Journal of Applied Pharmaceutical Science Vol. 8(09), pp 011-014, September, 2018
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2018.8903
ISSN 2231-3354

Stability Study of *Ipomoea reptans* Extract Self-Nanoemulsifying Drug Delivery System (SNEDDS) as Anti-Diabetic Therapy

Pinus Jumaryatno[1*], Lutfi Chabib[1,2], Farida Hayati[1], Rizki Awaluddin[1]

[1]Department of Pharmacy, Islamic University of Indonesia, Yogyakarta, Indonesia.
[2]Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia.

ARTICLE INFO

Article history:
Received on: 10/12/2017
Accepted on: 08/03/2018
Available online: 30/09/2018

Key words:
Ipomoea reptans, SNEDDS, Stability, Capryol 90, Diabetes Mellitus.

ABSTRACT

Diabetes mellitus (DM) is one of the metabolic syndromes that is characterized by the excessive accumulation of blood glucose, also called as hyperglycemia, and carbohydrate, fat, and protein metabolism disorder. The antioxidant compounds on *Ipomoea reptans* possess the pharmacological activity of DM with low absorption in the systemic circulation. Stability is one of the factors that affect the safety, quality, and efficacy of the SNEDDS (Self-Nanoemulsifying Drug Delivery) dosage form. This study aimed to evaluate the stability of *Ipomoea reptans* leaf extract (IPE) SNEDDS. The IPE SNEDDS was made using capryol 90 as the oil phase, tween 20 as surfactants, and polyethylene glycol (PEG) 400 as the cosurfactant. The stability study was conducted with several physical stability tests, which were centrifugation test, heating-cooling cycle test, and freeze-thaw cycle test. The result indicated that the particle size of the IPE SNEDDS was ≤100 nm and indicated good physical stability. It can be concluded that the IPE SNEDDS possesses good stability profile.

INTRODUCTION

Diabetes mellitus as the third most deadly health problem in the world can lead to complications that worsen the body organs condition such as chronic hyperglycemia, long-term damages, dysfunctions, and organ failures (Sucharitha and Estari, 2013). Free radicals are considered as one of the causes of several degenerative diseases such as hepatic cirrhosis, atherosclerosis, cancer, and diabetes mellitus (Uttara *et al.*, 2009). The activity of free radicals can initiate the lipid peroxidation, which stimulates the protein glycation, enzyme inactivation and generates long-term complication of diabetes (Lyons and Jenkins, 1997).

Antioxidants play a role to keep the body from the invasion of reactive oxygen species (Sabu and Kuttan, 2002). It has been reported that Asia and Africa have 56% of the medicinal plants spreading in the world. The contained pharmacological activities are related to the contents of chemical compounds such as phenolic, alkaloids, flavonoids, terpenoids, coumarin, and glycosides that produce positive effects (Mamun-or-rashid *et al.*, 2014).

In the previous study, the *Ipomoea reptans* leaf extract indicated the pancreatic protector activity in the streptozotocin-induced mice, which makes it considered to contains antioxidant compounds, which are β-carotene, riboflavin, vitamin A, tocopherol, 3-methoxy quercetin, 4-methoxy quercetin polyphenol, and anthocyanin (Hayati *et al.*, 2017; Manvar and Desai, 2013). In addition, *Ipomoea reptans* leaf extract has been shown to lower blood glucose level of mice with the dose of 2.23 g/kgBW, 4.46 g/kgBW, and 8.92 g/kgBW. However, a modification of the carrier preparation is required to improve the bioavailability of the extract (Hayati *et al.*, 2010).

Self-nano Emulsifying Drug Delivery System (SNEDDS) is a dosage form that can improve the bioavailability of lipophilic compounds that lead to an improvement of its clinical efficacy, simplify permeability of drugs, and lower the dose needed to generate clinical effects (Makadia *et al.*, 2013; Jain *et al.*, 2010). The stability of SNEDDS depends on the size of globules in the dispersed phase of SNEDDS. Small globules could improve the stability of SNEDDS by lowering the gravity and the Brownian motion that prevent the occurrence of creaming

*Corresponding Author
Pinus Jumaryatno, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia, Yogyakarta.
E-mail: pinus.jumaryatno @ uii.ac.id

and flocculation (Chabib *et al.*, 2017). In this study, the stability of the IPE SNEDDS was observed by conducting centrifugation test, heating-cooling cycle test, freeze-thaw cycle test that aims to review the physical stability and to obtain the stable IPE SNEDDS formula.

MATERIALS AND METHODS

Materials

The materials used were *Ipomoea reptans* leaf extract (obtained from Laboratorium Biologi Farmasi UII), aqua pro injection, tween 20 (Vivantis Inc.), polyethylene glycol 400 (Brataco), and capryol 90 (Gattefose).

Methods

Extraction of Ipomoea reptans leaf

Post-harvest treatments were sorting (leaf only), drying at 45°C-50°C for 2-3 days, and powdered using a grinder. *Ipomoea reptans leaf* powder was extracted by maceration for 6 days using 96% ethanol (ratio 1:10), and remaceration for 6 days with the same solvent. The viscous extract was obtained by evaporating the solvent using a rotary evaporator with a temperature of 60°C (Hayati *et al.*, 2015).

Formulation of the Ipomoea reptans leaf extract (IPE) SNEDDS

The formula of IPE SNEDDS was modified from Chabib, who conducted the previous study (Chabib *et al.*, 2017). The formula was presented in table 1.

Table 1: IPE SNEDDS formula.

Material	Function	Quantity
IPE	Active Ingredients	500 mg
Capryol 90	Oil phase	0.5 mL
Tween 20	Surfactant	3.5 mL
PEG 400	Co-surfactant	1 mL

The *Ipomoea reptans* leaf extract was weighed carefully, then it was dissolved into the oil phase (Capryol 90) until it was dissolved completely. The solution then was gradually added with the surfactant and co-surfactant and was ultrasonicated (Model 300 VT Biologics, Inc) for 2 minutes 4-7 times.

Centrifugation test

The IPE SNEDDS was diluted 100 times with aqua pro injection. Then, it was centrifugated using the centrifugator (Hanil MF 80) with speed of 3500 rpm for 30 minutes. Then, the phase separation was observed visually, the presence of phase separation indicates a difference in kinetic stability in nanoemulsion resulting in emulsion system instability, such as creaming, flocculation, cracking or coalescence (Shukla and Patel, 2010).

Heating-Cooling cycle test

The formula resulted from the centrifugation test was used in the heating-cooling cycle test. The test was conducted with six cycles at the temperature of 4°C and 40°C and stored for not less than 48 hours using Climatic Chamber (Climacell). The temperature of the stored formula was stabilized and centrifugated with speed of 3500 rpm for 15 minutes and observed visually to check the phase separation (Gupta *et al*., 2011).

Freeze-thaw cycle test

The formula resulted from the heating-cooling cycle test was used in the freeze-thaw cycle test. The test was conducted with six cycles at the temperature of −20°C and 25°C and stored for not less than 48 hours using Climatic Chamber (Climacell). The formula was stabilized at normal temperature and centrifugated with speed of 3500 rpm for 15 minutes and observed visually to check the phase separation (Gupta *et al*., 2011).

Endurance test

The formula resulted from the freeze-thaw cycle test was used to conduct the endurance test. The formula was diluted with dilutions of 25, 50, and 100 times with aqua pro injection. Then, the change of %transmittance, polydispersity index (PDI), and particle size of the formula were evaluated using Particle Size Analyzer (Horiba Sz 100) (Gupta *et al*., 2011).

RESULT AND DISCUSSION

IPE SNEEDS

Ipomoea reptans leaf extract (IPE) has characteristics of concentrated extract, greenish color (Hayati *et al.*, 2015). The SNEDDS formulation with the material ratio as table 1 consists of extract, oil phase, and surfactant. IPE SNEEDS exhibits dark color due to the formation of colloidal dispersion as in Figure 1. However, IPE SNEEDS forms an oil-in-water nanoemulsion (nanodroplet) when interacting with an aqueous medium (e.g. gastrointestinal fluid) that change the color into clear or cloudy as in Figure 2 tested durability by the effect of dilution (Yen *et al*., 2017).

Centrifugation test

The centrifugation test is conducted to assess the SNEDDS stability after an emulsion is formed, against the gravity force. The result of centrifugation that was shown in table 2 indicated that no phase separation occurred during the test.

Table 2: The result of the IPE SNEDDS stability test.

Replication	Centrifugation	Heat-Cool Cycle	Freeze-Thaw Cycle
1	No phase separation	No phase separation	No phase separation
2	No phase separation	No phase separation	No phase separation
3	No phase separation	No phase separation	No phase separation

Centrifugation describes the gravity force that occurs on the droplets. The small size of droplets can minimize the gravity force and Brownian motion on the particles that prevent the occurrence of phase separation (Fanun, 2012).

Heating-cooling and freeze-thaw test

Freeze-thaw cycle test is conducted to examine the effect of heating, cooling, and centrifugation against the stability of SNEDDS formula (Patel *et al.*, 2008). An emulsion tends

to be stable at the temperature of 40°C-45°C in few hours of storage. Heating and freezing are potential to damage or break the droplets of an emulsion (Anton and Thierry, 2011). Table 2 indicates that there was no phase separation occurred in the SNEDDS formula during the heating-cooling cycle and freeze-thaw cycle test.

Endurance test

The test is conducted to observe the character similarity of the nanoemulsion through various level of dilutions. The test is also can be used to ensure that the drug would not form a sedimentation. The result of the endurance test was shown in figure 2 and table 3.

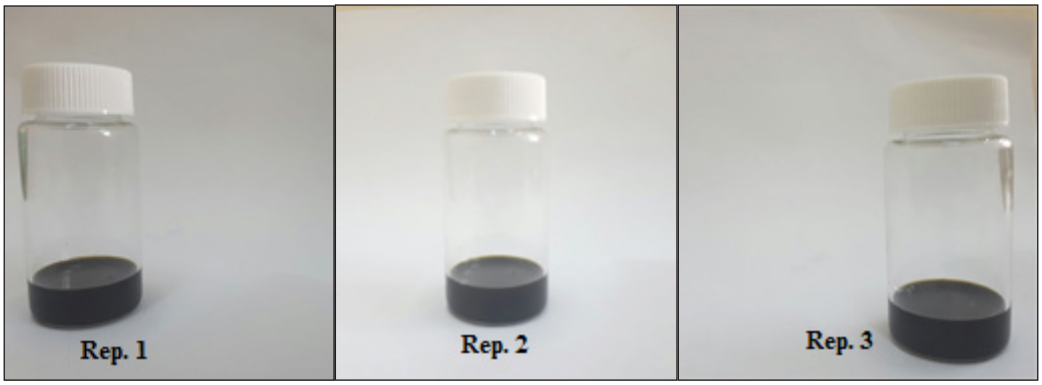

Fig. 1: IPE SNEDDS.

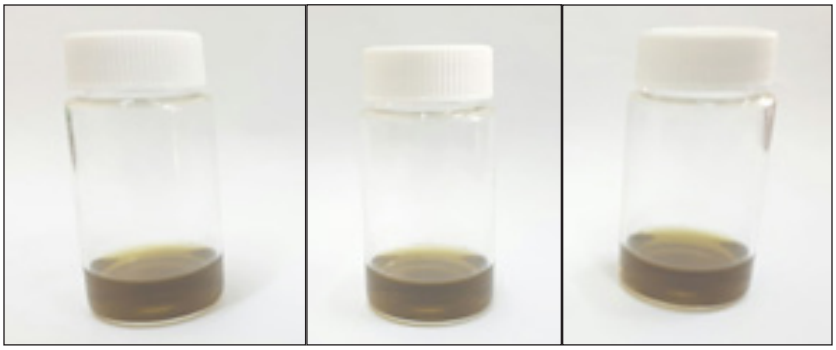

Fig. 2: The result of the endurance test with slightly greenish color.

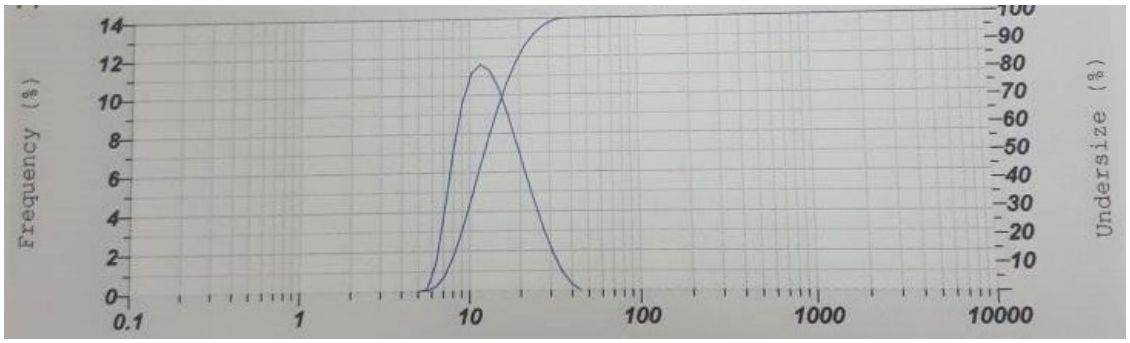

Fig. 3: Particle size analysis of IPE SNEEDS (one of the samples).

Based on the test using particle size analyzer, the particle size of the IPE SNEDDS formula was (15.5 ± 0.8 nm) and the PDI was 0.558 ± 0.04. Nanoemulsion is characterized by the particle size 0.1-100 nm with narrow particle size distribution and the particle size is still stable through dilutions (Dolati *et al.,* 2016; Shah *et al.*, 2010; Rao and Shao, 2008). In addition, the small particle size of the nanoemulsion will increase the permeability of absorption, that lead to an improvement of the oral bioavailability of compounds (Yen *et al.*, 2017).

Whereas, the PDI values from the study were between 0.2-0.7. The PDI value above 0.40 indicates wider particle size distribution and lower particle size uniformity (Chabib *et al.*, 2017; Mao *et al.*, 2009). Phase conversion of the dosage form can be considered as one of the kinetic and thermodynamic parameters in an optimal formula selection (Makadia *et al.*, 2013).

CONCLUSION

The IPE SNEDDS possesses good stability that is proven with no phase separation occurs during several tests such as centrifugation, heating-cooling cycle, and freeze-thaw cycle. The

particle size and PDI value obtained in the study indicated that the IPE SNEDDS possesses optimal characteristic as a nanoemulsion.

Table 3: The result of the endurance test.

Dilution	Particle size (nm)	PDI
25x	14.6	0.581
50x	15.5	0.586
100x	16.3	0.507
Average ± SD	15.5 ± 0.8	0.558 ± 0.04

ACKNOWLEDGMENT

This study was sponsored by Ministry of Research, Technology and Higher Education of The Republic of Indonesia under scheme Penelitian Terapan Unggulan Perguruan Tinggi 2017 (No. 032/ST-DirDPPM/70/DPPM/Penelitian Terapan Unggulan Perguruan Tinggi-KEMENRISTEKDIKTI/IV/2017) granted to F.H. The authors also would like to thank Department of Pharmacy Islamic University of Indonesia for the facilities.

REFERENCES

Anton N, Thierry V. Nano-emulsions and Micro-emulsions: Clarifications of the Critical Differences. Pharm. Res. 2011; 28:978–985.

Chabib L, Muhtadi WK, Ikawati Z, Martien R, Ismail H. Stability Study of Gamavuton (Gvt-0) Self-Nanoemulsifying Drug Delivery System (Snedds) with Myritol as The Oil Phase. Int. J. Curr. Inov. Res. 2017; 3:590–594.

Dolati S, Sadreddini S, Rostamzadeh D, Ahmadi M, ScienceDirect Utilization of nanoparticle technology in rheumatoid arthritis treatment. Biomed. Pharmacother. 2016; 80:30–41.

Gupta S, Chavhan S, Sawant KK. Self-Nanoemulsifying Drug Delivery System for Adefovir Dipivoxil: Design, Characterization, *In Vitro* and Ex Vivo Evaluation. Colloids Surf A Physicochem Eng Asp. 2011; 392:145–155.

Fanun M, Microemulsions as Delivery Systems. Curr. Opin. Colloid Interface Sci. 2012; 17:166–172.

Hayati F, Lulung W, Marsih L. The Effect Of Ipomoea reptans Poir Ethanolic Extract On The Histopathological Parameters Of Pancreas In Streptozotocin-Induced Diabetic Rats. Int. Conf. Chem. Chem. Process Eng. 2017; 20046.

Hayati F, Wibowo A, Jumaryatno P, Nugraha AT. Standardization of the Extract of Cultivated Ipomoea reptans Poir. Leaves from Sardonoharjo, Sleman and Its Potency as Antioxidant). J. Ilmu Kefarmasian Indones. 2015; 13.

Hayati F, Windyarini S, Helminawati. Efek Antihiperglikemik Infusa Kangkung Darat (Ipomoea reptans Poir) pada mencit jantan galur Swiss yang diinduksi Streptozotocin. J. Ilm. Farm. 2010; 7:13–22.

Jain N, Jain R, Thakur N, Gupta BP, Jain DK, Jain S. Nanotechnology: A Safe And Effective Drug Delivery System. Asian J. Pharm. Clin. Res. 2010; 3:159–165.

Lyons TJ, Jenkins AJ. Glycation, oxidation, and lipoxidation in the development of the complications of diabetes: a carbonyl stress hypothesis. Diabetes Rev (Alex), 1997; 5:365–391.

Makadia MHA, Bhatt MAY, Parmar RB, Paun MJS, Tank HM. Self-nano Emulsifying Drug Delivery System (SNEDDS): Future Aspects. Asian J. Pharm. Res. 2013; 3:21–27.

Mamun-or-Rashid ANM, Hossain S, Hassan N, Dash K, Sapon A, Sen MK. A review on medicinal plants with antidiabetic activity. 2014; 3:149–159.

Manvar M, Desai T. Phytochemical and Pharmacological Profile of Ipomoea Aquatica. Indian J. Med. Sci. 2013; 67:49–60.

Mao L, Xu D, Yang J, Yuan F, Gao Y, Zhao J. Effects of Small and Large Molecule Emulsifiers on the Characteristics of b-Carotene Nanoemulsions Prepared by High Pressure Homogenization. Food Technol. Biotechnol. 2009; 9862:336–342.

Patel P, GM C, A A. Self Emulsifying Drug Delivery System. Res. J. Pharm. Technol. 2008; 1.

Rao SVR, Shao J. Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs: I. Formulation development. Int. J. Pharm. 2008; 362:2–9.

Sabu MC, Kuttan R. Antidiabetic activity of selected medicinal plants and its possible mechanism of action Anti-diabetic activity of medicinal plants and its relationship with their antioxidant property. J. Ethnopharmacol. 2014.

Shah P, Bhalodia D, Shelat P. Nanoemulsion: A pharmaceutical review. Syst. Rev. Pharm. 2010; 1:24.

Shukla JB, Patel SJ. Formulation And Evaluation Of Self Micro Emulsifying System Of Candesartan Cilexetil. Int. J. Pharm. Pharm. Sci. 2010; 2:2–5.

Sucharitha E, Estari M. Evaluation of antidiabetic activity of medicinal plant extracts used by tribal communities in rural areas of Warangal district, Andhra Pradesh, India. Biology and Medicine. Biol. Med. 2013; 5:20–25.

Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options. Curr Neuropharmacol. 2009; 7:65-74.

Yen C, Chang C, Hsu M-C, Wu Y-T. Self-Nanoemulsifying Drug Delivery System for Resveratrol: Enhanced Oral Bioavailability and Reduced Physical Fatigue in Rats. Int. J. Mol. Sci. 2017; 18.

How to cite this article:
Jumaryatno P, Chabib L, Hayati F, Awaluddin R. Stability Study of *Ipomoea reptans* Extract Self-Nanoemulsifying Drug Delivery System (SNEDDS) as Anti-Diabetic Therapy. J App Pharm Sci, 2018; 8(09): 011-014.