Optimization of Labrasol and Tween 80 in Self Nano-Emulsiying Drug Delivery System (SNEDDS) Mefenamic Acid Using The Simplex Lattice Design Method

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Abstract.

Mefenamic acid is a derivative of anthranilic acid that functions as a nonsteroidal anti-inflammatory drug (NSAID), antipyretic, and analgesic. Mefenamic acid is included in the Biopharmaceutical Classification System (BCS) class II which has low solubility and high permeability. The manufacture of SNEDDS requires a non-ionic surfactant with an HLB (Hydrophilic-Lipophilic Balance) value of more than 10. Mefenamic acid has high solubility in the surfactant Labrasol which has HLB 12 and Tween 80 which has HLB 15. This study aims to develop mefenamic acid into a Self Nano-Emulsifying Drug Delivery System (SNEDDS) with the optimization of labrasol and tween 80 as surfactants. The optimization of mefenamic acid SNEDDS is made using the simplex lattice design method. In the optimization, 6 running SNEDDS formulas were obtained with mefenamic acid. Chemical physics testing includes organoleptic evaluation, pH, viscosity, percent of transmitters, emulsification time, stability, particle size, potential zeta, and level determination. The results showed that the optimal combination of labrasol and tweenat SNEDDS mefenamic acid 80, namely 24% Labrasol and 1% Tween 80, with a desirability value of 0.984, had a clear, non-rancid, homogeneous, liquid-shaped color, pH of 4.69, viscosity 31.33 cP, transmitter percentage 96.80%, emulsification time 29.11 seconds, particle size 44.30 nm, zeta potential -28.87 mV, and a polydispersivity index of 0.563, with a percentage of levels of 100.08%, 100.70%, and 99.87%, respectively.

Keywords: *Self Nano-Emulsifying Drug Delivery System (SNEDDS); Labrasol and Tween 80.*

I. INTRODUCTION

Mefenamic acid is often used as an anti-inflammatory and analgesic agent. Mefenamic acid is a non-narcotic analgesic group generally prescribed to treat acute pain felt after the effects of anesthesia begin to decrease in patients (Srivastava et al., 2019). This drug is used to treat postoperative pain, toothache, inflammation due to trauma, and swelling (Abdullah, 2022). In clinical studies, the use of mefenamic acid was reported to have an incidence of ADR (Adverse Drug Release) of abdominal pain with a percentage of 0-36% and nausea of 0-26% (Ocktavia, 2020).Until now, the common mefenamic acid preparations are still in the form of tablets. Mefenamic acid was developed into SNEDDS preparations because mefenamic acid is a class II Biopharmaceutical Classification System (BCS) (Sabiti, 2024). In an effort to develop the form of the preparation and reduce the side effects due to long-term consumption of mefenamic acid, mefenamic acid preparations were developed into a self nano-emulsiying drug delivery system (SNEDDS) (Yesika et al., 2025).

SNEDDS is a mixture of oils, surfactants and cosurfactants that spontaneously form nanoemulsions when mixed with water through gentle stirring in the digestive tract (Sapiun et al., 2023). SNEDDS has the ability to form nanoemulsions with a droplet size of ≤200 nm after contact with gastrointestinal fluids (Fitriani et al., 2021).The surfactants used in the SNEDDS formulation are labrasol and tween 80. Labrasol is a pale yellow oily liquid and functions as an emulsifying agent; modified-release agent; nonionic surfactants; penetration enhancer; Solubilizing agent with a concentration of oral products as a surfactant of 10-99%. Labrasol can be dispersed in hot water; freely soluble in methylene chloride. Tween 80 serves as a dispersing agent; emollient; emulsifying agent; nonionic surfactant; plasticizing agent; solubilizing agent; Suspending Agent. Tween 80 can be used as a surfactant with a concentration of 1-15% (Rowe, 2017).

II. METHODS

This study is an experimental research that aims to optimize formulations using the Simplex Lattice Design (SLD) method assisted by Design Expert software version 13. Optimization was carried out on the concentration of surfactants, namely labrasol and tween 80, in the Self Nano-Emulsifying Drug Delivery System (SNEDDS) preparation containing the active substance mefenamic acid, with the aim of evaluating the quality and physical characteristics of the preparation. The ingredients used include mefenamic acid, oleic acid as the oil phase, labrasol and tween 80 as surfactants, PEG 400 as co-surfactants, sodium benzoate, aquadest, CO_2-free water, and sodium hydroxide (NaOH). The tools used include computers, vortexes, sonicators (Branson), UV-Vis spectrophotometers, dissolution testers, measuring flasks, pH meters (Milwaukee), Stormer viscometers, beaker glass, mixing rods, vials, and test tubes. The SNEDDS formulation refers to the modified study of Norliani et al. (2024), with a preparation volume of 50 mL, in which mefenamic acid is weighed and mixed with surfactants (labrasol and tween 80), then vortex until homogeneous, PEG 400 and oleic acid are added, then sonicated for 15 minutes until a homogeneous mixture is formed.

The resulting preparations are then physicochemically tested, including organoleptic tests to assess homogeneity, clarity, and odor; pH test using a pH meter; viscosity test using Brookfield spindle viscometer number 3 at 50 rpm; percent test of transmitters using a UV-Vis spectrophotometer at a wavelength of 650 nm; and emulsification time test by stirring method in water at a temperature of 37°C. In addition, a stability test was conducted at storage conditions of 40°C ± 2°C/75% RH ± 5% RH for two weeks, with observations of changes in transmitters, particle size, and potential zetas. Particle size, polydispersity index, and potential zeta measurements were carried out using Particle Size Analyzer (PSA), while levels were determined by UV spectrophotometry method at a wavelength of 285 nm using a series standard solution. The data obtained was then analyzed using the SLD method through the Design Expert software to determine the optimal formulation, with model testing using ANOVA analysis which included p-value and lack of fit test.

III. RESULT AND DISCUSSION

Optimization of Analysis of Physical Characteristics of Mefenamic Acid SNEDDS Formula with SLD Method

Design Expert version 13.0 features 6 runs with a comparison of variations in the concentration of labrasol and tween 80 which are used as independent variables and physical tests such as pH, viscosity, % transmitter and emulsification time as bound variables that will determine the optimal formula.

Table 1. Run Results of Labrasol and Tween 80 Combination in Design Expert Version 13.0

Run	Factor 1A: Labrasol (%)	Factor 2B: Tween 80 (%)
1	10	15
2	24	1
3	17	8
4	13,5	11,5
5	24	1
6	20,5	4,5

Physical analysis of mefenamic acid SNEDDS preparations including pH test, viscosity test, % transmitter test and emulsification time test are included in the table in the simplex lattice design.

Fig 1. 6 Run SNEDDS Organoleptic Test Mefenamic Acid

The results of the organoleptic test of 6 runs were obtained in runs 1 and 4 had a clear yellow color, in runs 2 and 5 had a clear white color, and in runs 3 and 6 had a slight clear yellow color. All runs have a non-rancid, homogeneous odor and liquid form. A good SNEDDS preparation is a clear, homogeneous and non-rancid preparation (Sulistiana, 2017). So that all runs are included in a good SNEDDS setup. The preparations in runs 1 and 4 are thicker compared to other formulas. This is due to the 80's tween. The higher the concentration of tween 80 used, the thicker the preparation produced (Hastuti, 2020).

Table 2. Analysis of Mefenamic Acid SNEDDS Response

Run	Labrasol (%)	Tween 80 (%)	pH -	Viscosity (Cp)	Transmitter (%)	Time Emulsification (seconds)
1	10	15	5,80	46,99	90,53	38,46
2	24	1	4,69	29,15	98,58	28,55
3	17	8	5,14	37,23	94,44	33,45
4	13,5	11,5	5,52	43,80	92,40	36,22
5	24	1	4,70	28,78	98,38	28,40
6	20,5	4,5	4,92	34,50	95,59	31,72

The results obtained at 6 runs showed that all made mefenamic acid SNEDDS preparations entered a good pH range of 4.5 to 6 (Muslim et al., 2025). The viscosity test was carried out using Brookfield spindle viscometer number 3 with a speed of 50 rpm with a good viscosity range of 10-2000 Cp (Sari et al, 2015). In the results of the viscosity test, it can be seen that the higher the concentration value of tween 80, the higher the value of tween 80. The viscosity will be directly proportional to the concentration of the dispersed phase, if the increase in the concentration of a dispersed phase is increased and will be followed by the resulting increase in viscosity. The increase in viscosity is caused because the greater the concentration of tween 80 will decrease the size of the diameter of the globule, thereby increasing the surface area and the resistance of nanoemulsions to flow and increasing viscosity values (Hajrin et al., 2021). The results obtained show that runs 2 and 5 have. The highest transmitter % or close to 100% with values of 98.58% and 98.38%, respectively (Syukri, et al., 2020). A good emulsification time for SNEDDS should ideally be less than 1 minute. This time shows the formula is able to form a clear and homogeneous emulsion (Uno et al., 2015). The results obtained at 6 runs showed that all SNEDDS preparations made had a good emulsification time of less than 1 minute.

Table 3 . Analysis of ANOVA 6 Run Using Simplex Lattice Design Method

Analysis Parameters	p-value	Lack of Fit
pH	0,0002	0,1189
Viscosity	0,0010	0,1548
% Transmittan	0,0009	0,2032
Emulsification Time	0,0003	0,1757

ANOVA in the physical analysis of mefenamic acid SNEDDS preparations had good results, namely a significant p-value (<0.05) indicating that the ANOVA analysis was statistically valid and reliable to represent the relationship between the composition of the ingredients and the measured response. If the p-value model is >0.05, it means that the data is not significant, meaning that the change in the composition of the mixed material being tested does not have a statistically significant effect on the measured response. A good lack of fit is an insignificant one (>0.05) indicating the model conforms to the data without large systematic errors. If the lack of fit is significant (<0.05) indicates that the model is not suitable (Ministry of Health of the Republic of Indonesia, 2020).

Table 4. Quadratic Equations of Mefenamic Acid SNEDDS

Analysis Parameters	**Simplex Lattice Design Equation**
pH	$Y = 4.69\ (A) + 5.82\ (B) - 0.3127\ (AB)$
Viscosity	$Y = 29.04\ (A) + 47.24\ (B) + 1.14\ (AB)$
% Transmittan	$Y = 98.37\ (A) + 90.64\ (B) - 1.57\ (AB)$
Emulsification Time	$Y = 28.56\ (A) + 38.41\ (B) + 1.30\ (AB)$

The simplex lattice design equation for pH response shows that the proportion of tween 80 gives a positive response, namely increasing the pH value of mefenamic acid SNEDDS with a coefficient value of

5.82, which has a greater effect than labrasol with a coefficient value of 4.69. Mixing between labrasol and tween 80 in the preparation showed a negative coefficient value of -0.3127. Both components can be declared to be able to reduce the pH value of SNEDDS preparations of mefenamic acid.The simplex lattice design equation for viscosity response shows that the proportion of tween 80 gives a positive response, namely increasing the viscosity value of mefenamic acid SNEDDS with a coefficient value of 47.24, which has a greater effect than labrasol with a coefficient value of 29.04. Mixing between labrasol and tween 80 in the preparation showed a positive coefficient value of 1.14.

Both components can be declared to be able to increase the viscosity value of the SNEDDS preparation of mefenamic acid.The simplex lattice design equation for the % transmitter response shows that the proportion of labrasol gives a positive response, namely increasing the value of the % transmitter in the SNEDDS of mefenamic acid with a coefficient value of 98.37, which has a greater effect than tween 80 with a coefficient value of 90.64. Mixing between labrasol and tween 80 in the preparation showed a negative coefficient value of -1.57. Both components can be declared to be able to reduce the % transmitter value of SNEDDS preparations of mefenamic acid.The simplex lattice design equation for emulsification time response showed that the proportion of tween 80 gave a positive response, namely increasing the emulsification time value of mefenamic acid SNEDDS with a coefficient value of 38.41, which had a greater effect compared to labrasol with a coefficient value of 28.56. Mixing between labrasol and tween 80 in the preparation showed a positive coefficient value of 1.30. Both components can be declared to be able to increase the emulsification time value of SNEDDS preparations of mefenamic acid.

Solutions

1 Solutions found

	Number	labrasol	tween 80	pH	viskositas	% transmitan	waktu emulsifikasi	Desirability	
	1	24,000	1,000	4,693	29,040	98,369	28,558	0,984	Selected

Fig 2. Solutions Combination of Labrasol and Tween 80 on Mefenamic Acid SNEDDS

The optimization results were obtained from the optimal formula of SNEDDS preparations with a concentration of labrasol which is 24.% and tween 80 which is 1%. The selected solutions have a desirability value of 0.968. The desirability value in Simplex Lattice Design is a function that indicates the ability of the model or optimization program to meet the criteria that have been set on the final product. This desirability value ranges from 0 to 1, where the closer the value is to 1, the more the program's ability to produce the desired product will be more perfect and optimal (Hajrin et al., 2021).

Mefenamic Acid SNEDDS Stability Testing

The stability test of mefenamic acid SNEDDS preparations using a climatic chamber with a temperature condition of 40°C ± 2°C humidity of 75% RH ± 5% for 14 days then tested on days 0 and 14. The physical evaluation observed was organoleptic, pH, viscosity, percent of transmitters and emulsification time of mefenamic acid SNEDDS preparations.

Fig 3. Optimal Formula Stability Test SNEDDS Mefenamic Acid Day 0

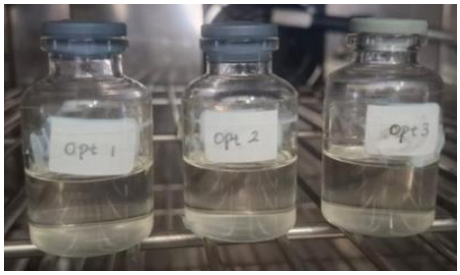

Fig 4. 14th Day Mefenamic Acid SNEDDS Optimal Formula Stability Test

The organoleptic test showed the same results before and after the stability test, namely with a clear color, a non-rancid odor, homogeneous preparations and liquid form. The results of organoleptic tests between before and after being put into the climatic chamber showed that the preparation of SNEDDS mefenamic acid was stable. This is in accordance with the requirements of a good SNEDDS preparation is a clear, homogeneous and non-rancid preparation (Syukri et al., 2020).

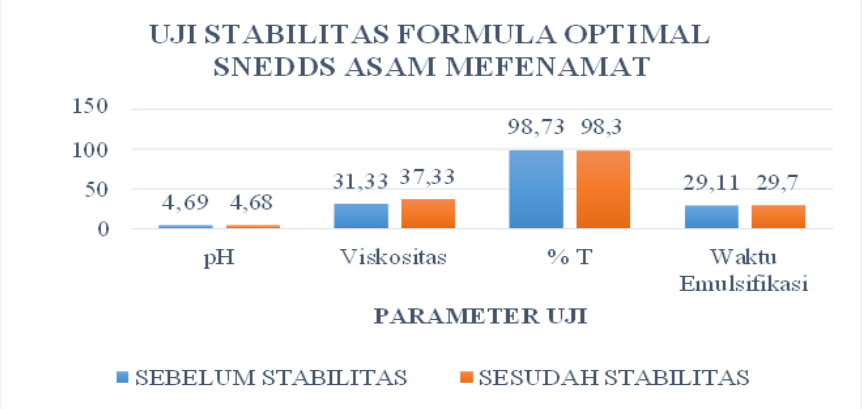

Fig 5. Mefenamic Acid SNEDDS Stability Test

The pH test showed that the pH decreased after the stability test was carried out, namely from pH 4.69 to 4.68. However, this decline is not too far away. The results of the pH test of mefenamic acid SNEDDS between before and after being put into the climatic chamber showed that the preparation of mefenamic acid SNEDDS was stable. The required pH range is between 4.5 to 6 (Muslim et al., 2025).

The results of the viscosity test of mefenamic acid SNEDDS preparations were obtained before the stability of 31.33 nm and after the stability of 37.33 nm. The results of the viscosity test of mefenamic acid SNEDDS between before and after being put into the climatic chamber showed that the preparation of mefenamic acid SNEDDS was stable. This result is in accordance with the requirement for a good viscosity range of 10-2000 Cp (Widyasanti et al., 2023).The transmittant percent test showed that the transmittant percentage decreased after the stability test was carried out, from 98.73% to 98.30%.

However, this decline is not too far away. The results of the percentage test of mefenamic acid SNEDDS transmittants between before and after being put into the climatic chamber showed that the preparation of mefenamic acid SNEDDS was stable and entered the range, which is close to 100% (Syukri et al., 2020).The results of the emulsification time test showed the same results before and after the stability test, which was 29.11 seconds to 29.70 seconds. These results showed that the emulsification time of the preparation of SNEDDS mefenamic acid before and after being introduced into the climatic chamber showed different results but the difference was not too great. The results of the emulsification time test of mefenamic acid SNEDDS are in accordance with the requirements of a good emulsification time for SNEDDS ideally less than 1 minute. This time shows the formula is able to form a clear and homogeneous emulsion (Uno et al., 2015).

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The results of the particle size test on the optimal preparation of mefenamic acid SNEDDS were obtained with a result of 44.30. From these results, it can be said that the particle size of the preparation falls within the range of SNEDDS. The results of the potential zeta test at the optimal concentration of mefenamic acid SNEDDS were obtained with a result of -28.87. It can be said that mefenamic acid SNEDDS preparations have good potential zeta values. A potential zeta value of -28.87 mV or minus indicates that the repulsive force between particles is strong enough to keep the particles separate and prevent clumping or flocculation (Sulistiana, 2017). Polydispersity index (PI) is the distribution of particles. In SNEDDS, mefenamic acid has a PI value of 0.563. A good PI value is less than 1 (Yesika et al., 2025). The results of particle size, potential zeta and PI are in accordance with the research of Syukri et al (2020), namely a particle size of 190.0

± 1.2 nm or <200 nm, PDI 0.469 ± 0.03 or <1, and zeta potential -44.1 ± 1.7 mV or -30 mV to +30 mV

(Sulistiana, 2017).

Rates

Determination of the level of the preparation is an analysis process that aims to determine the amount of active substance content in a drug preparation in order to ensure the quality, safety, and effectiveness of the drug during the shelf life and use. This process is important to ensure that the levels of active substances contained in drug preparations are in accordance with the standards set in pharmacopoeia or applicable regulations (Umar et al., 2021). The good level of mefenamic acid is between 98.0% - 102.0% (Ministry of Health of the Republic of Indonesia, 2020). The series starts at the lower limit of 4.762 ppm and the upper limit of 19.05 ppm. Made a series of 5 concentrations; 7,5; 10; 12,5; and 15 ppm with a wavelength of 285 nm obtained raw absorbance of mefenamic acid in the range of 0.2-0.8 (Nerdy, 2017).

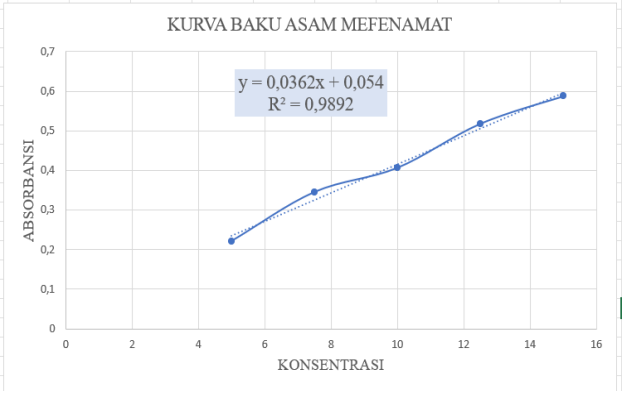

Fig 6. Mefenamic Acid Raw Curve

The absorbance obtained will then be calculated as the linear regression equation. Linear regression is calculated in excel with the result y = 0.0362x – 0.054 and the correlation coefficient or R2 is 0.9892. The value of the correlation coefficient is said to be good because it is close to 1 (Syukri et al., 2020). A correlation coefficient value (r) close to 1 expresses a linear relationship between the concentration and the resulting absorption, in other words the increase in the absorbance value of the analyte is directly proportional to the increase in its concentration (Uno et al., 2015).

Table 5. Result % of Mefenamic Acid Level in Mefenamic Acid SNEDDS

Sample	Absorbance	ppm	% Rate
1	0,4163	10,01	100,08
2	0,4189	10,08	100,70
3	0,4159	10,00	99,87

% of SNEDDS levels of mefenamic acid in sample 1 was 100.08%, sample 2 was 100.70% and sample 3 was 99.87%. This shows that the % of SNEDDS levels of mefenamic acid enter the range in the Indonesian Pharmacopoeia Edition VI, which is between 98.00% to 102.00% (Ministry of Health of the Republic of Indonesia, 2020).

IV. CONCLUSION

The combination of 24% Labrasol and 1% Tween 80 in SNEDDS mefenamic acid, with a desirability value of 0.984, had a clear, non-rancid, homogeneous, liquid color, pH of 4.69, viscosity of 31.33 cP, % of transmitter 96.80%, emulsification time of 29.11 seconds, particle size of 44.30 nm, zeta potential of -28.87 mV, and polydispersibility index of 0.563, with percentages of 100.08%, 100.70%, and 99.87%, respectively.

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REFERENCES

[1] Abdullah, A., & Tahar, N. (2022). Dissolution Improvement of Mefenamic Acid Through Cocrystallization with Aminobenzoic Acid Using Liquid-Assisted Grinding Method**.** ***Journal Of Pharmacy and Science),*** 5(2), 46–53.

[2] Ministry of Health of the Republic of Indonesia. (2020). Indonesian Pharmacopoeia Edition VI (Ministry of Health of the Republic of Indonesia, Ed.; VI). Ministry of Health of the Republic of Indonesia.

[3] Dilla, K. N., Adawiyah, R., Putri, N. C., Noval, N., & Mahdiyah, D. (2024). Formulation of Self-Nanoemulsifying Drug Delivery System Celery Extract (Apium graveolens L.) with Variation in Virgin Coconut Oil Concentration as Antihypertensive. ***Journal of Medical Radiation***, 10(2), 55–63. https://doi.org/10.33084/jsm.v10i2.7724

[4] Fitriani, H., Fitria, A., Miladiyah, I., & Syukri, Y. (2021). Development of Self-Nano Emulsifying System (SNES) of Temulawak Extract (Curcuma xanthorrhiza): Formulation, Characterization, and Stability. ***Journal of Pharmaceutical & Clinical Sciences***, 8(3), 332. https://doi.org/10.25077/jsfk.8.3.332-339.2021

[5] Hajrin, W., Subaidah, W. A., Juliantoni, Y., & Wirasisya, D. G. (2021). Application of Simplex Lattice Design Method on The Optimisation of Deodorant Roll-on Formula of Ashitaba (Angelica keiskei). ***Journal of Tropical Biology***, 21(2), 501–509. https://doi.org/10.29303/jbt.v21i2.2717

[6] Hastuti, E. D. (2020). Formulation of Self Nanoemulsifying Drug Delivery System (SNEDDS) Ethyl Acetate Extract of Parijoto Fruit (Medinilla speciosa Blume) and Physical Stability Test. ***Scholar Journal of Pharmacy***, 4. http://cjp.jurnal.stikescendekiautamakudus.ac.id

[7] Muslim, N. S., Hariyadi, P., & Andarwulan, N. (2025). Optimization of the Dry Vanilla (Vanilla tahitensis JW Moore) Maceration Process in Vanilla Extract Production Using RSM. ***Journal of Food Quality***: ***Indonesian Journal of Food Quality***, 12(1), 47–56. https://doi.org/10.29244/jmpi.2025.12.1.47

[8] Nerdy. (2017). Validation Of Ultraviolet Spectrophotometry Method For Determination Of Mefenamic Acid Level In Suspension Dosage Forms**.** ***Natural Journal***, 17(1), 17–22. https://doi.org/10.24815/jn.v17i1.6540

[9] Norliani, R., Noval, N., & Melviani, M. (2024). Stability Study of Self Nano Emulsifying Drug Delivery System (SNEDDS) Formulation of Serunai Leaf Extract as Anti-Diabetes with Variations in Oleic Acid Concentration. ***Scientific Journal of Ibn Sina (JIIS)***: Pharmaceutical and Health Sciences, 8(3), 13–24. https://doi.org/10.36387/jiis.v8i3.1646

[10] Ocktavia, R. P. (2020). Incidence of Side Effects of NSAID Use in Patients at Ngaglik 2 Sleman Health Center, Special Region of Yogyakarta.

[11] Rowe, R. C. (2017). Handbook of Pharmaceutical Excipients Eighth Edition (P. J. , C. W. G. , C. C. G. Sheskey, Ed.; 8th Edition). Pharmaceutical Press.