$$\text{Jumlah terpermeasi} = \text{konsentrasi dalam } 28 \text{ mL} + \text{Faktor koreksi}$$

$$= 0,452704 \text{ mg} + 0,04627 \text{ mg}$$

$$= 0,49897 \text{ mg}$$



Lampiran 4. Tabel Hasil Evaluasi

Lampiran 4.1 Tabel Kurva Baku TMN dalam etanol

Tabel 2. Kurva baku TMN dalam etanol

Konsentrasi (bpj)	Absorbansi				
	Replikasi 1	Replikasi 2	Replikasi 3	Rata-rata	SD
0,00	0,00	0,00	0,00	0,00	0,00
0,9375	1,126	1,149	1,164	1,14633333	0,015
1,875	0,6	0,595	0,627	0,60733333	0,014
3,75	0,272	0,304	0,311	0,29566667	0,016
7,5	0,132	0,136	0,201	0,15633333	0,031
15	0,074	0,059	0,089	0,074	0,012
30	0,052	0,073	0,034	0,053	0,015

Lampiran 4.2 Tabel kurva baku TMN dalam PBS-etanol 20%

Tabel 3. Kurva baku TMN dalam PBS-etanol 20%

Konsentrasi (bpj)	Absorbansi			Rata-rata	SD
	Replikasi 1	Replikasi 2	Replikasi 3		
0,00	0,00	0,00	0,00	0,00	0,00
0,9375	1,144	1,134	0,541	1,13533333	0,008
1,875	0,671	0,611	0,354	0,60766667	0,065
3,75	0,353	0,336	0,167	0,34766667	0,010
7,5	0,178	0,158	0,1	0,16766667	0,010
15	0,091	0,091	0,032	0,094	0,005
30	0,043	0,039	1,128	0,038	0,005

Lampiran 4.3 Tabel Hasil Uji pH

Tabel 4. Hasil Uji pH

Replikasi	Formula			
	F1	F2	F3	F4
1	5,11	5,19	5,91	5,86
2	5,33	5,61	5,86	5,41
3	5,91	5,94	5,13	5,73
Rata-rata	5,45	5,58	5,63	5,74
SD	0,41	0,37	0,43	0,22



Lampiran 4.4 Tabel Uji Kekuatan Mekanik

Tabel 4. Hasil uji kekuatan mekanik

Formula	Sebelum diberi beban	Sesudah diberi beban	% Reduksi	Rata-rata	SD
F1	787,52	685,66	12,93427469		
	651,27	549,19	15,67399082	15,3878	2,3237
	714,94	589,43	17,55531933		
F2	700,71	611,12	12,78560317		
	813,45	725,93	10,75911242	12,08496	1,1488
	863,56	753,8	12,71017648		
F3	686,97	590,61	21,30515161		
	731,39	680,87	6,907395507	10,7365	1,2675
	714,25	685,7	3,99719986		
F4	818,76	761,69	6,970296546		
	768,91	689,84	10,28338817	8,9409	1,6642
	867,47	789,91	8,940943203		

Lampiran 4.5 Tabel Hasil Uji Kemampuan Penetrasi

Tabel 5. Hasil uji kemampuan penetrasi

Lapisan	Lubang yang terbentuk							
	F1		F2		F3		F4	
	Rata-rata	SD	Rata-rata	SD	Rata-rata	SD	Rata-rata	SD
1	100	0,00	100	0,00	100	0,00	100	0,00
2	100	0,00	100	0,00	68	6,16	53	8,60
3	93,66	2,49	69	2,16	62,33	2,05	30,66	3,68
4	81,66	2,05	14,33	4,783	0,00	0,00	0,00	0,00
5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
6	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
7	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
8	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00

Lampiran 4.5 Tabel Hasil Uji Kandungan Obat

Tabel 6. Hasil Uji Kandungan Obat

Replikasi	Formula			
	F1	F2	F3	F4
1	94,1	94,8	98,93	98,96
2	98,63	98,6	94,89	99,88
	98,54	98,9	98,81	95,18
ta	97,09	97,43	97,54	98,06
	2,58	2,28	2,30	2,49



Lampiran 5. Hasil Evaluasi Statistik

Lampiran 5.1 Uji pH

Tests of Normality							
pH	Kolmogorov-Smirnov ^a				Shapiro-Wilk		
	Formula	Statistic	df	Sig.	Statistic	df	Sig.
	Formula 1	.281	3	.	.937	3	.515
	Formulas 2	.198	3	.	.995	3	.868
	Formula 3	.219	3	.	.987	3	.780
Formula 4	.274	3	.	.944	3	.	.543

a. Lilliefors Significance Correction

ANOVA

pH	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1120.250	3	373.417	.358	.785
Within Groups	8340.667	8	1042.583		
Total	9460.917	11			

Lampiran 5.2 Uji kandungan obat

Tests of Normality							
Kandungan_obat	Kolmogorov-Smirnov ^a				Shapiro-Wilk		
	Formula	Statistic	df	Sig.	Statistic	df	Sig.
	Formula 1	.385	3	.	.751	3	.002
	Formula 2	.362	3	.	.805	3	.125
	Formula 3	.376	3	.	.772	3	.050
Formula 4	.316	3	.	.890	3	.	.355

a. Lilliefors Significance Correction

TEST STATISTICS

Kandungan_ obat	
Kruskal-Wallis H	5.974
df	3
Asymp. Sig.	.113

a. Kruskal Wallis Test



Lampiran 5.3 Uji kekuatan mekanik

Tests of Normality

	Formula	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Mekanik	Formula 1	.216	3	.	.989	3	.796
	Formula 2	.374	3	.	.776	3	.058
	Formula 3	.224	3	.	.984	3	.761
	Formula 4	.293	3	.	.923	3	.461

a. Lilliefors Significance Correction

ANOVA

Mekanik

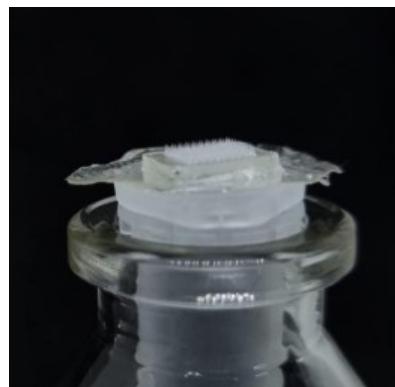
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	42064156.92	3	14021385.64	2.457	.138
Within Groups	45655021.33	8	5706877.667		
Total	87719178.25	11			



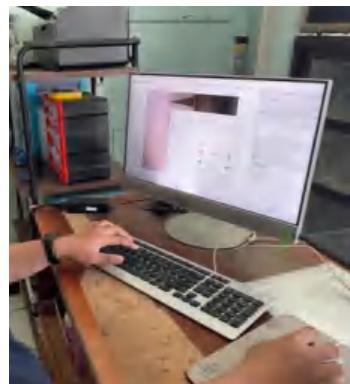
Lampiran 6. Dokumentasi Penelitian



Gambar 15. Formulasi sediaan



Gambar 16. Sediaan TMN-NC-DMN



Gambar 17. Pengamatan dibawah mikroskop



Gambar 18. Uji mekanik dan penetrasi



Gambar 19. Proses uji permeasi ex vivo



Gambar 20. Analisis dengan Spektrofotometer Uv-Vis

