

DAFTAR PUSTAKA

- Al-japairai, K.A.S., Mahmood, S., Almurisi, S.H., Reddy, J., Rebhi, A., Azmana, M., Raman, S., 2020. Current trends in polymer microneedle for transdermal drug delivery. *Int. J. Pharm.* 587.
- Ali, S., Shabbir, M., Shahid, N., 2015. The structure of skin and transdermal drug delivery system - A review. *Res. J. Pharm. Technol.* 8, 103–109.
- Alkilani, A.Z., McCrudden, M.T.C., Donnelly, R.F., 2015. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. *Pharmaceutics* 7, 438–470.
- Alrhia, L., Mohamad, I., 2021. Validation of the analytical method for determination of tetracycline residues in poultry chest, thigh and liver by HPLC-DAD technique. *J. Phys. Conf. Ser.* 1853.
- Baker, C., Retzik-Stahr, C., Singh, V., Plomondon, R., Anderson, V., Rasouli, N., 2021. Should metformin remain the first-line therapy for treatment of type 2 diabetes? *Ther. Adv. Endocrinol. Metab.* 12, 1–13.
- Chen, H.Y., Chen, C., 2022. Evaluation of Calibration Equations by Using Regression Analysis: An Example of Chemical Analysis. *Sensors* 22.
- Cheng, A., Sun, W., Xing, M., Zhang, S., Gao, Y., 2022. The hygroscopicity of polymer microneedles on the performance of dissolving behavior for transdermal delivery. *Int. J. Polym. Mater. Polym. Biomater.* 71, 72–78.
- Dange, Y.D., Honmane, S.M., Bhinge, S.D., Salunkhe, V.R., Jadge, D.R., 2017. Development and validation of uv-spectrophotometric method for estimation of metformin in bulk and tablet dosage form. *Indian J. Pharm. Educ. Res.* 51, S754–S760.
- Gaaz, T.S., Sulong, A.B., Akhtar, M.N., Kadhum, A.A.H., Mohamad, A.B., Al-Amiery, A.A., McPhee, D.J., 2015. Properties and applications of polyvinyl alcohol, halloysite nanotubes and their nanocomposites. *Molecules* 20, 22833–22847.

- Ghosal, S., 2019. The Side Effects Of Metformin - A Review. *Diabetes Metab. Disord.* 6, 1–7.
- González-Vázquez, P., Larrañeta, E., McCrudden, M.T.C., Jarrahan, C., Rein-Weston, A., Quintanar-Solares, M., Zehrun, D., McCarthy, H., Courtenay, A.J., Donnelly, R.F., 2017. Transdermal Delivery of Gentamicin Using Dissolving Microneedle Arrays for Potential Treatment of Neonatal Sepsis. *J. Control. Release* 265, 30–40.
- Guillot, A.J., Cordeiro, A.S., Donnelly, R.F., Montesinos, M.C., Garrigues, T.M., Melero, A., 2020. Microneedle-based delivery: An overview of current applications and trends. *Pharmaceutics* 12, 1–28.
- He, J., Zhang, Z., Zheng, X., Li, L., Qi, J., Wu, W., Lu, Y., 2021. Design and evaluation of dissolving microneedles for enhanced dermal delivery of propranolol hydrochloride. *Pharmaceutics* 13, 1–15.
- ICH, 2005. Technical Requirements for Registration of Pharmaceuticals for Human Use: The ICH Process, The Textbook of Pharmaceutical Medicine.
- Igarashi, T., Nishino, K., Nayar, S.K., 2007. The appearance of human skin: A survey. *Found. Trends Comput. Graph. Vis.* 3, 1–95.
- Jalikus, F.G., Reyes Gil, M., 2019. *Circulating Microparticles*, Third Edition, Transfusion Medicine and Hemostasis. Elsevier Inc.
- Kurakula, M., Rao, G.S.N.K., 2020. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information .
- Larrañeta, E., Moore, J., Vicente-pérez, E.M., González-vázquez, P., Lutton, R., Woolfson, A.D., Donnelly, R.F., 2014. A proposed model membrane and test method for microneedle insertion studies 472, 65–73.
- McCreight, L.J., Bailey, C.J., Pearson, E.R., 2016. Metformin and the

gastrointestinal tract. *Diabetologia* 59, 426–435.

Migdadi, E.M., Courtenay, A.J., Tekko, I.A., McCrudden, M.T.C., Kearney, M.C., McAlister, E., McCarthy, H.O., Donnelly, R.F., 2018. Hydrogel-forming microneedles enhance transdermal delivery of metformin hydrochloride. *J. Control. Release* 285, 142–151.

Mohamed, S.A., Hargest, R., 2022. Surgical anatomy of the skin. *Surg. (United Kingdom)* 40, 1–7.

Moosavi, S.M., Ghassabian, S., 2018. Linearity of Calibration Curves for Analytical Methods: A Review of Criteria for Assessment of Method Reliability. *Calibration Valid. Anal. Methods - A Sampl. Curr. Approaches*.

Nagarkar, R., Patel, J., 2019. Polyvinyl Alcohol : A Comprehensive Study. *Acta Sci. Pharm. Sci.* 3, 34–44.

Ondaral, S., Çelik, E., Kurtuluş, O.Ç., 2019. The adsorption of phosphate-buffered saline to model films composed of nanofibrillated cellulose and gelatin. *J. Appl. Biomater. Funct. Mater.* 17, 0–6.

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. *Eur. J. Pharm. Biopharm.* 154, 50–61.

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. *J. Control. Release* 316, 34–52.

Rena, G., Hardie, D.G., Pearson, E.R., 2017. The mechanisms of action of metformin. *Diabetologia* 60, 1577–1585.

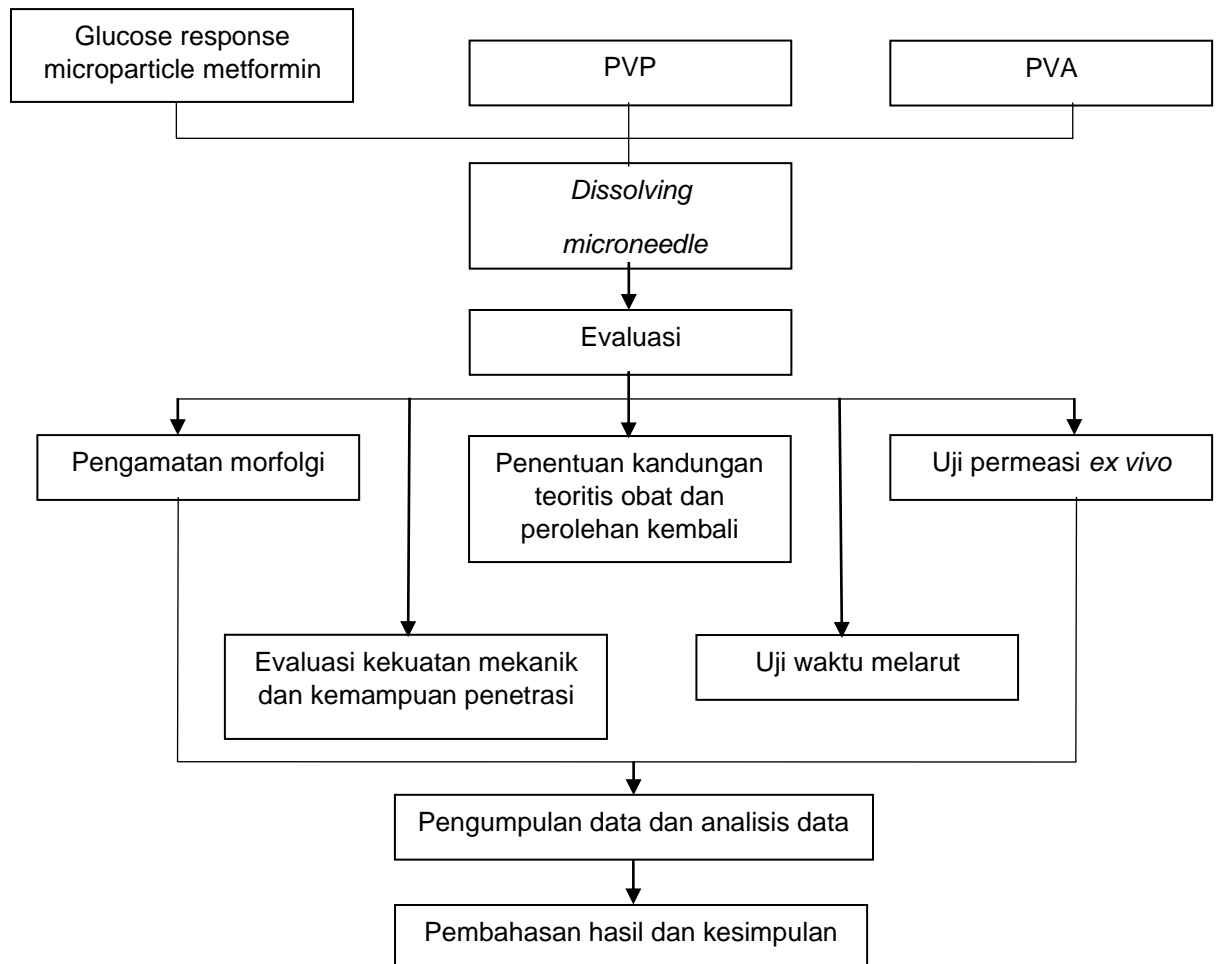
Rowe, R.C., Sheskey, P.J., Quinn, M.E., 2009. *Handbook of Pharmaceutical Excipients* 6th edition. Pharmaceutical Press, London.

- Shim, W.S., Hwang, Y.M., Park, S.G., Lee, C.K., Kang, N.G., 2018. Role of Polyvinylpyrrolidone in Dissolving Microneedle for Efficient Transdermal Drug Delivery: In vitro and Clinical Studies. *Bull. Korean Chem. Soc.* 39, 789–793.
- Sui, X., Chu, Y., Zhang, J., Zhang, H., Wang, H., Liu, T., Han, C., 2020. The Effect of PVP Molecular Weight on Dissolution Behavior and Physicochemical Characterization of Glycyrrhetic Acid Solid Dispersions. *Adv. Polym. Technol.* 2020.
- Sulistiawati, Enggi, C.K., Isa, H.T., Wijaya, S., Ardika, K.A.R., Asri, R.M., Donnelly, R.F., Permana, A.D., 2022. Validation of spectrophotometric method to quantify cabotegravir in simulated vaginal fluid and porcine vaginal tissue in ex vivo permeation and retention studies from thermosensitive and mucoadhesive gels. *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.* 267, 1–10.
- Teodorescu, M., Bercea, M., 2015. Poly(vinylpyrrolidone) – A Versatile Polymer for Biomedical and Beyond Medical Applications. *Polym. - Plast. Technol. Eng.* 54, 923–943.
- Waghule, T., Singhvi, G., Dubey, S.K., Pandey, M.M., Gupta, G., Singh, M., Dua, K., 2019. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. *Biomed. Pharmacother.* 109, 1249–1258.
- Walfish, S., 2006. Analytical Methods: A statistical perspective on the ICH Q2A and Q2B Guidelines for Validation of Analytical Methods. *Biopharm Int.* 19, 28–36.
- Wang, C., Lin, B., Zhu, H., Bi, F., Xiao, S., Wang, L., Gai, G., Zhao, L., 2019. Recent advances in phenylboronic acid-based gels with potential for self-regulated drug delivery. *Molecules* 24.
- Wang, J., Wang, Z., Yu, J., Kahkoska, A.R., Buse, J.B., Gu, Z., 2020. Glucose-Responsive Insulin and Delivery Systems: Innovation and Translation. *Adv. Mater.* 32, 1–19.
- Zhang, Y., Wu, M., Tan, D., Liu, Q., Xia, R., Chen, M., Liu, Y., Xue, L., Lei, Y., 2021. A dissolving and glucose-responsive insulin-releasing

microneedle patch for type 1 diabetes therapy. *J. Mater. Chem. B* 9, 648–657.

LAMPIRAN

Lampiran 1. Skema Kerja



Lampiran 2. Hasil uji kekuatan mekanik dan kemampuan penetrasi

Tabel 4. Hasil uji kekuatan mekanik

Formula	Sebelum evaluasi			Setelah evaluasi			Reduksi tinggi <i>needle</i>		
	Tinggi <i>needle</i> (μm)	Rata-rata (μm)	SD	Tinggi <i>needle</i> (μm)	Rata-rata (μm)	SD	Reduksi (%)	Rata-rata (%)	SD
F1	793			534			24,04		
	697	699,33	3,21	541	531,33	11,24	44,38	24,02	1,63
	698			519			35,64		
F2	701			668			4,71		
	700	699,33	2,08	644	663,33	17,47	8,00	5,14	2,66
	697			678			2,73		
F3	700			681			2,71		
	695	697,67	2,52	654	659,00	19,97	5,90	5,55	2,67
	698			642			8,02		
F4	703			614			12,66		
	697	700,67	3,21	624	621,33	6,43	10,47	11,32	1,17
	702			626			10,38		
F5	698			513			26,50		
	702	700,67	2,31	504	505,00	7,55	28,21	27,92	1,30
	702			498			27,92		

Contoh perhitungan persentase penurunan tinggi *needle*

Pada F1 replikasi 1 diketahui:

tinggi *needle* sebelum evaluasi= 793 μm

tinggi *needle* setelah evaluasi= 534 μm

Perhitungan dengan menggunakan persamaan (1):

$$\begin{aligned}
 \% \text{reduksi tinggi } needle &= \frac{\text{tinggi sebelum kompresi} - \text{tinggi setelah kompresi}}{\text{tinggi sebelum kompresi}} \times 100\% \\
 &= \frac{793 - 534}{793} \times 100\% \\
 &= 24,04\%
 \end{aligned}$$

Tabel 5. Hasil uji kemampuan penetrasi

Formula	Jumlah lubang yang terbentuk pada setiap lapisan							
	1	2	3	4	5	6	7	8
F1	100	72	38	0	0	0	0	0
	100	68	31	0	0	0	0	0
	100	63	42	0	0	0	0	0
F2	100	100	100	81	0	0	0	0
	100	100	96	71	0	0	0	0
	100	100	82	89	0	0	0	0
F3	100	100	68	18	0	0	0	0
	100	100	59	23	0	0	0	0
	100	100	71	21	0	0	0	0
F4	100	81	71	0	0	0	0	0
	100	73	68	0	0	0	0	0
	100	88	63	0	0	0	0	0
F5	100	83	29	0	0	0	0	0
	100	71	31	0	0	0	0	0
	100	81	38	0	0	0	0	0

Lampiran 3. Hasil penentuan densitas DMN

Tabel 6. Hasil penentan volume dan densitas balok DMN

Formula	Ukuran balok DMN (mm)			Volume (mm ³)	Bobot (mg)	Densitas (mg/mm ³)		
	Panjang	Lebar	Tinggi			Densitas	Rata-rata	SD
F1	10	10	5,85	585,48	592,62	1,01	1,01	0
	10	10	6,01	600,78	605,88	1,01		
	10	10	6,03	602,82	609,96	1,01		
F2	10	10	5,67	567,12	572,22	1,01	1,02	0,01
	10	10	5,75	575,28	583,44	1,01		
	10	10	5,79	579,36	594,66	1,03		
F3	10	10	5,31	531,42	533,46	1,00	1,02	0,02
	10	10	5,29	529,38	551,82	1,04		
	10	10	5,32	532,44	544,68	1,02		
F4	10	10	5,01	500,82	522,24	1,04	1,03	0,01
	10	10	5,08	507,96	518,16	1,02		
	10	10	5,13	513,06	521,22	1,02		
F5	10	10	4,81	481,44	491,64	1,02	1,03	0,01
	10	10	4,73	473,28	485,52	1,03		
	10	10	4,91	490,62	514,08	1,05		

a. Contoh perhitungan volume

Diketahui: panjang = 10 mm

Lebar = 10 mm

Tinggi = 5,85 mm

Maka,

Volume = panjang x lebar x tinggi

= 10 mm x 10 mm x 5,85

= 585 mm³

b. Contoh perhitungan densitas

Diketahui: Bobot = 592,62 mg

Volume = 585,48 mm³

Dengan menggunakan persamaan (3), maka

$$\begin{aligned}\rho &= \frac{\text{bobot}}{\text{volume}} \\ &= \frac{592,62 \text{ mg}}{585,48 \text{ mm}^3} \\ &= 1,01 \text{ mg/mm}^3\end{aligned}$$

Lampiran 4. Hasil penentuan LOD

Tabel 7. Data bobot basah dan kering serta penentuan LOD

Formula	Bobot basah (mg)	Bobot kering (mg)	LOD (%)			Jumlah <i>glucose-response microparticle metformin</i> dalam massa kering (%)		
			LOD	Rata-rata	SD	Jumlah	Rata-rata	SD
F1	501	316	36,93	36,95	0,03	39,64	39,65	0,02
	509	321	36,94			39,64		
	503	317	36,98			39,67		
F2	519	353	31,98	31,65	0,36	36,76	36,58	0,19
	511	349	31,70			36,60		
	515	354	31,26			36,37		
F3	509	372	26,92	27,23	0,27	34,21	34,35	0,13
	504	366	27,38			34,43		
	515	374	27,38			34,43		
F4	503	319	36,58	36,91	0,31	39,42	39,62	0,20
	500	314	37,20			39,81		
	509	321	36,94			39,64		
F5	501	283	43,51	42,22	0,96	44,26	43,44	0,73
	503	291	42,15			43,21		
	516	301	41,67			42,86		

a. Contoh perhitungan LOD

Diketahui: bobot basah = 501 mg

Bobot kering = 316 mg

Dengan menggunakan persamaan (4), maka

$$\begin{aligned} \%LOD &= \frac{\text{bobot basah}-\text{bobot kering}}{\text{bobot basah}} \times 100\% \\ &= \frac{501 - 316}{501} \times 100\% \\ &= 36,93\% \end{aligned}$$

b. Contoh perhitungan persentase *glucose-response microparticle* dalam massa kering

Diketahui: bobot metformin awal dalam formula = 25% b/b

LOD = 36,93%

Dengan menggunakan persamaan (5), maka

%jumlah *glucose-response microparticle* metformin dalam massa kering

$$\begin{aligned} &= \frac{\text{bobot metformin}}{100-\%LOD} \times 100\% \\ &= \frac{25}{100-36,93} \times 100\% \\ &= 39,64\% \end{aligned}$$

Lampiran 5. Hasil penentuan volume dan bobot *needle*

Tabel 8. Data dimensi DMN dan volume DMN

Panjang (mm)	Lebar (mm)	Tinggi (mm)	Volume (mm ³)	Volume 100 <i>needle</i> (mm ³)
0,2	0,2	0,7	0,00933	0,933

Contoh perhitungan volume DMN

Dengan menggunakan persamaan (6), maka

$$\begin{aligned}\text{Volume} &= \frac{1}{3} \times \text{panjang} \times \text{lebar} \times \text{tinggi} \\ &= \frac{1}{3} \times 0,2 \text{ mm} \times 0,2 \text{ mm} \times 0,7 \text{ mm} \\ &= 0,00933 \text{ mm}^3\end{aligned}$$

$$\begin{aligned}\text{Volume 100 needle} &= 100 \times \text{volume needle} \\ &= 100 \times 0,00933 \text{ mm}^3 \\ &= 0,933 \text{ mm}^3\end{aligned}$$

Tabel 9. Data bobot *needle* kering

Formula	Bobot <i>needle</i> kering (mg)			Rata-rata (mg)	SD
F1	0,94	0,94	0,94	0,94	0
F2	0,94	0,95	0,96	0,95	0,01
F3	0,94	0,97	0,95	0,95	0,02
F4	1,07	0,95	0,95	0,96	0,01
F5	0,95	0,96	0,98	0,96	0,01

Contoh perhitungan bobot *needle*

Diketahui: densitas polimer *blank* (ρ) = 1,01 mm³/mg

$$\text{Volume 100 needle} = 0,933 \text{ mm}^3$$

Dengan menggunakan persamaan (3),

$$\rho = \frac{\text{bobot}}{\text{volume}}, \text{ maka}$$

$$\text{Bobot} = \rho \times \text{volume}$$

$$= 1,01 \text{ mm}^3/\text{mg} \times 0,933 \text{ mm}^3$$

$$= 0,94 \text{ mg}$$

Lampiran 6. Hasil penentuan bobot teoritis metformin dalam DMN

Tabel 10. Hasil penentuan bobot teoritis metformin dalam DMN

Formula	Bobot <i>glucose-response microparticle</i> metformin dalam <i>needle</i> (mg)			Bobot metformin dalam DMN (μ g)		
	Bobot	Rata-rata	SD	Bobot	Rata-rata	SD
F1	0,37	0,37	0	78,35	78,25	0,16
	0,37			78,06		
	0,37			78,32		
F2	0,34	0,35	0	72,07	72,61	0,64
	0,35			72,45		
	0,35			73,32		
F3	0,32	0,33	0,01	67,34	68,63	1,29
	0,33			69,92		
	0,33			68,62		
F4	0,39	0,38	0,01	80,68	79,40	1,12
	0,38			78,92		
	0,38			78,60		
F5	0,41	0,42	0,01	86,63	87,51	1,21
	0,42			87,02		
	0,42			88,88		

a. Contoh perhitungan bobot *glucose-response* dalam *needle*

Diketahui: persentase *glucose-response microparticle* metformin dalam massa kering = 39,64%

Bobot *needle* = 0,94 mg

Dengan menggunakan persamaan (8)

Bobot *glucose-response microparticle* metformin

= % *lucose-response microparticle* metformin dalam massa kering x bobot
100 *needle*

= 39,64% x 0,98 mg

= 0,37 mg

b. Contoh perhitungan metformin dalam DMN

Diketahui:

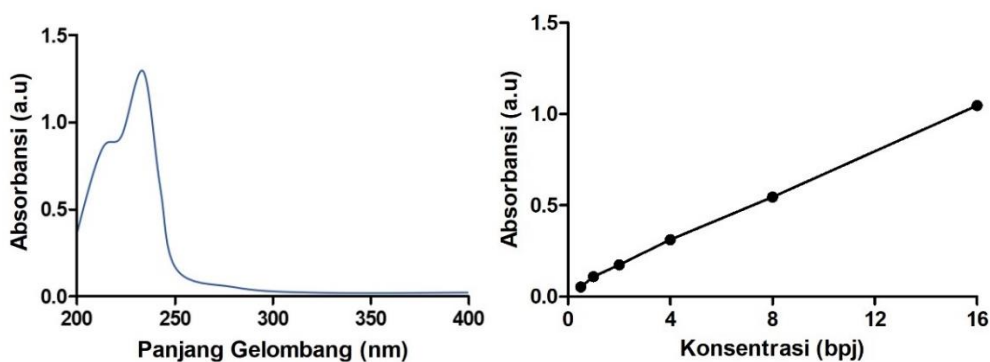
Bobot *glucose response microparticle* metformin dalam *needle* = 0,37 mg

Drug loading glucose response microparticle metformin = 20,93%

Maka

$$\begin{aligned}
 \text{Metformin dalam DMN} &= \text{drug loading} \times \text{bobot metformin} \\
 &= 20,93\% \times 0,37 \text{ mg} \\
 &= 0,07835 \text{ mg} \\
 &= 78,35 \mu\text{g}
 \end{aligned}$$

Lampiran 7. Kurva baku metformin dan validasi metode analisis spektrofotometri UV-Vis



Gambar 18. Panjang gelombang maksimum (A) dan kurva baku (B) metformin dalam media PBS

Tabel 11. Data absorbansi kurva baku metformin dalam media PBS

Konsentrasi (bpj)	Absorbansi (a.u)				
	Replikasi 1	Replikasi 2	Replikasi 3	Rata-rata	SD
16	1,053	1,037	1,050	1,047	0,008
8	0,546	0,538	0,551	0,545	0,007
4	0,313	0,315	0,306	0,312	0,005
2	0,178	0,174	0,169	0,174	0,004
1	0,111	0,105	0,113	0,109	0,004
0,5	0,053	0,055	0,051	0,053	0,002

Tabel 12. Data akurasi dan presisi metode analisis spektrofotometri UV-Vis metformin dalam media PBS

Presisi dan Akurasi <i>Intraday</i>					
Replikasi	Sampel	Konsentrasi sebenarnya (bpj)	Konsentrasi yang diperoleh (bpj) ± SD	Presisi (%RSD)	Akurasi (%RE)
1	HQC	12	13,33 ± 0,38	2,84	11,04
	MQC	7,5	7,99 ± 0,18	2,26	6,49
	LQC	4	4,45 ± 0,28	6,39	11,18
	LOQ	2,23	2,48 ± 0,09	3,53	11,16
2	HQC	12	12,57 ± 0,42	3,33	4,73
	MQC	7,5	8,20 ± 0,09	1,15	9,39
	LQC	4	4,34 ± 0,25	5,83	8,46
	LOQ	2,23	2,27 ± 0,16	6,92	1,99
3	HQC	12	12,23 ± 0,39	3,16	1,94
	MQC	7,5	7,87 ± 0,42	1,15	4,94
	LQC	4	4,10 ± 0,20	5,83	2,39
	LOQ	2,23	2,13 ± 0,12	6,92	4,48
Presisi dan Akurasi <i>Interday</i>					
Hari	Sampel	Konsentrasi sebenarnya (bpj)	Konsentrasi yang diperoleh (bpj) ± SD	Presisi (%RSD)	Akurasi (%RE)
1	HQC	12	11,86 ± 0,18	1,53	1,16
	MQC	7,5	7,85 ± 0,11	1,39	4,60
	LQC	4	4,17 ± 0,16	3,92	4,21
	LOQ	2,23	2,29 ± 0,06	2,71	2,64
2	HQC	12	13,09 ± 0,35	2,70	9,08
	MQC	7,5	8,07 ± 0,32	3,91	7,64
	LQC	4	4,35 ± 0,10	2,40	8,73
	LOQ	2,23	2,30 ± 0,16	7,12	3,18
3	HQC	12	12,94 ± 0,44	3,41	7,87
	MQC	7,5	8,12 ± 0,56	6,89	8,22
	LQC	4	4,31 ± 0,17	3,92	7,73
	LOQ	2,23	2,36 ± 0,05	2,23	5,70

Lampiran 8. Hasil penentuan kandungan metformin dalam DMN

Tabel 13. Hasil penentuan kandungan metformin dalam DMN

Formula	Absorbansi (a.u)	Konsentrasi ($\mu\text{g/mL}$)	Kandungan metformin (μg)	Perolehan kembali (%)	Rata-rata	SD
F1	0,561	8,23	82,30	105,04	103,08	2,17
	0,538	7,87	78,65	100,75		
	0,553	8,10	81,03	103,46		
F2	0,509	7,40	74,05	102,74	103,81	3,06
	0,532	7,77	77,70	107,25		
	0,511	7,44	74,37	101,43		
F3	0,501	7,28	72,78	108,08	103,32	4,12
	0,487	7,06	70,56	100,91		
	0,479	6,93	69,29	100,97		
F4	0,567	8,33	83,25	103,19	103,66	1,29
	0,533	8,10	81,03	102,67		
	0,563	8,26	82,62	105,11		
F5	0,603	8,90	88,97	102,70	103,24	0,50
	0,611	9,02	90,24	103,70		
	0,621	9,18	91,83	103,31		

Contoh perhitungan persentase perolehan kembali

Diketahui:

Kandungan teoritis metformin dalam DMN = 78,35

Kandungan metformin dalam DMN yang diperoleh = 82,30

Maka,

$$\begin{aligned}
 \text{Perolehan kembali} &= \frac{\text{Kandungan metformin dalam DMN yang diperoleh}}{\text{Kandungan teoritis metformin dalam DMN}} \times 100\% \\
 &= \frac{82,30}{78,35} \times 100\% \\
 &= 103,08\%
 \end{aligned}$$

Lampiran 9. Hasil uji permeasi *ex vivo*

Tabel 14. Data hasil uji permeasi *ex vivo* F2 dalam media PBS

Waktu (jam)	Absorbansi (a.u)	Konsentrasi (µg/ml)	Faktor pengenceran	Jumlah metformin dalam 8 ml (µg)	Faktor koreksi	Metformin yang terpermeasi (µg)	Rata-rata (µg)	SD
0,25	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,5	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,75	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
1	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
2	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
3	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
4	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
5	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
6	0,067	0,39	1	3,111	0,000	3,111	1,757	1,200
	0,049	0,10	1	0,825	0,000	0,825		
	0,053	0,17	1	1,333	0,000	1,333		

Lanjutan tabel 14

	0,070	0,44	1	3,492	0,389	3,881		
7	0,084	0,66	1	5,270	0,103	5,373	4,262	0,978
	0,069	0,42	1	3,365	0,167	3,532		
	0,103	0,96	1	7,683	0,825	8,508		
8	0,087	0,71	1	5,651	0,762	6,413	7,984	1,386
	0,109	1,06	1	8,444	0,587	9,032		
	0,119	1,21	1	9,714	1,786	11,500		
24	0,121	1,25	1	9,968	1,468	11,437	11,304	0,286
	0,116	1,17	1	9,333	1,643	10,976		

Tabel 15. Data hasil uji permeasi ex vivo F2 dalam media PBS + glukosa 1%

Waktu (jam)	Absorbansi (a.u)	Konsentrasi ($\mu\text{g/ml}$)	Faktor pengenceran	Jumlah metformin dalam 8 ml (μg)	Faktor koreksi	Metformin yang terpermeasi (μg)	Rata-rata (μg)	SD
0,25	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,5	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,75	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
1	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
2	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
3	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
4	0,053	0,17	1	1,333	0,000	1,333	0,571	0,672
	0,043	0,01	1	0,063	0,000	0,063		
	0,045	0,04	1	0,317	0,000	0,317		
5	0,062	0,31	1	2,476	0,167	2,643	4,283	1,525
	0,087	0,71	1	5,651	0,008	5,659		
	0,078	0,56	1	4,508	0,040	4,548		
6	0,101	0,93	1	7,429	0,476	7,905	9,296	1,248
	0,113	1,12	1	8,952	0,714	9,667		
	0,119	1,21	1	9,714	0,603	10,317		

Lanjutan tabel 15

	0,132	1,42	1	1,365	1,405	12,770		
7	0,121	1,25	1	9,968	1,833	11,802	12,331	0,490
	0,126	1,33	1	10,603	1,817	12,421		
	0,143	1,60	1	12,762	2,825	15,587		
8	0,131	1,40	1	11,238	3,079	14,317	15,524	1,176
	0,149	1,69	1	13,524	3,143	16,667		
	0,191	2,36	1	18,857	4,421	23,278		
24	0,178	2,15	1	17,206	4,484	21,690	23,310	1,635
	0,201	2,52	1	20,127	4,833	24,960		

Tabel 16. Data hasil uji permeasi ex vivo F2 dalam media PBS + glukosa 2%

Waktu (jam)	Absorbansi (a.u)	Konsentrasi ($\mu\text{g/ml}$)	Faktor pengenceran	Jumlah metformin dalam 8 ml (μg)	Faktor koreksi	Metformin yang terpermeasi (μg)	Rata-rata (μg)	SD
0,25	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,5	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,75	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
1	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
2	0,044	0,02	1	0,190	0,000	0,190	0,360	0,408
	0,049	0,10	1	0,825	0,000	0,825		
	0,043	0,01	1	0,063	0,000	0,063		
3	0,065	0,36	1	2,857	0,024	2,881	2,563	0,344
	0,059	0,26	1	2,095	0,103	2,198		
	0,063	0,33	1	2,603	0,008	2,611		
4	0,098	0,88	1	7,048	0,381	7,429	7,069	0,927
	0,087	0,71	1	5,651	0,365	6,016		
	0,101	0,93	1	7,429	0,333	7,762		
5	0,111	1,09	1	8,698	1,262	9,960	10,235	0,708
	0,121	1,25	1	9,968	1,071	11,040		
	0,109	1,06	1	8,444	1,262	9,706		
6	0,132	1,42	1	11,365	2,349	13,714	13,820	0,579
	0,129	1,37	1	10,984	2,317	13,302		
	0,138	1,52	1	12,127	2,317	14,444		

Lanjutan tabel 16

7	0,136	1,48	1	11,873	3,770	15,643	15,976	0,537
	0,137	1,50	1	12,000	3,690	15,690		
	0,143	1,60	1	12,762	3,833	16,595		
8	0,153	1,75	1	14,032	5,254	19,286	20,127	1,973
	0,149	1,69	1	13,524	5,190	18,714		
	0,176	2,12	1	16,952	5,429	22,381		
24	0,243	3,18	1	25,460	7,008	32,468	36,119	3,767
	0,271	3,63	1	29,016	6,881	35,897		
	0,298	4,06	1	32,444	7,548	39,992		

Tabel 17. Data hasil uji permeasi ex vivo F2 dalam media PBS + glukosa 4%

Waktu (jam)	Absorbansi (a.u)	Konsentrasi ($\mu\text{g/ml}$)	Faktor pengenceran	Jumlah metformin dalam 8 ml (μg)	Faktor koreksi	Metformin yang terpermeasi (μg)	Rata-rata (μg)	SD
0,25	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,5	0,000	0,00	1	0,000	0,000	0,000	0,000	0,000
	0,000	0,00	1	0,000	0,000	0,000		
	0,000	0,00	1	0,000	0,000	0,000		
0,75	0,043	0,01	1	0,063	0,000	0,063	0,275	0,264
	0,047	0,07	1	0,571	0,000	0,571		
	0,044	0,02	1	0,190	0,000	0,190		
1	0,067	0,39	1	3,111	0,008	3,119	2,595	0,483
	0,059	0,26	1	2,095	0,071	2,167		
	0,062	0,31	1	2,476	0,024	2,500		
2	0,098	0,88	1	7,048	0,397	7,444	5,878	1,362
	0,079	0,58	1	4,635	0,333	4,968		
	0,081	0,61	1	4,889	0,333	5,222		
3	0,119	1,21	1	9,714	1,278	10,992	9,447	1,502
	0,109	1,06	1	8,444	0,913	9,357		
	0,098	0,88	1	7,048	0,944	7,992		
4	0,106	1,01	1	8,063	2,492	10,556	11,429	0,817
	0,118	1,20	1	9,587	1,968	11,556		
	0,124	1,29	1	10,349	1,825	12,175		
5	0,129	1,37	1	10,984	3,500	14,484	13,780	1,151
	0,131	1,40	1	11,238	3,167	14,405		
	0,116	1,17	1	9,333	3,119	12,452		
6	0,132	1,42	1	11,365	4,873	16,238	17,339	1,103
	0,143	1,60	1	12,762	4,571	17,333		
	0,154	1,77	1	14,159	4,286	18,444		

Lanjutan tabel 17

	0,165	1,94	1	15,556	6,294	21,849		
7	0,187	2,29	1	18,349	6,167	24,516	23,251	1,339
	0,179	2,17	1	17,333	6,056	23,389		
	0,198	2,47	1	19,746	8,238	27,984		
8	0,209	2,64	1	21,143	8,460	29,603	29,492	1,456
	0,221	2,83	1	22,667	8,222	30,889		
	0,354	4,94	1	39,556	10,706	50,262		
24	0,398	5,64	1	45,143	11,103	56,246	53,093	3,005
	0,371	5,21	1	41,714	11,056	52,770		

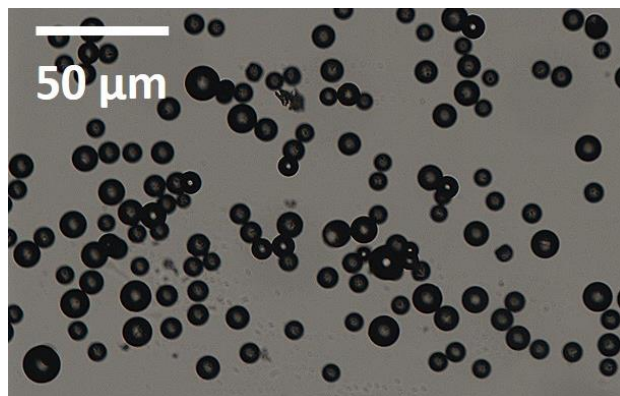
Lampiran 10. Data analisis statistika

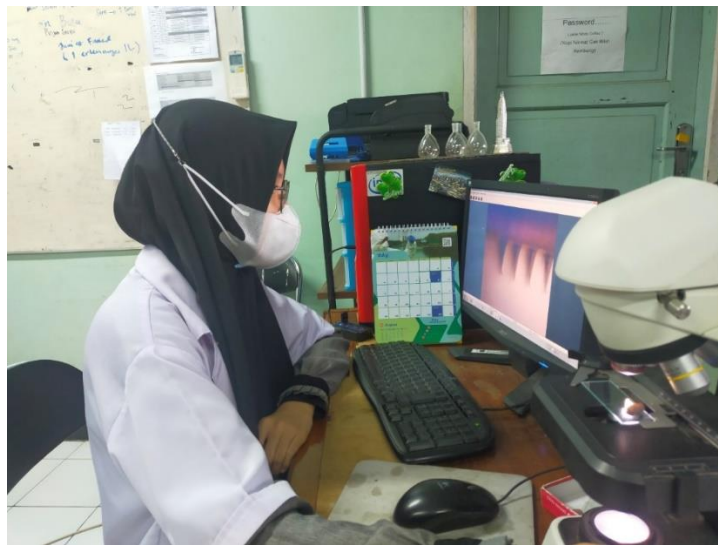
Analisis statistika evaluasi kekuatan mekanik

1way ANOVA Tabular results						
1	Table Analyzed	Kekuatan Mekanik				
2						
3	One-way analysis of variance					
4	P value	< 0.0001				
5	P value summary	***				
6	Are means signif. different? (P < 0.05)	Yes				
7	Number of groups	5				
8	F	84.38				
9	R square	0.9712				
10						
11	ANOVA Table	SS	df	MS		
12	Treatment (between columns)	1345	4	336.2		
13	Residual (within columns)	39.84	10	3.984		
14	Total	1385	14			
15						
16	Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
17	F1 vs F2	18.88	16.38	Yes	***	13.51 to 24.24
18	F1 vs F3	18.48	16.03	Yes	***	13.11 to 23.84
19	F1 vs F4	12.70	11.02	Yes	***	7.339 to 18.07
20	F1 vs F5	-3.901	3.385	No	ns	-9.264 to 1.462
21	F2 vs F3	-0.4000	0.3471	No	ns	-5.763 to 4.963
22	F2 vs F4	-6.175	5.358	Yes	*	-11.54 to -0.8117
23	F2 vs F5	-22.78	19.77	Yes	***	-28.14 to -17.41
24	F3 vs F4	-5.775	5.011	Yes	*	-11.14 to -0.4117
25	F3 vs F5	-22.38	19.42	Yes	***	-27.74 to -17.01
26	F4 vs F5	-16.60	14.41	Yes	***	-21.97 to -11.24

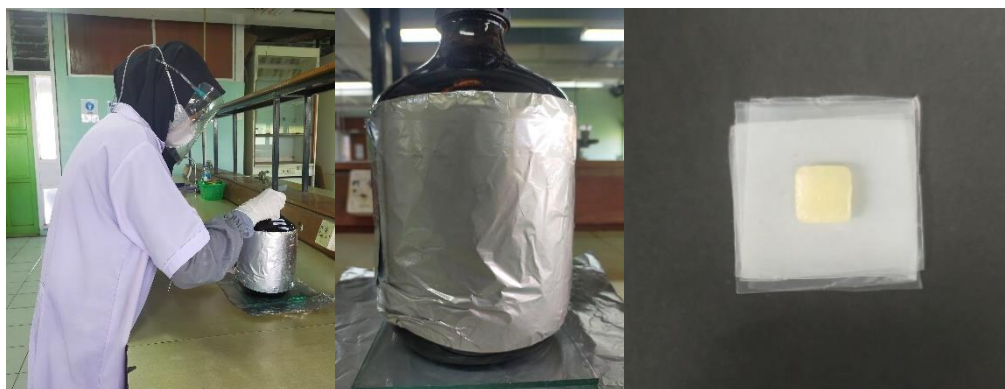
Analisis statistika uji permeasi ex vivo

1way ANOVA Tabular results					
1	Table Analyzed				
2					
3	One-way analysis of variance				
4	P value				
5	P value summary				
6	Are means signif. different? (P < 0.05)				
7	Number of groups				
8	F				
9	R square				
10					
11	ANOVA Table	MS			
12	Treatment (between columns)	7017			
13	Residual (within columns)	45.53			
14	Total				
15					
16	Tukey's Multiple Comparison Test	Significant? P < 0.05?	Summary	95% CI of diff	
17	PBS vs PBS+Glukosa 1%	Yes	**	-42.00 to -6.716	
18	PBS vs PBS+Glukosa 2%	Yes	***	-111.8 to -76.47	
19	PBS vs PBS+Glukosa 4%	Yes	***	-111.8 to -76.56	
20	PBS+Glukosa 1% vs PBS+Glukosa 2%	Yes	***	-87.39 to -52.11	
21	PBS+Glukosa 1% vs PBS+Glukosa 4%	Yes	***	-87.48 to -52.20	
22	PBS+Glukosa 2% vs PBS+Glukosa 4%	No	ns	-17.73 to 17.55	

Lampiran 11. Gambar penelitian**Gambar 19. Morfologi MP-MTF-GR****Gambar 20. Formulasi DMN****Gambar 21. Proses pengeringan DMN**



Gambar 22. Pengamatan morfologi DMN



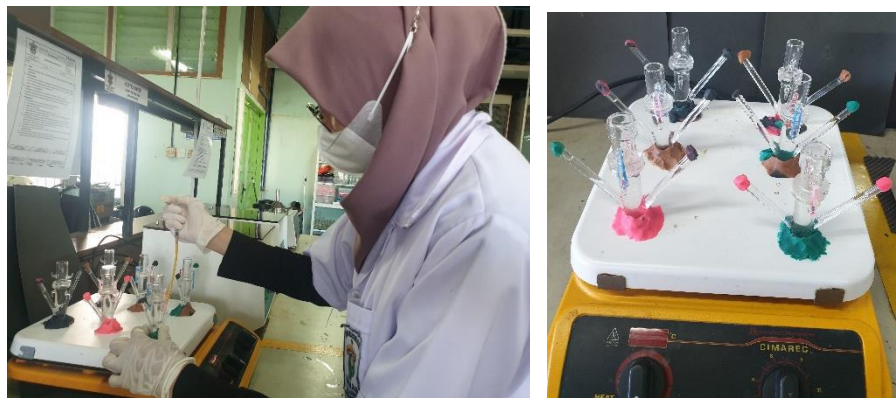
Gambar 23. Uji kekuatan mekanik dan kemampuan penetrasi



Gambar 24. Penentuan kandungan metformin dalam DMN



Gambar 25. Persiapan uji permeasi ex vivo



Gambar 26. Uji permeasi ex vivo