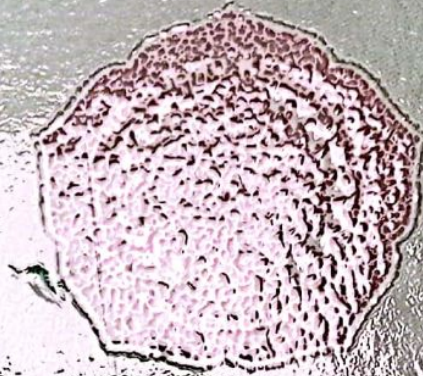


SKRIPSI

SEKRINING KOMPONEN SELF EMULSIFYING
EKSTRAK ETANOL BROTOWALI (*Thespora crispa* L.)
MENGUNAKAN FRACTIONAL FACTORIAL DESIGN 2^{5-2}
DAN ANALISIS KEMOMETRIK



OLEH
TIRA URYANI
194620163031

PROGRAM STUDI SI-FARMASI
SEKOLAH TINGGI ILMU KESEHATAN AISYIYAH
PALEMBANG
2023

SKRIPSI
SKRINING KOMPONEN *SELF EMULSIFYING*
EKSTRAK ETANOL BROTOWALI (*Tinospora crispa* L.)
MENGGUNAKAN *FRACTIONAL FACTORIAL DESIGN 2⁶⁻²*
DAN ANALISIS KEMOMETRIK



Oleh:
TIKA UMMAMI
194820103034

PROGRAM STUDI S1-FARMASI
SEKOLAH TINGGI ILMU KESEHATAN 'AISYIYAH
PALEMBANG
2023

**LEMBAR PENGESAHAN
SKRIPSI**

**SKRINING KOMPONEN *SELF EMULSIFYING* EKSTRAK ETANOL
BROTOWALI (*Tinospora crispa* L.) MENGGUNAKAN *FRACTIONAL
FACTORIAL DESIGN 2⁶⁻²* DAN ANALISIS KEMOMETRIK**

Oleh :

Tika Ummami
NIM. 194820103034

Telah dipertahankan didepan Tim Penguji pada 15 Mei 2023.

Dosen Penguji

I. apt. Galih Pratiwi, M.Pharm.Sci.
NIP. 2015.09.059

(.....)

II. apt. Aninditha Rachmah R., M.Si.
NIP. 2018.01.071


(.....)

III. Yudi Arina, S.Si., M.Kes.
NIP. 2004.10.025

(.....)

IV. Dr. apt. Shaum Shiyan, M.Sc.
NIP. 198605282012121005

(.....)


Mengetahui,
Ketua STIKES 'Aisyiyah Palembang'
..... SKM., M.Kes.
NIP. 2000.12.014

SEKOLAH TINGGI ILMU KESEHATAN 'AISYIYAH PALEMBANG PROGRAM STUDI SI FARMASI

Skripsi, Mei 2023

Tika Ummami

Skrining Komponen *Self emulsifying* Ekstrak Etanol Brotowali (*Tinospora Crispa* L.) Menggunakan *Fractional Factorial Design* 2^{6-2} dan Analisis Kemometrik

122 Halaman, 23 Tabel, 19 Gambar, 21 Daftar Singatan, 12 Lampiran

INTISARI

Latar belakang: Brotowali (*Tinospora crispa* L.) merupakan tanaman obat tradisional yang secara empiris dan ilmiah dapat menyembuhkan berbagai penyakit. Salah satu kandungan fitokimia ekstrak brotowali yang dapat memberikan efek tonik dari golongan alkaloid yaitu berberin. Hambatan pengembangan formula ekstrak brotowali adalah kelarutan ekstrak brotowali yang rendah didalam air. Pengembangan ekstrak brotowali dalam bentuk *Self emulsifying*(SE) dilakukan untuk meningkatkan kelarutan dan bioavailabilitas oral ekstrak brotowali. **Tujuan:** Mengetahui karakteristik formula SE ekstrak brotowali dengan pengaruh komponen penyusun berupa minyak, surfaktan, dan kosurfaktan dan korelasi antar respon dengan pendekatan kemometrik. **Metode:** Skrining formula SE dirancang dengan metode FrFD 2^{6-2} pada piranti lunak *design expert* untuk menentukan masing-masing komponen penyusun. Komponen minyak yang digunakan meliputi asam oleat dan miglyol, surfaktan tween 80 dan PEG 40, ko-surfaktan PEG 400 dan propilen glikol. Parameter evaluasi SE meliputi visualisasi, pH, *drug load*, persen transmittan SE, persen transmittan emulsi, viskositas, waktu emulsifikasi SGF, waktu emulsifikasi SIF, dan waktu emulsifikasi *aquadest*. **Hasil:** formula terpilih tersusun dari komponen minyak miglyol 10%, PEG 40 30%, dan propilen glikol 20%. Formula terpilih memiliki nilai *drug load* 97,90 mg/mL, persen transmittan SE 83,086%, persen transmittan emulsi 98,086%, viskositas 6.61 mPa.s, waktu emulsifikasi 1,21; 1,51; 1,22 detik pada media SGF, SIF dan *aquadest*. **Kesimpulan:** Variasi komponen minyak, surfaktan, dan ko-surfaktan serta parameter respon dalam skrining SE ekstrak brotowali memenuhi karakteristik sediaan SE.

Kata kunci: SE, ekstrak brotowali, FrFD 2^{6-2} , kemometrik.

Daftar Pustaka: 97 (2006-2022)

SEKOLAH TINGGI ILMU KESEHATAN 'AISYIYAH
PALEMBANG PROGRAM STUDI SI FARMASI

Skripsi, Mei 2023

Tika Ummami

Screening Of Self emulsifying Components Of Ethanol Extract Of Brotowali
(*Tinospora Crispa* .L) Using Fractional Factorial Design 2^{6-2} And
Chemometric Analysis

122 Pages, 23 Tables, 19 Figures, 21 List of Abbreviations, 12 Appendices

ABSTRACT

Background: Brotowali (*Tinospora crispa* L.) is a traditional medicinal plant which empirically and scientifically can cure various diseases. One of the phytochemicals contained in brotowali extract which can provide a tonic effect is from the alkaloid group, namely berberine. The obstacle to the development of the brotowali extract formula was the low solubility of the brotowali extract in water. The development of brotowali extract in the form of Self emulsifying(SE) was carried out to increase the solubility and oral bioavailability of extra brotowali. **Objective:** To determine the characteristics of the brotowali extract SE formula with the influence of constituent components such as oil, surfactants, and cosurfactants and the correlation between responses with chemometric approaches. **Methods:** The SE formula screening was designed using the FrFD 2^{6-2} method in design expert software to determine each constituent component. The components of the oil used include oleic and miglyol acids, tween 80 and PEG 40 surfactants, PEG 400 co-surfactants and propylene glycol. SE evaluation parameters included visualization, pH, drug load, percent transmittance of SE, percent transmittance of emulsion, viscosity, emulsification time in SGF, SIF emulsification time, and aquadest emulsification time. **Results:** The selected formula was composed of 10% miglyol oil, 30% PEG 40, and 20% propylene glycol. The selected formula has a drug load value of 97.90 mg/mL, transmittance percentage of SE 83.086%, percent transmittance of emulsion 98.086%, viscosity 6.61 mPa.s, emulsification time 1.21; 1.51; 1.22 seconds on SGF, SIF and distilled water media. **Conclusion:** Variation of oil, surfactant, and co-surfactant components as well as response parameter in SE screening of brotowali extract meet the characteristics of SE preparations.

Keywords: SE, brotowali extract, FrFD 2^{6-2} , chemometrics.

Bibliography: 97 (2006-2022)

DAFTAR ISI

HALAMAN SAMPUL	i
HALAMAN JUDUL.....	ii
LEMBAR PERSETUJUAN	iii
LEMBAR PERSEMBAHAN	v
RIWAYAT HIDUP.....	vi
KATA PENGANTAR.....	ix
DAFTAR ISI.....	xiii
DAFTAR TABEL.....	xvii
DAFTAR GAMBAR	xix
DAFTAR LAMPIRAN.....	xx
DAFTAR SINGKATAN.....	xxi
BAB I PENDAHULUAN.....	1
A. Latar Belakang.....	1
B. Rumusan Masalah.....	3
C. Tujuan Penelitian	4
D. Manfaat Penelitian	4
BAB II TINJAUAN PUSTAKA.....	6
A. TINJAUAN PUSTAKA.....	6
1. Brotowali	6
a. Klasifikasi Tanaman Brotowali (<i>Tinospora crispa</i> L.)	6
b. Mofologi Tanaman Brotowali (<i>Tinospora crispa</i> L.)	7
c. Kandungan Tanaman Brotowali (<i>Tinospora crispa</i> L.)	7
d. Manfaat Tanaman Brotowali (<i>Tinospora crispa</i> L.)	7
2. Emulsi.....	8
3. <i>Self emulsifying</i> (SE)	9
4. Komponen Minyak dalam Formulasi SE	10
a. Miglyol	10

b. Asam Oleat	11
5. Komponen Surfaktan dalam Formula SE.....	12
a. Tween 80	12
b. Hydrogenated Castor Oil (PEG 40)	14
6. Komponen Ko-Surfaktan dalam Formulasi SE	15
a. Polietilen Glikol 400 (PEG 400).....	15
b. Propilen Glikol.....	17
7. Pendekatan Statistika <i>Fractional Factorial Design</i> (FrFD).....	18
a. Model Linier <i>Fractional Factorial Design</i> (FrFD).....	19
b. Menggunakan <i>Fractional Factorial Design</i> (FrFD).....	19
c. Pembentukan dan Pemilihan Struktur Rancangan FrFD 2^{k-p}	20
d. Pembentukan Rancangan dengan Fraksi $\frac{1}{4}$ dari Rancangan 2^k	20
8. Kemometrik	20
B. Landasan Teori	21
C. Hipotesisi.....	23
BAB III METODE PENELITIAN.....	25
A. Jenis Penelitian	25
B. Waktu dan Tempat Penelitian.....	25
C. Variabel Penelitian.....	25
1. Variabel Bebas.....	25
2. Variabel Terkendali.....	25
3. Variabel terikat	26
D. Alat dan Bahan.....	26
E. Jalannya Penelitian.....	27
1. Pembuatan Ekstrak Brotowali	27
2. Rancangan Percobaan dan Penentuan <i>Run</i> Menggunakan <i>Fractional Factorial Design</i> (FrFD)	27

3. Orientasi dan Preparasi Komponen SE Ekstrak Brotowali	29
4. Penentuan persentase transmitan	29
5. Bobot Jenis SE	29
6. Pengukuran Viskositas	29
8. Pengukuran <i>Drug Load</i>	30
9. Pengukuran Waktu Emulsifikasi	30
10. Stabilitas Termodinamika.....	31
F. Analisis Data.....	31
BAB IV HASIL DAN PEMBAHASAN	33
A. Pembuatan Ekstrak Brotowali	33
B. Preparasi SE Ekstrak Brotowali.....	33
C. Skrining Komponen Penyusun SE Menggunakan <i>Fractional Factorial Design</i> (FrFD).....	38
1. Respon <i>Drug Load</i> (R_1).....	42
2. Respon Persen Transmitan SE.....	44
3. Respon Persen Transmitan Emulsi	47
4. Respon Viskositas (R_4).....	50
5. Respon Waktu Emulsifikasi SGF, SIF dan <i>Aquadest</i> (R_5, R_6, R_7)	52
D. Formula Terpilih dan Verifikasi Hasil	60
E. Karakteristik Dan Evaluasi Komponen Formula Terpilih	63
1. Penampakan Visual SE Ekstrak Brotowali	63
2. Penetapan <i>Drug Load</i>	65
3. Persen Transmitan.....	66
4. Viskositas	67
5. Waktu Emulsifikasi	68
6. Uji Stabilitas Termodinamika SE	69
F. Pengolahan Data dengan Analisis Kemometrik	74

1. Analisis <i>Scree Plot</i>	74
2. Analisis <i>Score Plot</i> dan Dendogram	75
3. Analisis <i>Loading Plot</i>	78
BAB V KESIMPULAN DAN SARAN	81
A. Kesimpulan.....	81
B. Saran.....	81
DAFTAR PUSTAKA	83
LAMPIRAN	93

BAB V

KESIMPULAN DAN SARAN

A. Kesimpulan

1. Variasi komponen penyusun SE berupa minyak (miglyol 812N dan asam oleat), surfaktan (tween 80 dan PEG 40), ko-surfaktan (PEG 400 dan propilen glikol) pembawa ekstrak botowali mampu memenuhi karakteristik sediaan SE.
2. Komponen terpilih SE pembawa ekstrak brotowali adalah miglyol dengan konsentrasi 10% sebagai fase minyak, PEG 40 dengan konsentrasi 30% sebagai fase surfaktan, dan propilen glikol dengan konsentrasi 20% sebagai fase ko-surfaktan.
3. Korelasi positif ditunjukkan pada respon persen transmitan dengan waktu emulsifikasi SIF, viskositas. Korelasi negatif ditunjukkan pada respon drug load dengan waktu emulsifikasi *aquades* dan SIF, persen transmitan SE dengan waktu emulsifikasi *aquades*.

B. Saran

Berdasarkan penelitian yang telah dilakukan disarankan:

1. Perlu dilakukan evaluasi *drug content* untuk mendapatkan jumlah zat aktif yang terlarut dengan metode analisis yang tepat untuk sistem SE.
2. Diperlukan penelitian lebih lanjut terkait formula terpilih yang didapat pada level optimasi yang lebih komperhensif.

3. Menggunakan lemari pendingin atau freezer yang sesuai dengan temperatur suhu yang dibutuhkan dan melakukan pengukuran secara berkala pada pendingin yang digunakan.

DAFTAR PUSTAKA

- Akbar, N. D., Nugroho, A. K., & Martono, S. (2021). Review Article: Optimization of Snedds Formulation By Simplex Lattice Design and Box Behnken Design. *Jurnal Ilmiah Farmako Bahari*, 13(1), 90–100.
- Amin, A. (2016). Determinasi dan Analisis Finger Print Daun Miana (*Coleus scutellarioides* Linn.) Sebagai Bahan Baku Obat Tradisional Dengan Metode Speltrofotometri FT-IR dan Kemometrik. *Jf Fik Uinam*, 4(2), 58–64.
- Ananda, N. C. R., Sulaiman, S., & Suwarni. (2017). Pengaruh Peningkatan Tween 20 Sebagai Surfaktan Terhadap karakteristik dan Kestabilan Fisik Sediaan Self Emulsifying Drug Delivery System (SNEDDS) Simvastatin. *Media Farmasi Indonesia*, 10(2), 940–948.
- Anindhita Anung, M., & Oktaviani, N. (2016). Formulasi Self-Emulsifying Drug Delivery System (SNEDDS) Ekstak Daun Pepaya (*Carica papaya* L.) dengan Virgin Coconut Oil (VCO) sebagai Minyak Pembawa. *Jurnal Pena Medika*, 6(2), 103–111.
- Annisa, R., Yuwono, M., & Hendradi, E. (2020). Design and optimization of eleutherine palmifolia extract-loaded snedds using hlb approach. *Journal of Research in Pharmacy*, 24(6), 943–951. <https://doi.org/10.35333/jrp.2020.254>
- Arina, Y., Shiyan, S., & Suprayetno, S. (2022). Analisis Kemometrik Ekstrak Akar Tunjuk Langit (*Helminthostachys Zeylanica* (L)) Melalui Analisis Fourier Transformed Infrared Dari Berbagai Daerah Sumatera Selatan. *Jurnal 'Aisyiyah Medika*, 7(1), 243–258.
- Azeem, A., Rizwan, M., Ahmad, F. J., Iqbal, Z., Khar, R. K., Aqil, M., & Talegaonkar, S. (2009). Emulsion components screening and selection: A technical note. *AAPS PharmSciTech*, 10(1), 69–76.
- Bali, V., Ali, M., & Ali, J. (2011). Nanocarrier for the enhanced bioavailability of a cardiovascular agent: In vitro, pharmacodynamic, pharmacokinetic and stability assessment. *International Journal of Pharmaceutics*, 403(1–2), 46–56.
- Baloch, J., Sohail, M. F., Sarwar, H. S., Kiani, M. H., Khan, G. M., Jahan, S., Rafay, M., Chaudhry, M. T., Yasinzai, M., & Shahnaz, G. (2019). Self-emulsifying drug delivery system (Snedds) for improved oral bioavailability of chlorpromazine: In vitro and in vivo evaluation. *Medicina (Lithuania)*, 55(5), 1–13.
- Beandrade, M. U. (2018). Formulasi dan Karakterisasi SNEDDS Ekstrak Jinten Hitam (*Nigella Sativa*) dengan Fase Minyak Ikan Hiu Cucut Botol (*Centrophorus* Sp) serta Uji Aktivitas Imunostimulan. *JPSCR: Journal of*

- Pharmaceutical Science and Clinical Research*, 3(1), 50.
- Biswasroy, P., Panda, S., Das, C., Das, D., Kar, D. M., & Ghosh, G. (2020). *Tinospora cordifolia*— a plant with spectacular natural immunobooster. *Research Journal of Pharmacy and Technology*, 13(2), 1035–1038.
- Brilliant, V. G., Hutomo, S., Sooi, C. M., & Merry, M. S. (2022). Aktivitas Penghambatan *Candida krusei* oleh Ekstrak Etanol Batang Brotowali (*Tinospora crispa* L.). *Jurnal Kedokteran Meditek*, 28(2), 120–125.
- Brotowali, P., & Hook, L. (2019). *Sebagai Pestisida Nabati*. 18(1), 28–39.
- Cahyani, S. E., Nugroho, B. H., & Syukri, Y. (2020). Stability studies of mefenamic acid Self-Emulsifying drug delivery system (SNEEDS) preparation with oleic acid as the oil phase. *Jurnal Ilmiah Farmasi*, 16(2), 130–143.
- Cardona, M. I., Dominguez, G. P., Echeverry, S. M., Valderrama, I. H., Bernkop-Schnürch, A., & Aragón, M. (2021). Enhanced oral bioavailability of rutin by a self-emulsifying drug delivery system of an extract of calyces from *Physalis peruviana*. *Journal of Drug Delivery Science and Technology*, 66(September).
- Chiappetta, D. A., & Sosnik, A. (2007). Poly(ethylene oxide)-poly(propylene oxide) block copolymer micelles as drug delivery agents: Improved hydrosolubility, stability and bioavailability of drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, 66(3), 303–317.
- Chintalapudi, R., Murthy, T. E. G. K., Lakshmi, Kr., & Manohar, Gg. (2015). Formulation, optimization, and evaluation of self-emulsifying drug delivery systems of nevirapine. *International Journal of Pharmaceutical Investigation*, 5(4), 205.
- Choi, S. J., & McClements, D. J. (2020). Emulsions as delivery systems for lipophilic nutraceuticals : strategies for improving their formulation , stability , functionality and bioavailability. *Food Science and Biotechnology*, 29(2), 149–168.
- Cui, F., Kim, M., Park, C., Kim, D., Mo, K., & Kim, M. (2021). Application of principal component analysis (PCA) to the assessment of parameter correlations in the partial-nitrification process using aerobic granular sludge. *Journal of Environmental Management*, 288(January), 112408.
- Date, A. A., Desai, N., Dixit, R., & Nagarsenker, M. (2010). Self-emulsifying drug delivery systems: Formulation insights, applications and advances. *Nanomedicine*, 5(10), 1595–1616.
- Dewi, R., Anwar, E., & Yunita, K. S. (2014). Uji Stabilitas Fisik Formula Krim yang Mengandung Ekstrak Kacang Kedelai (*Glycine max*) Absrak. 1(3), 194–208.

- Engelen, A., Sugiyono, & Budijanto, S. (2015). Optimasi proses dan formula pada pengolahan mi sagu kering (Metroxylon sagu). *Agritech*, 35(4), 359–367.
- Fatimah, S., Jumar, J., & Ronny, M. (2021). Uji Efektivitas Ekstrak Batang Brotowali (*Tinospora crispa* (L.) Miers.) pada Hama Padi Wereng Batang Coklat (*Nilaparvata lugens* Stal.) dalam Skala Rumah Kaca. *Agritrop: Jurnal Ilmu-Ilmu Pertanian (Journal of Agricultural Science)*, 19(1), 19–26.
- Gao, H., Lv, C., Song, Y., Zhang, Y., Zheng, L., Wen, Y., Peng, J., & Yu, H. (2015). Chemometrics data of water quality and environmental heterogeneity analysis in Pu River, China. *Environmental Earth Sciences*, 73(9), 5119–5129. <https://doi.org/10.1007/s12665-015-4233-x>
- García, L. F., & Morgado, A. (2021). *Journal of Archaeological Science : Reports Reflectance spectroscopy in combination with cluster analysis as tools for identifying the provenance of Neolithic flint artefacts*. 37(May 2020).
- Halder, S., Islam, A., Muhit, M. A., Shill, M. C., & Haider, S. S. (2021). Self-emulsifying drug delivery system of black seed oil with improved hypotriglyceridemic effect and enhanced hepatoprotective function. *Journal of Functional Foods*, 78, 104391. <https://doi.org/10.1016/j.jff.2021.104391>
- Handoyo Sahumena, M., Suryani, S., & Rahmadani, N. (2019). Formulasi Self-Emulsifying Drug Delivery System (SNEDDS) Asam Mefenamat menggunakan VCO dengan Kombinasi Surfaktan Tween dan Span. *Journal Syifa Sciences and Clinical Research*, 1(2), 37–46.
- Hartati Yuliani, S., Hartini, M., Pudyastuti, B., & Perdana Istyastono, E. (2016). Comparison of Physical Stability Properties of Pomegranate Seed Oil Emulsion Dosage Forms With Long-Chain Triglyceride and Medium-Chain Triglyceride As the Oil Phase Perbandingan Stabilitas Fisis Sediaan Emulsi Minyak Biji Delima Dengan Fase Minyak. *Traditional Medicine Journal*, 21(2), 2016.
- Harwansh, R. K., Mukherjee, P. K., Kar, A., Bahadur, S., Al-Dhabi, N. A., & Duraipandiyar, V. (2016). Enhancement of photoprotection potential of catechin loaded emulsion gel against UVA induced oxidative stress. *Journal of Photochemistry and Photobiology B: Biology*, 160, 318–329.
- helio duvaizem, J. (2009). *farmakope indonesia edisi 5*. 12–42.
- Hernawan Nugroho, B., & Permata Sari, N. (2018). Formulation of Self Nano Emulsifying Drug Delivery System (SNEDDS) Karamunting Leaf Extract (*Rhodymyrtus tomentosa* (Ait.) Hassk) Fomulasi Self Nano Emulsifying Drug Delivery System (SNEDDS) Ekstrak Daun Karamunting (*Rhodymyrtus tomentosa* (Ait.) Hassk). *Jurnal Ilmiah Farmasi*, 14(1), 1–8.
- Heshmati, N., Cheng, X., Eisenbrand, G., & Fricker, G. (2013). Enhancement of Oral Bioavailability of E804 by Self-Emulsifying Drug Delivery System

- (SNEDDS) in Rats. *Journal of Pharmaceutical Sciences*, 102(10), 3792-3799.
- Hidayat, I. R., Zuhrotun, A., & Sopyan, I. (2020). Design-Expert Software sebagai Alat Optimasi Formulasi Sediaan Farmasi. *Majalah Farmasetika*, 6(1), 99-120.
- Hiral, M., Bhatt, M. A. Y., Parmar, R. B., Paun, M. J. S., & Tank, H. M. (2013). Self-nano Emulsifying Drug Delivery System (SNEDDS): Future Aspects. *Asian J.Pharm. Res.*, 3(1), 21-27.
- Huda, N., & Wahyuningsih, I. (2018). Karakterisasi Self-Emulsifying Drug Delivery System (SNEDDS) Minyak Buah Merah (*Pandanus conoideus* Lam.). *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 3(2), 49.
- Huynh-ba, K. (2009). Handbook of Stability Testing in Pharmaceutical Development. *Handbook of Stability Testing in Pharmaceutical Development*.
- Iaboni, D. S. M., Farrell, S. R., & Chauhan, B. C. (2020). Morphological multivariate cluster analysis of murine retinal ganglion cells selectively expressing yellow fluorescent protein. *Experimental Eye Research*, 196(February), 108044.
- Indriani, V., Tobing, N. E. K. P., & Rijai, L. (2018). Formulasi Self-Emulsifying Drug Delivery System (SNEDDS) Ekstrak Biji Ramania (*Bouea macrophylla* Griff) dengan Asam Oleat (Oleic Acid) sebagai Minyak Pembawa. *Proceeding of Mulawarman Pharmaceuticals Conferences*, 8(November 2018), 276-284.
- Irawaty, I., Anisa, A., & Herdiani, E. T. (2018). Perbandingan Nilai Fraksi pada Rancangan Faktorial Fraksional 2k dengan Metode Bissell dan Aplikasinya pada Kasus Perkecambahan Kacang Hijau. *Jurnal Matematika Statistika Dan Komputasi*, 14(2), 192.
- Jaworska, M., Sikora, E., & Ogonowski, J. (2014). *The influence of glicerides oil phase on O / W emulsion formation by pic method*. 58, 43-48.
- Juaeni, I. (2014). Dampak Penerapan Principal Component Analysis (Pca) Dalam Clustering Curah Hujan Di Pulau Jawa , Bali , Dan Lombok [Impact of Principal Component Analysis (Pca) Implementation on Rainfall Clustering Over Java , Bali and Lombok Islands]. *Jurnal Sains Dirgantara*, 11, 97-108.
- Kanwal, T., Kawish, M., Maharjan, R., Ghaffar, I., Ali, H. S., Imran, M., Perveen, S., Saifullah, S., Simjee, S. U., & Shah, M. R. (2019). Design and development of permeation enhancer containing self-emulsifying drug delivery system (SNEDDS) for ceftriaxone sodium improved oral pharmacokinetics. *Journal of Molecular Liquids*, 289, 111098.

- Kartini, K., Putri, L. A. D., & Hadiyat, M. A. (2020). FTIR-based fingerprinting and discriminant analysis of *Apium graveolens* from different locations. *Journal of Applied Pharmaceutical Science*, 10(12), 62–67.
- Khan, A. W., Kotta, S., Ansari, S. H., Kumar, R., & Ali, J. (2015). Self-emulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid Naringenin: design, characterization, in vitro and in vivo evaluation water-soluble grapefruit flavonoid Naringenin: design, characterization, .. 7544.
- Kotta, S., Khan, A. W., Pramod, K., Ansari, S. H., Sharma, R. K., & Ali, J. (2012). Exploring oral emulsions for bioavailability enhancement of poorly water-soluble drugs. *Expert Opinion on Drug Delivery*, 9(5), 585–598.
- Leuner, C., & Dressman, J. (2010). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
- Listyorini, N.L.P.D. Wijayanti, K. W. A., & Progam. (2018). Optimasi Pembuatan Emulsi Virgin Coconut Oil. *Universitas Udayana*.
- Makadia, Bhatt, M. A. Y., Parmar, R. B., Paun, M. J. S., & Tank, H. M. (2013). Self-nano Emulsifying Drug Delivery System (SNEDDS): Future Aspects. *Asian J.Pharm. Res.*, 3(1), 21–27.
- Meesathien, N., & Phromyothin, D. (2016). Preparation and Characterization of Nano-cream from Squalene in olive oil and Virgin Coconut Oil by Emulsions method. *Thai J*, 1(1), 30–36.
- Muttaqin, B. I. A. (2019). Telaah Kajian dan Literature Review Design of Experiment (DoE). *Journal of Advances in Information and Industrial Technology*, 1(1), 33–40.
- Nainggolan, R., & Eviyanti Purba. (2020). The Cluster Analysis of Online Shop Product Reviews Using K-Means Clustering. *Data Science: Journal of Computing and Applied Informatics*, 4(2), 111–121.
- Nugroho, B. H., Citrariana, S., Sari, I. N., Oktari, R. N., & Munawwarah, M. (2017). Formulasi dan evaluasi SNEDDS (Self Emulsifying Drug Delivery System) ekstrak daun pepaya (*Carica papaya L.*) sebagai analgesik. *Jurnal Ilmiah Farmasi*, 13(2), 77–85. <https://doi.org/10.20885/jif.vol13.iss2.art5>
- Nurmiah, S., Syarief, R., Sukarno, S., Peranginangin, R., & Nurmata, B. (2013). Aplikasi Response Surface Methodology Pada Optimalisasi Kondisi Proses Pengolahan Alkali Treated Cottonii (ATC). *Jurnal Pascapanen Dan Bioteknologi Kelautan Dan Perikanan*, 8(1), 9.
- Pamudji, J. S., Darijanto, S. T., & Rosa, S. (2012). Formulasi dan Evaluasi Mikroemulsi Minyak dalam Air Betametason 17-Valerat. *Acta Pharmaceutica Indonesia*, 37(4), 140–146.

- Patel, J., Kevin, G., Patel, A., Raval, M., & Sheth, N. (2011). Design and development of a self-emulsifying drug delivery system for telmisartan for oral drug delivery. *International Journal of Pharmaceutical Investigation*, 1(2), 112.
- Patel, J., Patel, A., Raval, M., & Sheth, N. (2011). Formulation and development of a self-emulsifying drug delivery system of irbesartan. *Journal of Advanced Pharmaceutical Technology and Research*, 2(1), 9–16.
- Pradhan, D., Kar, D. M., & Ghosh, G. (2020). Bioassay-guided fractionation of anti-microbial principle from ethanolic extract of *tinospora cordifolia* and its characterization. *Research Journal of Pharmacy and Technology*, 13(3), 1415–1422.
- Pratiwi, G., Martien, R., & Murwanti, R. (2019). Chitosan nanoparticle as a delivery system for polyphenols from meniran extract (*Phyllanthus niruri* L.): Formulation, optimization, and immunomodulatory activity. *International Journal of Applied Pharmaceutics*, 11(2), 50–58.
- Pratiwi, G., Ramadhiani, A. R., & Shiyan, S. (2022). Understanding the combination of fractional factorial design and chemometrics analysis for screening super-saturable quercetin-self nano emulsifying components. *Pharmacia*, 69(2), 273–284.
- Pratiwi, G., Susanti, S., & Shiyan, S. (2020). Application of Factorial Design for Optimization of PVC-HPMC Polymers in Matrix Film Ibuprofen Patch-Transdermal Drug Delivery System. *Indonesian Journal of Chemometrics and Pharmaceutical Analysis*, 1(1), 11.
- Pratiwi, L., Fudholi, A., Martien, R., & Pramono, S. (2018). Uji Stabilitas Fisik dan Kimia Sediaan SNEDDS (*Self-emulsifying Drug Delivery System*) dan Emulsi Fraksi Etil Asetat Kulit Manggis (*Garcinia mangostana* L.) Physical and Chemical Stability Test of SNEDDS (*Self-emulsifying Drug Delivery System*) a. *Traditional Medicine Journal*, 23(2), 84–90.
- Priani, S. E., Annisa, A., & Darma, G. C. E. (2018). Dissolution enhancement of atorvastatin calcium by self-emulsifying drug delivery system using cremophor RH 40 and Transcutol P as surfactants. *Drug Invention Today*, 10(Special Issue 5), 3768–3772.
- Pujiyanto, S. R. I., Lestari, Y., Suwanto, A., Budiarti, S. R. I., & Darusman, L. K. (2012). *Actinomycetes Isolated From Some Indonesian Diabetic Medicinal Plants*. 4(pH 7).
- Purnomo, E., B. Sitanggang, A., S. Agustin, D., Hariyadi, P., & Hartono, S. (2012). Formulation and Process Optimization of Muffin Produced From Composite Flour of Corn, Wheat and Sweet Potato. *Jurnal Teknologi Dan Industri Pangan*, 23(2), 165–172.
- Rachmawati, H., Novel, M. A., Ayu, S., Berlian, G., Tandrasasmita, O. M.,

- Tjandrawinata, R. R., & Anggadiredja, K. (2017). The in vitro-in vivo safety confirmation of PEG-40 hydrogenated castor oil as a surfactant for oral emulsion formulation. *Scientia Pharmaceutica*, 85(2).
- Rafi, Widia Citra Anggundari, T. T. I. (2016). Info Artikel. *Edaj*, 2(3), 3-8.
- Ragavee, A., Choedar, T., Suman, S., & Asha Devi, S. (2018). Evaluation of bioactive constituents and antioxidant activity of mucilage isolated from *tinospora cordifolia*. *Research Journal of Pharmacy and Technology*, 11(7), 2747-2751.
- Ramadhani, R. A., Riyadi, D. H. S., Triwibowo, B., & Kusumaningtyas, R. D. (2017). Review Pemanfaatan Design Expert untuk Optimasi Komposisi Campuran Minyak Nabati sebagai Bahan Baku Sintesis Biodiesel. *Jurnal Teknik Kimia Dan Lingkungan*, 1(1), 11.
- Ramadhiani, A. R., Pratiwi, G., Fitriani, E., & Kurniawaty. (2021). Activity of Ethanol Extract of *Tinospora crispa* (L.) Hook in Increasing Swimming Endurance on Male Mice Using Natatory Exhaustion Method. *Research Journal of Pharmacy and Technology*, 14(10), 5439-5442.
- Ramli, S., Chyi, K. T., Zainuddin, N., Mokhtar, W. N. A. W., & Abdul Rahman, I. (2019). The influence of surfactant/co-surfactant hydrophilic-lipophilic balance on the formation of limonene-based microemulsion as Vitamin C carrier. *Sains Malaysiana*, 48(5), 1035-1042. <https://doi.org/10.17576/jsm-2019-4805-12>
- Renato Cesar, D. A. R., Barreto, S. M. A. G., Ostrosky, E. A., Da Rocha-Filho, P. A., Verissimo, L. M., & Ferrari, M. (2015). Production and characterization of cosmetic emulsions containing *Opuntia ficus-indica* (L.) Mill extract as moisturizing agent. *Molecules*, 20(2), 2492-2509.
- Risal, Y. (2020). Analisis Kemometrik Senyawa Inhibitor Tirosinase Menggunakan Spektrofotometer IR (FTIR). *Majalah Farmasi Dan Farmakologi*, 24(2), 59-62.
- Rosyidi, N. N., & Khamidina. (2020). Analisis Lemak Bakso Tikus dalam Bakso Sapi di Sleman Menggunakan Spektroskopi Inframerah (Fourier Transform Infrared). (*IJHS*) *Indonesian Journal of Halal Science*, 001(01), 12-23.
- Rowe. (2020). Pharmaceutical excipients. In *Remington: Handbook of Pharmaceutical Excipients* (pp. 633-643).
- Senapati, P. C., Sahoo, S. K., & Sahu, A. N. (2016). Mixed surfactant based (SNEDDS) self-emulsifying drug delivery system presenting efavirenz for enhancement of oral bioavailability. *Biomedicine and Pharmacotherapy*, 80, 42-51.
- Shafii, N. Z., Saudi, A. S. M., Pang, J. C., Abu, I. F., Sapawe, N., Kamarudin, M. K. A., & Saudi, H. F. M. (2019). Application of chemometrics techniques to

- solve environmental issues in Malaysia. *Heliyon*, 5(10).
- Shafirany, M. Z., Susilawati, Y., & Musfiroh, I. (2019a). Aplikasi Kemometrik dalam Penentuan Mutu Tumbuhan Obat. *Pharmauho: Jurnal Farmasi, Sains, Dan Kesehatan*, 4(2), 6–14.
- Shafirany, M. Z., Susilawati, Y., & Musfiroh, I. (2019b). Aplikasi Kemometrik dalam Penentuan Mutu Tumbuhan Obat. *Pharmauho: Jurnal Farmasi, Sains, Dan Kesehatan*, 4(2).
- Shahba, A. A. W., Mohsin, K., & Alanazi, F. K. (2012). Novel self-emulsifying drug delivery systems (SNEDDS) for oral delivery of cinnarizine: Design, optimization, and in-vitro assessment. *AAPS PharmSciTech*, 13(3), 967–977.
- Shiyan, S., Hertiani, T., Martien, R., & Nugroho, A. K. (2018). Optimization of a novel kinetic-assisted infundation for rich-egcg and polyphenols of white tea (*Camellia sinensis*) using central composite design. *International Journal of Applied Pharmaceutics*, 10(6), 259–267.
- Shiyan, S., Zubaidah, & Pratiwi, G. (2021). Chemometric Approach to Assess Response Correlation and its Classification in simplex centroid design for Pre-Optimization stage of Catechin-SNEDDS. *Research Journal of Pharmacy and Technology*, 14(11), 5863–5870.
- Suanda, I. W. (2021). *Manisnya Brotowali Sebagai Fitofarmasida*.
- Suhandy, D., Waluyo, S., & Sugianti, C. (2017). Studi Penggunaan Uv-Vis Spectroscopy Dan Kemometrika Untuk Mengidentifikasi Pemalsuan Kopi Arabika Dan Robusta Secara Cepat [*Study On The Use Of Uv-Vis Spectroscopy And Chemometrics To Quickly Identify The Falsification Of Arabica And Robusta Coffees*]. 6(1), 43–52.
- Syukri, Y., Kholidah, Z., & Chabib, L. (2020). Fabrikasi dan Studi Stabilitas Self-Nano Emulsifying Propolis menggunakan Minyak Kesturi sebagai Pembawa. *Jurnal Sains Farmasi & Klinis*, 6(3), 265.
- Syukri, Y., Martien, R., Lukitaningsih, E., & Nugroho, A. E. (2018). Novel Self-Nano Emulsifying Drug Delivery System (SNEDDS) of andrographolide isolated from *Andrographis paniculata* Nees: Characterization, in-vitro and in-vivo assessment. *Journal of Drug Delivery Science and Technology*.
- Syukri, Y., Nugroho, B. H., & Istanti, I. (2020). Penggunaan D-Optimal Mixture Design untuk Optimasi dan Formulasi Self-Nano Emulsifying Drug Delivery System (SNEEDS) Asam Mefenamat. *Jurnal Sains Farmasi & Klinis*, 7(3), 180.
- Syukri, Y., Taher, M., Martien, R., Lukitaningsih, E., Nugroho, A. E., & Zakaria, Z. A. (2021). Self-emulsifying delivery of andrographolide: Ameliorating islet beta cells and inhibiting adipocyte differentiation. *Advanced Pharmaceutical Bulletin*, 11(1), 171–180.

- Talekar, S. D., Haware, R. V., & Dave, R. H. (2019). Evaluation of self-emulsifying drug delivery systems using multivariate methods to optimize permeability of captopril oral films. *European Journal of Pharmaceutical Sciences*, 130, 215–224.
- Tran, T. H., Guo, Y., Song, D., Bruno, R. S., & Lu, X. (2014). Quercetin-containing self-emulsifying drug delivery system for improving oral bioavailability. *Journal of Pharmaceutical Sciences*, 103(3), 840–852.
- Ujilestari, T., Martien, R., Ariyadi, B., Dono, N. D., & Zuprizal. (2018). Self-emulsifying drug delivery system (SNEDDS) of Amomum compactum essential oil: Design, formulation, and characterization. *Journal of Applied Pharmaceutical Science*, 8(6), 14–21.
- Warsinah, Baroroh, H. N., & Harwoko. (2020). Phytochemical analysis and antioxidant activity of brotowali (*Tinospora crispa* L. Mier) stem. *Molekul*, 15(2), 73–78.
- Wendersteyt, N. V., Wewengkang, D. S., & Abdullah, S. S. (2021). Uji Aktivitas Antimikroba Dari Ekstrak Dan Fraksi Ascidian *Herdmania Momus* Dari Perairan Pulau Bangka Likupang Terhadap Pertumbuhan Mikроба *Staphylococcus aureus*, *Salmonella typhimurium* DAN *Candida albicans*. *Pharmakon*, 10(1), 706.
- Widyaningsih, W., Widyarini, Y., Agustina, A., & Sofia, V. (2009). Efek Antipiretik Dari Fraksinasi Ekstrak Etanol Batang Brotowali (*Tinospora Crispa*, L) Pada Tikus Putih Jantan Galur Wistar. *Media Farmasi*, 8(1), 33–38.
- Widyastuti Indah, Prof. Dr. apt. Abdul Rohman, M. S. (2020). *Aktivitas Antioksidan Temulawak (Curcuma xanthorrhiza) dan Profil Pengelompokannya dengan Kemometrik*.
- Winarni, S., Sunengsih, N., & Anugrah, R. I. (2019). Penerapan Desain Fractional Factorial dalam Menentukan Faktor Berpengaruh pada Eksperimen Pelindian Konsentrat Galena (Pbs). *STATISTIKA Journal of Theoretical Statistics and Its Applications*, 19(2), 83–92. 7
- Yadav, P., Yadav, E., Verma, A., & Amin, S. (2014). In vitro characterization and pharmacodynamic evaluation of furosemide loaded self nano emulsifying drug delivery systems (SNEDDS). *Journal of Pharmaceutical Investigation*, 44(6), 443–453.
- Yulia, N., & Setiyabudi, L. (2022). Skrining Fitokimia dan Uji Aktivitas Antibakteri Ekstrak Jeringau dan Brotowali terhadap *Streptococcus pyogenes*. *Prosiding Seminar Nasional ...*, September, 36–41.
- Zhao, T. (2015). Self-emulsifying drug delivery systems (SNEDDS) for the oral delivery of lipophilic drugs. *Self-Emulsifying Drug Delivery Systems* (

SNEDDS) for the Oral Delivery of Lipophilic Drugs, November, 1-120.

Zulfa, E., Novianto, D., & Setiawan, D. (2019). Formulasi Emulsi Natrium Diklofenak dengan Variasi Kombinasi Tween 80 Dan Span 80: Kajian Karakteristik Fisik Sediaan. *Media Farmasi Indonesia, 14*(1), 1471-1477.