Homepage :
https://journal.ubaya.ac.id/index.php/MPI/index
DOI 10.24123/mpi.v7i1.7440

Research Article
p-ISSN 2527-6298 | e-ISSN 2527-9017

Development of A Self Nanoemulsifying Drug Delivery System for Atenolol using Soybean Oil, Olive Oil and Virgin Coconut Oil

Endang Wahyu Fitriani, Helma Malini, Vestiana Rosita, and Yella Handika

Pharmaceutics Department, Faculty of Pharmacy, University of Surabaya, Surabaya 60293, Indonesia

Korespondensi: Endang Wahyu Fitriani
Email: endangwahyu@staff.ubaya.ac.id

Submitted : 10-04-2025, *Revised* : 22-04-2025, *Accepted* : 07-05-2025, *Published regularly*: *June 2025*

ABSTRACT: *Oral formulations remain the primary method of drug delivery, however, the solubility and lipophilicity of compounds such as atenolol present significant obstacles. Atenolol, a β1-selective antihypertensive agent, exhibits limited solubility in both aqueous and gastrointestinal environments. Atenolol is developed in a lipid-based delivery system, specifically the Self-Nanoemulsifying Drug Delivery System (SNEDDS), to enhance its bioavailability and resolve this issue. SNEDDS can improve drug solubility by generating spontaneous nanoemulsions in the gastrointestinal tract. This study aims to evaluate and improve the main components of SNEDDS, specifically oil, surfactant, and co-surfactant, according to the parameters of % transmittance, polydispersity index (PI), and zeta potential. The research findings suggest that the nine formulas have not yet achieved the optimal attributes, concerning clarity and durability against dilution. Differences in oil types and amounts of surfactants and cosurfactants influence droplet size, polydispersity index, and zeta potential. Formulas 2 (soybean oil), 7, and 9 (olive oil) exhibit physicochemical parameters that meets the criteria and possess potential for further advancement.*

Keywords: *atenolol; cosurfactant; self nanoemulsifying drug delivery system (SNEDDS); surfactant*

1. Introduction

Atenolol is an antihypertensive agent classified as a β-blocker (β1-selective) with low solubility in both water and gastric fluid [1,2]. Conventional atenolol tablet formulations have been documented to induce variations in plasma drug levels. This situation induces adverse effects or diminishes drug concentration at the receptor [3,4]. Consequently, to improve its solubility and bioavailability, and to attain optimal therapeutic outcomes, atenolol must be developed into non-traditional oral formulations, such as lipid-based systems.

Lipid-based delivery mechanisms have become popular for drugs with low aqueous solubility and bioavailability, particularly for oral administration. This delivery method is thought to facilitate drug transport into the body through lymphatic pathways via Peyer patches situated along the gastrointestinal tract, therefore bypassing enterohepatic circulation [5]. The self nanoemulsifying drug delivery system (SNEDDS) is a lipid-based delivery system under extensive investigation. SNEDDS consists of an isotropic mixture of oil, surfactant, co-surfactant, and drug, which can spontaneously produce an oil-in-water nanoemulsion in the gastrointestinal tract [6]. SNEDDS, as a drug delivery system, has numerous advantages, such as transparent formulations, enhanced stability, simple manufacturing, and the capacity to serve as carriers for hydrophobic medicines or those with limited solubility in water [7,8]. This delivery strategy can improve bioavailability by increasing solubility and maintaining the drug in a dissolved state throughout its passage in the gastrointestinal tract [9,10].

The main components of SNEDDS include oil, surfactants, and co-surfactants [11]. The oil content within the SNEDDS formulation will determine the size of the resulting nanoemulsion. The choice of oil is determined by its capacity to dissolve the active substances and its ability to spontaneously generate nanoemulsions. Oils composed of medium-chain triglycerides are easier to emulsified than those containing long-chain triglycerides. Oils containing long-chain triglycerides have an advantage over those with medium-chain triglycerides, as they facilitate drug delivery via the lymphatic system, hence diminishing first-pass metabolism [12]. The surfactants frequently used in SNEDDS formulations are nonionic surfactants with hydrophilic characteristics, distinguished by HLB values ranging from 15 to 21 [6]. Nonionic surfactants are selected due to their safety, low toxicity, and minimal pH sensitivity.

The screening and optimization of SNEDDS components are essential to achieve an optimal formulation and reduce the potential side effects. This process involves a series of preliminary steps in the formulation of SNEDDS. This phase includes the primary components of SNEDDS, specifically oil, surfactant, and co-surfactant, evaluated according to the parameters of % transmittance, polydispersity index (PI), and zeta potential [13,14].

This study involved the screening and optimization of the components—oil, surfactant, and co-surfactant—to formulate atenolol SNEDDS. The oils selected are soybean oil, olive oil, and virgin coconut oil. The surfactant employed was tween 80, while the cosurfactants utilized was PEG 400. The choice of oil, surfactant, and co-surfactant were determined by the characteristics of each component and the accessibility of these materials. This research contributes in determining an optimal formulation of oil, surfactant, and cosurfactant for the SNEDDS of atenolol.

2. Materials and methods

2.1. Materials

Atenolol (Refarmed Chemicals, Lugano, Switzerland), food-grade soybean oil (PT. Indofood, Indonesia), virgin coconut oil (Indonesia), olive oil (Bertolli, Italy), tween 80 (Evonik Industries), PEG 400 (Arrow Fines Chemicals), and demineralized water(Universitas Surabaya, Indonesia).

Table 1. Formula of SNEDDS atenolol

Component	Atenolol	Soybean oil	VCO	Olive oil	Tween 80	PEG 400
Function	Active ingredients		Oil phase		Surfactant	Cosurfactant
Formula	Amount in formulas (%)					
F1	1	49	-	-	45	5
F2	1	49	-	-	40	10
F3	1	49	-	-	35	15
F4	1	-	49	-	45	5
F5	1	-	49	-	40	10
F6	1	-	49	-	35	15
F7	1	-	-	49	45	5
F8	1	-	-	49	40	10
F9	1	-	-	49	35	15

2.2. Instrument

Analytical balance (Scout® Pro Digital), magnetic stirrer (Cimarec®), UV-VIS spectrophotometer (Shimadzu® UV-1800), particle size analyzer (Microtrac®-Nanotrac Wave II), high-shear stirrer (Ultra Turrax, IKA® T25), and glassware (Pyrex®).

2.3. Methods

2.3.1. Preparation methods of atenolol SNEDDS

The main components of the atenolol SNEDDS formulation are presented in Table 1. To prepare atenolol SNEDDS, the oil phase, surfactant, and cosurfactant were combined in a beaker and stirred with a magnetic stirrer at 300 rpm for 5 minutes. The mixture was afterwards stirred with an ultra turrax at a speed of 20,000 rpm for 2 minutes.

2.3.2. The preliminary orientation of the atenolol SNEDDS formulation

The preliminary orientation of the atenolol SNEDDS formulation involved surfactant and co-surfactant concentration ratios of 50:0, 45:5, 40:10, 35:15, and 30:20, maintaining an identical oil concentration of 49%. The prepared SNEDDS were diluted 250-fold in demineralized water, after which their clarity was visually assessed.

2.3.3. Determination of % transmittance

One milliliter of the atenolol SNEDDS base was pipetted with a micropipette and dispersed in 250 milliliters of aquabidest, then swirled gently with a magnetic stirrer to create a nanoemulsion. The % transmittance was measured by a UV spectrophotometer at a wavelength of 650 nm, located within the visible spectrum. The clarity of the formulated SNEDDS correlated positively with the transmittance achieved.

2.3.4. Robustness to dilution

The assessment of robustness to dilution is performed to ascertain the formulas resilience against different dilution ratios in an aqueous dissolution media. This study evaluated robustness exclusively in demineralized water dissolving media in volumes of 50 ml, 100 ml, and 1000 ml. Following the dilution of the SNEDDS preparation, it was held for 12 hours and monitored for indications of phase separation or precipitation, while the particle size was assessed using a particle size analyzer (PSA).

2.3.5. Determination of particle size, polydispersity index, and zeta potential

The primary constituents of the atenolol SNEDDS base, in varying ratios of 1 mL each, were dispersed in 250 mL of aquabidest (250X dilution) and gently swirled with a magnetic stirrer to create a nanoemulsion. The atenolol SNEDDS base samples were analyzed for particle

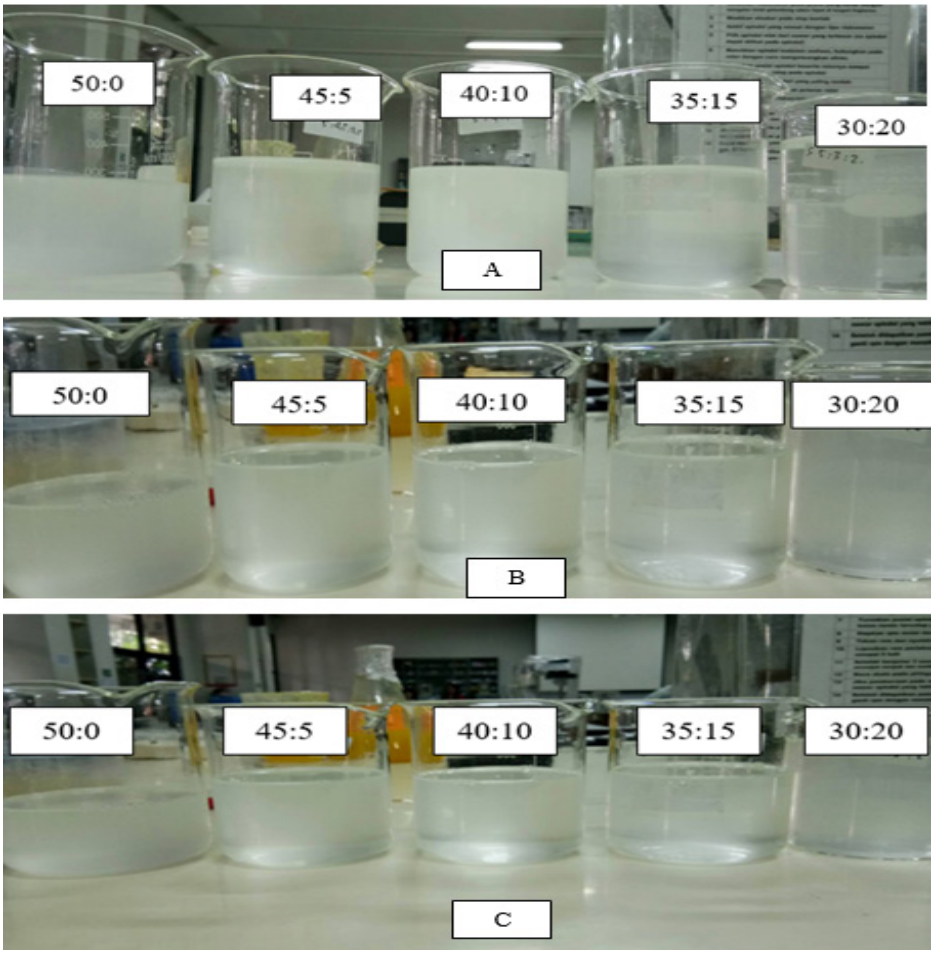

Figure 1. The initial orientation results of atenolol SNEDDS after being diluted with aquadem up to 250 ml. (A). formula with soybean oil; (B) formula with virgin coconut oil; (C) formula with olive oil

size, polydispersity index, and zeta potential.

3. Result and Discussion

Based on the preliminary orientation results, the chosen oil phases for the formulation of atenolol SNEDDS preparations were virgin coconut oil (VCO), soybean oil, and olive oil, with surfactant concentration ratios of 45:5, 40:10, and 35:15. The orientation results indicated that the three concentration ratios yield clearer atenolol SNEDDS following a 250x dilution in demineralized water. The outcomes of diluting SNEDDS in demineralized water are illustrated in Figure 1.

The appropriate oil for SNEDDS formulation is one with a medium-chain fatty acid composition due to its enhanced emulsification properties. Long-chain oils facilitate higher drug transport via the lymphatic system, consequently diminishing first-pass metabolism [12]. Virgin coconut oil (VCO) was selected due to its composition of medium-chain fatty acids, which were readily metabolized and oxidized by the body, thereby averting accumulation [15]. Soybean oil has been demonstrated to serve as a fat the base in SNEDDS formulations [12]. This oil includes lecithin, an emulsifying agent with a structure similar to tween or span, featuring both polar and non-polar groups, hence facilitating the formation of nanoemulsions in the gastrointestinal tract. The choice of olive oil as the oil phase was predicated on its capacity to breakdown water-insoluble active compounds and to enhance the permeability of active substances inside the digestive system.

The result regarding the % transmission of SNEDDS atenolol is presented in Table 2. The results indicated that all SNEDDS atenolol formulations fail to meet the transmission percentage

Table 2. Percentage transmission of SNEDDS atenolol using a spectrophotometer at a wavelength of 650 nm

Formula	Percentage transmission (%)		
	Peak 1	Peak 2	Peak 3
F1	25.821	25.710	25.507
F2	26.973	26.541	26.442
F3	19.557	19.618	19.644
F4	23.653	23.628	23.618
F5	51.025	51.166	51.178
F6	32.996	32.985	32.773
F7	51.224	51.134	51.018
F8	56.621	47.200	30.046
F9	69.318	69.315	70.749

Table 3. Particle size of atenolol SNEDDS after robustness to dilution test at various dilution concentrations

Formula	Particle size (nm)		
	Dillution 1:50	Dillution 1:100	Dillution 1:1000
F1	185.7	286.0	236.1
F2	192.8	272.0	167.0
F3	683.0	192.7	177.4
F4	273.1	1108	271.8
F5	1591	302.0	141.7
F6	124.8	167.8	211.4
F7	5450	180.2	5820
F8	207.6	366.0	210.5
F9	712.0	136.4	567.0

criteria, since they remain below 80%. This is attributable to the properties of the active component atenolol, which exhibits poor solubility in both aqueous and lipid environments [2]. Atenolol exhibits suboptimal solubility in the oil phase, leading to the resultant SNEDDS being less clear and translucent. Surfactants and co-surfactants are anticipated to diminish surface tension, thus enhancing the solubility of atenolol. Nonetheless, the quantity of surfactants and co-surfactants did not markedly enhance the solubility of the active ingredient atenolol in oil, leading to a SNEDDS preparation that remained relatively opaque, thereby yielding a low percentage transmission value [12].

The findings from the robustness to dilution assessment are presented in Table 3. The assessment of robustness to dilution was performed to ascertain the formulas resistance against different dilution ratios in an aqueous dissolution media. This study evaluated robustness using demineralized water dissolving media in quantities of 50 ml, 100 ml, and 1000 ml. Following the dilution of the SNEDDS preparation, it was held for 12 hours and monitored for indications of phase separation or precipitation. The examination of droplet size measurement for SNEDDS showed variations in droplet size at each dilution, as determined by a particle size analyzer (PSA). This signifies that the developed SNEDDS atenolol formulation were lack resistance to dilution. Formula 6 had superior dilution resistance properties relative to the other formulas.

The outcomes of the particle size, polydispersity index, and zeta potential assessments are illustrated in Figures 2 and 3. The droplet size test was performed to ascertain if the generated droplets conform to the criteria for nano-sized droplets, defined as being less than 200 nm. The nanoemulsion size is anticipated to enhance the

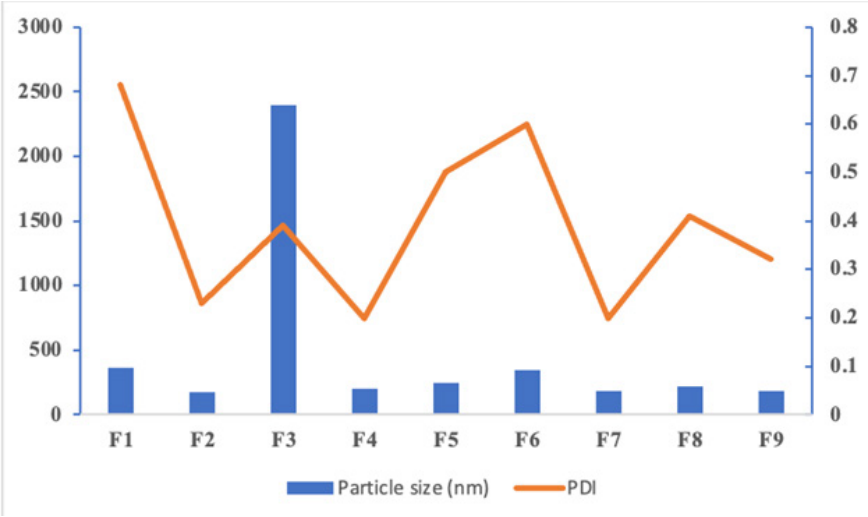

Figure 2. Particle size and polidispersity index of atenolol SNEDDS

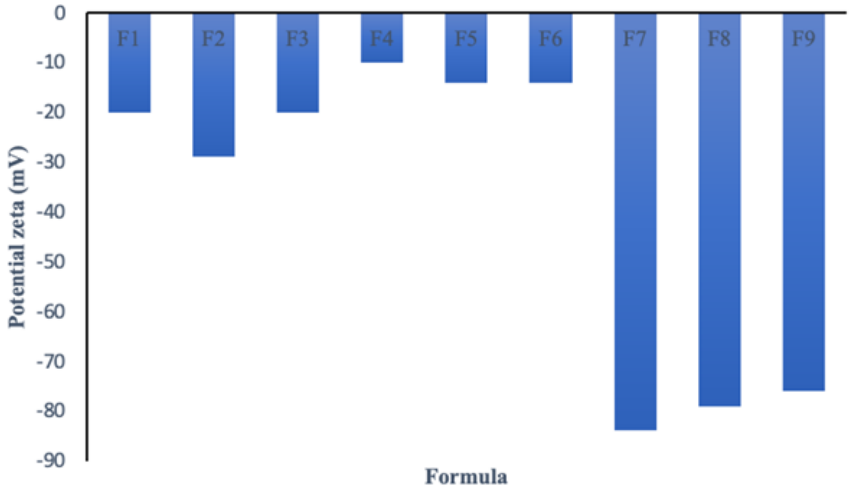

Figure 3. Zeta potential of atenolol SNEDDS

surface area, facilitating rapid absorption of the active ingredient [11]. Particle sizes under 200 nm induce Brownian motion, enabling SNEDDS to prevent sedimentation or creaming. Sedimentation or creaming is a prevalent issue encountered in emulsion formulations. SNEDDS with a size of less than 200 nm are anticipated to yield a formulation with enhanced stability [16]. The result of SNEDDS particle size indicates that F2, F4, F7, F8 and F9 produced particle sizes that meet the criteria (< 200 nm). The findings demonstrate that droplet size is affected by the oil constituents of SNEDDS, as well as the concentrations of surfactants and co-surfactants. The concentration ratio of surfactant to co-surfactant substantially influences droplet size, although an ideal value exists that will produce nanoemulsion size. According to these findings, future study needs the optimization of the formulation by adjusting the quantities of surfactant and oil in the SNEDDS formulation. The homogenization of SNEDDS requires the use of effective shear stirring [10].

The assessment of the polydispersity index (PI) by the particle size analyzer (PSA) indicated the uniform particle size of the SNEDDS formulation. All formulations showed a polydispersity index (PI) ranging from 0.01 to 0.7. An excessively high polydispersity index signifies inadequate consistency in droplet size distribution. The inadequate droplet size distribution results from

the emulsifier diminished efficacy or insufficient concentration to adequately adsorb onto the surfaces of the oil droplets formed during stirring, resulting in a fragile protective membrane that fails to safeguard the droplets, thereby causing aggregation.

The assessment of the zeta potential is a method for predicting the stability of the atenolol SNEDDS. A high zeta potential signifies enhanced stability of the preparation, as it mitigates the likelihood of aggregation. A zeta potential of ± 60 mV signifies a formulation with commendable stability. Stable in that aggregation does not readily transpire [13]. This investigation reveals a negative zeta potential value, signifying the presence of free fatty acids in the formulation, and indicates potential repulsion between droplets in the nanoemulsion, hence inhibiting their coalescence into bigger droplets. The zeta potential test results indicated that the three formulations with VCO as the oil phase resulted zeta potential values below ± 60 mV.

4. Conclusion

The findings suggest that the nine SNEDDS atenolol formulations have not demonstrated optimal characteristics regarding dilution resistance and clarity (% transmittance). The variation in the oil phase type and the concentration of surfactant-co-surfactant in the formulation influences the properties of the resultant atenolol SNEEDS. The impact of various oil phase types and surfactant-co-surfactant concentrations can be seen in the parameters of the droplet size, polydispersity index, and zeta potential. F2, F7, and F9 represent potential formulas with better optimization, since they all satisfy the criteria of droplet particle size, polydispersity index, and zeta potential.

References

1. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A pathophysiologic approach, seventh edition, 139-140. New York: McGraw-Hill; 2008.
2. Sweetman SC. Martindale the complete drug reference thirty-six edition, 1217-1218. London: Pharmaceutical Press; 2009.
3. Kumare MM, Marathe RP, Kawade RM, Ghante MH, Shendarkar RR. Design of fast dissolving tablet of atenolol using novel co-processed superdisintegrant. *Asian Journal of Pharmaceutical and Clinical Research.* 2013;6(3):81-85.
4. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system: Optimization for formulation variables using response surface methodology. *Journal of Controlled Release.* 1997;45:121-130.
5. Lynas K. A step forward for medication safety: Stakeholders agree to a common standard for barcoding pharmaceutical. *Clinical Pharmaceutical Journal.* 2010;143(2):220-225.
6. Patel MJ, Patel NM, Patel RB, Patel RP. Formulation and evaluation of self-microemulsifying drug delivery system of lovastatin. *Asian Journal Pharm. Sci.* 2010;5(6):266-267.
7. Subudhi B, et all. Self-microemulsifying drug delivery system formulation and study intestinal permeability of ibuprofen in rats. *Journal of Pharmaceutics*. 2013;15(3):1-6.
8. Gutierrez JM, et all. Nano-emulsions: New applications and optimization of their preparation. *Current Opinion in Colloid & Interface Science*. 2008;13(02):245-251.
9. Weerapol Y, Limmatvapirat S. Spontaneous emulsification of nifedipine- loaded self-nanoemulsifying drug delivery system. *American Association of Pharmaceutical Scientists.* 2015;16(2):435-443.
10. Gupta S, et all. Self-nanoemulsifying drug delivery systems for adefovir dipivoxil: Design, characterization, in vitro and ex vivo evaluation, colloids and surfaces a physicochemical and engineering aspects. *International Journal of*

Pharmaceutics. 2011;392(10):145-155.

11. Abbaspour M, Jalayer N, Makhmalzadeh BS. Development and evaluation of a solid self-nanoemulsifying drug delivery system for loratadin by extrusion-spheronization. APB. 2014;4(2):113-119
12. Sapra K, Sapra A, Singh SK, Kakkar S. Self-emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs. *Int. J. Pharm. Sci.* 2012;2(3):314-320.
13. Debnath S, Satayanarayana, Kumar GV. Nanoemulsion a method to improve the solubility of lipophilic drugs. *Pharmanest.* 2011;2(2):72-76.
14. Shah P, Balodhia D, Shelat P. Review article nanoemulsion: A pharmaceutical review. *Sys. Rev. Pharm*. 2010;1(1):29-30.
15. Rukmini A, Raharjo S, Hastuti P, et al. Formulation and stability of water-in-virgin coconut oil microemulsion using ternary food grade nonionic surfactants. *International Food Research Journal.* 2012;19.
16. Makhmalzadeh BS, Torabi S, Azarpanah A. Optimization of ibuprofen delivery through rat skin from traditional and novel nanoemulsion formulation. *Iranian Journal of Pharmaceutical Research*. 2012;11(1);47- 58.