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Economic Evaluation Analysis of PEGylated Poly(amidoamine) Dendrimer Production by Divergent Synthesis Method

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ABSTRACT

The purpose of this study is to evaluate the viability of a large-scale divergent growth synthesis PEGylated dendrimer poly(amidoamine) (PAMAM) production project. Engineering and economic evaluations were used to determine the results of this feasibility study. Engineering evaluation is based on a review of the initial plant design and stoichiometry calculations. While a number of factors, including the payback period, gross profit margin, cumulative net present value, etc., are used to evaluate the economic evaluation. The results of this analysis confirm that PEGylated PAMAM dendrimer may be produced on an industrial scale. In this project, 250 grams of PEGylated PAMAM dendrimer was obtained per cycle and the total profit earned was USD 4,656,187,677.16 in 20 years. Payback Period analysis shows that the investment will be profitable after more than two years. To ensure project feasibility, projects are estimated from ideal to worst conditions in production, including salaries, sales, raw materials, utilities, and external conditions such as taxes.

1. Introduction

Dendrimers are globular, three-dimensional, and well-ordered synthetic polymetric nanoparticles (Narmani *et al.*, 2019; Nikdouz *et al.*, 2022). The three main components that make up this molecule are the multifunctional initiator nucleus, which acts as a "germination seed" or anchor point for dendrimer growth; the inner layer along with the branches that will form generations; and the outer layer which is the terminal branch (Lyu *et al.*, 2019). The poly(amidoamine) (PAMAM) dendrimer was one of the first dendrimer families to be synthesized and characterized (Mahmoudi *et al.*, 2019). The PAMAM dendrimer is an ideal option for use in drug-loading vehicles due to its small size (1-100 nm) and loading characteristics (Narmani *et al.*, 2019). Besides size, the number of generations of PAMAM dendrimer formation will also greatly affect its structure. Based on prior research, it is known that PAMAM dendrimer with low generation (G0-G3) will tend to form open and amorphous structures so that they do not show clear internal characteristics, whereas for PAMAM dendrimer with high generation (G4-G10) will produce dendrimer structures that are round and has high stiffness (Sorroza-Martínez *et al.*, 2020).

PAMAM dendrimer modifications such as PAMAM PEGylation dendrimer (Ho *et al.*, 2019), PAMAM-Pyrrolidine dendrimer (Singhania *et al.*, 2020), PAMAM carboxymethyl chitosan dendrimer (Zhou *et al.*, 2021), PAMAM termination amino dendrimer (Cheng & Kaifer, 2022), and PAMAM acylation of dendrimer (Lee *et al.*, 2020) have all been studied in the context of research. The PAMAM PEGylation dendrimer is one of those modifications that are widely used. This is due to the fact that polyethylene glycol (PEG) is a synthetic polymer that is highly soluble in water, non-toxic, non-immunogenic, is excellent biocompatibility, is cost-effective, and is used extensively in a variety of industries and fields of medicine (Nguyen *et al.*, 2019; Wang *et al.*, 2018; Xiangbin Liu *et al.*, 2020). Due to these characteristics, PEG is often used in conjunction with PAMAM dendrimer for drug delivery applications to increase circulation time and reduce aggregation formation (Mahmoudi *et al.*, 2019; Tsujimoto *et al.*, 2021). PEGylated PAMAM dendrimer can be produced using various synthesis methods. Synthesis methods that can be used are divergent growth, convergent growth, double exponential growth, double-stage convergent, and hypermonomer (Irfan *et al.*, 2020; Kumar *et al.*, 2021; Nikzamir *et al.*, 2021; Sadhu *et al.*, 2022). Of the several synthesis methods, the divergent method is the most preferred method for preparing PEGylated PAMAM dendrimer because it has the advantages of fast synthesis, production in large quantities, and symmetrical high-generation dendrimer products. In addition, the resulting dendrimer product divergent method can be modified with certain functional groups. Therefore, the divergent growth synthesis method is used as a method for synthesizing PEGylated PAMAM dendrimer which will be analyzed through industrial scale economic evaluation. **Figure** 1 shows a schematic diagram of the preparation of PEGylated PAMAM dendrimer.

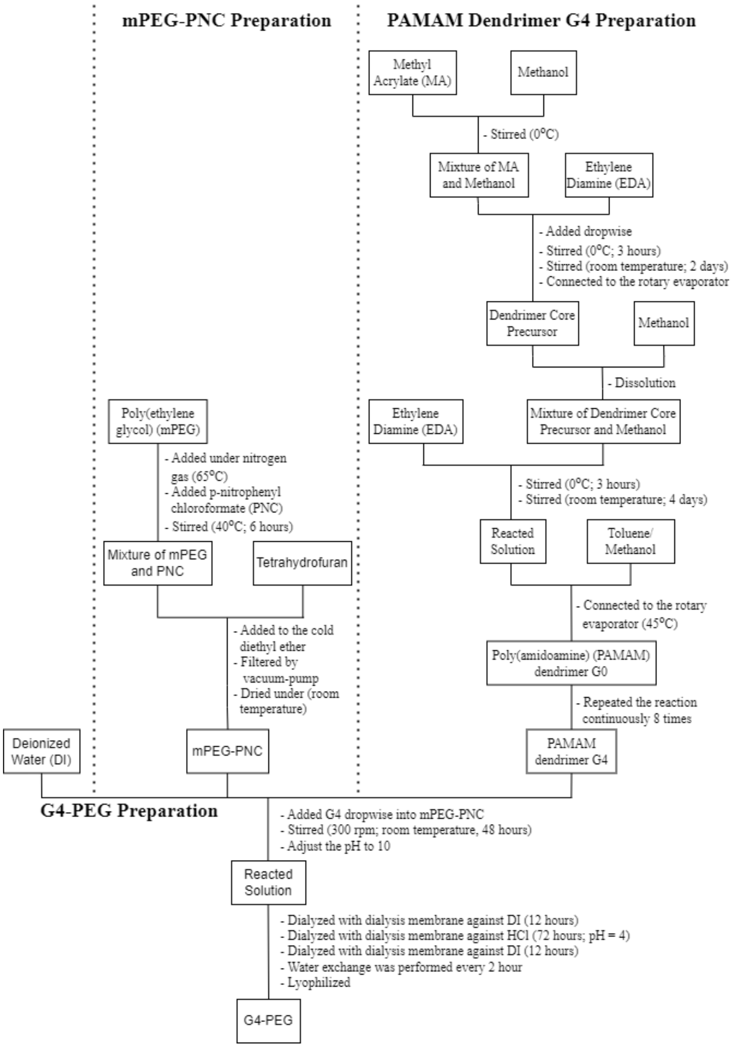

Figure 1. Schematic of the dendrimer manufacturing process.

Several studies have studied the synthesis of PEGylated PAMAM dendrimer using the divergent growth synthesis method. However, there has been no study studying the industrial-scale economic evaluation of the synthesis of PEGylated PAMAM dendrimer using the divergent growth synthesis method. This evaluation was carried out from two perspectives, namely a technical perspective and an economic perspective. From an engineering perspective it can be determined using stoichiometric calculations and evaluation of the initial plant design. Meanwhile, from an economic perspective, it is determined by several parameters to determine the feasibility of the project to be established, namely Gross Profit Margin, Payback Period, and Cumulative Net Present Value under certain conditions.

2. Method

In this study, the process for preparing PEGylated PAMAM dendrimer published by Ho *et al* (2019) was used as the main reference (Ho *et al.*, 2019). In an economic evaluation, an analysis of equipment prices and utilities for the manufacture of magnesium oxide nanoparticles was obtained from online shopping sites Amazon and Alibaba. Price analysis for chemicals was obtained from the Sigma-Aldrich (Merck) website. The electricity price per kWh is obtained based on electricity cost data from the Indonesian State Electricity Company. the data is calculated using Microsoft Excel with reference to several parameters, such as Gross Profit Margin, Payback Period, and Cumulative Net Present Value with various cost variables. Calculations were made based on literature (Nandiyanto, 2018; Ragadhita *et al.*, 2019; Veronica *et al.*, 2021). Economic evaluation is carried out using the calculation of the following parameters.

Gross Profit Margin (GPM) is the first analysis to determine the level of profitability of a project. This analysis is estimated by reducing the cost of selling the product with the cost of raw materials. GPM calculation is shown by Equation (1).

$$GPM = \sum_{tr=1}^{tr}(S.\eta - RM)PC.Q.t \qquad (1)$$

S is total sales, RM is total raw materials, PC is production capacity, Q is capacity of raw materials included and used in the process (kg/hour), and t is production time.

Payback Period (PBP) is a calculation to predict the length of time required for an investment to return the initial capital expenditure. In short, the Payback Period is calculated when the Cumulative Net Present Value reaches zero.

Cumulative Net Present Value (CNPV) is the total value of Net Present Value (NPV) from the beginning of the factory construction until the end of the factory operation. The NPV calculation is shown by Equation (2).

$$NPV = \sum_{tr=1}^{tr}\left(\frac{R_t}{(1+i)^{tr}}\right) \quad (2)$$

Rt is the net cash inflows minus outflows over a period of tr, i is the discount rate that can be obtained in alternative investments, tr is the project time (in a year), and Tr is the last year of the project.

3. Results and Discussion

3.1 Engineering Perspective

In this study, several assumptions were used based on the synthesis process of PEGylated PAMAM dendrimer (**Figure** 2). Based on these assumptions, by improving stoichiometric calculations from industrial projects, the manufacture of PEGylated PAMAM dendrimer can produce 250 grams in one cycle. The assumptions used are:

1. All raw materials are increased to five times the laboratory scale in the literature.
2. The material used is a material with a high level of purity (ACS Reagent).
3. The reaction precursors shown in Table 1 are reacted to produce a high purity level of PEGylated PAMAM dendrimer product.
4. Losses during the process of transferring, drying, and product picking are 2%.

Economic evaluation analysis is carried out with several assumptions needed to analyze and predict several possibilities that may occur during an industrial project. The assumptions used include:

1. All analyzes are performed in USD (1 USD = Rp 14,738)
2. Based on existing commercial prices, prices of precursors are shown in Table 1
3. All materials are estimated using stoichiometric calculations
4. When the project land has been purchased, land costs are added at the beginning of the factory construction year and reacquired at the end of the project
5. Total Investment Cost (TIC) is calculated based on the Lang Factor (Garrett, 2012)
6. TIC is calculated in two stages: the first stage is 40% in the first year and the second stage is 60% during the project development
7. Depreciation is estimated using direct calculations
8. One cycle of PEGylated PAMAM dendrimer manufacturing process takes 44 days
9. Dendrimer products are sold at a price of 3,799.48 USD/pack (1 gram).
10. A one-year project is 264 days (and the remaining days are used to clean and organize the process)
11. To simplify utility, utility units can be described and converted into charge. The unit of electricity (kWH) is multiplied by the cost of electricity. The assumed annual utility cost is 1,615.8682 USD/kWh.
12. Total salary/labor is assumed to be at fixed value of 25,50 USD/day
13. Discount rate 15% per year
14. Income tax is 10% per year
15. The duration of the project operation is 20 years

Table 1. Assumed reagent prices for the production of PEGylated PAMAM dendrimer.

Material	Price (USD)
Methyl Acrylate (MA)	85.20
Methanol	23.80
Ethylene Diamine (EDA)	35.59
Toluene	58.62
Poly(ethylene glycol) (mPEG)	85.20
Tetrahydrofuran	95.38
p-nitrophenylchloroformate (PNC)	4,116.90
Diionized Water (DI)	29.10
Diethyl Ether	127.05
Chloride Acid (HCl)	65.75
Dialysis membrane with MWCO 3500 Da	69.75

Economic evaluation is carried out to test the feasibility of a project. Economic evaluation is carried out in various conditions by varying the value of raw materials, utilities, sales, salaries, and taxes in various conditions. Variations in raw materials, utilities, sales, and salaries are carried out at 50, 75, 100, 125, 150, 175, and 200%, while tax variations are carried out at 10, 25, 50, 75, and 100%.

Figure 2 shows the process of making PEGylated PAMAM dendrimer using the divergent growth synthesis method based on a literature study by Ho et al (2019) (Ho et al., 2019). All symbols shown in **Figure** 2 are presented in Table 2. PEGylated PAMAM dendrimer using the divergent growth synthesis method were initiated by mixing methyl acrylate (MA) with methanol at 0oC. After mixing the MA solution with methanol homogeneously, ethylene diamine (EDA) was dripped using an automatic burette. The mixed solution was stirred for three hours at 0^{o}C and continued at room temperature for two days. The reaction mixture was connected to a rotary evaporator to remove unreacted methanol and MA to produce dendrimer core precursor products. The dendrimer core precursor was dissolved in methanol and put into EDA. The mixed solution was stirred for three hours at 0oC and continued at room temperature for four days. The toluene/methanol mixture was added to the mixed solution to remove the residue and remaining EDA solvent. Excess toluene and methanol were then removed using a rotary evaporator at 45^{o}C to produce PAMAM dendrimer generation 0.0 (G0). To obtain PAMAM generation 4.0 (G4) dendrimer, the same steps were carried out eight times.

The precursor to be conjugated with the PAMAM G4 dendrimer was prepared by reacting PEG under nitrogen gas at 65oC for one hour. After that, p-nitrophenyl chloroformate (PNC) was added and stirring was carried out for six hours before the temperature was reduced to 40oC. All chemical mixtures were dissolved using tetrahydrofuran and precipitated using cold diethyl ether. The PEG-PNC precipitate was filtered using a vacuum pump and dried under vacuum at room temperature. PEG-PNC conjugation with PAMAM G4 dendrimer was carried out by dissolving PEG-PNC in deionized water (DI) and stirring with PAMAM G4 dendrimer solution (300 rpm) at room temperature for 48 hours. All solutions used were prepared in phosphate buffer (pH = 10). Adding the PAMAM G4 dendrimer to the PEG-PNC solution by dripping so that the conjugation formed is homogeneous. The resulting solution was dialyzed using a dialysis membrane (MWCO 12-14 kDA) against DI water for the first 12 hours, against acidic medium (pH = 4) for 72 hours, and finally against DI for 12 hours. Water exchange is carried out every two hours. The dialysis results were then lyophilized to obtain dry G4-PEG.

In this process, one cycle produces 250 grams of PEGylated PAMAM dendrimer. In one month, the project can produce 5500 gram, and in one year, the project can produce 66000 gram of PEGylated PAMAM dendrimer. From an engineering point of view, the total cost of purchasing raw materials for one year is USD 281,435.86, while the total sales for one year are USD 250,765,847.08. The profit for one year is 232,808,752.23 USD. The price for the equipment cost analysis is 63,871.0541 USD. Total Investment Cost must be less than 36,406.50 USD. The project life is 20 years. In 20 years, producing PAMAM dendrimer are PEGylated with Cumulative Net Present Value/Total Investment Cost reaching 21.894%. The payback period is reached in the third year.

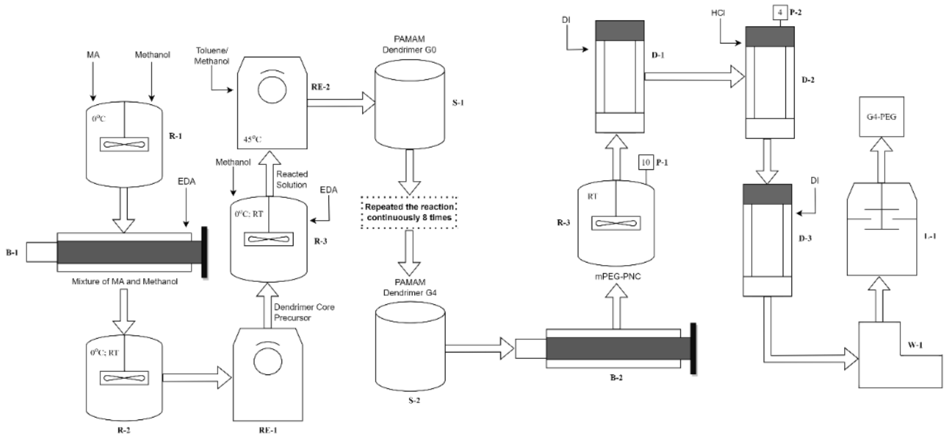

Figure 2. Flowchart illustration for manufacturing dendrimer.

Table 2. Symbols used in flowcharts.

No	Symbol	Information
1	R-1	Reactor-1
2	R-2	Reactor-2
3	R-3	Reactor-3
4	R-4	Reactor-4
5	B-1	Automatic Burette-1
6	B-2	Automatic Burette-2
7	RE-1	Rotary Evaporator-1
8	RE-2	Rotary Evaporator-2
9	S-1	Storage-1
10	S-2	Storage-2
11	D-1	Dialyzer-1
12	D-2	Dialyzer-2
13	D-3	Dialyzer-3
14	W-1	Washer-1
15	L-1	Lyophilizer-1
16	P-1	pH Meter-1
17	P-2	pH Meter-2

3.2 Economic Evaluation

3.2.1 Ideal Condition

The graph of the relationship between Cumulative Net Present Value/Total Investment Cost to time is shown in **Figure** 3. The y-axis is Cumulative Net Present Value/Total Investment Cost and the x-axis is the 20 year service life. The curve shows a decrease in the Cumulative Net Present Value/Total Investment Cost to be negative (value below zero) in the first year to the second year. This decrease occurred because in the first two years the initial capital costs were still calculated for tools, materials, and industrial development for the production of PEGylated PAMAM dendrimer. In the third year, the graph shows a fairly rapid increase in income, this condition is also known as the Payback Period. The profit earned can cover the initial capital that has been issued and continues to increase thereafter until the twentieth year. A more detailed value of the Cumulative Net Present Value/Total Investment Cost can be seen in Table 3. Thus, PEGylated PAMAM dendrimer production can be considered as a profitable industrial project because it takes a short time to recover investment costs.

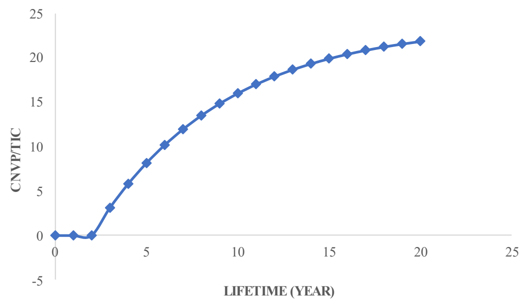

Figure 3. Ideal conditions for Net Present Value/Total Investment Cost for lifetime (years) [sb. x CNP/TIC; sb y lifetime]

Table 3. CNPV/TIC value for 10 years.

Lifetime	CNPV/TIC
0	0
1	-0.000591629
2	-0.00974648
3	3.098379316
4	5.8010974
5	8.151287038
6	10.1949302
7	11.97201121
8	13.51729905
9	14.8610276
10	16.02948721
11	17.04553905
12	17.92906239
13	18.69734355
14	19.36541412
15	19.94634506
16	20.45150239
17	20.89076964
18	21.27274116
19	21.60489031
20	21.89371565

3.2.2 Effect of External Condition

The success of a project can be influenced by external factors. One of these factors is the taxes levied on projects by the state to finance various societal expenditures. **Figure** 4 shows a graph of the Cumulative Net Present Value/Total Investment Cost with various tax variations for 20 years. The y-axis is the Cumulative Net Present Value/Total Investment Cost (%) and the x-axis is the useful life of 20 years.

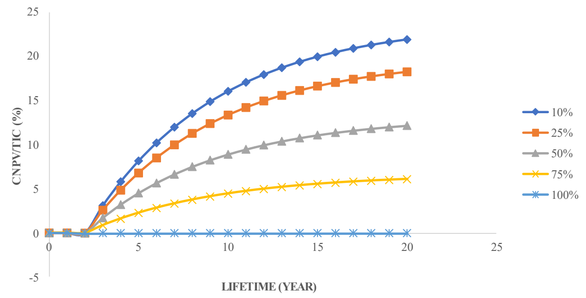

Figure 4. Cumulative Net Present Value/Total Investment Cost curve of tax variations.

Figure 4 shows that the conditions from the beginning of the year to the second year show the same results because the Cumulative Net Present Value/Total Investment Cost is under variations in taxes and there are ongoing project developments.

In addition, from the beginning of the year until the second year there is no income, but there is a decrease from the ideal condition chart. Profits continued to increase after reaching the Payback Period until the second year. Cumulative Net Present Value/Total Investment Cost (%) for the twentieth year for every variation of 10, 25, 50, 75, and 100% is 21.894; 18.243; 12.159; 6.075, and -0.009%. Therefore, the maximum tax for obtaining a Break-Even Point (a point where there are gains and losses in the project) is 75%. Tax changes that are worth more than 75% which will cause failure of the project.

3.2.3 Change in Sales

The graph of the relationship between Cumulative Net Present Value/Total Investment Cost and various sales variations is shown in **Figure** 5. The y axis is the Cumulative Net Present Value/Total Investment Cost (%) and the x axis is the 20 year service life. **Figure** 5 displays the Payback Period results. The second year is the initial condition of the project, where the Cumulative Net Present Value/Total Investment Cost in various variations is the same. This can happen because the effect of sales during project construction on the Cumulative Net Present Value/Total Investment Cost can only be obtained during the initial conditions of the second year, when the project construction has been completed. If the greater the sales value, the more profit will be obtained from the project being implemented. However, if there are conditions that cause product sales to decline, then the project's profits will fall from the ideal state.

Based on the results of the analysis, the Payback Period for selling variations of 50, 75, 100, 125, 150, 175 and 200% can be achieved in the third year. Profits continue to increase after reaching the Payback Period. The profit margin generated each year increases as sales increase from ideal conditions. Cumulative Net Present Value/Total Investment Cost (%) in the twentieth year for each variation 50, 75, 100, 125, 150, 175, and 200% is 11.182; 16.538; 21.894; 27.249; 32.605; 37.961, and 43.316. The minimum sales to reach the Break Even Point (the point where the project gains or loses) is 50%, so sales of PEGylated PAMAM dendrimer will be more profitable if sales increase by more than 50%. This is because the graph shows a higher positive Cumulative Net Present Value/Total Investment Cost (%), so industrial projects are feasible to run.

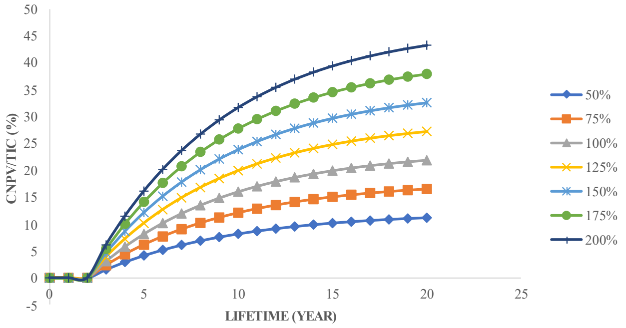

Figure 5. Cumulative Net Present Value curve of sales variation.

3.2.4 Variable Cost Changes (Raw Material Costs, Salaries, and Utilities)

Several internal factors can affect the success of an industrial project, namely the cost of raw materials, salaries, and utilities. Cumulative Net Present Value/Total Investment Cost of raw materials is shown graphically in **Figure 6**. The y-axis is Cumulative Net Present Value/Total Investment Cost and the x-axis is the service life in 20 years. The analysis is carried out by reducing and increasing the cost of raw materials by 50, 75, 100, 125, 150, 175, and 200%. The ideal cost of raw materials is 100%.

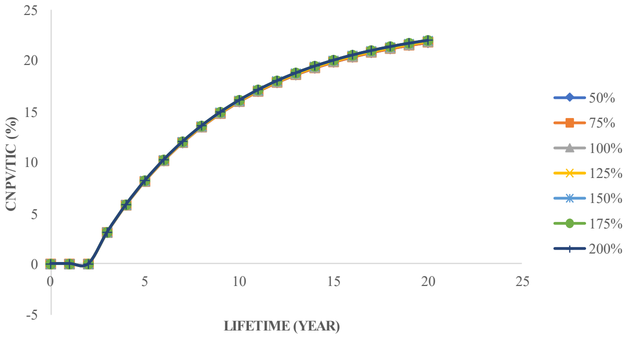

Figure 6. Cumulative Net Present Value curve of raw material variation.

The payback period results for raw materials are obtained in the 3rd year as shown in **Figure 6**. The value of the cumulative net present value/total investment cost in the first and second years is the same. The conditions from the beginning of the year to the second year of the project are cumulative net present value at various costs. raw material variable is the same because it is still in the stage of industrial project development. The effect of raw material costs on the Cumulative Net Present Value can be obtained after the industrial project has been running for 2 years from the initial conditions. The graph in **Figure 6** displays the same situation for each variation in the cost of raw materials that is carried out. This shows that the cost of raw materials does not have much effect on profits because it is already covered by high selling costs.

Based on the Payback Period analysis, profits continued to increase from the third year to the twentieth year. However, the profit margins obtained each year were getting smaller in line with the increase in raw material costs from ideal conditions. On the other hand, the annual profit margin increases as raw material costs decrease from ideal conditions. Cumulative Net Present

Value/Total Investment Cost in the twentieth year for each variation 50, 75, 100, 125, 150, 175, and 200% is 21.808; 21.851; 21.894; 21.937; 21.980; 22.023, and 22.065. From the variable cost of raw materials it is known that industrial projects can continue to run and generate profits.

The graph of Cumulative Net Present Value/Total Investment Cost with various employee salary variations is shown in **Figure 7**. The y axis is Cumulative Net Present Value/Total Investment Cost and the x axis is the 20 year service life. Analysis was carried out by varying employee salaries by 50, 75, 100, 125, 150, 175, and 200%. The ideal salary is 100%. Payback Period results for variations in employee salaries are obtained in the third year as shown in **Figure 7**. The cumulative Net Present Value/Total Investment Cost for employee salary variations in the first and second years is the same because the industrial project is still under construction. The effect of employee salaries on Cumulative Net Present Value/Total Investment Cost is obtained after the industrial project has been made for 2 years from the initial conditions. The graph in **Figure 7** displays the same situation for each employee salary variation. This shows that the costs for employee salaries do not have much effect on profits because they are already covered by high selling costs. Even so, the Cumulative Net Present Value/Total Investment Cost is different for each year. The difference in values for each variation of 50, 75, 100, 125, 150, 175, and 200% is 21.825; 21.859; 21.894; 21.928; 21,962; 21.997, and 22.031. From the variations in salary, it is known that the project can continue and generate profits.

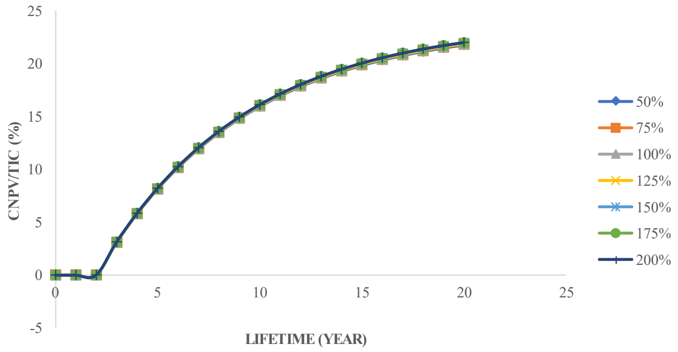

Figure 7. Cumulative Net Present Value curve of salaries variation.

Figure 8 shows a graph of Cumulative Net Present Value/Total Investment Cost with a variety of utilities. The y-axis is Cumulative Net Present Value/Total Investment Cost, and the x-axis is 20 years of service life. Utility variation analysis was performed with values of 50%, 75%, 100%, 125%, 150%, 175%, and 200%. Payback Period is obtained from the results of utility variations. The Payback Period results are shown in **Figure 8**. The conditions from the beginning of the year to the second year of the Cumulative Net Present Value/Total Investment Cost for various utility variations are the same. That way, there is no significant variation in the Cumulative Net Present Value/Total Investment Cost. This shows that the costs incurred for utilities do not have much effect on profits because they are already covered by high selling costs.

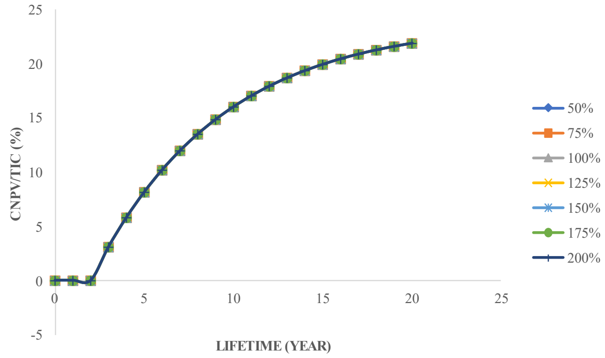

Figure 8. Cumulative Net Present Value curve of utilities variation.

However, the Cumulative Net Present Value/Total Investment Cost will be different in the tenth year for each variation. The difference in values for each variation of 50, 75, 100, 125, 150, 175, and 200% is 21.8934; 21.8935; 21.8937; 21.8938; 21.8940; 21.8941, and 21.8943. Payback Period for each variation of utility is still reached in the third year. From the variety of utilities, it can be concluded that the project can still run and generate profits.

4. Conclusion

Based on the economic evaluation analysis that has been carried out, the synthesis of PEGylated PAMAM dendrimer from an engineering point of view shows that the synthesis can be carried out using available tools. Payback Period analysis shows that the investment will experience profit after more than two years. This can happen because of the use of raw materials in the synthesis process of PEGylated PAMAM dendrimer using a cheap divergent growth synthesis method, requiring a short time to produce PEGylated PAMAM dendrimer, and produce symmetrical high-generation dendrimer products. From the economic analysis that has been done, it is concluded that this project is feasible to run.

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