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The Increased Dissolution Rate of Furosemide with PEG 6000 and PVP K30 on Microcapsule Preparations.

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ABSTRACT

Furosemide is a diuretic drug included BCS class two, so the bioavailability was low. An oral administration only about 60% absorbed, therefore an effort in this problem. The increased solubility of furosemide using a combination of two polymers i.e PEG 6000 and PVP K30 which is hydrophilic polymers by used solvent evaporation emulsification method with four formula. The microcapsules is evaluate the shape and morphology using SEM (Scanning Electron Microscope), particle size distribution, quantitave analysis and retrieval determination, FTIR analysis, X-ray diffraction analysis, and dissolution test. SEM photo results show that the form of furosemide microcapsules in all formulas almost spheres form. Particle Size determination in all four formulas was included the microcapsule preparation requirements. FTIR analysis of the four formulas showed has no chemical interaction between the active ingredients and the polymer. The peak from X-ray diffraction results that show the crystalline form. The dissolution test with a phosphate buffer medium of pH 5.8 shows After 90 minutes there is most an increased for the percentage of dissolution from formula 4 = 92.74%. This research can be concluded that the furosemide microcapsule used a combination of PEG 6000 polymer and PVP K30 can increase the rate of furosemide dissolution.

Keywords: furosemide, dissolution, microcapsule, PEG 6000, PVP K30

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INTRODUCTION

Furosemide is an active Pharmaceutical drug ingredient with diuretic indications and most commonly used in patients with heart failure. This drug inhibits the reabsorbtion of sodium and chloride in the distal tubule and henle curve [1][2]

Furosemide is a powerful diuretic drug group, effective for the treatment of udem due to heart, liver or kidney and hypertensive disorders. Treatment with furosemide often caused oral bioavailability problems. The problem of bioavailability that arises was often associated with a low rate of furosemide dissolution. Furosemide has a high melting point of 206 ° C and is practically insoluble in water (3)

Furosemide had a solubility value of 0.01 mg / ml, C log P 1.9 and log P 0.74 and pKa value of 3.9. Based on log P values, furosemide was classified into 4th Class (BCS) Biopharmaceutics Classification System (BCS), i.e as a drug having low solubility and low permeability in accordance with Biopharmaceutics Classification System (BCS) (4)

The initial work of Furosemide occurs within 0.5-1 hours after oral administration, with a relatively short working period of ± 6-8 hours. Rapid absorption of furosemide in the gastrointestinal tract, its bioavailability is 60-69% in normal subjects, and ± 91-99% of the drug is bound by protein plasma. Maximum blood levels were achieved 0.5-2 hours after oral administration, with a biological half-life of ± 2 hours (4)

Microencapsulation is one of the techniques used to control drug release. This technique has a way of coating / coating a core substance (in this case active drug) with a polymer so that it becomes micro-sized particles with a size range between 1-5000 micrometers. Due to the wall layers of this polymer, the core substances will be released rapidly by using hydrophilic polymers or slowly using a hydrophobic polymer according to the purpose of preparing the microcapsules. One technique that can be used in the manufacture of microcapsules is the solvent evaporation emulsification technique (5)

The solvent evaporation emulsification method has the principle of preparation by dissolving the polymer in a volatile solvent, and then the drug was dispersed or dissolved in polymer solution. The drug-containing polymer solution was emulsified in the dispersing phase, and let the polymer solvent evaporate and then the microcapsules are collected by washing, filtration, and drying (6)

One method to increase the rate of drug dissolution was by microencapsulation technique. The polymers which may be used are hydrophilic polymers, such as: polyvinyl pyrrolidone (PVP) and PEG 6000 which were often used as additives in formulations to increase solubility of soluble drugs. PVP is a synthetic polymer, water-soluble polymer and can be found in various drug delivery systems such as microspheres, nanoparticles, liposomes and conjugate polymers. This polymer is hydrophilic in nature, it can be used as a hydrophobic coating of drugs such as Furosemide so it is expected to increase Furosemid dissolution rate and produce increased bioavailability [6]

MATERIALS AND METHODS

Chemical materials:

The materials used in this research were Furosemid (Indofarma), Polivinilpirolidon K30 (Kollidon®), Polyethylene Glycol 6000, n-Hexan, Chloroform, Span 60, liquidum paraffin (Brataco), aquadest and used phosphate buffer pH ± 5,8.

Instruments:

The equipment used was Homogenizer (IKA® RW 20 Digital), Analytic balance (O-Hau160D), Spectrophotometer UV-Visible (Shimadzu UV-1800), Oculo Micrometer, Binocular Microscope (Olympus), pH meter (Hanna Instrument)

Methods:

Procedure 1: Preparation of Furosemide microcapsules

0.5 grams of Polyvinylpyrrolidone K30 and 0.5 grams of PEG 6000 dissolved in 25 ml of chloroform and then dispersed 1 gram of furosemide into it (first solution). Then, 125 ml of liquidum paraffin was inserted into other glass shaker, stirring using homogenizer. Add 0.5 span of 0.5 gram which has been melted using waterbath (second solution). Dissolve solution 1 into solution 2 to form an emulsion, and stirred with homogenizer at a rate of 700 Rpm (Rotation per minute) for 5 hours at room temperature (15 ° - 30 ° C) until chloroform had evaporated and microcapsules are deposited. The Solid Result (Microcapsule) was separated by Filtering (paper filter), the precipitated microcapsules were washed with n-Hexane to remove the liquid paraffin attached and dried at room temperature (25 ° C) for 24 hours (8)

Procedure 2: Microcapsule evaluation (9)((10)

Sub Procedure 1 : The weight of microcapsules obtained

The weight of the obtained microcapsules is weighed using an analytic scale.

Sub Procedure 2 : Examination The shape and surface of the particles by using the Electron Microscope Scanning (SEM) tool.

The powder was attached to the holder by a special glue, then inserted into an evaporator vacuum to coat with gold (Au). At a certain vacuum level the gold will evaporate and coat the powder particles on the holder, then the samples inserted into the SEM device are then observed.

Sub Procedure 3 : Determination of particle siza analysis

The method of determining particle size distribution by microscopic method was equipped with an oculo micrometer tool, a number of samples placed on a glass object dropped with liquid paraffin, covered with a cover glass. Observe under a microscope of 1000 particles. Particles are grouped on specific sizes. Then amount of each group was determined. Before the calculation, the oculo micrometer was calibrated using a stage micrometer by determining a scale on graph paper (1mm) equal to 100 scales on a micrometer so that the scale at a micrometer equals 10 µm

Sub Procedure 4 : Examination of Furosemide levels in microcapsules

Determination of percentage entrapment eficiency (% EE) Furosemide in microcapsules was : The percentage of entrapment eficiency (% EE) was obtained from the determination of Furosemide content in microcapsules on microcapsule weight:

Sub Procedure 5 : FTIR Analysis

Microcapsule analysis by wave equation by using Fourier Transformation Infrared Spectroscopy (FTIR). This analysis was used to identify the functional group produced from a drug and to know whether in the microcapsule formula is made there is chemical or physical interaction that occurs in each material used in microcapsule preparations.

Sub Procedure 6: X-ray Diffraction Analysis

X-ray diffraction was a technique that used to identify the presence of crystalline phases in materials and powders, and to analyze the properties of structures (such as grain size, crystal oriented phase composition, and crystal defects) of each phase.

The intensity of the peak of the diffractogram showed the number of crystal phases in the test sample. The sharper of the peak, the larger the crystalline phase, the smaller the peak intensity the smaller

was the crystal phase. The intensity of the diffractogram was generated by the X-ray diffraction pattern that affects the surface of the crystal by certain diffraction angles

Sub Procedure 7 : Dissolution profile

An equivalent microcapsule of 1 gram Furosemide was determined by the dissolution profile by rowing method (type 2), by inserting the test substance into the capsule and then inserting into the medium at a rate of 30 rpm as the dissolution medium was phosphate buffer pH 5.8 at 37 ± 0.7ºC As much as 900 ml.

Dissolution test was carried out for 8 hours with solution taken 5 ml after 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480 minutes. The solution taken was replaced by an amount equal to the dissolution medium of phosphate buffer pH 5.8 to the volume of the fixed medium.

The sample was analyzed by UV-visible spectrophotometry to obtain absorbance at its maximum wavelength then calculated using the regression equation .

Data Analysis

The data were analyzed using simple calculations on microcapsule preparation. The evaluation of the preparation includes:

1. Determination of particle size analysis using the formula :

$$d_{In} = \frac{\sum nd}{\sum n}$$

2. Determination of percentage entrapment efficiency (% EE) Furosemide in microcapsules using linear regression (on this research linier regression y= 0,07845x + 0,08686) With y as the absorbance obtained at the wavelength 273,6 nm so we get% EE with the formula :

$$\% \text{ EE} = \frac{\text{x}}{\text{Initial microcapsule to be analyzed}} \text{ x } 100 \text{ \%}$$

3. The dissolution profile was obtained from absorbent data obtained from sampling at any given time (triplo) substituted in linear regression Y = 0,11245x – 0,05740 derived from the solution of the active ingredient in a series of concentrations at the wavelength 273,6 nm. And the levels obtained at certain minutes are calculated by the formula:

$$\% \text{ dissolution} = \frac{\text{level obtained}}{\text{initial dosage levels}} \text{ x } 100 \text{ \%}$$

$$\text{correction factor} = \frac{\text{sample volume}}{\text{medium}} \text{ x levels obtained from linier regresion}$$

RESULTS AND DISCUSSION

The preparation of the microcapsule preparation begins with the determination of the optimum conditions of the microencapsulation on process of furosemide which included the determination of stirring rate, emulsifier concentration and the ratio of solvent to the carrier phase. These factors influence the manufacturing process of microcapsules. At the time of this research, the researchers found difficulties in determining the optimum conditions of the furosemide microcapsules preparation. Furosemide could not be perfectly coated and this constraint is due to the nature of PVP K30 which had a fine shape and very hygroscopic powders (11)

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Determination of the particle size distribution using a camera-equipped microscope. The average diameter of the microcapsule Furosemide long known that the number of coatings added to the microencapsulation process the greater the diameter of the particle size obtained. According to the particle surface area phenomenon, the smaller the particle diameter the greater the ability to coat the drug. From the Figure 1. showed that the furosemide microcapsules had the largest particle size in the average diameter range of 25-475.5 µm particles from 1000 particles. All the results obtained fulfill the requirements for the particle size of the microcapsules by a solvent evaporation emulsification method that is between 5-5000 µm.

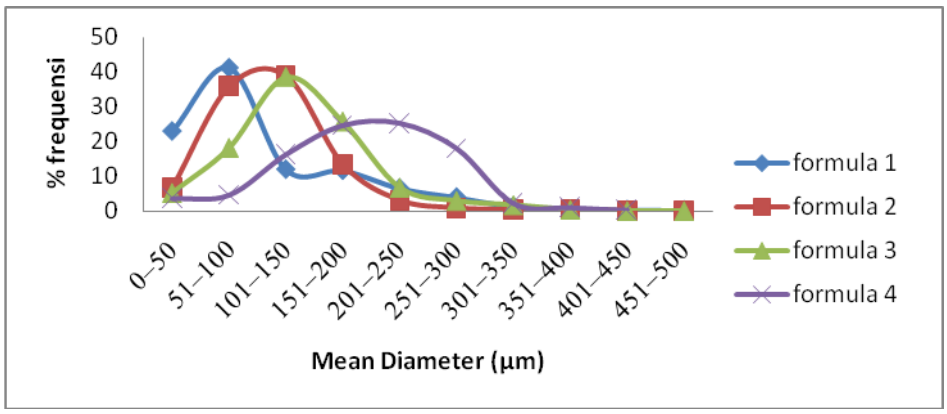

Figure 1: % Frequensi vs mean diameter microcapsule

The result of determination of efficiency entrapment (% EE) of active substance was obtained furosemide with mixture of PVP K30 and PEG 6000 in microcapsule for formula 1 = 73,026%, formula 2 = 100,5%, formula 3 = 87,84% and formula 4 = 70,72%. The purpose of recovery was to know whether the levels of Furosemide in the microcapsules are equivalent to the weight of the active ingredient in the supposed microcapsules. Of the percentages obtained all formulas had a recovery of more than 60% and all formulas meet the requirements of recovery.

Further recovery results will be used in the furosemide microcapsule dissolution profile test that could showed how many microcapsules are weighed and used. For example seen from the formula 1 obtained recovery rate of 73.026%. To find out how many microcapsules weights used for the dissolution test of formula 1, 100% multiplied by 40 mg then divided by 73.026%. The result that was 54.775 mg. Thus, the formula 1 for his dissolution test was weighed as much as 54.775 mg. The dissolution profile that showed on figure 2:

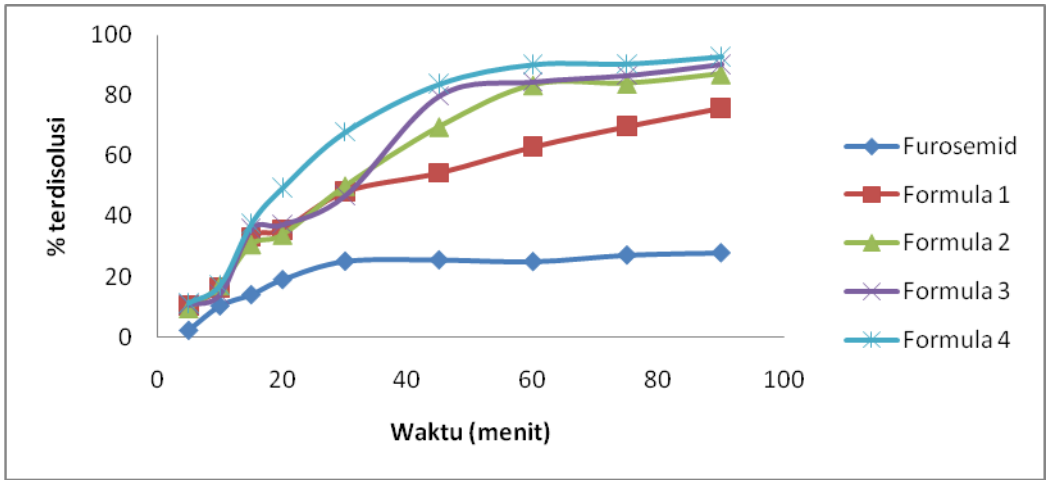

Figure 2: Dissolution profile Furosemide microcapsule

From the results of the dissolution percentages obtained, the more coating added to the furosemide microcapsule production the faster the dissolution rate was produced. In addition, the increased speed of furosemide release from microcapsules was caused by PVP K30 and PEG 6000 were hydrophilic, so easy to

dissolve in water and easy to inflate, resulting in fluid penetration to diffuse faster and bigger. Therefore the time required to release some drugs becomes faster.

In this study, microcapsules and morphology examination was done using Scanning Electron Microscope (SEM) all formulas at 50x and 300x magnification to see whether the microcapsules have spheris / round shape. The microcapsule image of furosemide could be seen the microcapsule had not been fully encapsulated, so that the form looked uneven as it is the result of formula 1, formula 2 and formula 3. While in Formula 4, the microcapsules are almost formed, but not evenly distributed. This can happen because in the process of making the time was still less and difficult to determine the optimum time so that encapsulation was not perfect. The Shape could be shown at figure 3 : (12)

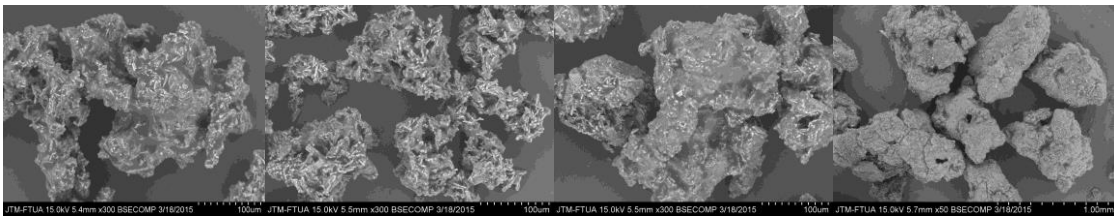

Figure 3: Shape and surface of microcapsules using SEM 50x magnification for the all formulas

From the result of FTIR spectroscopy of furosemide microcapsules it could be seen that the valleys formed show clusters possessed by furosemide as the active ingredient, PVP K30 and PEG 6000 as a coating. However, some of the missing peaks of the furosemide microcapsules are particularly evident in the formulas 2,3 and 4, ie peaks at 2347.81 cm-1 wave numbers belonging to PVP K30. This can be caused by the amount of PVP K30 added less than the amount of active ingredient and PEG 6000 so that the possibility was not detected by the tool used. The lack of measurement of IR spectroscopy devices with small amounts of PVP K30 may also cause some peaks not to appear as in formula 3, ie, at 2853.81 cm-1 wave numbers owned by PEG 6000 (13)

From X-ray diffraction at the fourth formulas there was decreased in the degree of crystallinity, although not too large. Formula 1, the crystals in the furosemid microcapsule were reduced when compared to the comparative substances, as did the formulas 2,3 and 4 which showed that fewer crystals were formed. The more the amount of polymer used the crystals to become smaller so that the crystalline index decreases, this may occur because the possibility of furosemide was uniformly distributed and the effect of amorphous polymer having structure (14)

Results from measurements of particle size on all four formulas, % EE and % dissolution was :

Table 1: Results of evaluation microcapsule of Furosemide

Parameter	F1	F2	F3	F4
Determination particle size (µm)	105,0325	114,1165	140,7235	245,3115
% EE	73,026	100,5	87,84	70,72
% dissolution at 90 minutes	75,93	87,18	90,37	92,74

CONCLUSIONS

The furosemide with a PVP polymer K30 combined with PEG 6000 in microcapsules can increased dissolution rate which meets the requirements of microcapsule preparations of size, No chemical interactions, increasing dissolution percentage after 90 minutes. However the shape of this furosemide microcapsule had not been completely spherical

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