Microcapsule from PCL/PEG as Controlled Nifedipine Drug Delivery Carrier

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Abstract. Problems related to controlled drug release are important to immediately find a solution because of the dangers of drug side effects if consumed repeatedly every day. The drug used is Nifedipine which is a hydrophobic drug. This research used a synthetic combination of poly(caprolactone) and poly(ethylene glycol) with surfactants in the form of tween 80 and span 80 while the method used was microencapsulation. Microencapsulation is a process in which active substances are coated by extremely small capsules. Once the drug was in the intestine, it was released in a controlled manner so as to minimize side effects and maximize drug release. The results showed that the composition of the best poly(caprolactone) (PCL): (PEG) poly(ethylene glycol) combination was 80:20 with a molecular weight of PEG 400 g/mol. The result of the encapsulation efficiency percentage obtained 97.84% ± 0.01 and the result of dissolution test was 44.77%.

Keyword: nifedipine, polyethylene-glikol, polycaprolactone, polyblend, drug delivery.

1. Introduction

The controlled drug delivery system is one of the centers of research at this time. That is because the number of hydrophobic drugs when taken orally has not been able to release optimally. A number of compounds that act as carriers and various technical encapsulation have been evaluated to produce microcapsules with sustained drug release properties with the aim of resolving the drug release problem. However, several studies that have been carried out have not yet succeeded in achieving the maximum drug release results. The drug nifedipine [1] is an example of a drug that is not soluble in water so its solution in the body is very low, as a result it has side effects on the body. Nifedipine is a short acting calcium antagonist formulated into several different oral preparations, each of which may have different effects on haemodynamics and autonomic nerve function. Short acting calcium antagonists on nifedipine cause increased activation of sympathetic nerves and reflex tachycardia. In addition, the clinical use of short-acting calcium antagonists is limited by the emergence of adverse side effects such as headaches, flushing, dizziness, and palpitations. It is thought that these side effects...
are caused by acute vasodilation and reflex activation of the sympathetic nervous system. These side effects can be overcome by doing controlled release of nifedipine. The controlled release of nifedipine exerts less influence on the autonomic nervous system and heart rate [2]. Based on the problems that occur in nifedipine, controlled drug delivery is needed, which is one alternative to solve the problem of oral drug administration including repeated drug consumption, drug side effects caused and the time of rapid drug elimination [3]. The technique used was microencapsulation in which the technique has been widely used in the design and development of drugs as microcapsules to protect drugs from degradation first and prevent the body from potential toxicity from drugs [4]. Drugs would be conjugated and embedded into the polymer walls resulting in drug stabilization and controlled drug release [5]. This study used synthetic biocompatible polymers in the form of a combination. The purpose of forming a polyblend was to have better mechanical properties as a drug coating matrix. The polyblend used are poly (caprolactone) (PCL) and polyethylene-glycol (PEG).

2. Material and Methods

2.1 Materials

The materials that used in this research included poly(ethylene glycol) (Average Mw = 400 g/mol) and polycaprolactone (PCL) (Average MW = 50,000 g/mol) from Changchun Foliaplast Bio.Tech co.,Ltd, Nifedipine from PT. Dexa Medica, Span 80 and Tween 80 from Evonik Industries AG and also the material from Merck such as dichloromethane (CH$_2$Cl$_2$), KH$_2$PO$_4$.3H$_2$O, K$_2$HPO$_4$, NaCl, HCl 37%.

2.2 Optimization of the Composition of the Polyblend

Optimization of microcapsules was performed with the aim of obtaining optimum conditions to obtain the best microcapsules seen from the value of encapsulation efficiency and percent dissolution. The composition of polyblend namely poly(caprolactone) and poly(ethylene glycol) was varied beforehand with 10 types of variations as in Table 1.

| Sample | PCL: PEG |
|--------|----------|
| N1     | 10 : 0   |
| N2     | 9 : 1    |
| N3     | 8 : 2    |
| N4     | 7 : 3    |
| N5     | 6 : 4    |
| N6     | 5 : 5    |
| N7     | 4 : 6    |
| N8     | 3 : 7    |
| N9     | 2 : 8    |
| N10    | 1 : 9    |

2.3 Nifedipine Encapsulation Efficiency Test

20 ml of filtrate obtained at the nifedipine microcapsule dispersion stage was measured for absorbance at the wavelength that had been obtained using a UV-Vis spectrophotometer (UV-2450 Shimadzu, Japan). The concentration of the drug obtained was used to determine the mass of the drug that was not coated. The efficiency of nifedipine encapsulation in microcapsules was calculated by [6]:

Percent Efficiency of Encapsulation ($\%$EE) = \( \frac{\text{NIFL} - \text{NIFR}}{\text{NIFL}} \times 100\% \)

NIFL: the mass of the drug inserted
NIFR : mass of drug that is not coated
2.4 Nifedipine Dissolution Test
The best nifedipine microcapsules were wrapped in nylon cloth and tied to a magnetic stirrer. The wrapped and bound microcapsules were then immersed in 900 mL of a pH 1.2 solution and stirred with a magnetic stirrer at 100 rpm for 3 hours. 10 mL of filtrate was taken every hour. Each time taking 10 mL of filtrate was carried out adding a solution of pH 1.2 of 10 mL into the media so that the volume remained. The filtrate that had been taken was measured its absorbance at the maximum wavelength of nifedipine using a UV-VIS spectrophotometer (UV-2450 Shimadzu, Japan). After 3 hours the microcapsules that had been wrapped and bound to the magnetic stirrer were transferred to 900 mL of a buffer solution of 7.4 and stirred with a magnetic stirrer at a speed of 100 rpm.

3. Results and Discussion
This research used polymers namely poly(caprolactone) and poly(ethylene glycol) as coatings of the drug nifedipine to produce nifedipine microcapsules. This study used a solvent evaporation method. Solvent evaporation is a technique in which a polymer is dissolved in a volatile organic solvent and is insoluble in water such as dichloromethane (DCM) or chloroform [7]. Microencapsulation is one of the applications of polymers to protect specific functional materials and to release them into the outer phase for a long period of time [8]. In general, the formation of microcapsules by solvent evaporation method occurs in three stages, namely core, coat material / protective material, and liquid manufacturing vehicle (LMV) [9]. The first stage was the stage in which the polymer support material was dissolved in volatile organic solvents. The second stage of the organic phase was emulsified by stirring in a dispersing phase consisting of non-polymeric solvents, which do not mix with organic solvents. Stirring was done at 900 rpm for 1 hour. The third stage was the stirring stage which was maintained until the solvent has completely evaporated. Then the microcapsules were filtered, washed and dried.

![Image](image.png)

**Figure 1. Nifedipine Microcapsules**

The microcapsules successfully formed as shown in Figure 1. The microcapsules were proven by the results of the characterization using FTIR (Thermo Scientific-Nicolet i550 FTIR + NIR Spectrometer) and XRD (Phillips Analytical PW3710). The first FTIR analysis was to compare PCL and PEG functional groups to the PCL and PEG combination that formed the microspheres. The second FTIR analysis was to compare pure nifedipine functional groups with nifedipine that had interacted with polyblend.
Based on Figure 2, the results showed that the absorption band that appears on the microcapsules (2a) was a combination of absorption bands found in the absorption band PEG, microcapsules (2d) (representing the PCL absorption band) and nifedipine. There were no missing or increased absorption bands that showed no chemical reaction between PCL and PEG in the microspheres and only physical interactions occurred [10]. The presence of nifedipine in microcapsules (2a) was indicated by the absorption band 3329 cm\(^{-1}\) which is the wave number of the \(-\text{NH}\) group. This shows that the drug can interact well because of the small samples used when characterization has been able to show the absorption of the \(\text{NH}\)-band which is a typical functional group of nifedipine.

Based on Figure 3a, there were 2 specific peaks at an angle of \(2\theta = 21.5190\) and 23.8250. Then in Figure 3b also showed 2 specific peaks at angles \(2\theta = 21.5690\) and 23.7910. This was consistent with the previous reported [11] that PCL has two strong diffraction peaks at an angle of \(2\theta = 21.3\) ° and 23.6 °. This showed that there was no change in angle at the two specific peaks of PCL after being combined with another polymer, PEG.

After the nifedipine microcapsules had formed successfully, it was followed by testing the encapsulation efficiency. The aim was to find out the percentage of the ability of polyblend in coating
drugs. Following the results of the efficiency of nifedipine microcapsules from all variations of the composition along with the percentage of nifedipine microcapsules produced was shown in Graph 1.

![Graph 1](image1)

**Graph 1.** Percent Efficiency [□] and Solid Microcapsules [■] Obtained from The Optimization of The Composition of The Nifedipine Microcapsule Composition

Based on Graph 1, the average encapsulation efficiency had a value above 90% which showed that the drug was well coated. The highest value of encapsulation efficiency was in N3 microcapsules which was 97.84 ± 0.01%. Then obtained also various microcapsule solids in each composition variation. In microcapsules N6, N7, N8, N9, N10 the number of microcapsules solids obtained was getting smaller. That was because the variations in the composition of the number of PEG added more and more. PEG itself has hydrophilic properties so it dissolved easily with the aqueous phase during the dispersing stage. The lack of regularity resulted in the encapsulation efficiency of any variation in composition due to the lack of stability of the PCL and PEG polyblend.

After all variations of the composition were calculated the value of the encapsulation efficiency then the dissolution test was entered. The dissolution test was carried out on 10 variations of the composition whose results were depicted in Graph 2.

![Graph 2](image2)

**Graph 2.** Dissolution Profile of Nifedipine Microcapsules from Various Variations in the Composition of PCL and PEG 400

Based on Graph 2 showed that there were two compositions of variations in combination with the best drug release results, namely N1 and N3. The molecular weight of PEG used is 400 gram / mol
where small molecular weights were used to increase dissolution yield. N1 without the addition of PEG had a slightly greater dissolution result than the N3 that PEG had added. This showed that PEG had less effect on the percentage of microcapsule dissolution. However, the optimized microcapsules N3 was chosen because it had the largest encapsulation efficiency value of all variations. The efficiency value of N3 microcapsules obtained 97.84 ± 0.01%, and the dissolution percent after 3 hours (pH 1.2) and 52 hours (pH 7.4) was 44.77%.

**Figure 4.** The Appearance of N3 Microcapsules by Cross Section Using SEM

Based on the Figure 4, it was confirmed that N3 microcapsules were selected to be the most optimum composition variation where the composition of PCL: PEG used was 80:20 with a molecular weight of PEG 400 g/mol. SEM (Carl Zeiss EVO MA 10 Scanning Electron Microscope) cross section result showed the formation of many holes as a way out of the drug.

4. Conclusion and Future Work
This study succeeded in producing dissolution percent after 3 hours (pH 1.2) and 52 hours (pH 7.4) of 44.77% with the optimum composition of PCL (80): PEG (20). Subsequent research is testing in vivo to find out that the optimization results obtained are able to achieve therapeutic drugs.

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