International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.6, pp 148-151, 2017

Design and Formulation Quercetin Formula In The Phytosomes System as Novel Drug Delivery

Ayu Lestari[1]*, Effionora Anwar[1], Yahdiana Harahap[1]

[1]Department of Pharmacy, Faculty of Pharmacy, Universitas Indonesia, Depok 16424, Indonesia

Abstract : Quercetin has many pharmacological activities but it has low bioavailability and absorption. The purpose of this research is to get the best formula composition for quercetin phytosome intended for oral administration. Three different formula have been prepared in this study using thin layer hydration method, namely F1, F2, F3 with concentration of quercetin in a row is 1%, 1.5% and 2%. Phosphatidylcholine and cholesterol were used in the composition.Each formula had evaluated by characterization including vesicle morphology, entrapment efficiency, particle size, polydispersity index, and zeta potential. The results show that F1 is the best formula with spherical vesicle morphology, entrapment efficiency 96.57 ± 5.61%, average particle size 266.6 ± 1.37 nm, polydispersity index 0.01 ± 0.388 and zeta potential -29,43 ± 0.75 mV. That formula can be used in the next research.
Keywords : bioavailability, quercetin, formula, phytosome.

Introduction

Quercetin is a hydrophobic crystalline bioactive component and also a bioflavonoid found in various natural products. Quercetin have a broad range of therapeutic effects. The results of in vitro assays and in vivo studies showed that quercetin can act as antioxidants, anti-inflammatory and anticancer, and antidiabetic[1,2,3,4]. Quercetin can also be used in cardiovascular protection by reducing the oxidative damage caused by LDL (Low Density Lipoprotein) by collecting free radicals and transition metal ions. However, although it has a broad therapeutic activity, as well as other flavonoid compounds, quercetin has limitations in bioavailability and absorption[4,5,6].

Poor absorption of flavonoids are caused by two factors: first, flavonoids have a double-ring molecules which are too broad to be absorbed by simple diffusion system. Second, the flavonoid molecule has a bad miscibility with oil and other lipids, which limits the ability of flavonoids to pass through the outer membrane of enterocytes of the small intestine which is rich in lipids. These flavonoids including quercetin can be converted into lipid-compatible molecular complex, called phytosome[5,6]. Another study says that absorption of quercetin is low due to three factors, namely first quercetin solubility in lipids is low, second sugar cluster increases the hydrophilicity of the molecule, third molecular size of quercetin is large so that it can't be absorbed through passive diffusion from the small intestine into the bloodstream[7].

Studies show that phytosome system is proven to generate compound bioavailability of active natural ingredients better than the conventional delivery systems. Phytosome is formed through binding of medicinal compounds with phospholipids, mainly phosphatidylcholine which produce compatible molecular complex lipids. Phytosome generate pharmacokinetic and pharmacodynamic profile better than conventional delivery systems. Phytosome as a nanolipid vesicles can alter the composition of the cell environment being

environmentally friendly to lipid, so that the active substance can be brought into the cell membrane and finally to the blood circulation[8,9]. Therefore, design and optimization formula will be conducted in this research to optimize the use of quercetin as an active therapeutic agent. It is expected these formulation can increase quercetin bioavailability, so that it can provide the desired therapeutic effect in accordance with the intended use.

Experimental

Material

The chemicals used include the phospholipids of soybean lipoid P 30 (phosphatidylcholine 30% non-GMO) (GmbH Lipoid Germany), quercetin, cholesterol (Sigma Aldrich, Singapore), maltodextrin, methanol (Merck, Germany) , ethanol 96% (Merck, Germany), aqua bidestillata, aqua demineralisata (BRATACO, Indonesia), sodium hydroxide (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany), and disodium hydrogen phosphate (Merck, Germany).

Methods

Quercetin phytosome was prepared using thin layer hydration method. Design formulation quercetin phytosome formula in this research refers to research done before by Rasaie, Ghanbarzadeh, Mohammadi, and Hamishehkar (2014) with modification[7,10]. The comparison of its formula composition shown in Table 1. Quercetin phytosome formula resulted was characterized including vesicle morphology, entrapment efficiency, particle size distribution, polydispersity index and zeta potential. Determination phytosome formula is based on the results of the above characterization, that have a formula with the spherical morphology, highest percentage of drug adsorbed, polydispersity index <0.8 and zeta potential> ± 30mV.

Table 1. Design Optimization Quercetin Phytosome Formula

Material	Concentration (%w/w)		
	F1	F2	F3
Quercetin	1	1,5	2
Phosphatidylcholine	2	2	2
Cholesterol	0,2	0,2	0,2
Phosphate buffer pH 5	Add to 100	Add to 100	Add to 100

F1= 1st Formula; F2= 2nd Formula; F3= 3rd Formula

Result and Discussion

Design and formulation studies of quercetin phytosome were done to get the best formula for quercetin delivery intended for oral administration. Characterizations of each design formula show that formula quercetin phytosome 1 (F1) has the most optimum characteristics. F1 has formed spherical particles with a particle size 266.6 ± 1.37 nm and polydispersity index 0.388 ± 0.01, and the zeta potential -29.43 ± 0.75 mV, and entrapment efficiency 96.57 ± 5.61 %. Characterization results can be seen in Table 2.

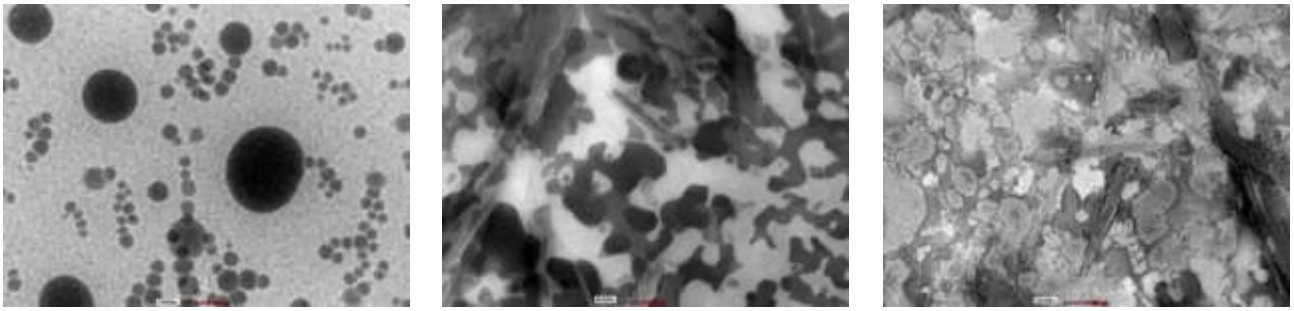
Table 2. Characterization of Quercetin Phytosome Formula

Formula	Vesicle Morphology	Z-Average (nm)	Polidispersity Index	Zeta Potential	Entrapment Efficiency
F1	Spheris	266.6 ± 1.37	0.388 ± 0.01	-29.43 ± 0.75	96.57 ± 5.61
F2	Spheris	316.2 ± 4.69	0.311 ± 0.02	-30.40 ± 0.80	46.75 ± 3.12
F3	Not spheris	363 ± 12.40	0.454 ± 0.01	-32.03 ± 0.12	29.18 ± 1.53

F1= 1st Formula; F2= 2nd Formula; F3= 3rd Formula

Measurement of particle size distribution, polydispersity index and zeta potential was conducted using PSA (Particle Size Analyzer) by DLS (Dynamic Light Scattering) method. Polydispersity index stated the

particles level heterogeneity. Polydispersity index obtained in this research has value of less than 0.5. This indicates that the sample has low level particle size heterogeneity or homogeneous particle size[11].



(a) (b) (c)

Fig 1. Vesicle morphology of each phytosome quercetin formula: (a) F1; (b) F2; and (c) F3.

The phytosome formula was conducted by comparing the concentration of quercetin, phosphatidylcholine and cholesterol. Phosphatidylcholine and cholesterol concentration was fixed for each formula while the concentration of quercetin made different. This is done to determine the optimum adsorption effect of the third formula. Phytosome formula composition can be seen in Table 1. Phytosome main constituent material consisting of phospholipid (Phospolipon P 30) and quercetin.Phospholipids used is Phospolipon P 30 is hydrogenated phospholipids derived from soybeans in the form of powder. This powder form is an important prerequisite when aiming to produce a final product in powder form to be administered orally.

Research on the comparison of the composition of active substances and phospholipids have been carried out by Keerthi, Pingali, and Srinivas (2014). The study formulates five formulas with active substance concentration was fixed but the concentration of phosphatidylcholine was made to increase in each formula. Comparison of the concentration of active substances and phospholipids in the formula is 1: 1; 1: 2; 1: 3 .; 1: 4 and 1: 5 respectively. The entrapment efficiency test results in each formula is 60%; 84%; 90.1%; 83% and 84% sequentially. These results indicate although the concentration of the phospholipid further increased, but it did not increase the entrapment efficiency (formulas 4 and 5), while the optimum entrapment efficiency is obtained from the formula 3 is 90.1%[12].

Based on these descriptions, it is known that increasing the concentration of active ingredient to the concentration of phospholipids, do not necessarily increase the entrapment efficiency phytosome formula. The entrapment efficiency resulting from a formula determined by the capacity of phospholipids in adsorb the active substances on the most optimum composition, wherein the composition in this study were obtained on a formula F1. Formula F1 has a ratio of quercetin and phospholipids in an amount that is equivalent ratio of 1: 1, while in the formula F2 and F3, the concentration of quercetin increased but the amount of phospholipid stays. Total phospholipids that form a bond with quercetin decreased, so that the amount of the bond that is formed fewer and fewer. This causes the entrapment efficiency formulas F2 and F3 decreases.

Conclusion

Based on the results obtained in this study, it can be concluded that quercetin can be formulated into nanovesicle phytosome. The best formula is F1 which has quercetin and fosfolipid in the same ratio 1:1. F1 has formed spherical particles with a particle size 266.6 ± 1.37 nm and polydispersity index 0.388 ± 0.01, and the zeta potential -29.43 ± 0.75 mV, and entrapment efficiency 96.57 ± 5.61 %.

Acknowledgement

The authors wish to thank Indonesia Endowmentfor Education (LPDP) for the financial assistance in this research.

References

1. Pool, H., Mendoza, S., Xiao, H., & McClements, D.J. Encapsulation and Release of Hydrophopic Bioactive Components in Nanoemulsion-Based Delivery Systems: Impact of Physical Form on Quercetin Bioaccessibility. Food Function, 2012, 4;162.
2. Mojsin, M., Vicentic, J.M., Schwirtlich, M., Topalovic, V., Stevanovic, M. Quercetin Reduces Pluripotency, Migration and Adhesion of Human Tetracarcinoma Cell Line NT2/D1 By Inhibiting Wnt/β-Catenin Signaling. Food Function, 2014, 5;2564-2573.
3. Kawabata, K., Mukai, R., Ishisaka, A. Quercetin and Related Polyphenols: New Insights and Implications For Their Bioactivity and Bioavailability. The Royal Society of Chemistry, Food & Function, 2015, 6;1399.
4. Torres-Piedra, M., Ortiz-Andrade, R., Villalobos-Molina, R., Singh, N., Medina-Franco, J. L., Webster, S. P., Binnie, M., Navarrete-Vazquez, G., & Estrada-Soto, S. A comparative study of flavonoid analogues on streptozotocin-nicotinamide induced diabetic rats: quercetin as a potential antidiabetic agent acting via 11β-hidroxysteroid dehydrogenase type 1 inhibition. European Journal of Chemistry, 2010, 45:2606-2612.
5. Sindhumol, P.G., Thomas, M. & Mohanachandran, P.S. Phytosomes: A Novel Dosage Form for Enhancement of Bioavailability of Botanicals and Neutraceuticals. International Journal of Pharmacy and Pharmaceutical Science, 2010, 2;4.
6. Shivanand, P. & Kinjal, P. Technical Revolution in Phytomedicine, International Journal of PharmTech Research, 2010, 2 (1) :627-631.
7. Rasaie, S., Ghanbarzadeh, S., Mohammadi, M., & Hamishehkar, H. Nano Phytosomes of Quercetin: A Promising Formulation for Fortification of Food Products with Antioxidants. Pharmaceutical Sciences, 2014, 20;96-101.
8. Gandhi, A., Dutta, A., Pal., & Bakshi, P. Recent Trends of Phytosomes for Delivering Herbal Extract with Improved Bioavailability. Journal of Pharmacognosy and Phytochemistry, 2012, 1(4); 6-14.
9. Zhang, J., Tang, Q., Xu, X., & Li, N. Development and Evaluation of A Novel Phytosome-Loaded Chitosan Microsphere System for Curcumin Delivery. International Journal of Pharmaceutics, 2013, 448;168-174.
10. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (Eds.)., Handbook of Pharmaceutical Excipients, 6th ed., Pharmaceutical Press, London, 2009.
11. Malvern Instruments. Dynamic Light Scattering Common Terms Defined, 2011, 1–6.
12. Keerthi, B., Pingali, P. S & Srinivas, P. Formulation and Evaluation of Capsules of Ashwagandha Phytosomes, 2014, 29(25);138–142.

*****