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Submission date: 28-May-2020 07:02PM (UTC+0700)
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File name: cek_plagiat.docx (20.16K)
Word count: 1840
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Preparation and Characterization of Reserpine-High-Risk Drug into Sub-Micron Particles for a Safe Drug with Minor Side Effects

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Abstract – The major effort to decrease the side effects of drugs is the development of delivery processes the active-pharmaceutical-ingredients (API). Delivery processes of API are growing in line with advances in nanotechnology. Reserpine which is one of the antihypertensive drugs is rarely manufactured by pharmaceutical companies because of its side effects that were difficult to control. On this occasion, the researcher was motivated to lay the early foundation in the delivery of reserpine by presenting it as sub-micron particles. The method for preparation of particles was an emulsion solvent evaporation. The amount of reserpine were weighed as much 4 mg and poly(lactide-co-glycolide) (PLGA) were 50 mg with three variations of the stabilizer weight of poly(vinyl-alcohol) (PVA) of 40, 80, and 120 mg as formula F1, F2, and F3. Selection of the best formula was based on the percentage of encapsulation efficiency (% EE) indicated that F2 and F3 were 71% and 80%. Further F2 and F3 were characterized by using their physical properties. Three kinds measurements for characterization of physical properties were applied i.e transmission electron microscopy (TEM), particles size analyzer (PSA), and atomic forced microscopy (AFM). These three sophisticated instruments provided an overview of the particles which were spheric shape, smooth surface, with the size range 302 ± 23 nm, polydispersity index (PDI) 0.31 and zeta potential -8 ± 0.4 mV. Based on morphology, size, PDI, surface appearance, zeta potential, and the % EE, indicated at the initial steps that the particles were potential to be developed further for security purposes for human health.

1. INTRODUCTION

The development dosage form containing reserpine into suspension is an alternative option for the comparison to a tablet, especially for patients with difficulty in swallowing. The creation became suspension is not an easy task to prepare because reserpine is unstable in water. Submicron-sized particles can be applied in the creation of suspension by using the principles of technology particle [1-3].

The development of technology particle has succeeded in manufacturing the coated drug ingredient in biopolymer to produce stable particles in water. This aspect is required by reserpine. Besides, the problem of stability in water, reserpine molecule (Fig.1) has chemical interactions in a free state with compounds of the human body. It is hard to avoid, because of the interaction, reserpine is known as a drug has many side effects. Side effects of reserpine include disorders of the central nervous system (CNS), sedation and unable to concentrate or perform complex activities [4].

Figure 1. Chemical structure of reserpine

With the coating technique, it is expected that reserpine side effects can be reduced as the hallmarks of targeted drug delivery in the prevention of disease [5,6].

Figure 2. Chemical structure of PLGA

For coating procedure, the pharmaceutical biodegradable polymers have been used such as poly (lactide coglycolic acid) (PLGA) Fig 2. The drug coating will be optimized when the active substance is coated by the polymer even equipped with a stabilizer such as polyvinyl alcohol (PVA) Fig.3. To improve the stability of the particles, the use of more than one layer has been reported [7] by Nafee 2008.

Figure 3. Chemical structure of PVA

2. METHODS

2.1 Chemicals

The chemicals used in this study were namely reserpine (Sigma-Aldrich), ethyl acetate (Merc), ethanol 96% (Merc), aqua bidest, PLGA (Sigma-Aldrich), and PVA (Kuraray).

2.2 Procedures

Dissolving of Materials

Reserpine powder was weighed 2.7 g put in a glass beaker and dissolved in 8 mL ethyl acetate. Furthermore, reserpine was stirred for 4 hours at a speed of 75 rpm. The solution was allowed to stand up to the rest of reserpine soluble homogeneous powder. The phase of reserpine in solution was pipetted as much as 500 mL for each containing 4 mg of reserpine. PLGA powder weighed as much as 500 mg inserted into a glass beaker and dissolved in 15 mL ethyl acetate. Furthermore, PLGA was stirred for 4 hours at a speed of 75 rpm. The solution was allowed to stand up to the rest of the PLGA powder settles. PLGA solution formulation stage pipette 2 mL

each containing 50 mg of PLGA for each formula.
Preparation of PVA 2.5% using PVA powder weighed 2.5 g put in a glass beaker and then dissolved in 100 mL of distilled water at a temperature of 60ºC. Then, the mixture was stirred for 24 hours at a speed of 75 rpm to produce a white cloudy PVA solution and was homogenized by vortex. PVA solution formulation stage was pipetted of 1.5 mL each carries 40 mg PVA (F1), 2 mL bring 50 mg PVA (F2), and 2.5 mL of carrying 60 mg PVA (F3).

Formulation

In this study there are three formulas and differentiated on the use of PVA as a stabilizer. F1 using PVA 1.5 mL, 2 mL F2 using PVA, and F3 using PVA 2.5 mL.

Particles PLGA-Reserpine Formation.

Preparation and characterization of particles by Mardiyanto, 2015. Starting with the preparation of particles: reserpine solution of 60 mL contains 4 mg of reserpine was mixed with a solution of PLGA as much as 2 ml contains 50 mg of PLGA using a magnetic stirrer (mass 1). PVA solution 2.5%, as much as 1.5 mL for formula 1, 2 mL of 2.5% PVA for formula 2, and 2.5 mL of 2.5% PVA for formula 3 were prepared on a magnetic stirrer (mass 2). Mass 1 was dropped using a micropipette 10 mL into the mass 2 by using a magnetic stirrer. Forwarded homogenization process was set for 1 hour at a speed of 750 rpm. The process of particle homogeneity was also done using ultra Turrax with a speed of 12,000 rpm for 30 seconds. The emulsion was diluted by adding 30 mL distilled water and evaporated for 24 hours over a magnetic stirrer to remove organic solvents.

Determination of Percentage Encapsulation efficiency (% EE)

The suspension of particles was inserted into the centrifuge tube and was centrifuged for 15 minutes, at a speed of 13,000 rpm. Determination of % EE was done by measuring the absorbance of each formula with UV-Vis spectrophotometer at a wavelength of 358 nm. A calibration curve was made on a series of reserpine concentrations of 10, 20, 30, 40, 50 µg / mL of the stock solution.

Determination of Diameter, PDI, and Zeta Potential

The equipment was used in this test was PSA. Measurement of the average diameter, particle size distribution, and zeta potential using DLS method. The suspension of particles that have done through the stage of purification wass taken about 2 mL, and then inserted into the cuvette Zetasizer. Measurement of particle diameter, PDI, and zeta potential do with the scattering angle 90o.

Determination of Particle Shape and Morphology

Determination of particle shape and morphology using a TEM. Particles suspension were diluted with aquabidest. After that the sample was placed on a TEM grid which made of copper, then the electron beam passes through the sample and was captured by the detector with the acceleration voltage of 100 kV or more.

3. RESULTS AND DISCUSSION

Preparation of PLGA resulted in the conduction of solvation by adding ethyl acetate then was stirred about 5

minutes in which the PLGA was dissolved in ethyl acetate in the form of a clear viscous solution. Results were obtained in the form of a clear solution, it happened because of PLGA dissolves in one semi-polar solvent ethyl acetate (Mardiyanto, 2015). Reserpine is also soluble in ethyl acetate. PVA powder that had been prepared, further was mixed with distilled water. Dissolving PVA in hot distilled water was taken about 24 hours to produce a homogeneous solution became a bit white turbid and it happens because of decreasing temperature. During the drop by drop process (Fig.4), the initial emulsion was formed then became more turbid according to the amount of PLGA-reserpine which was dropped. Stirring for 1 hour was a precondition before come into homogenizing step. Removing organic solvent after dilution of homogenizing emulsion (Fig.5) was recognized by the tracing odor of ethyl acetate.

Figure 4. Process of drop by drop to perform emulsion

Data of % EE of formula 1, 2 and 3 was processed based on the amount of reserpine that were not fit into particles to obtain an efficient yield. This yield was visibly different from one formula to others: formula 1 of 60,75 % ± 1,5, formula 2 of 73 % ± 2,6, and formula 3 of 65 % ± 3,8 but statistical tests were still needed. So that the obtained data were performed first by Shapiro-Wilk normality test, and resulted that the data are normally distributed. Then the normally distributed data were analyzed using ANOVA (one-way) to see the difference between formula 2 and 3 were chosen by further follow-up testing done with Tukey Post Hoc test and LSD (Least Significant Difference) in SPSS 21®.

Figure 5. Resulting particles in aquadest

Not only data of % EE, to see the difference between a formula, but also the particle of around 300 nm in diameter by PSA data (Fig.6) were processed first by the statistical test, and the data were known to be uneven distributed. Further data were transformed into a logarithm so that data could normally be distributed.

Figure 6. Avarage diameter by PSA measurement

Normally distributed data were statistically analyzed using independent t-test in SPSS 21® indicated there was no significant difference between formula 2 and 3. Obtained image of TEM (Fig.7) and AFM (Fig.8) were processed by using ImageJ® program with same contrast and visualization of pict area.

Figure 7. TEM image of particles

Figure 8. AFM image of particles

4. CONCLUSIONS

The stable colloid system of three formula was resulted using reserpine into emulsion solvent evaporation method. % EE of formula 1, 2 and 3 were 60,75 % ± 1,5, 73 % ± 2,6, and 65 % ± 3,8. The particle of around 300 nm in diameter and negatively charge were recognized by PSA. Obtained image of TEM and AFM were represented the homogenous and spherical particles.

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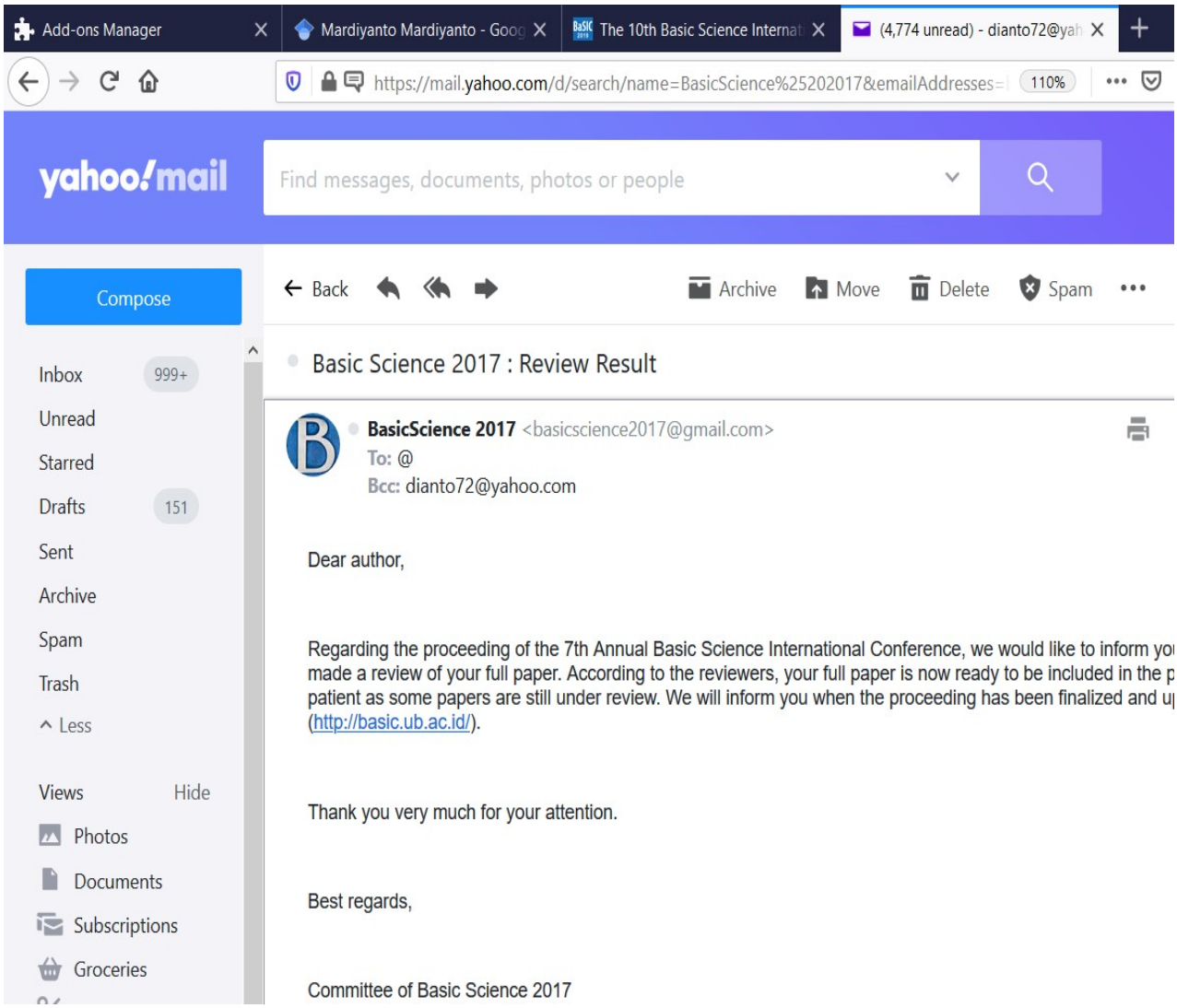
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