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Optimization of PVA Concentration in the Preparation of Amlodipine Besylate Microparticles with Ethyl Cellulose Polymer Based on Entrapment Efficiency

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Abstract

Amlodipine besylate is an anti-hypertensive drug that is degraded due to an acidic pH (pH 3) of 55.35%. Microparticles are one strategy that can be used for targeted drug delivery systems. The polymer ethylcellulose can be used to make microparticles. In the production of microparticles, polyvinyl alcohol (PVA) acts as a stabilizing agent. The goal of this study is to see how different PVA concentrations affect the absorption efficiency of amlodipine besylate microparticles with polymer ethylcellulose and to find the best PVA concentration for the microparticle system. The solvent evaporation method is used to create amlodipine besylate microparticles from the polymer ethylcellulose. The entrapment efficiency was evaluated using UV-Vis spectrophotometry at a wavelength of 237 nm. When 50:50 mg is made with 1% PVA, the ideal entrapment effectiveness is 49.964 percent. The percentage entrapment efficiency of amlodipine besylate in the microparticle increases in direct proportion to the concentration of PVA, although at specific concentrations of PVA (1.5 percent), the entrapment efficiency decreases.

Keywords: microparticles, amlodipine besylate, ethylcellulose, PVA, entrapment efficiency.

INTRODUCTION

Amlodipine is a long-acting dihydropyridine calcium channel blocker (CCB) that is commonly used to treat hypertension [1]. Based on research conducted by Wajiha, it was found that amlodipine besylate is unstable under acidic conditions, even degraded by 55.50% at pH 3[2].

Amlodipine besylate, which is degraded at acidic pH, makes amlodipine besylate less suitable for targeting the stomach. Therefore, it is more suitable for targeted delivery systems to the intestine.

A Targeted Drug Delivery System (TDDS) refers to the development of drug delivery technology using polymers to deliver drugs to specific body parts depending on time and dose [3]. Delivery systems that have the potential to deliver drugs selectively and target them to various parts of the body are microparticles [4]. Microparticles are a sort of multiparticulate drug delivery technology that is designed for long-term or controlled drug administration. The aim is to increase the bioavailability or stability of drugs and to target drugs to specific body parts.

Ethylcellulose, as a polymer, can also be used for controlled release into the intestine [5]. Polymers such as ethyl cellulose are insoluble in water due to the difference in polarity, thus forming two phases when preparing microparticles by the solvent evaporation method. Two phases will form when mixed at high speed, which unfortunately causes instability. A stabilizer or stabilizing agent is required to stabilize the organic phase (polymer and solvent) and the aqueous phase. One option is to use polyvinyl alcohol (PVA) as a stabilizer [6]. Because it includes a large number of hydroxyl groups that can form hydrogen bonds, PVA is employed as a stabilizer. The higher the hydrogen bond, the higher the viscosity, where this increase in viscosity affects the increase in the entrapment efficiency [7].

The goal of this study is to see how the amount of PVA in the ethyl cellulose polymer affects the efficiency of entrapment of amlodipine besylate microparticles. The method used for the manufacture of amlodipine besylate microparticles is the solvent evaporation method (solvent evaporation). Each amlodipine besylate microparticle formula was evaluated, including organoleptic, percent yield, particle size, and entrapment efficiency, to determine the optimum PVA formula.

MATERIALS

Amlodipine besylate (Dexa Medica), polyvinyl alcohol (PVA) (PT. Triam Pharmaceutical Industries), ethyl cellulose (Corel Phar Chem), ethanol, dichloromethane (DCM), aquabidest (PT. Whidatra Bhakti), and methanol (Merck).

METHODS

Preparation of Ethyl Cellulose Amlodipine Besylate Microparticles

In this research, 3 formulas of ethyl cellulose amlodipine besylate microparticles were made with 3 variations of PVA concentration in table 1. The three microparticle formulas were prepared by the solvent evaporation method. Dissolving PVA in distilled water was used to make the PVA solution. The mixture was then thoroughly dissolved using a magnetic stirrer at 500 rpm and 50 °C. In this experiment, 50 mg of amlodipine besylate and 50 mg of ethyl cellulose were dissolved in a 1:1 mix of ethanol and dichloromethane (DCM) in a 20 ml organic solvent (10 ml of ethanol and 10 ml of DCM). Amlodipine besylate – ethyl cellulose solution was mixed by dripping slowly into various concentrations of PVA solution, then stirred at 500 rpm for 120 minutes at room temperature. Furthermore, solid droplets of amlodipine besylate microparticles were filtered, washed several times with distilled water, and dried at room temperature.

Characterization of amlodipine besylate microparticles

The characterization of amlodipine besylate microparticles included organoleptic observations, particle size measurements using an optical microscope, and determination of yield percent.

Determination of the Percentage Efficiency of Amlodipine Besylate Entrapment in Microparticles

The formed amlodipine besylate microparticles were weighed at as much as 6 mg and dissolved in 10 ml of methanol. The mixture was then vortexed for five minutes. Dilute as much as 1 mL of the microparticle solution, made up to 5 mL using methanol in a volumetric flask. Then the amlodipine besylate content was measured using a UV spectrophotometer at the maximum wavelength. The percent entrapment efficiency (% EE) is calculated using the formula:

$$\% \text{ EE} = \frac{\text{Measured Drug Level}}{\text{Initial Drug Level}} \text{ x } 100\%$$

RESULTS AND DISCUSSION

This study is an experiment that aims to provide an overview of microparticle manufacturing optimization. Microparticulate drug delivery systems have recently attracted a lot of attention in comparison to single unit systems because of their prospective benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, and predictable gastric emptying [8]. To estimate the intended results, it is critical to optimize the components in the microparticle manufacturing process.

The solvent evaporation method was used to make amlodipine besylate microparticles. It is a method of making microparticles that uses organic solvents dispersed in a receiving medium or water to form microparticles. Amlodipine besylate and ethyl cellulose have good solubility in organic solvents, so the choice of this method is suitable for the active substances and polymers used in this study [9].

The preparation of amlodipine besylate microparticles begins with the preparation of the receiving medium in the form of a solution of polyvinyl alcohol (PVA) in water. The addition of PVA serves as a stabilizing agent or stabilizer because it can increase the viscosity of the water medium. PVA will also help in the formation of spherical particles and prevent the incorporation of particles with one another during the microparticle manufacturing process [10]. The PVA used varies, ranging from 0.5%, 1%, and 1.5% (w/v) dissolved in 100 ml of water. PVA is formulated into three different formulas. This aims to determine the effect of PVA concentration on the entrapment ability, which is seen as a percentage of the entrapment efficiency in the microparticle system.

The active substances, amlodipine besylate, and ethyl cellulose polymer were then dissolved in a mixture of organic solvents. The choice of ethanol and dichloromethane as organic solvents is because the solvent used in the manufacture of microparticles must be able to dissolve the active substance and polymer. The ratio of the concentration of ethanol to DCM used was 1:1 in 20 mL [11]. The active substance and polymer in this organic solvent were then dropped into the receiving medium, which was stirred at 500 rpm for 2 hours [12]. Solid particles of microspheres dispersed in aquadest medium in the manufacturing process will then be filtered using Whatman filter paper. The filtered results were then washed using distilled water so that the unadsorbed amlodipine besylate could be separated from the formed microparticles. The solids retained on the filter paper were then dried at room temperature and weighed. The dried amlodipine besylate microparticles were then separated from the filter paper by dredging.

The physically formed amlodipine besylate microparticles are white and odorless. The percent yield or weight of the amlodipine besylate microparticle yield was calculated by comparing the dry weight of the microparticles with the theoretical weight of microparticles [13]. The percent yield, or weight of the amlodipine besylate microparticle yield, increased in direct proportion to the increase in PVA concentration. The result of the percent yield test is that formula 1 is 71%, formula 2 is 83%, and formula 3 is 93%. The results show that the average particle size of Formula 1 is 44.39 µm, Formula 2 is 45.09 µm, and Formula 3 is 45.94 µm.

Entrapment efficiency can be defined as how much of the active ingredient of the drug amlodipine besylate can be adsorbed by the ethyl cellulose polymer in the microparticle system. The resulting microparticles were weighed as a whole as the yield weight. A total of 6 mg of microparticles were weighed and dissolved in 10 ml of methanol. A UV-Vis spectrophotometer with a maximum wavelength of 237 nm was used to measure the levels of amlodipine besylate. In formula 1 and formula 2, dilution is required, with 1 mL diluted into 10 mL of methanol. This was done because the absorbance obtained did not fall within the range of Lambert-Beer's law (0.2-0.8) [14]. In formula 3, no dilution is necessary because it is already in the range of Lambert-Beer's law. The data percentage efficiency of amlodipine besylate entrapment in microparticles can be seen in Table 2.

Table 1: Formulation of Amlodipine Besylate Ethyl Cellulose Microparticles with Variations in PVA Concentration

No	Ingredients	Formula		
		F1	F2	F3
1	*Amlodipine besylate* (mg)	50	50	50
2	PVA (%)	0,5	1	1,5
3	Ethanol: Dichloromethane (1:1) (ml)	20	20	20
4	Ethyl Cellulose (mg)	50	50	50

Table 2: Amlodipine Besylate Microparticles Entrapment Efficiency

Formula	Ingredients			% EE ± SD
	Amlodipine besylate (mg)	Ethyl Cellulose (mg)	PVA (%)	
F1	50	50	0,5	40,17 ± 0,24
F2	50	50	1	49,96 ± 0,17
F3	50	50	1,5	2,44 ± 0,12

The concentration of PVA as a stabilizer affects the percentage of amlodipine besylate entrapment efficiency in microparticles. This is to the theory, which states that increasing the concentration of stabilizer will increase the efficiency of drug entrapment in the microparticles. The use of the optimum concentration of PVA in the formula will result in the formation of more stable microparticles, with spherical microparticles. However, in formula F3, it can be seen that the level of entrapment amlodipine besylate decreased significantly. This could be due to the addition of PVA, which would increase the viscosity of the receiving medium [15]. Receiving medium that has high viscosity or viscosity will make the organic phase droplets unstable, so it will be easy to aggregate. This makes the formed microparticles less spherical [16][17]. The size of the nonspherical microparticles allows the drug to be more easily diffused out of the microparticles, resulting in a reduced concentration of the adsorbed drug [18].

The results of the percentage of entrapment efficiency obtained were analyzed using the SPSS One-Way ANOVA statistical analysis program to see if there were significant differences between each formula. Based on the results of Shapiro and Wilk's analysis, if the Asymp Sig value is greater than or equal to 0.05, then the data is normally distributed. Levene Test statistical analysis obtained a sig value of 0.540, more than equal to 0.05, so it can be concluded that the data is homogeneous. The One-Way ANOVA test results show a significance value of less than 0.05, which means that there is a significant difference between each formula. Formula F2 was chosen as the optimum formula because it produces the highest optimal percentage of amlodipine besylate entrapment in the microparticle system, where this formula contains 1% PVA with an entrapment efficiency value of 49.964%. Similar results were also seen in the study of pentazocine microparticles using ethyl cellulose and PVA polymers. The optimum formula is obtained from a 1% concentration of PVA [19].

CONCLUSION

Variations in the concentration of PVA as a stabilizer affect the percentage of entrapment efficiency of amlodipine besylate microparticles of ethyl cellulose polymers. The percentage of amlodipine besylate entrapment efficiency in the microparticle increased in direct proportion to the increase in PVA concentration, but at a particular concentration, the entrapment efficiency decreased. Formula F2 (PVA 1%) was chosen as the optimum formula for ethyl cellulose polymer amlodipine besylate microparticles because it provided the most optimal entrapment efficiency, amounting to 49,964%.

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REFERENCE

[1] T. Wang *et al.*, "Evaluation of pharmacokinetics and safety with bioequivalence of Amlodipine in healthy Chinese volunteers: Bioequivalence Study Findings," *J. Clin. Lab. Anal.*, vol. 34, no. 6, pp. 1–10, 2020, doi: 10.1002/jcla.23228.

[2] W. Gul, S. Basheer, F. Karim, and S. Ayub, "Effect of Acid, Base, Temperature and U.V Light on Amlodipine Besylate," *Int. J. Adv. Res. Chem. Sci.*, vol. 2, no. 9, pp. 21–24, 2015.

[3] J. Zhan, X. L. Ting, and J. Zhu, "The Research Progress of Targeted Drug Delivery Systems," *IOP Conf. Ser. Mater. Sci. Eng.*, vol. 207, no. 1, 2017, doi: 10.1088/1757-899X/207/1/012017.

[4] B. Pilicheva, "A Concise Review on Microspheres for Targeted Drug Delivery," *Glob. J. Pharm. Pharm. Sci.*, vol. 5, no. 2, 2018, doi: 10.19080/gjpps.2018.05.555664.

[5] S. Prasertmanakit, N. Praphairaksit, W. Chiangthong, and N. Muangsin, "Ethyl cellulose microcapsules for protecting and controlled release of folic acid," *AAPS PharmSciTech*, vol. 10, no. 4, pp. 1104–1112, 2009, doi: 10.1208/s12249-009-9305-3.

[6] Y. Samati, N. Yüksel, and N. Tarimci, "Preparation and characterization of poly(D,L-lactic-co-glycolic acid) microspheres containing flurbiprofen sodium," *Drug Deliv. J. Deliv. Target. Ther. Agents*, vol. 13, no. 2, pp. 105–111, 2006, doi: 10.1080/10717540500313331.

[7] P. E. Savitry and N. Wathoni, "Karakterisasi Efesiensi Penjerapan Pada Nanopartikel Natrium Diklofenak Dalam Sediaan Topikal," *Farmaka*, vol. 16, no. 2, pp. 493–507, 2018.

[8] P. V. Lakshmi, K. P. R. Chowdary, A. P. Rani, and S. V. U. M. Prasad, "Design and Evaluation of Starch Acetate-Glipizide Microparticulate Drug Delivery Systems for Oral Controlled Release : Invitro Studies," vol. 1, no. 5, pp. 55–58, 2018.

[9] B. S. G. P. V. R. M. Gupta2 and N. Devanna3, "Microspheres As Drug Delivery System-A Review," *Indian J. Pharm. Sci.*, vol. 63, no. 6, pp. 450–458, 2001.

[10] A. K. Joshi, T. J. Mehta, M. R. Patel, K. R. Patel, and N. M. Patel, "Design and development of gastroretentive floating microspheres of glipizide," *Der Pharm. Lett.*, vol. 3, no. 5, pp. 189–201, 2011.

[11] A. M. Avachat, P. N. Bornare, and R. R. Dash, "Sustained release microspheres of ropinirole hydrochloride: Effect of process parameters," *Acta Pharm.*, vol. 61, no. 4, pp. 363–376, 2011, doi: 10.2478/v10007-011-0032-4.

[12] J. Y. Mukund, B. R. Kantilal, and R. N. Sudhakar, "Floating microspheres: A review," *Brazilian J. Pharm. Sci.*, vol. 48, no. 1, pp. 17–30, 2012, doi: 10.1590/S1984-82502012000100003.

[13] D. M. Hariyadi, E. Hendradi, and O. L. V. Piay, "Optimasi mikrosfer Ovalbumin-Alginat yang diproduksi dengan teknik aerosolisasi," *Pharma Sci.*, vol. 2, no. 1, pp. 21–30, 2013.

[14] S. Ahmed, N. Mustaan, M. A. Sheraz, S. A. A. un Nabi, and I. Ahmad, "Validation of a UV Spectrometric Method for the Assay of Tolfenamic Acid in Organic Solvents," *J. Pharm.*, vol. 2015, pp. 1–8, 2015, doi: 10.1155/2015/216249.

[15] F. Cui *et al.*, "Preparation and characterization of melittin-loaded poly (DL-lactic acid) or poly (DL-lactic-co-glycolic acid) microspheres made by the double emulsion method," *J. Control. Release*, vol. 107, no. 2, pp. 310–319, 2005, doi: 10.1016/j.jconrel.2005.07.001.

[16] S. R. Patel, V. P. Patel, and S. Road, "Optimization of Formulation of Insulin Microspheres for Oral Delivery," *Asian J. Pharm. Res. Dev.*, vol. 1, no. 5, pp. 28–32, 2013.

[17] Y. M. Jagtap, R. K. Bhujbal, A. N. Ranade, and N. S. Ranpise, "Effect of various polymers concentrations on physicochemical properties of floating microspheres," *Indian J. Pharm. Sci.*, vol. 74, no. 6, pp. 512–520, 2012, doi: 10.4103/0250-474X.110578.

[18] B. Liu *et al.*, "Preparation, characterization, and pharmacodynamics of exenatide-loaded poly(DL-lactic-co-glycolic acid) microspheres," *Chem. Pharm. Bull.*, vol. 58, no. 11, pp. 1474–1479, 2010, doi: 10.1248/cpb.58.1474.

[19] A. Jabar *et al.*, "Statistically optimized pentazocine loaded microsphere for the sustained delivery application: Formulation and characterization," *PLoS ONE*, vol. 16, no. 4 April. 2021, doi: 10.1371/journal.pone.0250876.