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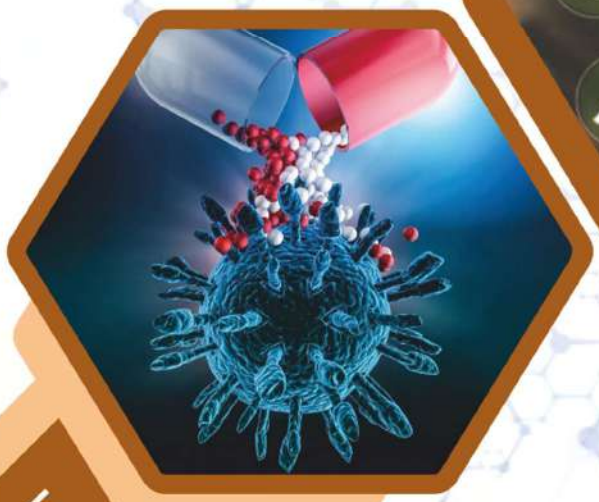

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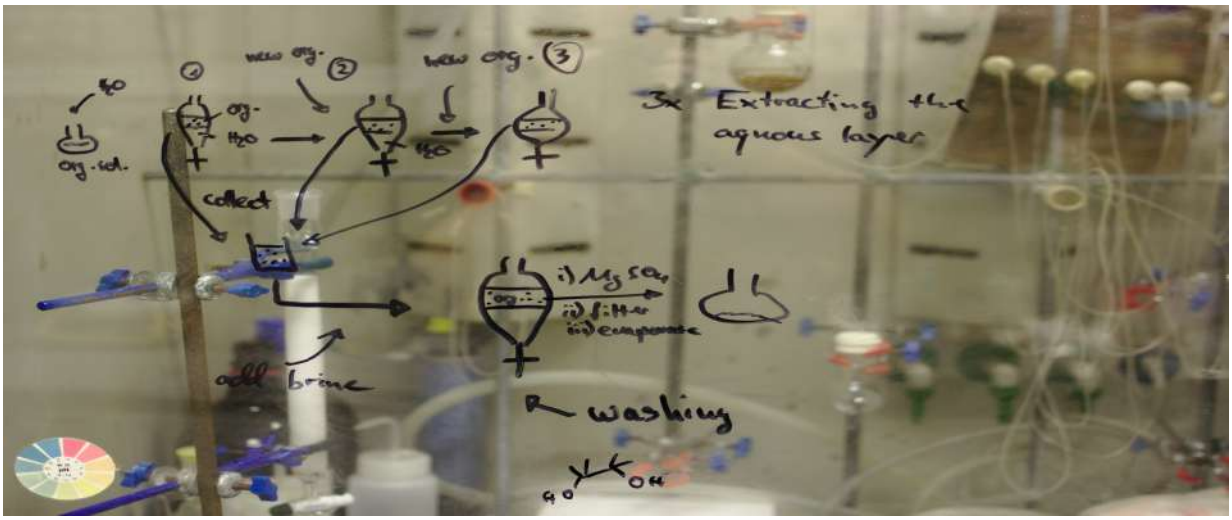

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THE IMPACT OF PULVERIZATION DURATION ON THE HOMOGENEITY AND CHEMICAL STABILITY OF PULVERIZED PREPARATIONS CONTAINING A COMBINATION OF KETOTIFEN FUMARATE AND CYPROHEPTADINE HCl

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ABSTRACT

Drug compounding is carried out by trained healthcare professionals following established standards to ensure both the safety and effectiveness of drugs. This study examines the practice of preparing compounded drugs. The quality can be determined by their homogeneity and stability during storage, ensuring that they remain effective and safe to use. This study aims to evaluate how the duration of pulverisation affects the homogeneity and stability of a combined pulverised preparation containing Cyproheptadine HCl and Ketotifen Fumarate, which are two drugs used to treat allergy symptoms. This research employs UV spectrophotometry in conjunction with the partial least squares chemometric model. The pulverisation durations used for homogeneity and chemical stability tests were 30, 60, 120, and 150 seconds. The evaluation of chemical stability was conducted over a storage period extending to 90 days. This study revealed that the homogeneity and stability of a compounded preparation containing ketotifen fumarate and cyproheptadine HCl can be attained with pulverisation times of 120 and 150 seconds, respectively. This study highlights the significance of controlling pulverisation duration to preserve the quality and stability of drug preparations and to guarantee accurate dosage for optimal therapeutic effects. Further, this study contributes to improving the quality of drugs and relates to SDG-3 of good health and well-being.

Keywords: Pulverizers, Cyproheptadine HCl, Ketotifen Fumarate, Stability, Homogeneity

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INTRODUCTION

Drug compounding is only done by healthcare specialists in accordance with established guidelines to ensure safety and reproducibility.[1] In the Special Region of Yogyakarta, 94% of community pharmacists provide prescriptions that include compounded preparations. Compounded prescriptions make up 11.55% of the total prescriptions each month.[2] Divided powder is a solid compounded dosage form containing an active ingredient powder that is evenly ground and divided in accordance with the Indonesian Pharmacopoeia.[2,3] Drug compounding presents risks such as overdose, underdose, formula incompatibility, and reduced chemical stability, all of which impact both effectiveness and safety.[4,5] One key factor in assessing the chemical stability of drug ingredients is the beyond-use date (BUD), which refers to the time restriction for use after the compound or primary package is opened.[6] In contrast with licensed drugs, compounded prescriptions are susceptible to drug interactions and incompatibilities, which affect the stability of the final product.[7,8] The preparation of divided powder for patients involves the pulverization or reduction of the particle size of the tablet formulation. This procedure is taken since there are no other options due to the lack of pure powder that can be combined into pulverized products. Pulverization is used to create pulverized tablets through manual techniques or tools like blenders. The use of blenders in pulverization is noted to speed up the process; however, it may compromise the levels of active substances due to degradation caused by the particle contact area.[9,10] The combination of cyproheptadine HCl and ketotifen fumarate is commonly prescribed for children as pulverized combination.[11,12] This study used cyproheptadine HCl and ketotifen fumarate, antihistamines indicated for allergies and asthma, which have a history of reduced stability during manual grinding.[12,14] This research was designed to assess how pulverization duration affects the homogeneity and stability of the

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cyproheptadine HCl and ketotifen fumarate mixture, ensuring the effectiveness and safety of the therapy. This study will significantly contribute to the enhancement of the quality of extemporaneous preparations and implement the Sustainable Development Goal of good health and well-being (SDG-3).[15]

EXPERIMENTAL

Material and Methods

Ketotifen fumarate (BPFI) and cyproheptadine HCl (BPFI) standards were obtained through the Indonesian Food and Drug Authority (BPOM). The solvents used in this study included Methanol Pro Analysis sourced from Smart-Lab, while ketotifen fumarate and cyproheptadine HCl tablets were obtained from a pharmacy in Sleman, Yogyakarta, Indonesia.

Instrument and Software

Ohaus® analytical balance with 0.001 accuracy, Shimadzu® double beam UV spectrophotometer, RStudio® application version 2024.6.14 with RGui 4.4.1, Pyrex® beakers, Pyrex® volumetric flasks (5 and 10 mL), Pyrex® droppers, Whatman® filter paper, Socorex® 825 micropipettes (1-10 µl, 10-100 µl, 100-1000 µl), white tip, yellow tip, and blue tip, pulverizer and climatic chamber.

General Procedure

A multivariate model was created using standard solutions that consisted of a combination of ketotifen fumarate and cyproheptadine HCl, each at varying concentrations. The study used 60 pulverized samples for the homogeneity test and 140 pulverized samples for the chemical stability test.

Developing a Multivariate Model

10 mg of ketotifen fumarate were weighed and dissolved in 10 ml of methanol to prepare a 1000 ppm standard solution of ketotifen fumarate. The same procedure was conducted using the cyproheptadine HCl standard solution to produce a 1000 ppm standard solution. Both solutions were pipetted using the randomization method, resulting in 30 calibration solutions and 15 validation solutions. Ketotifen fumarate has a concentration range of 24-36 ppm, while cyproheptadine HCl has a range of 48-60 ppm, as indicated in Table-1.

Divided Powder Sample Compounding

This study used powders comprising 1 mg of Ketotifen Fumarate tablets and 4 mg of Cyproheptadine HCl tablets. Compounding was conducted in the Laboratory of the Faculty of Pharmacy at Sanata Dharma University, Yogyakarta, Indonesia. The samples were prepared following the specified recipe.

R/ Ketotifen Fumarate 1 mg 1/2
Siproheptadin HCl 4 mg 1/4
M F Pull dtd no. VIII

For the homogeneity test, 4 tablets of Ketotifen Fumarate 1 mg and 2 tablets of Cyproheptadine HCl 4 mg were placed in a pulverizer for 30 seconds and then divided into eight equal units using an analytical balance. The process was conducted for batches with mixing durations of 60, 120, and 150 seconds. Upon completion of the mixing duration, the batches were sealed in plastic and covered with silica gel. For the chemical stability test: 4 tablets of Ketotifen Fumarate (1 mg) and 2 tablets of Cyproheptadine HCl (4 mg) were separately ground using a pulverizer for 30 seconds, next to division into 8 equal units using an analytical balance. The procedure was conducted for batches with mixing durations of 60, 120, and 150 seconds. The samples were pulverized, stored at room temperature, and assayed on days 0, 7, 14, 21, 28, 60, and 90.

Table-1: Concentration Sets for Calibration and Validation of Ketotifen Fumarate and Cyproheptadine HCl

Codes	Calibration concentration set(ppm)		Codes	Calibration concentration set(ppm)		Codes	Validation concentration set(ppm)	
	KF	CH		KF	CH		KF	CH
C1	26	51	C16	35	60	V1	25	50
C2	28	52	C17	36	48	V2	28	57
C3	33	55	C18	33	55	V3	30	50

C4	29	57	C19	31	55	V4	33	60
C5	35	59	C20	26	50	V5	25	52
C6	34	48	C21	30	55	V6	26	52
C7	28	55	C22	29	51	V7	36	55
C8	34	48	C23	26	49	V8	29	54
C9	30	49	C24	32	58	V9	25	49
C10	26	55	C25	26	59	V10	31	56
C11	34	51	C26	33	49	V11	32	58
C12	30	51	C27	28	52	V12	29	59
C13	28	51	C28	36	55	V13	29	49
C14	36	56	C29	34	52	V14	25	60
C15	26	49	C30	24	58	V15	24	50

Notes: KF: ketotifen fumarate; CH: Cyproheptadine HCl.

Sample Preparation

The divided powder sample was dissolved in pro-analyse methanol solvent in a 10 mL volumetric flask and then filtered through Whatman filter paper. Afterwards, 1 mL was transferred to a 5 mL volumetric flask, and solvent was added to the calibration mark.

Detection Method

The calibration and validation sets, along with sample solutions, were examined using double-beam UV-Vis spectrophotometry at wavelengths of 210-395 nm at 2 nm intervals. The findings included the absorption spectra of ketotifen fumarate and cyproheptadine HCl. The calibration and validation sets were utilised to predict the test samples for the homogeneity and stability tests.

Data Analysis

The prepared solutions underwent scanning with a UV-Vis spectrophotometer spanning a wavelength range of 200-400 nm at 2 nm intervals. During the scanning process, absorbance values for each wavelength point were gathered and subjected to statistical analysis using R Studio software. The absorbance data obtained from calibration and validation solutions were converted into five types of UV-Vis spectra: original spectrum, first derivative, second derivative, standard normal variate (SNV), and Savizky-Golay (SG).[16] A multivariate calibration model was developed to analyze the five types of spectra, including Principal Component Regression (PCR) and Partial Least Squares Regression (PLS). The optimal calibration model was identified and applied to determine the levels of ketotifen fumarate and cyproheptadine HCl.

RESULTS AND DISCUSSION

Before creating the multivariate model, a singular spectral profile reading was conducted for each prescription drug. Standard solutions were subjected to scans at a 1:4 ratio.

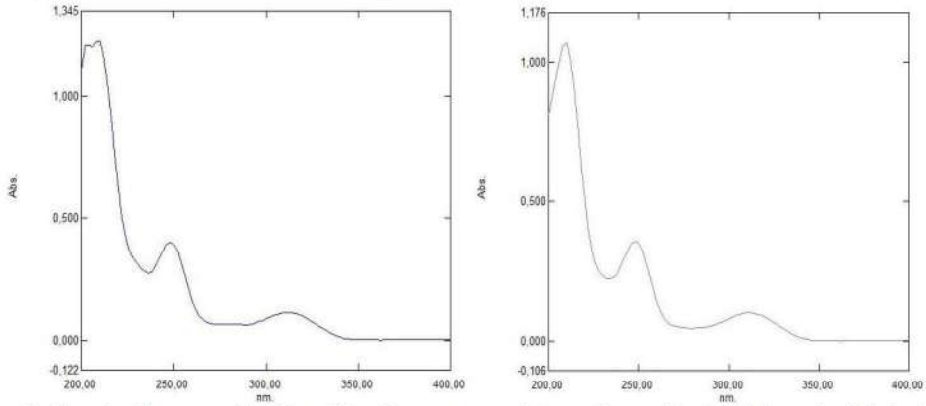

Fig.-1: Standard spectra for Ketotifen Fumarate and Cyproheptadine HCl Standard Solutions

The objective of optimising the maximum wavelength is to identify the wavelength of the compound that produces the maximum absorbance response. Standard solutions at varying concentrations of 2, 4, 6, 8,

and 10 ppm were analyzed for absorbance within the 200-400 nm wavelength range using a UV-Vis spectrophotometer.

Table-2: Maximum Absorbance Wavelength (λmax) Observations for Ketotifen Fumarate and Cyproheptadine HCl Standards

Ketotifen Fumarate Standard			Cyproheptadine HCl Standard		
Concentration(ppm)	λmax (nm)	Absorbance	Concentration(ppm)	λmax (nm)	Absorbance
2	300	0.137	2	286	0.206
4	300	0.204	4	286	0.261
6	300	0.286	6	286	0.319
8	300	0.340	8	286	0.377
10	300	0.380	10	286	0.432

The maximum wavelength of ketotifen fumarate is 300 nm,[17] whereas the maximum wavelength of cyproheptadine HCl is 286 nm.[13] Based on Table-3, the Partial Least Squares Technique (PLS) was selected as the model. For ketotifen fumarate, the R_{cal}^2 value was 0,901, R_{CV}^2 was 0.907, and R_{Val} was 0.989. For cyproheptadine HCl, the R_{Cal}^2 value was 0.997, R_{CV}^2 was 0,906, and R_{Val}^2 was 0,954. This decision was made based on the R^2 value approaching 1 and the RMSE value approaching 0. The coefficient of determination, R^2, quantifies the proportion of variance in variable Y (concentration) that can be accounted for by variable X (predictor). A higher R^2 value indicates a better model. Prediction accuracy is measured by the difference between the actual concentration (variable Y) and the predicted value (Y). The difference is subsequently squared to derive the Mean Squared Error (MSE) value. A lower MSE value indicates better model quality. The Root Mean Square Error (RMSE) represents the mean of the squared prediction errors.[18] Additionally, the Predicted Residual Error Sum of Squares (PRESS) value is computed to evaluate the calibration model's performance. A smaller PRESS value indicates superior predictive ability of the model.[19] The selected selection model is then used to determine and calculate stability and homogeneity values.

Table-3: Results of PCR and PLS Multivariate Calibration Model Analysis for Ketotifen Fumarate and Cyproheptadine HCl

Analytes	Techniques	Type of Spectra	Number of components	RCal ^{2}	RMSEC	RCV^2	RMSECV	RVal^2	RMSEP
Ketotifen Fumarate	PCR	Original	1	0.889	2.089	0.840	3.143	0.954	1.134
		MSC	1	0.921	2.929	0.545	5.326	0.558	4.567
		SNV	5	0.889	2.453	0.570	5.465	0.598	4.873
		SG	4	0.838	2.342	0.835	3.156	0.912	2.098
		1st der	12	0.876	1.522	0.765	4.029	0.865	2.542
		2nd der	1	0.857	1.354	0.876	3.094	0.950	1.109
	PLS	Original	4	0.870	2.210	0.845	2.465	0.965	1.043
		MSC	1	0.834	2.389	0.828	2.405	0.932	1.125
		SNV	1	0.789	2.985	0.732	3.092	0.876	2.367
		SG	7	0.746	3.098	0.678	3.432	0.687	3.654
		1st der	1	0.895	1.985	0.887	1.990	0.943	1.065
		2nd der	2	0.901	1.462	0.907	2.543	0.979	0.989
Cyproheptadine HCl	PCR	Original	2	0.903	0.094	0.907	0.674	0.931	0.726
		MSC	14	0.897	0.142	0.901	0.805	0.815	1.189
		SNV	13	0.890	0.140	0.834	0.987	0.824	1.180
		SG	8	0.945	0.078	0.899	0.704	0.932	0.643
		1st der	2	0.979	0.070	0.704	0.987	0.923	0.768
		2nd der	1	0.981	0.069	0.602	0.929	0.932	0.768
	PLS	Original	13	0.991	0.060	0.903	0.680	0.931	0.728

		MSC	1	0.981	0.132	0.838	0.890	0.839	1.111
		SNV	1	0.989	0.78	0.842	0.870	0.845	1.009
		SG	4	0.976	0.138	0.789	0.990	0.921	0.890
		1st der	8	0.997	0.135	0.906	0.698	0.954	0.893
		2nd der	1	0.986	0.067	0.678	0.999	0.899	0.881

Note: the selected calibration model for each compound is indicated in bold

Table-4: Homogeneity Test Results of Ketotifen Fumarate and Cyproheptadine HCl

Time (s)	Ketotifen Fumarate			Cyproheptadine HCl		
	Mean (%)	SD	CV	Mean	SD	CV
30	105.5093	4.84853	4.59536	98.3913	2.7746	2.81996
60	102.6283333	3.944	3.84299	101.341	3.73471	3.6853
120	106.5326667	3.97057	3.72709	99.6217	1.54357	1.54943
150	105.684	3.64151	3.44566	99.7197	2.43375	2.44059

The concentrations obtained, as indicated in the table above, were either above or below 100%. This may result from variations in drug content when samples are collected from commercially available drug products. The results of the homogeneity test produced differing coefficients of variance; however, these findings conform to established literature standards, which indicate that a satisfactory %CV is less than 5%.[20,21] The homogeneity test for ketotifen fumarate produced a coefficient of variation of 3.44566 following a pulverization duration of 150 seconds. The homogeneity test for cyproheptadine HCl produced a coefficient of variation of 1.5493 after 120 seconds. The highest CV for homogeneity was obtained at a 30 seconds pulverization duration, which found that too short a mixing time can result in uneven distribution of the active ingredient.[22] The compounding process for the preparation containing ketotifen fumarate and cyproheptadine HCl ensures quality when conducted for a minimum duration of 120 seconds. The stability of the ketotifen fumarate and cyproheptadine HCl combination was evaluated over a 90-day storage period. Figure-2 indicates that the application of a pulverizer did not significantly affect the stability of the resulting drug.

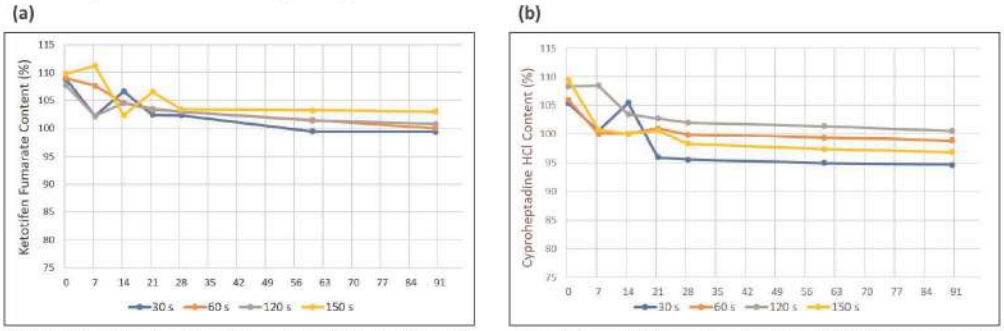

Fig.-2: Stability Evaluation Results of Ketotifen Fumarate (a) and Cyproheptadine HCl (b) during 90 Days of Observation at different Pulverization Treatment Times

The Indonesian Pharmacopoeia, Edition VI, specifies that cyproheptadine HCl tablets must contain a minimum of 90% and a maximum of 110.0% of the labelled amount. In conclusion, cyproheptadine in the pulverization mixture demonstrates stability over a 90-day storage period, maintaining a concentration range of 99.838% to 108.74%. Ketotifen fumarate, as specified in the European Pharmacopoeia 6.0, has a content range of 98.5% to 101%.[23] The results indicate that ketotifen exhibited stability in the pulverization mixture, with a concentration range of 95.67% to 105%. The results of the stability test were consistent with those of the homogeneity test. The homogeneity test indicated a homogeneous mixture, with the lowest coefficient of variance observed for ketotifen fumarate and cyproheptadine HCl at 120 and 150 seconds, respectively. The stability test results indicate that ketotifen fumarate and cyproheptadine HCl showed analyte stability at 120 and 150 seconds, with a content percentage above 95%. It can be stated that the pulverization duration may affect the homogeneity and chemical stability of extemporaneous preparations containing ketotifen fumarate and cyproheptadine HCl. This study provides useful information for pharmacists to improve the quality of their technical skills in compounding

preparation. Further, this research can be linked with the relevant SDG of good health and well-being (SDG-3) for sustainability improvement for health care services, especially from the pharmacist.

CONCLUSION

This study, which examined the impact of pulverisation duration on the homogeneity and stability of a ketotifen fumarate and cyproheptadine HCl combination, was successful. All evaluated pulverisation times met the criteria for homogeneity and stability. The optimal quality mixture was attained with a pulverization duration of no less than 120 seconds. This offers advantages and relevant information for pharmacists to utilise the duration of pulverization to achieve compounded preparations that meet homogeneity and stability criteria, particularly for formulations containing ketotifen fumarate and cyproheptadine HCl. This result reflects the connection between pulverization duration and the quality of the divided powder as an implementation of SDG-3.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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REFERENCES

1. W. Widyastiwi, G. Sugihartina, and I. Pamudjo, *Indonesian Journal Of Clinical Pharmacy,* **6**, 99(2017), https://doi.org/10.15416/ijcp.2017.6.2.99
2. R. Widyaswari, and C. Wiedyaningsih, *Majalah Farmaseutik*, **8**, 227(2017)
3. D. M. Karunia, A. Putri and D. C. A. Putri, In *Proceedings of Seminar Nasional Matematika dan Sains* (SENAM 2024), Yogyakarta, Indonesia, pp.35–42 (2024).
4. K. K. R. Indonesia, Farmakope Indonesia Edisi VI, Kementrian Kesehatan Republik Indonesia, Jakarta, (2020)
5. R. Yulianita, I. Sopyan, A. M. Gazzali, and M. Muchtaridi, *Indonesian Journal of Pharmacy*, **32**, 458(2021), https://doi.org/10.22146/ijp.2730
6. Z. Na, Chinese Journal Clinical Pharmacology, **37**, 1(2022), https://doi.org/10.13699
7. S. W. Turwewi, *CHM-K Pharmaceutical Scientific Journal*, **1,** 53(2018)
8. A. K. Mohiuddin, *Innovative Journal of Medical and Health Science*, **9**, 252(2019), https://doi.org/10.15520/ijmhs.v9i1.2420
9. M. D. P. Santoso, and V. Nopiyanti, CERATA *Jurnal Ilmu Farmasi*, **13**, 50(2022), https://doi.org/10.61902/cerata.v13i1.457
10. A. N. Bestari, T. N. Sulaiman, and D. A. Purnamasari, *Majalah Farmaseutik*, **13**, 45(2017).
11. M. I. A. Nindi and R. A. Maria, *Journal Kesehatan*, **9**, 34(2021), https://doi.org/10.55912/jks.v9i2.33

12. M. S. Dewi, Thesis, Department of Pharmacy, Universitas Sanata Dharma, Yogyakarta, Indonesia (2021).
13. A. Indarwati, A. S. Fitriana and N. Rahmawati, *Journal of Natural Sciences and Mathematics Research,* **10**, 82(2024).
14. X. Y. Dou and W. Zhang, *International Journal of Ophthalmology*, **16**, 286(2023), https://doi.org/10.18240/ijo.2023.02.17
15. https://sdgs.un.org/goals/goal3
16. F. D. O. Riswanto, A. Rohman, S. Pramono and S. Martono, *Journal of Applied Pharmaceutical Science*, **11**, 154(2021), https://doi.org/10.7324/JAPS.2021.110318
17. A. Gumieniczek, A. B. Rycerz, U. Hubicka, P. Żmudzki, K. Lejwoda and P. Kozyra, *Pharmaceutics*, **12**, 1(2020), https://doi.org/10.3390/pharmaceutics12060560
18. D. Hendrati, A. Mutalib, M. Pratiwi and R. P. Fauzia, *Chimica et Natura Acta*, **5**, 43(2017), https://doi.org/10.24198/cna.v5.n1.12821
19. A. Rohman and Y. B. C. Man, *Middle-East Journal of Scientific Research*, **7**, 726(2011)
20. M. E. Aulton and K. M. G. Taylor, Aulton's Pharmaceutics: The Design and Manufacture of Medicines Fifth Edition, London, New York, p.177(2018)
21. A. Ainurofiq and N. Azizah, *Journal of Pharmaceutical Science and Clinical Research,* **1,** 1(2016), https://doi.org/10.20961/jpscr.v1i1.682
22. A. Gandhi, S. O. Sen, D. Manna, C. Roy, K. K. Sen and S. D. Roy, *Indian Research Journal of Pharmacy and Science,* **1**, 887(2017), https://doi.org/10.21276/IRJPS.2017.4.1.3
23. EDQM. European Pharmacopoeia 6.0. Council of Europe. 2221(2007).

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