

## DAFTAR PUSTAKA

- Adamczyk-Woźniak, A., Gozdalik, J. T., Kaczorowska, E., Durka, K., Wieczorek, D., Zarzeczańska, D., & Sporzyński, A. (2021). (Trifluoromethoxy)phenylboronic acids: Structures, properties, and antibacterial activity. *Molecules*, 26(7). <https://doi.org/10.3390/molecules26072007>
- Association, A. D. (2022). Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clinical Diabetes*, 40(1), 10–38. <https://doi.org/10.2337/cd22-as01>
- Bruschi, M. L. (Ed.). (2015). 5 - Mathematical models of drug release. In *Strategies to Modify the Drug Release from Pharmaceutical Systems* (pp. 63–86). Woodhead Publishing. <https://doi.org/https://doi.org/10.1016/B978-0-08-100092-2.00005-9>
- Danaei, M., Dehghankhold, M., Ataei, S., Hasanzadeh Davarani, F., Javanmard, R., Dokhani, A., Khorasani, S., & Mozafari, M. R. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. In *Pharmaceutics* (Vol. 10, Issue 2). MDPI AG. <https://doi.org/10.3390/pharmaceutics10020057>
- Farhangi, M. A., Dadashzadeh, S., & Bolourchian, N. (2017). Biodegradable Gelatin Microspheres as Controlled Release Intraarticular Delivery System: The Effect of Formulation Variables. *Indian Journal of Pharmaceutical Sciences*, 79, 105–112.
- Fox, M., & Zilberman, M. (2015). Drug delivery from gelatin-based systems. *Expert Opinion on Drug Delivery*, 12(9), 1547–1563. <https://doi.org/10.1517/17425247.2015.1037272>
- Gabel, S. A., Duff, M. R., Pedersen, L. C., DeRose, E. F., Krahn, J. M., Howell, E. E., & London, R. E. (2017). A Structural Basis for Biguanide Activity. *Biochemistry*, 56(36), 4786–4798. <https://doi.org/10.1021/acs.biochem.7b00619>
- Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, 21(17). <https://doi.org/10.3390/ijms21176275>
- Ghosal, S. (2019). The Side Effects Of Metformin - A Review. *Diabetes & Metabolic Disorders*, 6(1), 1–7. <https://doi.org/10.24966/DMD-201X/100030>

- Gong, J., Jaiswal, R., Dalla, P., Luk, F., & Bebawy, M. (2015). Microparticles in cancer: A review of recent developments and the potential for clinical application. *Seminars in Cell & Developmental Biology*, 40, 35–40. <https://doi.org/https://doi.org/10.1016/j.semcd.2015.03.009>
- Gong, L., Goswami, S., Giacomini, K. M., Altman, R. B., & Klein, T. E. (2012). Metformin pathways: Pharmacokinetics and pharmacodynamics. *Pharmacogenetics and Genomics*, 22(11), 820–827. <https://doi.org/10.1097/FPC.0b013e3283559b22>
- International Diabetes Federation. (2021). *IDF Diabetes Atlas, 10th edition edn. Brussels*.
- Lengyel, M., Kállai-Szabó, N., Antal, V., Laki, A. J., & Antal, I. (2019). Microparticles, microspheres, and microcapsules for advanced drug delivery. In *Scientia Pharmaceutica* (Vol. 87, Issue 3). MDPI AG. <https://doi.org/10.3390/scipharm87030020>
- Mady, O. Y., Donia, A. A., Al-Shoubki, A. A., & Qasim, W. (2019). Paracellular pathway enhancement of metformin hydrochloride via molecular dispersion in span 60 microparticles. *Frontiers in Pharmacology*, 10. <https://doi.org/10.3389/fphar.2019.00713>
- Maqbool, I., Noreen, S., Pervaiz, F., Ijaz, M., & Farooq, I. (2019). Micro Particles: A Review of Recent Developments, Microencapsulation Method, and Therapeutic Strategies. *Global Pharmaceutical Sciences Review*, IV(I), 28–39. [https://doi.org/10.31703/gpsr.2019\(iv-i\).04](https://doi.org/10.31703/gpsr.2019(iv-i).04)
- Ma, Q., Zhao, X., Shi, A., & Wu, J. (2021). Bioresponsive functional phenylboronic acid-based delivery system as an emerging platform for diabetic therapy. In *International Journal of Nanomedicine* (Vol. 16, pp. 297–314). Dove Medical Press Ltd. <https://doi.org/10.2147/IJN.S284357>
- Marín-Peñalver, J. J., Martín-Timón, I., Sevillano-Collantes, C., & Cañizo-Gómez, F. J. del. (2016). Update on the treatment of type 2 diabetes mellitus. *World Journal of Diabetes*, 7(17), 354. <https://doi.org/10.4239/wjd.v7.i17.354>
- Naguib, Y. W., Givens, B. E., Ho, G., Yu, Y., Wei, S. G., Weiss, R. M., Felder, R. B., & Salem, A. K. (2021). An injectable microparticle formulation for the sustained release of the specific MEK inhibitor PD98059: in vitro evaluation and pharmacokinetics. *Drug Delivery*

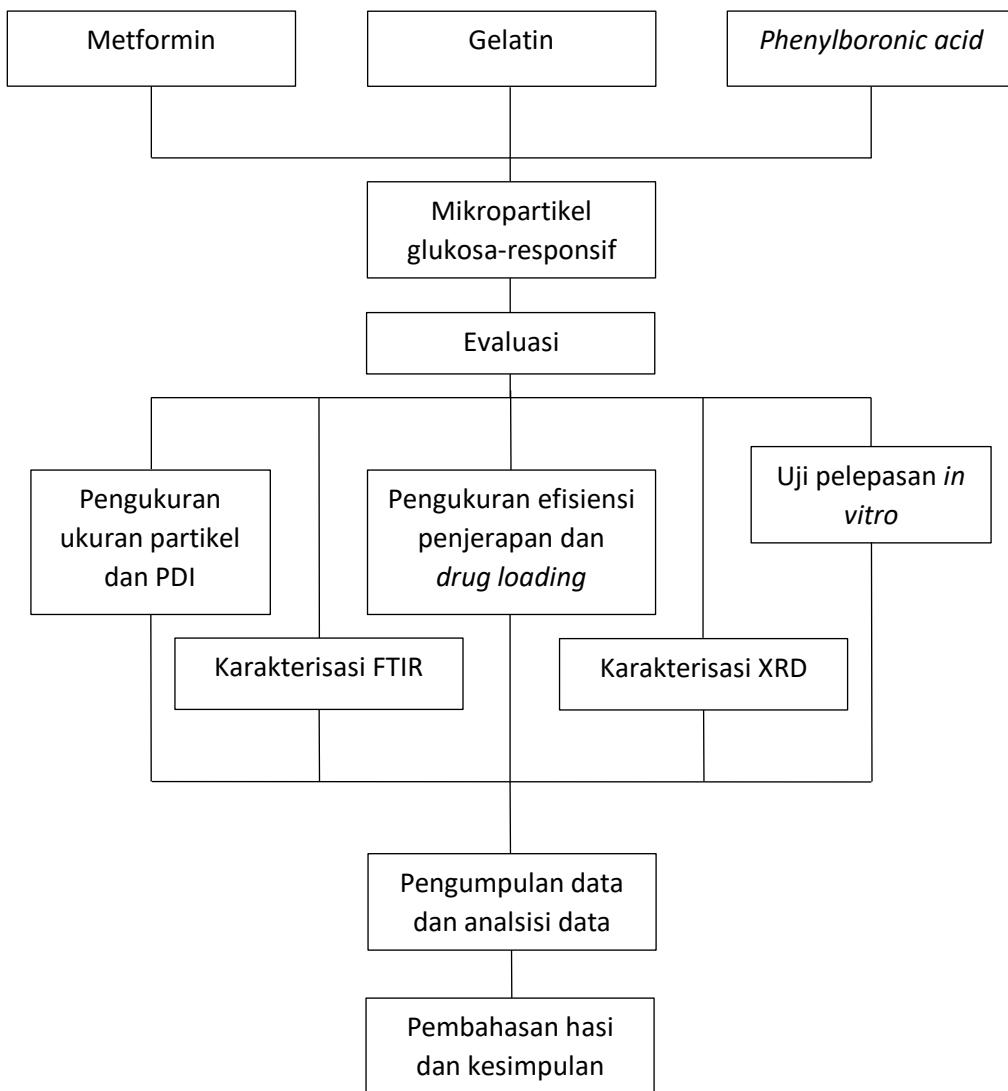
- and Translational Research*, 11(1), 182–191.  
<https://doi.org/10.1007/s13346-020-00758-9>
- Nii, T. (2021). Strategies using gelatin microparticles for regenerative therapy and drug screening applications. In *Molecules* (Vol. 26, Issue 22). MDPI. <https://doi.org/10.3390/molecules26226795>
- Perkumpulan Endokrinologi Indonesia. (2021). *PEDOMAN PENGELOLAAN DAN PENCEGAHAN DIABETES MELITUS TIPE 2 DEWASA DI INDONESIA*. PB Perkeni.
- 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), 346–368. <https://doi.org/10.3390/pharmaceutics11070346>
- Prieto, C., Evtoski, Z., Pardo-Figuerez, M., & Lagaron, J. M. (2021). Bioavailability enhancement of nanostructured microparticles of carvedilol. *Journal of Drug Delivery Science and Technology*, 66. <https://doi.org/10.1016/j.jddst.2021.102780>
- Rafiee, M. H., & Rasool, B. K. A. (2022). An Overview of Microparticulate Drug Delivery System and its Extensive Therapeutic Applications in Diabetes. In *Advanced Pharmaceutical Bulletin* (Vol. 12, Issue 4, pp. 730–746). Tabriz University of Medical Sciences. <https://doi.org/10.34172/apb.2022.075>
- Raza, H., Javeria, S., & Rashid, Z. (2020). Sustained released Metformin microparticles for better management of type II diabetes mellitus: In-vitro studies. *Materials Research Express*, 7(1). <https://doi.org/10.1088/2053-1591/ab6c0f>
- Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. In *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* (Vol. 14, pp. 3567–3602). Dove Medical Press Ltd. <https://doi.org/10.2147/DMSO.S319895>
- Rena, G., Hardie, D. G., & Pearson, E. R. (2017). The mechanisms of action of metformin. In *Diabetologia* (Vol. 60, Issue 9, pp. 1577–1585). Springer Verlag. <https://doi.org/10.1007/s00125-017-4342-z>
- Saeed, M., & Elshaer, A. (2019). Glucose-sensitive materials for delivery of antidiabetic drugs. In *Engineering Drug Delivery Systems* (pp. 203–228). Elsevier. <https://doi.org/10.1016/B978-0-08-102548-2.00009-3>

- Sulistianiati, 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. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 267, 1386–1425. <https://doi.org/10.1016/j.saa.2021.120600>
- Volpatti, L. R., Matranga, M. A., Cortinas, A. B., Delcassian, D., Daniel, K. B., Langer, R., & Anderson, D. G. (2020). Glucose-Responsive Nanoparticles for Rapid and Extended Self-Regulated Insulin Delivery. *ACS Nano*, 14(1), 488–497. <https://doi.org/10.1021/acsnano.9b06395>
- Wang, X., Wei, B., Cheng, X., Wang, J., & Tang, R. (2016). Phenylboronic acid-decorated gelatin nanoparticles for enhanced tumor targeting and penetration. *Nanotechnology*, 27(38). <https://doi.org/10.1088/0957-4484/27/38/385101>
- Webber, M. J., & Anderson, D. G. (2015). Smart approaches to glucose-responsive drug delivery. In *Journal of Drug Targeting* (Vol. 23, Issues 7–8, pp. 651–655). Taylor and Francis Ltd. <https://doi.org/10.3109/1061186X.2015.1055749>
- Wu, J. Z., Williams, G. R., Li, H. Y., Wang, D. X., Li, S. de, & Zhu, L. M. (2017). Insulin-loaded plga microspheres for glucose-responsive release. *Drug Delivery*, 24(1), 1513–1525. <https://doi.org/10.1080/10717544.2017.1381200>
- Yao, Y., Ji, K., Wang, Y., Gu, Z., & Wang, J. (2022). Materials and Carriers Development for Glucose-Responsive Insulin. *Accounts of Materials Research*, 3(9), 960–970. <https://doi.org/10.1021/accountsmr.2c00094>
- Yasmin, R., Shah, M., Khan, S. A., & Ali, R. (2017). Gelatin nanoparticles: A potential candidate for medical applications. In *Nanotechnology Reviews* (Vol. 6, Issue 2, pp. 191–207). Walter de Gruyter GmbH. <https://doi.org/10.1515/ntrev-2016-0009>
- Zhao, L., Xiao, C., Wang, L., Gai, G., & Ding, J. (2016). Glucose-Sensitive Polymer Nanoparticles for Self-Regulated Drug Delivery. *Chem. Commun.*, 52, 7633–7652. <https://doi.org/10.1039/C6CC02202B>
- Zhong, P., Zeng, H., Huang, M., He, G., & Chen, Z. (2021). Efficacy and Safety of Subcutaneous and Oral Semaglutide Administration in

Patients with Type 2 Diabetes: A Meta-Analysis. *Frontiers in Pharmacology*, 12, 1–11. <https://doi.org/10.3389/fphar.2021.695182>

## LAMPIRAN

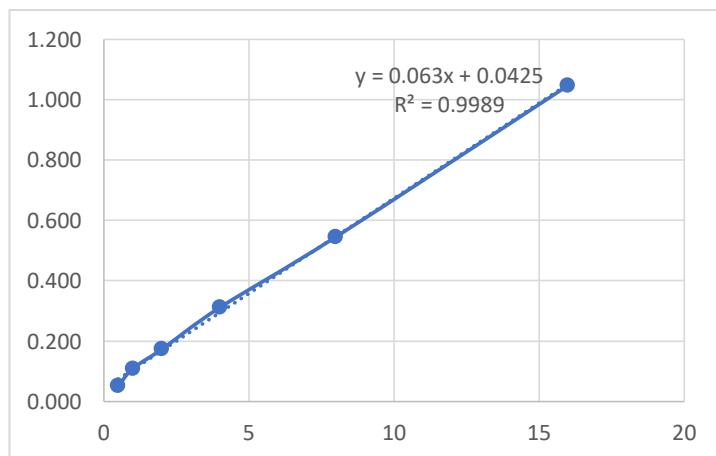
### Lampiran 1. Skema Kerja



## Lampiran 2. Absorbansi pembuatan kurva baku

**Tabel 2. Hasil pengukuran absorbansi kurva baku metformin media PBS**

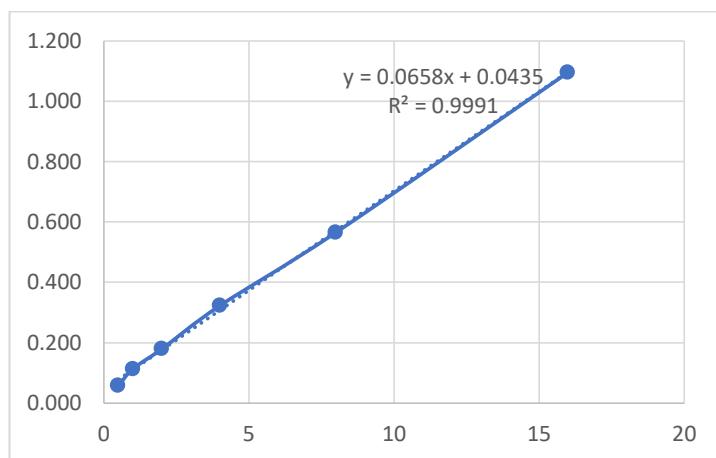
Konsentrasi	Absorbansi rep-1	Absorbansi rep-2	Absorbansi rep-3	Rata-rata
16	1,053	1,037	1,050	1,047
8	0,546	0,538	0,551	0,545
4	0,313	0,315	0,306	0,312
2	0,178	0,174	0,169	0,174
1	0,111	0,105	0,113	0,109
0,5	0,053	0,055	0,051	0,053



**Gambar 15. Grafik kurva baku metformin dalam media PBS**

**Tabel 3. Hasil pengukuran absorbansi kurva baku metformin media PBS + glukosa 1%**

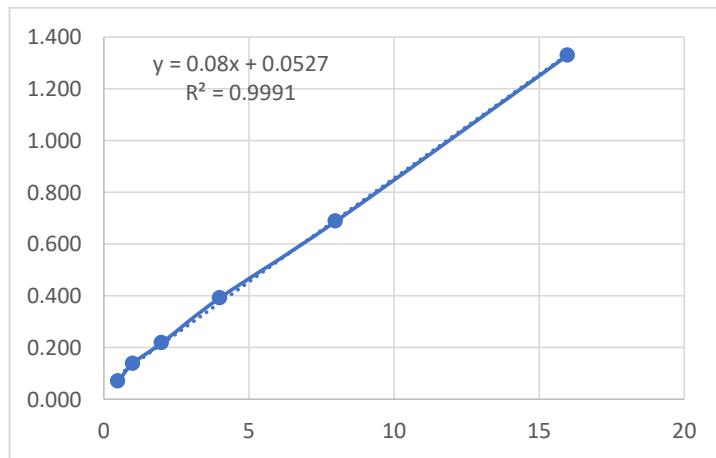
Konsentrasi	Absorbansi rep-1	Absorbansi rep-2	Absorbansi rep-3	Rata-rata
16	1,105	1,088	1,092	1,095
8	0,573	0,549	0,574	0,565
4	0,329	0,322	0,318	0,323
2	0,187	0,177	0,176	0,180
1	0,116	0,107	0,117	0,113
0,5	0,066	0,056	0,053	0,058



**Gambar 16.** Grafik kurva baku metformin dalam media PBS + glukosa 1%

**Tabel 4.** Hasil pengukuran absorbansi kurva baku metformin media PBS + glukosa 2%

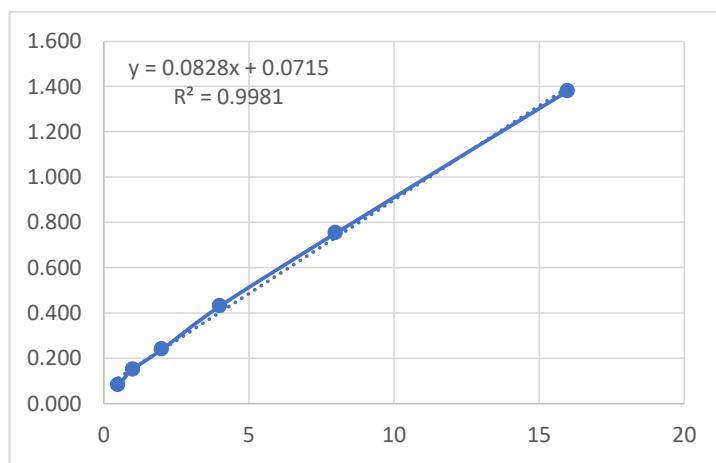
Konsentrasi	Absorbansi rep-1	Absorbansi rep-2	Absorbansi rep-3	Rata-rata
16	1,194	1,167	1,627	1,329
8	0,619	0,589	0,855	0,688
4	0,355	0,345	0,474	0,392
2	0,201	0,190	0,262	0,218
1	0,125	0,115	0,174	0,138
0,5	0,071	0,060	0,079	0,070



**Gambar 17.** Grafik kurva baku metformin dalam media PBS + glukosa 2%

**Tabel 5. Hasil pengukuran absorbansi kurva baku metformin media PBS + glukosa 4%**

Konsentrasi	Absorbansi rep-1	Absorbansi rep-2	Absorbansi rep-3	Rata-rata
16	1,331	1,398	1,412	1,380
8	0,638	0,784	0,837	0,753
4	0,366	0,459	0,465	0,430
2	0,207	0,253	0,257	0,239
1	0,129	0,153	0,171	0,151
0,5	0,091	0,080	0,078	0,083



**Gambar 18. Grafik kurva baku metformin dalam media PBS + glukosa 4%**

**Lampiran 3. Hasil Pengukuran Efisiensi Penjerapan dan Drug Loading**

**Tabel 6. Persentase efisiensi penjerapan dan drug loading**

Formula	Efisiensi penjerapan (%) (rata-rata ± SD)	Drug loading (%) (rata-rata ± SD)
F1	28,32 ± 2,13	12,09 ± 1,15
F2	32,12 ± 3,04	13,43 ± 1,24
F3	41,39 ± 4,31	18,21 ± 1,38
F4	69,53 ± 6,46	20,93 ± 1,63
F5	72,09 ± 6,98	18,02 ± 1,28

**Contoh perhitungan persen efisiensi penjerapan**

Diketahui berat metformin awal: 100 mg

Berat metformin bebas untuk F4: 30,47 mg

$$\% \text{ EP} = \frac{(100 \text{ mg} - 30,47 \text{ mg})}{100 \text{ mg}} \times 100$$

$$\% \text{ EP} = \frac{69,53 \text{ mg}}{100 \text{ mg}} \times 100$$

$$\% \text{ EP} = 69,53\%$$

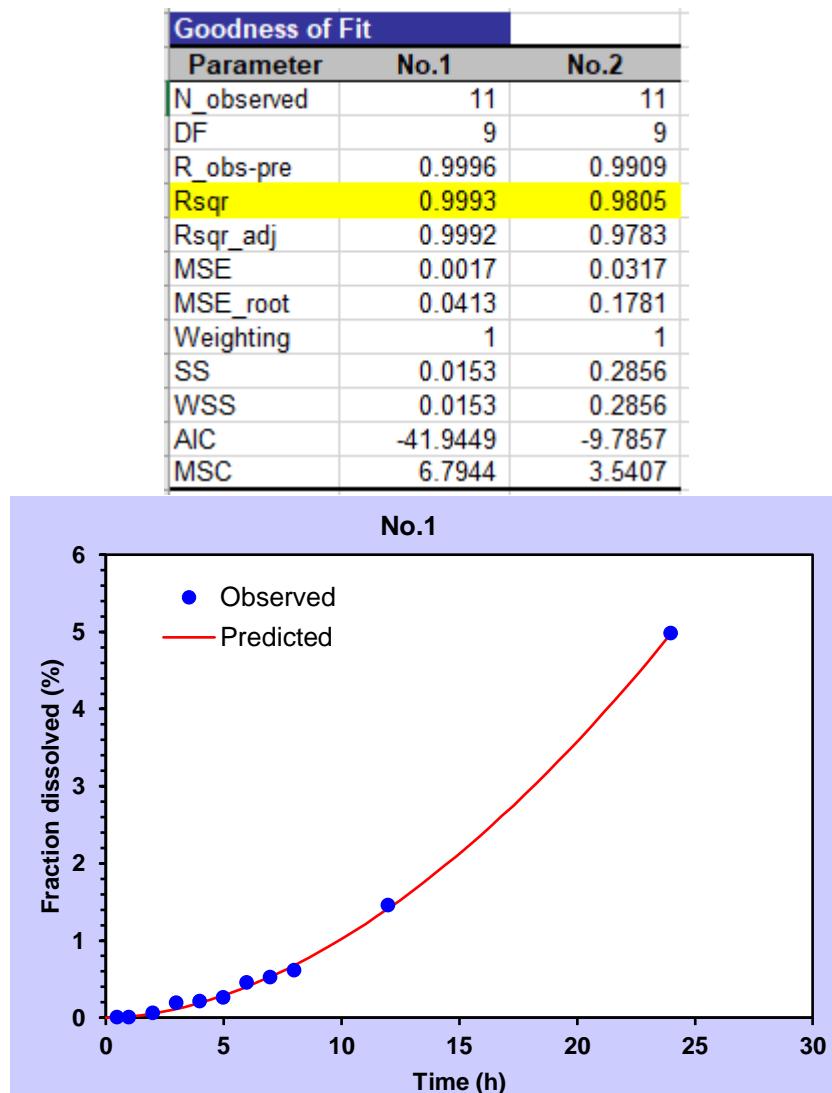
**Contoh perhitungan persen drug loading**

Diketahui berat total mikropartikel untuk F4: 332,02 mg

$$\% \text{ DL} = \frac{69,53}{332,02} \times 100$$

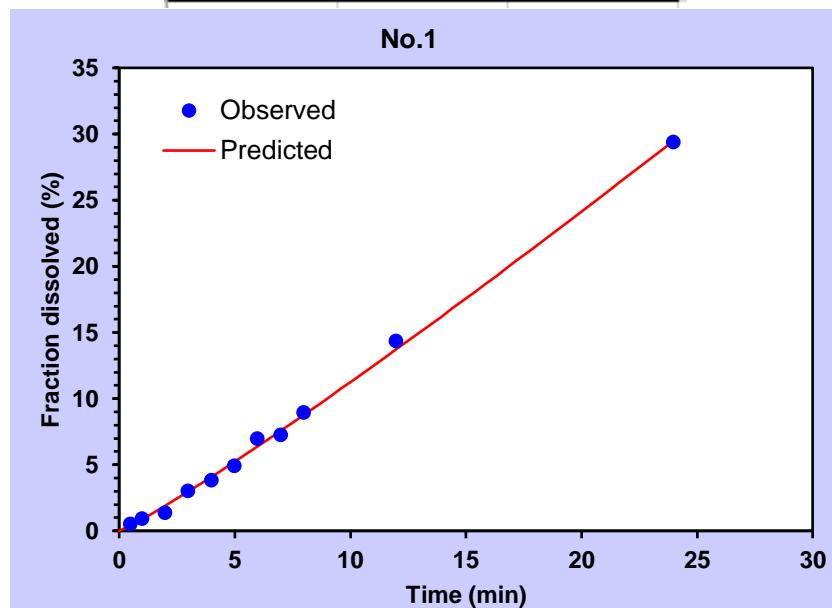
$$\% \text{ DL} = 20,93\%$$

**Lampiran 4. Analisis model kinetika pelepasan metformin dalam formula F4**

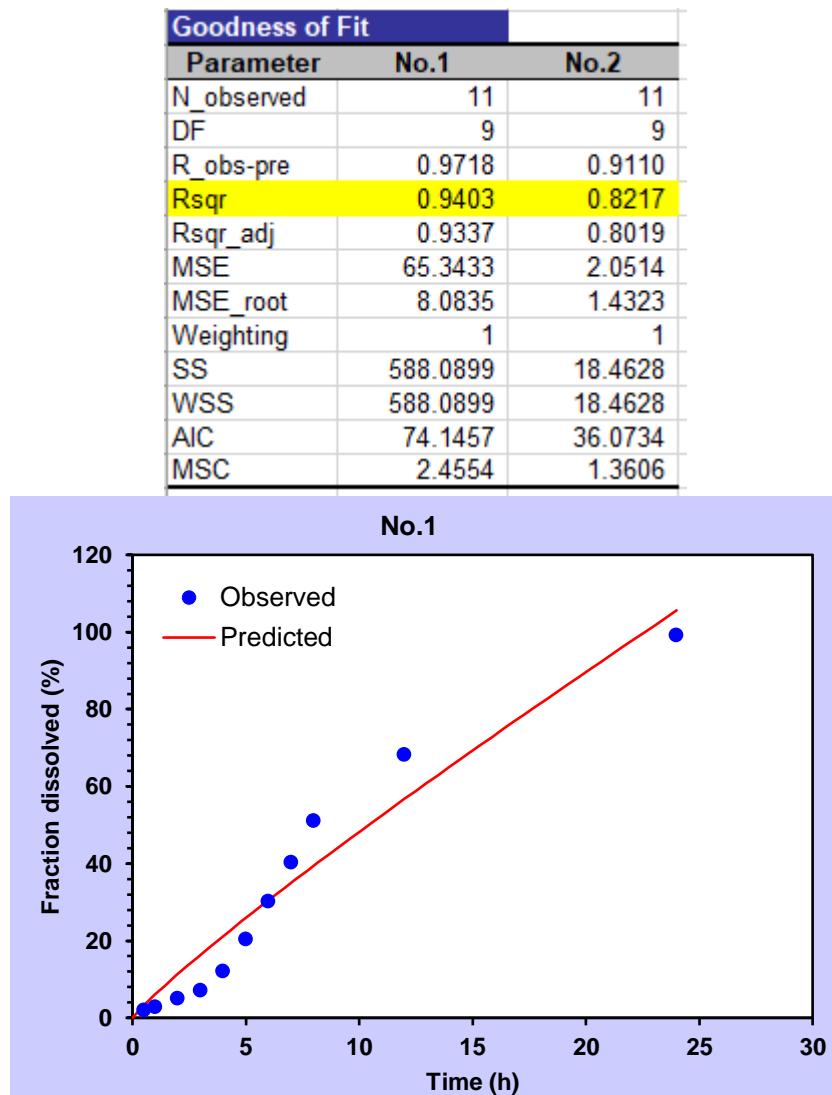


**Gambar 19. Model kinetika pelepasan Korsmeyer-Peppas dalam media PBS**

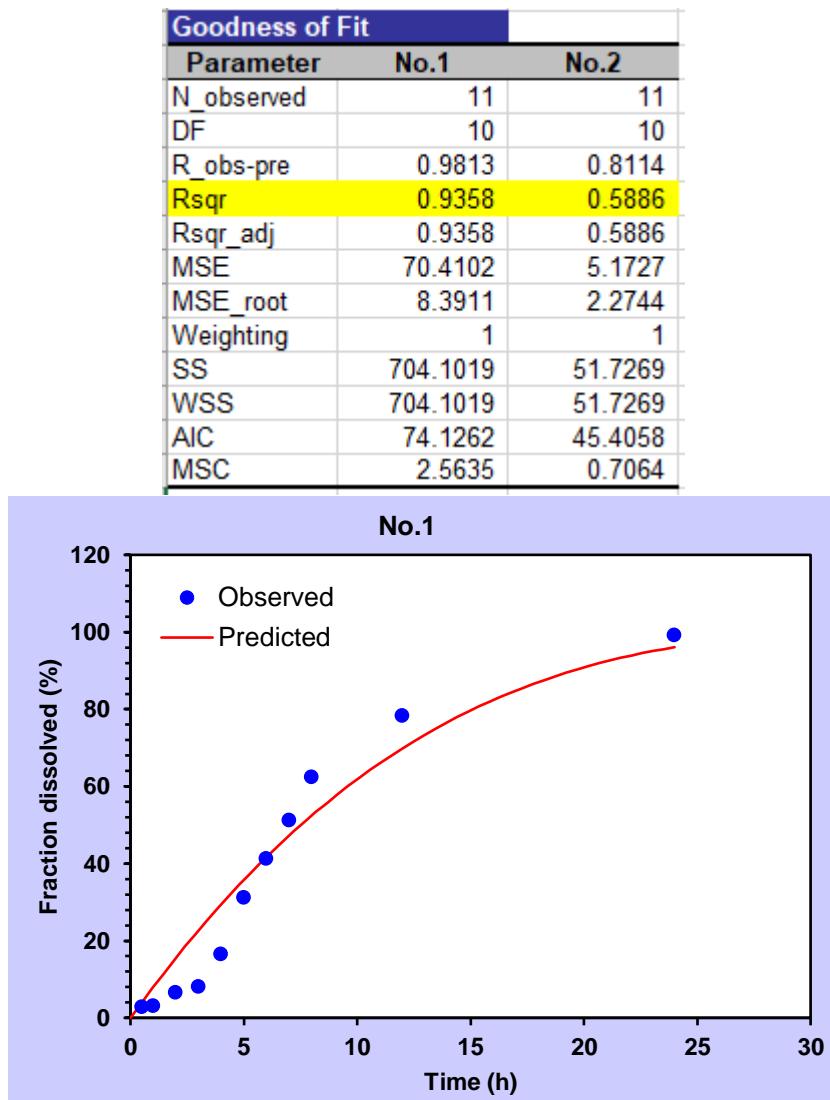
Goodness of Fit		
Parameter	No.1	No.2
N_observed	11	11
DF	9	9
R_obs-pre	0.9990	0.9865
Rsqr	0.9980	0.9719
Rsqr_adj	0.9978	0.9688
MSE	0.1527	0.0187
MSE_root	0.3908	0.1367
Weighting	1	1
SS	1.3745	0.1681
WSS	1.3745	0.1681
AIC	7.4987	-15.6143
MSC	5.8657	3.2083



Gambar 20. Model kinetika pelepasan Korsmeyer-Peppas dalam media PBS+glukosa 1%



Gambar 21. Model kinetika pelepasan Korsmeyer-Peppas dalam media PBS+glukosa 2%



Gambar 22. Model kinetika pelepasan Hixson Crowell dalam media PBS+glukosa 4%

## Lampiran 5. Data Analisis Statistika

### Lampiran 5.1 Analisis statistika data ukuran partikel

One-way analysis of variance					
P value	< 0.0001				
P value summary	***				
Are means signif. different? (P < 0.05)	Yes				
Number of groups	5				
F	66.92				
R square	0.9640				
ANOVA Table					
Treatment (between columns)	SS	df	MS		
128.0	4		32.00		
Residual (within columns)	4.782	10	0.4782		
Total	132.8	14			
Tukey's Multiple Comparison Test					
	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F1 vs F2	-2.150	5.385	Yes	*	-4.008 to -0.2919
F1 vs F3	-2.990	7.489	Yes	**	-4.848 to -1.132
F1 vs F4	-4.150	10.39	Yes	***	-6.008 to -2.292
F1 vs F5	-8.790	22.02	Yes	***	-10.65 to -6.932
F2 vs F3	-0.8400	2.104	No	ns	-2.698 to 1.018
F2 vs F4	-2.000	5.009	Yes	*	-3.858 to -0.1419
F2 vs F5	-6.640	16.63	Yes	***	-8.498 to -4.782
F3 vs F4	-1.160	2.905	No	ns	-3.018 to 0.6981
F3 vs F5	-5.800	14.53	Yes	***	-7.658 to -3.942
F4 vs F5	-4.640	11.62	Yes	***	-6.498 to -2.782

### Lampiran 5.2 Analisis statistika data efisiensi penjerapan

One-way analysis of variance					
P value	< 0.0001				
P value summary	***				
Are means signif. different? (P < 0.05)	Yes				
Number of groups	5				
F	52.66				
R square	0.9547				
ANOVA Table					
Treatment (between columns)	SS	df	MS		
5174	4		1293		
Residual (within columns)	245.6	10	24.56		
Total	5420	14			
Tukey's Multiple Comparison Test					
	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F1 vs F2	-3.800	1.328	No	ns	-17.12 to 9.517
F1 vs F3	-13.07	4.568	No	ns	-26.39 to 0.2465
F1 vs F4	-41.21	14.40	Yes	***	-54.53 to -27.89
F1 vs F5	-43.77	15.30	Yes	***	-57.09 to -30.45
F2 vs F3	-9.270	3.240	No	ns	-22.59 to 4.047
F2 vs F4	-37.41	13.07	Yes	***	-50.73 to -24.09
F2 vs F5	-39.97	13.97	Yes	***	-53.29 to -26.65
F3 vs F4	-28.14	9.835	Yes	***	-41.46 to -14.82
F3 vs F5	-30.70	10.73	Yes	***	-44.02 to -17.38
F4 vs F5	-2.560	0.8947	No	ns	-15.88 to 10.76

### Lampiran 5.3 Analisis statistika data *drug loading*

One-way analysis of variance				
P value				
P value summary				
Are means signif. different? (P < 0.05)				
Number of groups				
F				
R square				
ANOVA Table	df	MS		
Treatment (between columns)	4	40.29		
Residual (within columns)	10	1.812		
Total	14			
Tukey's Multiple Comparison Test	q	Significant? P < 0.05?	Summary	95% CI of diff
F1 vs F2	1.724	No	ns	-4.957 to 2.277
F1 vs F3	7.875	Yes	**	-9.737 to -2.503
F1 vs F4	11.37	Yes	***	-12.46 to -5.223
F1 vs F5	7.630	Yes	**	-9.547 to -2.313
F2 vs F3	6.151	Yes	**	-8.397 to -1.163
F2 vs F4	9.650	Yes	***	-11.12 to -3.883
F2 vs F5	5.906	Yes	*	-8.207 to -0.9731
F3 vs F4	3.500	No	ns	-6.337 to 0.8969
F3 vs F5	0.2445	No	ns	-3.427 to 3.807
F4 vs F5	3.744	No	ns	-0.7069 to 6.527

### Lampiran 5.4 Analisis statistik data pelepasan metformin dalam media PBS setelah 24 jam

One-way analysis of variance					
P value	< 0.0001				
P value summary	***				
Are means signif. different? (P < 0.05)	Yes				
Number of groups	3				
F	320.5				
R square	0.9907				
ANOVA Table	SS	df	MS		
Treatment (between columns)	17507	2	8754		
Residual (within columns)	163.9	6	27.31		
Total	17671	8			
Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F4 vs F4 without PBA	-92.03	30.50	Yes	***	-105.1 to -78.94
F4 vs Pure MTF	-95.02	31.49	Yes	***	-108.1 to -81.93
F4 without PBA vs Pure MTF	-2.990	0.9909	No	ns	-16.08 to 10.10

### Lampiran 5.5 Analisis statistik data pelepasan metformin dalam media PBS+Glukosa 1% setelah 24 jam

One-way analysis of variance					
P value	< 0.0001				
P value summary	***				
Are means signif. different? (P < 0.05)	Yes				
Number of groups	3				
F	169.0				
R square	0.9826				
ANOVA Table					
	SS	df	MS		
Treatment (between columns)	9571	2	4785		
Residual (within columns)	169.9	6	28.31		
Total	9741	8			
Tukey's Multiple Comparison Test					
	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F4 vs F4 without PBA	-67.59	22.00	Yes	***	-80.92 to -54.26
F4 vs Pure MTF	-70.66	23.00	Yes	***	-83.99 to -57.33
F4 without PBA vs Pure MTF	-3.070	0.9993	No	ns	-16.40 to 10.26

### Lampiran 5.6 Analisis statistik data pelepasan metformin dalam media PBS+Glukosa 2% setelah 24 jam

One-way analysis of variance					
P value	0.9483				
P value summary	ns				
Are means signif. different? (P < 0.05)	No				
Number of groups	3				
F	0.05356				
R square	0.01754				
ANOVA Table					
	SS	df	MS		
Treatment (between columns)	6.016	2	3.008		
Residual (within columns)	337.0	6	56.16		
Total	343.0	8			
Tukey's Multiple Comparison Test					
	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F4 vs F4 without PBA	1.090	0.2519	No	ns	-17.68 to 19.86
F4 vs Pure MTF	-0.9100	0.2103	No	ns	-19.68 to 17.86
F4 without PBA vs Pure MTF	-2.000	0.4622	No	ns	-20.77 to 16.77

### Lampiran 5.7 Analisis statistik data pelepasan metformin dalam media PBS+Glukosa 2% setelah 24 jam

One-way analysis of variance					
P value	0.9845				
P value summary	ns				
Are means signif. different? (P < 0.05)	No				
Number of groups	3				
F	0.01563				
R square	0.005182				
ANOVA Table					
	SS	df	MS		
Treatment (between columns)	1.705	2	0.8524		
Residual (within columns)	327.3	6	54.55		
Total	329.0	8			
Tukey's Multiple Comparison Test					
	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
F4 vs F4 without PBA	0.1800	0.04221	No	ns	-18.32 to 18.68
F4 vs Pure MTF	-0.8200	0.1923	No	ns	-19.32 to 17.68
F4 without PBA vs Pure MTF	-1.000	0.2345	No	ns	-19.50 to 17.50

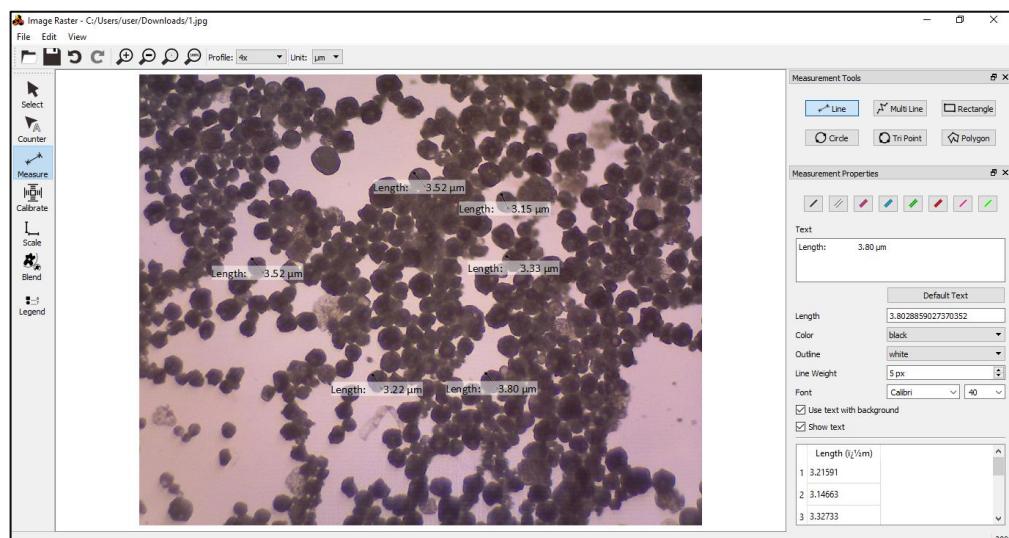
### Lampiran 7. Gambar Penelitian



**Gambar 23. Pengukuran panjang gelombang maksimum dan pembuatan kurva baku**



**Gambar 24. Proses formulasi mikropartikel metformin glukosa-responsif**



**Gambar 25. Pengamatan dan pengukuran ukuran partikel**



Gambar 26. Pengukuran efisiensi penyerapan dan drug loading



Gambar 27. Uji pelepasan in vitro