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van

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onderwerp:

PENICILLIN PROCESS, with growth coupled production and reactive extraction in a tubular centrifuge.

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1. **Summary**

Penicillin is produced by the fungus *P. chrysogenum* during a two hundred hours lasting fermentation performed in a 250m$^3$ reactor. The development of the broth in time is described by a growth coupled production model. Optimizing the administration of the growth limiting substrate glucose resulted in a final concentration of penicillin of 18.7 g/l.

After conventional separation of mycelium and liquid with a rotating vacuum drum filter, the penicillin is extracted according to the principle of continuous reactive extraction, using a tubular centrifuge with an axial countercurrent flow of the liquid phases. Inside the extractor the phases are alternately being mixed and separated in order to enhance mass transfer.

The aqueous flow entering the crystallization section contains 660.6 g penicillin/l. Losses of the reactive amine are recovered from the wastewater using butyl acetate in a carrier recovery section.
2. Conclusions and recommendations

The production of penicillin can be divided into two parts.

- The fermentation, the actual production of penicillin.
- The extraction of penicillin.

2.1 The fermentation

The fermentation is the part of the process which is aimed at the quantity of penicillin. The fermentation is also the cost determining step of the process, it determines the price of penicillin. This is probably the reason why still so much time is spent on optimizing the fermentation.

This optimization concerns models describing the dependency of the process on the parameters such as temperature, pH, substrate etc. An important parameter is the substrate feed rate, because of its direct influence on the price of penicillin. We have investigated the optimization of an linearly increasing substrate feed rate.

Because of the dependency of so many parameters such as temperature and pH, production values in practice however may differ from the results. Another reason why practical fermentation results may differ from results obtained by simulation, is the physiology and the physical properties of mycelial broths.

There are many difficulties describing the viscosity of the broths. Therefore models describing oxygen and heat transfer are mostly very poor. For example most models are based on substrate limitation, but towards the end of the fermentation oxygen, because of transfer phenomena, may become the limiting nutrient.

2.2 The extraction.

The extraction is the part of the process which is aimed at quality of the penicillin. This indicates that a separation has to be achieved between penicillin and other fermentation products and not consumed nutrients. Phenylacetic acid is in this objective important because of its toxicity. It can be concluded that with the used model of reactive extraction no selective extraction can be achieved.

An advantage of the reactive extraction however is the recovery of penicillin at high pH values. The reactive extraction therefore does not need to be performed in extractors with short contact times. In this perspective it is competitive with the conventional process of physical absorption. The, in this objective designed, tubular centrifuge extractor offers good prospects which makes more closely investigations wanted.
3. Introduction

The antibioticum penicillin was incidently discovered by A. Fleming in 1928. Its enormous potential of anti-inflammatory working however was discovered during world war 2. The need for penicillin and the lack of good production processes, especially with regards to the purification, led to very high prices ($8000/kg in 1946). After the war, production plants of penicillin increased in capacity and the price dropped. It was not until the end of the sixties that major improvements of the purification of penicillin were achieved. The price of penicillin has now dropped to about $40/kg. The annual production of penicillin is 15,000 tons. Gist-brocades produces about 20%.

Penicillin is produced by P. Chrysogenum, a fungus growing under aerobic conditions. The fermentation is usually performed in fermentors which are operated as a fedbatch. In time many models describing the fermentation kinetics of the substrate limited growth of P. Chrysogenum and its production of penicillin, have been developed. Most of these models are based on a separation of the growth phase and the production phase. The model developed by J.J. Heijnen a.o. is based on a growth coupled production. This model was used in this plant design.

Most recent processes use a physical absorption in an organic phase like butyl acetate. The problem of this extraction method is that in order to obtain high extraction factors the pH has to be low. Because the stability of penicillin rapidly decreases with decreasing pH, the purification section usually has a large penicillin loss. In order to minimize these losses special extractors have been developed, like the Podbielniak, in which very short contact times are possible. Another method of minimizing the penicillin losses is by trying to extract the penicillin at higher pH values. This can be achieved by reactive extraction. In this method a carrier molecule, a secondary amine, is dissolved in an organic phase and reacts with the penicillin in the aqueous phase.

Because the conventional method of extracting the penicillin was not used, the short-contact-time extractors were not needed. Therefore it was decided to perform the extraction in a tubular centrifuge in which mixing and settling zones accomplished the mass transfer.
4. Flowsheet

The flowsheet can be divided into three parts:

1. Discontinuous production of penicillin, filtration and cooling.
2. Continuous upgrading of the penicillin.
3. Regeneration of the organic phase of the extraction.

ad. 1.

In the fermentor (R13) the penicillin is being produced. The fermentation is fedbatch and the weight increases from 100 ton to 185 ton. During the 200 hours of fermentation glucose, ammonia, phenylacetic acid and sulphuric acid are continuously being fed. Compressed air (11) is supplied. The fermentor is cooled with water and stirred. The air leaving the fermentor (12) contains the produced CO2.

After the fermentation the broth (1) is pumped (P12) to the rotating vacuum drum filter (M3). From the filtrate tank (V9), the filtrate (2) is being pumped (P8) through the heat exchanger (H5) to the storage tank (V14). In this tank the acid is added to obtain the right pH value for the extraction. Acid is supplied from vessel (V6).

ad. 2.

From the storage tank the filtrate (3) is continuously being pumped (P15) to the absorber (M19). In the absorber the filtrate is countercurrently extracted with carrier dissolved in butyl acetate (8 and 10). The organic phase leaving the absorber (4) is reextracted with water in the desorber (M18).

The penicillin is now concentrated. Before the aqueous phase (5) is sent to the crystallization it is purified by coalbed absorption (M20 and M22). The flow leaving the coalbed absorber (6) is sent to the crystallization section.

ad. 3.

The organic phase leaving the desorber is divided into two flows; 25% is being regenerated (9) and 75% is directly sent back to the absorber (8).

The regeneration of the carrier is performed by pH shifts. First the organic phase is treated with acid to precipitate the proteins in a stirred tank (R25). The proteins are being filtered off (M26 and M27) and the two phases are being separated (V30).

The next step is the cleaning of the carrier by treatment with lye in a stirred tank (R34). The two phases are again separated (V36). The cleaned organic phase is sent back to the absorber (10).

For table flow numbers see Appendix N.
Fig 5.1 Simulation results with respect to total broth weight (G), total biomass (GCX), total penicillin mass (GCP) and total mass of glucose (GCS), all in kg.
According to the model of Heijnen (4) two hundred hours of fermentation result in a total weight of 184,884 kg per fermentor (see fig. 5.1). With a broth density of 1037 kg/m³ (see Appendix A) the broth volume becomes 178 m³.

Based upon a 15% gas holdup and a working volume of 85% the volume of the fermentor amounts to 250 m³. Standard geometries were used to design the fermentor dimensions²:

- \( D_T \) diameter of fermentor = 5.40 m
- \( H_T \) height of fermentor = 10.80 m
- \( D_S \) diameter of six bladed agitator = 1.80 m
- \( D_W \) height of blades of agitator = 0.30 m
- \( C \) position of first agitator with reference to bottom of fermentor = 0.90 m
- \( C' \) position of second agitator with reference to bottom of fermentor = 5.00 m

The second agitator has been positioned in such a way that when starting the fed batch procedure the blades of the agitator be just under the liquid surface (under aerated circumstances).

Our factory produces about 20% of the world’s sodium benzylpenicillin production and can therefore be compared to Gist brocades in Delft \( (3 \times 10^6 \text{ kg Pen/yr} = 8417.5 \text{ kmol Pen/yr}) \).

Each fermentation yields 9972.5 mol penicillin. The minimum number of fermentations per year can be calculated as:

\[
\frac{8417.5 \times 10^3}{9972.5} = 844.1 \quad (1)
\]

To estimate the number of fermentors needed we assumed a period of hundred hours to sterilize, fill, empty and clean a fermentor:

\[
\frac{844.1 \times (200 + 100)}{8760} = 28.9 \quad (2)
\]

With an overall penicillin recovery of 92% (see Appendix L) 31.4 fermentors are needed. This factory has been designed for 30 fermentors.
6. Fermentation

6.1. Introduction

The fermentation is carried out in a reactor of 250 m$^3$ under aseptic conditions. The process begins with the inoculation derived from a seed developing section, resulting in an initial broth weight of $10^5$ kg with a mycelial concentration of 1 g DM/kg.

Sterile air at relative high pressure ($\approx 2.5$ bar), obtained from air compressors and filtered through one or more air filters, enters the fermentor through a sparger at the bottom of the tank. To prevent infection the tank is operated under a positive pressure of about 0.7 bar.

Temperature and pH are closely controlled. The optimum values with respect to penicillin production are 25-27°C and pH=7.0.

The glucose feed rate is regulated in such a way that a specific growth rate profile, consistent with a maximal penicillin production is achieved. Because glucose has been chosen as the growth limiting component, all other nutrients should be added such that their concentration is just in excess of the minimum requirements which are dictated by the specific growth rate and penicillin production rate. All necessary medium components are heat sterilized prior to addition.

The precursor phenylacetic acid is also fed continuously. This to avoid a toxic level for the mycelium and to minimize the hydroxylation by the organism. Continuous feeding of phenylacetic acid leads to a conversion of precursor into the penicillin side chain of more than 90%.

During fermentation an antifoam agent has to be added continuously. The ideal defoamer should be completely non-toxic to the organism and effective in relatively small amounts. Typical defoamers used are lard oil containing 2% octadecyl alcohol or lard oil containing 6% Alkaterge C.

The duration of the fermentation is limited to about two hundred hours. The reasons involved are:
- build up of toxicants and inhibitors (even penicillin itself can act as inhibitor)
- volume of the fermentor
- development of mutants of lower productivity
- limitation of oxygen transfer capacity of the fermentor (although theoretically sufficient, practically probably occurring).
6.2. Description of model

Until now the production of penicillin has always been considered as a two phased process in which a phase of rapid growth without product formation (trophophase) and a phase without growth but with formation of the penicillin (idiophase) can be discerned.

However, Heijnen, Roels and Stouthamer\textsuperscript{4} developed a model in which these two phases are not separated any longer but exist at the same time. Product and biomass are formed side by side during the process of fermentation.

Therefore it is not necessary to have two separate fermentors, one of which is used for the production of biomass while the other functions as a production vessel.

The model is based on a balance for the six relevant elements C, H, O, N, P and S, an enthalpy balance and five kinetic equations.

The elementary balance\textsuperscript{5} can be written as:

\[ \frac{dC_8}{dt} = r \cdot \alpha \cdot E + \phi \cdot E \]  

(6.1)

where:
- \( C_8 \) vector of concentrations of the elements (g atom/m\(^3\))
- \( \alpha \) stoichiometric matrix
- \( \phi \) vector of exchange
- \( E \) elementary matrix
- \( r \) vector of conversion rates

Because no conversion of elements occurs it follows:

\[ r \cdot \alpha \cdot E = 0 \]  

(6.2)

or:

\[ r \cdot E = 0 \]  

(6.3)
For the components involved in the fermentation (see table 6.1), the elementary matrix becomes:

\[
E = \begin{bmatrix}
6 & 12 & 6 & 0 & 0 & 0 & 0 \\
1 & 1.64 & 0.52 & 0.16 & 0.0054 & 0.0046 \\
16 & 18 & 4 & 2 & 0 & 1 \\
8 & 8 & 2 & 0 & 0 & 0 \\
16 & 20 & 5 & 2 & 0 & 1 \\
0 & 0 & 2 & 0 & 0 & 0 \\
0 & 2 & 1 & 0 & 0 & 0 \\
0 & 3 & 0 & 1 & 0 & 0 \\
0 & 2 & 4 & 0 & 0 & 1 \\
0 & 3 & 4 & 0 & 1 & 0 \\
1 & 0 & 2 & 0 & 0 & 0 \\
\end{bmatrix}
\]
Table 6.1: relevant compounds in penicillin fermentation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical formula</th>
<th>Conversion rate (mol/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>C₆H₁₂O₆</td>
<td>rₛ</td>
</tr>
<tr>
<td>Mycelium</td>
<td>CH₁₆H₄O₅₂N₀₁₆S₀₀₀₄₆P₀₀₅₄</td>
<td>rₓ</td>
</tr>
<tr>
<td>Penicillin</td>
<td>C₁₆H₁₈O₄N₂S</td>
<td>rₚ</td>
</tr>
<tr>
<td>Phenyl acetic acid</td>
<td>C₈H₁₈O₂</td>
<td>rₚₐ</td>
</tr>
<tr>
<td>Penicilloic acid</td>
<td>C₁₆H₂₀O₂N₂S</td>
<td>rₚ₀</td>
</tr>
<tr>
<td>Oxygen</td>
<td>O₂</td>
<td>rₒ</td>
</tr>
<tr>
<td>Water</td>
<td>H₂O</td>
<td>rₜ</td>
</tr>
<tr>
<td>Ammonia</td>
<td>NH₃</td>
<td>rₘ</td>
</tr>
<tr>
<td>Sulphuric acid</td>
<td>H₂SO₄</td>
<td>rₛᵤ</td>
</tr>
<tr>
<td>ortho-Phosphoric acid</td>
<td>H₃PO₄</td>
<td>rₛₚ</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>CO₂</td>
<td>rₛₖ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molweight (g/mol)</th>
<th>Molar enthalpy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>180</td>
<td>-303</td>
</tr>
<tr>
<td>Mycelium</td>
<td>24.52</td>
<td>-28.1</td>
</tr>
<tr>
<td>Penicillin</td>
<td>334</td>
<td>-115</td>
</tr>
<tr>
<td>Phenyl acetic acid</td>
<td>136</td>
<td>-69</td>
</tr>
<tr>
<td>Penicilloic acid</td>
<td>352</td>
<td>-183</td>
</tr>
<tr>
<td>Oxygen</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Water</td>
<td>18</td>
<td>-68</td>
</tr>
<tr>
<td>Ammonia</td>
<td>17</td>
<td>-19</td>
</tr>
<tr>
<td>Sulphuric acid</td>
<td>98</td>
<td>-194</td>
</tr>
<tr>
<td>ortho-Phosphoric acid</td>
<td>98</td>
<td>-319</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>44</td>
<td>-94</td>
</tr>
</tbody>
</table>
With the vector of conversion rates ($\mathbf{r}$) given by:

$$
\mathbf{r} = [ r_s, r_x, r_p, r_{pa}, r_{po}, r_o, r_w, r_n, r_{su}, r_{ph}, r_c ]
$$

(6.4)

the multiplication of $\mathbf{E}$ and $\mathbf{r}$ results in the following relationship for the conversion rates:

**Carbon balance:**

$$
6r_s + r_x + 16r_p + 8r_{pa} + 16r_{po} + r_c = 0
$$

(6.5)

**Hydrogen balance:**

$$
12r_s + 1.64r_x + 18r_p + 8r_{pa} + 20r_{po} + 2r_w + 3r_n + 2r_{su} + 3r_{ph} = 0
$$

(6.6)

**Oxygen balance:**

$$
6r_s + 0.52r_x + 4r_p + 2r_{pa} + 5r_{po} + 2r_o + r_w + 4r_{su} + 4r_{ph} + 2r_c = 0
$$

(6.7)

**Nitrogen balance:**

$$
0.16r_x + 2r_p + 2r_{po} + r_n = 0
$$

(6.8)

**Sulphur balance:**

$$
0.0046r_x + r_p + r_{po} + r_{su} = 0
$$

(6.9)

**Phosphorus balance:**

$$
0.0054r_x + r_{ph} = 0
$$

(6.10)
After algebraic manipulation of the above equations the following relations for the conversion rates of oxygen ($r_o$), carbon dioxide ($r_c$), ammonia ($r_n$), sulphuric acid ($r_{su}$) and phosphoric acid ($r_{ph}$) are obtained:

$$
-r_o = -6r_s - 9r_{pa} - 1,044r_x - 18,5r_p - 18,5r_{po} \quad (6.11)
$$

$$
r_c = -6r_s - 8r_{pa} - r_x - 16r_p - 16r_{po} \quad (6.12)
$$

$$
-r_n = 0,16r_x + 2r_p + 2r_{po} \quad (6.13)
$$

$$
-r_{su} = 0,0046r_x + r_p + r_{po} \quad (6.14)
$$

$$
-r_{ph} = 0,0054r_x \quad (6.15)
$$

The metabolic heat production can be described by:

$$
r_H = r \times h \quad (6.16)
$$

in which $h$ is the vector of molar enthalpies of the components involved. This leads to:

$$
r_H = 303r_s + 28,1r_x + 115r_p + 69r_{pa} + 183r_{po} + 68r_n + 194r_{su} + 319r_{ph} + 94r_c \quad (6.17)
$$

With equations (6.11) - (6.15) this leads to:

$$
r_H = -669r_s - 955r_{pa} - 110,1r_x - 1961r_p - 1961r_{po} \quad (6.18)
$$

In order to be able to calculate $r_o$, $r_c$, $r_n$, $r_{su}$, $r_{ph}$ and $r_H$, five kinetic equations have to be known. In these equations the glucose uptake rate ($r_s$), the penicillin formation rate ($r_p$), the biomass formation rate ($r_x$), the phenylacetic acid consumption rate ($r_{pa}$) and the penicilloic acid formation rate ($r_{po}$) are described.

For the glucose uptake rate a Michaelis-Menten type of relation is used:

$$
-r_s = q_{s, max} \times C_s \times C_x \times G / \left( K_s + C_s \right) \quad (6.19)
$$

where:
- $q_{s, max}$: maximum specific glucose uptake rate (mol/moleDM h)
- $C_s$: glucose concentration in broth (mol/kg)
- $C_x$: biomass concentration in broth (mol/kg)
- $G$: total broth weight (kg)
- $K_s$: Michaelis constant for glucose uptake (mol/kg)
The sugar consumed is used not only for maintenance and the formation of biomass but also for the formation of penicillin and its hydrolyzed product penicilloic acid. The following equation gives us an expression for the biomass formation rate \( r_x \):

\[
-r_s = r_x/Y_{xs} + m_s C_x G + (r_p + r_{po}) / Y_{ps}
\]  

(6.20)

in which:
- \( Y_{xs} \) true yield for biomass on substrate (mol/mol)
- \( Y_{ps} \) true yield for product on substrate (mol/mol)
- \( m_s \) maintenance constant (mol/molDM h)

The penicillin production rate can be described by:

\[
\begin{align*}
    r_p + r_{po} &= q_{p,max} \cdot C_x \cdot G & \mu \geq \mu_{cr} \\
    r_p + r_{po} &= q_{p,max} \cdot C_x \cdot G / (\mu/\mu_{cr}) & \mu < \mu_{cr}
\end{align*}
\]

(6.21) and (6.22)

where:
- \( q_{p,max} \) maximum specific penicillin synthesis rate (mol/molDM/h)
- \( \mu \) specific growth rate (h\(^{-1}\))
- \( \mu_{cr} \) critical specific growth rate for penicillin production (h\(^{-1}\))

Most data in literature more or less agree with the kinetic behaviour proposed by Humphrey and Jefferis, meaning a stable specific rate of penicillin synthesis at growth rates lower than the critical value \( \mu_{cr} \). However the specific rate of penicillin synthesis is not constant below this critical value \( \mu_{cr} \) but decreases with decreasing specific growth rate. A reasonable value for \( \mu_{cr} \) is 0.01h\(^{-1}\).

Assuming the precursor phenylacetic acid is not used in reactions other than penicillin synthesis the rate of conversion of the precursor is given by:

\[
-r_{pa} = r_p + r_{po}
\]

(6.23)

in which the rate of penicillin hydrolysis \( r_{po} \) can be described by a first order reaction:

\[
r_{po} = k \cdot C_p \cdot G
\]

(6.24)

with:
- \( k \) first order rate constant (h\(^{-1}\))
- \( C_p \) penicillin concentration in broth (mol/kg)
A mass balance for biomass (DM), penicillin and glucose can be formulated:

For biomass:

\[
\frac{d(GC_x)}{dt} = C_x \frac{dG}{dt} + G \frac{dc_x}{dt} = r_x
\]  
(6.25)

For penicillin:

\[
\frac{d(GC_p)}{dt} = C_p \frac{dG}{dt} + G \frac{dc_p}{dt} = r_p
\]  
(6.26)

For glucose:

\[
\frac{d(GC_s)}{dt} = C_s \frac{dG}{dt} + G \frac{dc_p}{dt} = r_s + \Phi_s
\]  
(6.27)

where \(\Phi_s\) is the flow of glucose into the fermentor (mol/hr).

The broth weight (G) as a function of the fermentation time can be calculated as follows:

\[
G(t) = \int_t \left( \sum \Phi_i + 0.032r_o + 0.044r_c \right) dt
\]  
(6.28)

where: - \(\Phi_i\) flow rate of component i to the system (mol/hr)

The fermentation according to this growth-coupled penicillin production model has been simulated using the modeling program PSI. Values of the parameters used are listed in table 6.2. A listing of the program is given in Appendix B. Process conditions are summarized in table 6.3.
Table 6.2: values of parameters used in the growth coupled penicillin production model\textsuperscript{4, 6}.

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
<th>unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$q_{s, \text{max}}$</td>
<td>0.045</td>
<td>mol/molDM/hr</td>
</tr>
<tr>
<td>$K_s$</td>
<td>0.0011</td>
<td>mol/kg</td>
</tr>
<tr>
<td>$Y_{xs}$</td>
<td>4.20</td>
<td>mol/mol</td>
</tr>
<tr>
<td>$Y_{ps}$</td>
<td>0.61</td>
<td>mol/mol</td>
</tr>
<tr>
<td>$m_s$</td>
<td>0.0027</td>
<td>mol/molDM/hr</td>
</tr>
<tr>
<td>$q_{p, \text{max}}$</td>
<td>0.00033</td>
<td>mol/molDM/hr</td>
</tr>
<tr>
<td>$k$</td>
<td>0.002</td>
<td>h\textsuperscript{-1}</td>
</tr>
</tbody>
</table>

Table 6.3: process conditions during fermentation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air flow rate</td>
<td>50 Nm$^3$/ton/\text{hr}</td>
</tr>
<tr>
<td>Broth weight after inoculation</td>
<td>$10^5$ kg</td>
</tr>
<tr>
<td>Initial mycelium concentration</td>
<td>1 gDM/kg</td>
</tr>
<tr>
<td>Ammonia feed concentration</td>
<td>250 g/kg</td>
</tr>
<tr>
<td>Sulfuric acid feed concentration</td>
<td>250 g/kg</td>
</tr>
<tr>
<td>Phenylacetic acid concentration</td>
<td>250 g/kg</td>
</tr>
<tr>
<td>Duration of fermentation</td>
<td>200 hr</td>
</tr>
<tr>
<td>Glucose concentration in feed</td>
<td>500 g/kg</td>
</tr>
</tbody>
</table>

Before inoculation ortho-phosphoric acid is added to the batch in an amount sufficient for the duration of the fermentation (200 hrs). Feed rates of ammonia, sulphuric acid and phenylacetic acid are supplied at rates equal to their conversion rates ($r_n$, $r_s$, $r_{pa}$).

Simulations were performed with different rates of glucose feed. Heijnen\textsuperscript{4} showed that both a constant feed rate as well as a decreasing feed rate were inferior to a linearly increasing glucose feed rate with respect to biomass production and penicillin production. Varying the feed rate according to:

$$\Phi_s = \Phi_{s0} + b \times t$$

(6.29)

where:
- $t$ time (h)
- $\Phi_{s0}$ glucose feed rate at $t=0$ h (mol/hr)
- $b$ increase of feed rate per hour (mol/hr\textsuperscript{2})

showed a varying penicillin yield in reference to biomass production. An optimal value for the glucose feed rate was found to be:
Fig 6.1 Simulation results with respect to total amount of added oxygen (IRO), glucose (IPHIS) and removal of carbon dioxide (IRC) and water (IH2O) in kg.

Fig 6.2 Simulation results with results to total amount added of ammonia (IRN), phenylacetic acid (IRPA) and glucose (IRSU).
\[ \Phi_s = 11.0 \times t \]  \hspace{1cm} (6.30)

in which case the amount of penicillin mass was at a maximum and the amount of remaining not metabolized substrate at a minimum. The final results of the simulation are summarized in table 6.4. Figures 6.1 and 6.2 show the course of the fermentation. These results are used in designing the fermentation equipment and the downstream processing equipment.

**Table 6.4: results of simulation with a glucose feed rate of \( \Phi_s = 11t \) (t is time (hr)).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total broth weight</td>
<td>184,884 kg</td>
</tr>
<tr>
<td>Penicillin</td>
<td>9972.5 mol</td>
</tr>
<tr>
<td>Non-metabolized glucose</td>
<td>24.6 mol</td>
</tr>
</tbody>
</table>
Fig 6.3  Rheological equations
6.3. Rheology

Mycelial broths are highly viscous fluids. Because the viscosity is an important aspect of a fermentation process in describing transport phenomena. A constitutive equation, i.e. a relationship between shear stress, shear rate and their time dependency, would be required. Unfortunately there is no such equation.

In order to be able to assess the viscosity empirically relations have been developed to describe the pseudoplastic behaviour of mycelial broths. Two frequently used expressions are the power law and Casson equation (see fig.6.3):

**Power law:**

\[ \tau = K \cdot (\dot{\gamma})^n \]  

(6.31)

where:  
- \( \tau \) shear stress (N/m²)  
- \( K \) consistency index (N.s^n/m²)  
- \( n \) flow behaviour index (-)  
- \( \dot{\gamma} \) shear rate (s⁻¹)

Both the influence of the mycelial concentration as well as the shape of the mycelial aggregate is incorporated in both the consistency index (\( K \)) and the flow behaviour index (\( n \)). With increasing mycelial concentration \( K \) increases and \( n \) decreases. The same relationship holds for an increasing particle size; an increase of mycelial aggregate is coupled with an increasing consistency index (\( K \)) and a decreasing flow behaviour index (\( n \)).

**Casson:**

\[ \sqrt{\tau} = \sqrt{\tau_0} + K_c \cdot \sqrt{\dot{\gamma}} \]  

(6.32)

where:  
- \( \tau \) yield stress (N/m²)  
- \( K_c \) Casson constant (N^0.s^-n/m)

For mould suspensions the Casson equation parameters \( \tau_0 \) and \( K_c \) can be estimated by means of the following equations:

\[ \tau = 1.67 \times 10^{-4} \times (C_m)^{2.5} \times (L_e)^{0.8} \]  

(N/m²)  

(6.33)

\[ K_c = 5.454 \times (C_m)^{1.0} \times (L_{h_g u})^{0.6} \]  

(N^0.5.s^-0.5/m)  

(6.34)

where:  
- \( C_m \) biomass concentration (kgDM/m³)  
- \( L_e \) dimensional hyphal length (-)  
- \( L_{h_g u} \) length of the hyphal growth unit (m)
In case of a mould of \textit{P. chrysogenum} typical values for the dimensionless hyphal length and the hyphal growth unit are:

\[ L_e = 55 \]
\[ L_{h_g_u} = 80 \mu m \]

The main difference between the power law and the Casson equation is the inability of the power law to predict a limiting viscosity for infinite shear rates. Another difference is a poor agreement of experimental results in the low shear range with the power law\textsuperscript{9,10}.

In order to determine the apparent viscosity with the above mentioned, empirical relations of the actual flow conditions in the fermentor are required. That is one needs to know the shear rate (\( \tau \)).

Calderbank and Moo-Young\textsuperscript{7} proposed a relation in which the average shear rate (\( \tau_{av} \)) for a flow around a turbine impeller in a stirred tank reactor can be estimated:

\[ \tau_{av} = k_s \cdot N_s \]  \hspace{1cm} (6.35)

where:
- \( \tau_{av} \) average shear rate (s\textsuperscript{-1})
- \( k_s \) constant
- \( N_s \) impeller speed (s\textsuperscript{-1})

For laminar flow conditions the value of the constant \( k_s \) lies between 10 and 15. According to van 't Riet and Smith\textsuperscript{12} the value of \( k_s \) under turbulent aerated conditions amounts to 10 to 50. We use an average value of 30 for \( k_s \).

A crude estimation for the mean bulk shear rate (\( \tau_{bulk} \)) for a vessel with standard geometry is given by Nagata\textsuperscript{13}:

\[ \tau_{bulk} \approx 0.2 \cdot N_s \]  \hspace{1cm} (6.36)

Because the viscosity is shear rate dependent an apparent viscosity (\( \mu_a \)) is defined:

\[ \mu_a = \frac{d\tau}{d\tau \tau=\tau_0} \]  \hspace{1cm} (6.37)

where:
- \( \mu_a \) apparent viscosity at shear rate \( \tau_0 \) (s\textsuperscript{-1})
- \( \tau_0 \) shear rate at defined impeller speed (s\textsuperscript{-1})
Therefore an estimation of the apparent viscosity according to the power law and Casson equation becomes:

Power law:

\[ \mu_a = K \cdot n \cdot (\tau)^{n-1} \] (Pa.s) \hspace{1cm} (6.38)

Casson:

\[ \mu_a = \frac{K_c}{\sqrt{\tau}} \cdot (\sqrt{\tau_0} + K_c \cdot \sqrt{\tau}) \] (6.39)

Results of the calculations are listed in table 6.5. As can be seen the values of the two types of apparent viscosity (\(\mu_a\)), in the bulk or near the impeller, mutually differ a factor four to five. For the most part this originates from the calculation of the apparent viscosity at different broth ages.

Table 6.5: results of calculations of apparent viscosity (\(\mu_a\)) for different values of the Power Law constants (K,n) and Casson constants (\(\tau_0, K_c\)). Value of \(k_s=30\). Mycelium concentration \(X = 63\) kgDM/m\(^3\). Rotational speed of agitator \(N_s = 2s^{-1}\).

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>K (Pas(^n))</th>
<th>n (-)</th>
<th>(\mu_a) Impeller (Pas)</th>
<th>(\mu_a) Bulk (Pas)</th>
<th>Literature source</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>58</td>
<td>0.11</td>
<td>0.17</td>
<td>14.4</td>
<td>14</td>
</tr>
<tr>
<td>39</td>
<td>15.5</td>
<td>0.37</td>
<td>0.44</td>
<td>10.2</td>
<td>15</td>
</tr>
<tr>
<td>62</td>
<td>57.8</td>
<td>0.23</td>
<td>0.57</td>
<td>26.9</td>
<td>15</td>
</tr>
<tr>
<td>90</td>
<td>70.9</td>
<td>0.23</td>
<td>0.70</td>
<td>33.0</td>
<td>15</td>
</tr>
<tr>
<td>111</td>
<td>103.3</td>
<td>0.18</td>
<td>0.65</td>
<td>39.4</td>
<td>15</td>
</tr>
<tr>
<td>53</td>
<td>205.0</td>
<td>0.04</td>
<td>0.16</td>
<td>19.8</td>
<td>16</td>
</tr>
<tr>
<td>113</td>
<td>106.3</td>
<td>0.048</td>
<td>0.10</td>
<td>12.2</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(\sqrt{\tau_0}) (Pa)</th>
<th>(K_c) (Pa(^s)s(^{-1}))</th>
<th>(\mu_a) Impeller (Pas)</th>
<th>(\mu_a) Bulk (Pas)</th>
<th>Literature source</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.39</td>
<td>1.20</td>
<td>3.20</td>
<td>23.1</td>
<td>10</td>
</tr>
</tbody>
</table>
A final estimation of the apparent viscosity is based upon the following assumptions:

1. In the high shear range \((N_s > 0.2 \, \text{s}^{-2})\) the power law probably gives a better estimation of the apparent viscosity than the Casson equation\(^9,^{10}\). The apparent viscosity near the impeller is therefore calculated with the power law.

2. The flow behaviour index \((n)\) is fairly constant and is equal to about 0.23 on the average\(^10\).

3. The consistency index \((K)\) is time dependent i.e. varies with the broth age. However it does not increase with time continuously, as one would expect, but decreases again towards the end of the fermentation. Based upon the data of Bongenaar\(^{14}\) the value of \((K)\) after 200 hours of fermentation is estimated at 58.

This all leads to the following estimation of the apparent viscosity near the impeller:

\[
(\mu_a)_{\text{impeller}} = K \cdot n \cdot (30 \cdot N_s)^{n-1} \\
= 58 \cdot 0.23 \cdot (30 \cdot 2)^{0.77} \\
= 0.57 \, \text{Pa.s}
\]
6.4 Power Input

The two criteria of importance in determining the minimum rotational speed of the agitator are the necessity to keep the broth in suspension and the necessity to achieve a good dispersion of the air.

To fulfill the criterion of suspension the Re number must have a value of at least 85, in case of two standard turbine agitators mounted on one shaft. This leads to a minimum rotational speed of:

$$N_{\text{min}} = \frac{\text{Re} \cdot \mu_a}{\nu_b \cdot D_s^2} = \frac{85 \cdot 0.57}{1037 \cdot 1.8^5}$$

$$= 1.44 \times 10^{-2} \text{ s}^{-2} = 0.87 \text{ rpm}$$

Fulfilling the criterion of dispersion the minimum rotational speed (towards the end of the fermentation) is estimated according to Zwietering:

$$N_{\text{min}} = \frac{\Phi_g \cdot g}{16 \cdot D_s^4} \cdot \frac{D_t}{D_s} = \frac{50 \cdot 185 \cdot 9.8}{3600 \cdot 16 \cdot 1.8^4}$$

$$= 1.78 \text{ s}^{-1} \approx 107 \text{ rpm}$$

It is obvious the criterion of dispersion is far more important than the criterion of suspension. Including a ten percent margin the operational speed of revolution becomes:

$$N_s = 2 \text{ s}^{-1} = 120 \text{ rpm}$$

(6.43)

The power input ($P_0$) can be estimated as:

$$P_0 = P_v \cdot \rho_b \cdot N_s^3 \cdot D_s^5$$

(6.44)

where $P_v$ the Power number. In case of a turbine impeller with six blades (2):

$$P_v = 5$$

(6.45)
Therewith:

\[ P_0 = 5 \times 1037 \times 2^3 \times 1.8^5 \]
\[ = 783.8 \text{ kW} \]  \hspace{1cm} (6.46)

However under aerated conditions the necessary power input is reduced. The exact amount of reduction is difficult to estimate especially for non-Newtonian liquids. As deduced in appendix B we estimated the ratio of gassed to ungassed power input \((P_g/P_0)\) to be a half.

If two impellers are mounted on one shaft, the power input increases with \(\sqrt{2}\). This results in:

\[ P_g = P_0 \times 0.5 \times \sqrt{2} \]  \hspace{1cm} (6.47)
\[ = 783.8 \times 0.5 \times \sqrt{2} \]
\[ = 554.2 \text{ kW} \]
6.5 Oxygen supply

The model used describes a glucose limiting growth of the microorganism \textit{P.chrysogenum}. This means all other nutrients should be present in ample amounts. Achieving this is no problem with respect to the added salts, but it can be a problem with respect to oxygen.

A lot of factors are involved which influence the oxygen concentration in the bulk of the broth:
- airflow
- the number and speed of agitators
- viscosity of the broth
- coalescence of air bubbles

In order to check if the used airflow (50Nm$^3$/ton/hr) is sufficient to keep the broth from oxygen limitation the following calculation has been made:

$$\text{OTR} = k_L a \cdot (C^* - C) \quad (6.48)$$

where:
- $\text{OTR}$ oxygen transfer rate \hspace{1cm} (mol/m$^3$/s)
- $k_L a$ oxygen transfer coefficient \hspace{1cm} (s$^{-1}$)
- $C^*$ oxygen concentration at saturation in broth \hspace{1cm} (mol/m$^3$)
- $C$ oxygen concentration in bulk of broth \hspace{1cm} (mol/m$^3$)

The oxygen transfer coefficient ($k_L a$) can be estimated by:

$$k_L a = 1.025 \cdot (P/V)^{0.4} \cdot v_s^{0.5} \cdot N_s^{0.5} \quad (6.49)$$

with:
- $P/V$ power input \hspace{1cm} (kW/m$^3$)
- $v_s$ superficial gas velocity \hspace{1cm} (m/s)
- $N_s$ agitator speed \hspace{1cm} (s$^{-1}$)

This leads to:

$$k_L a = 1.025 \cdot (554.2 / 180)^{0.4} \cdot (50 \cdot 185 / (3600 \cdot 0.25 \cdot \pi \cdot 5.4^2)^{0.5} \cdot 2$$

$$= 7.61 \cdot 10^{-2} \text{ s}^{-1}$$

The saturated oxygen concentration ($C^*$) is given by:

$$x_{O_2} = \frac{P_{O_2}}{H} \quad (6.50)$$

where:
- $x_{O_2}$ molefractio of oxygen in liquid \hspace{1cm} (-)
- $P_{O_2}$ partial oxygen pressure in air \hspace{1cm} (N/m$^2$)
- $H$ Henry coefficient \hspace{1cm} (N/m$^2$)
The average pressure of the gas in the fermentor is given by:

\[ P_{\text{gas}} = P_A + \left( P_h + P_B \right)/2 \quad (6.51) \]

where:
- \( P_{\text{gas}} \) average pressure in fermentor (N/m\(^2\))
- \( P_A \) atmospheric pressure (N/m\(^2\))
- \( P_h \) hydrostatic pressure at the bottom of fermentor (N/m\(^2\))
- \( P_B \) back pressure (N/m\(^2\))

Values are:
- \( P_A = 1.013 \times 10^5 \) N/m\(^2\)
- \( P_h = \rho_b \times g \times h \)
  \[ = 1037 \times 9.8 \times 7.86 = 0.8 \times 10^5 \text{ N/m}^2 \]
- \( P_B = 10 \text{ p.s.i} = 0.689 \times 10^5 \text{ N/m}^2 \)

This leads to:

\[ P_{\text{gas}} = 1.76 \times 10^5 \text{ N/m}^2 \quad (6.52) \]

Given a 21 vol% of oxygen in air the partial oxygen pressure becomes:

\[ P_{O_2} = 0.21 \times 1.76 \times 10^5 = 0.370 \times 10^5 \text{ N/m}^2 \quad (6.53) \]

The Henri coefficient at \( T=25^\circ C \) is:

\[ H = 4.4 \times 10^9 \text{ N/m}^2 \quad (6.54) \]

With this the mol fraction of oxygen in water becomes:

\[ X_{O_2} = \frac{0.370 \times 10^5}{4.4 \times 10^9} = 8.41 \times 10^{-6} \quad (6.55) \]

Assuming the oxygen saturation concentration in the broth can be compared to the oxygen saturation concentration in water, it follows:

\[ C^* = 8.41 \times 10^{-6} \times 55.6 \approx 0.47 \text{ mol/m}^3 \quad (6.56) \]

The presence of ions leads to a decrease of the saturation concentration. This effect however can be neglected compared to the effect of antifoam on the oxygen transfer coefficient. Depending on the amount added it can result in a decrease of the \( k_L a \) of 40%.
This run needed 303.38 seconds

Fig 6.4 Simulation of oxygen uptake rate \( r_o \) as function of time (hr).
Further it is assumed that the oxygen concentration in the bulk has to be at least 10% of the oxygen saturation concentration in order to prevent an oxygen limiting situation for the microorganism.

Now the maximal achievable oxygen transfer rate (OTR) can be calculated:

\[
OTR = 0.6 \times k_L a \times 0.9 \times C^* \\
= 0.6 \times 7.61 \times 10^{-2} \times 0.9 \times 0.47 \\
= 0.019 \text{ mol/m}^3/\text{s}
\]  
(6.57)

The oxygen uptake rate (OUR) towards the end of the fermentation amounts (see fig. 6.4):

\[
\text{OUR} = \frac{8663}{180 \times 3600} = 0.013 \text{ mol/m}^3/\text{s}
\]  
(6.58)

Therefore because the oxygen transfer rate exceeds the oxygen uptake rate, the used airflow (50Nm$^3$/ton.hr) is sufficient in preventing an oxygen limiting situation for the mycelium.
Fig. 6.5 Simulation result with respect to metabolic heat production ($r_H$).
6.6 **Heat balance**

The broth is to be kept at a constant temperature of 25°C. Because more heat is generated than lost by for example evaporation, cooling devices are required.

The heat sources (all in J/s) are:

1. $r_{HS}$ = heat dissipated by agitator
2. $r_{Hm}$ = metabolic heat production
3. $r_{HE}$ = heat loss resulting from evaporation
4. $r_{HW}$ = heat loss through fermentor wall
5. $r_{HA}$ = heat generated by throughflowing air
6. $r_{HR}$ = all other heat sources

Ad 1. Assuming all the agitating energy is dissipated as heat, $r_{HS}$ amounts to:

$$r_{HS} = 554.2 \text{ kW} \quad (6.59)$$

Ad 2. The metabolic heat production towards the end of the fermentation (see fig.6.5):

$$r_{HM} = 912.6 \text{ kW} \quad (6.60)$$

Ad 3. To calculate the maximum amount of energy loss by evaporation we assume that the incoming air contains no water, while the outgoing air is saturated. The massflow of evaporated water can be described by:

$$\Phi_w(t) = 0.016 * G(t) * 50*10^3 \quad (\text{kg/hr}) \quad (6.61)$$

Total broth weight at the end of the fermentation amounts to:

$$G(200 \text{ hr}) = 184,884 \text{ kg} \quad (6.62)$$

leading to:

$$\Phi_w(200 \text{ hr}) = 147.9 \text{ kg/hr} \quad (6.63)$$

The heat of vaporization of water at $T=25^\circ C$ being 585 kcal/kg the total vaporization energy ($r_{HE}$) becomes:

$$r_{HE} = 147.9 * 585 * 4.2 / 3600 = 100.9 \text{ kW} \quad (6.64)$$
Ad 4. The heat loss through the fermentor wall to the surroundings is given by:

\[ r_{HW} = h_w * A_F * (T_b - T_s) \]  \hspace{1cm} (6.65)

with:
- \( h_w \) total heat transfer coefficient (W/m\(^2\) °C)
- \( A_F \) surface of fermentor (m\(^2\))
- \( T_b \) broth temperature (°C)
- \( T_s \) temperature of surroundings (°C)

The value of the above parameters is:
- \( h_w = 10 \) W/m\(^2\) °C
- \( A_F = 206.1 \) m\(^2\)
- \( T_b = 25°C \)
- \( T_s = 20°C \)

Therefore the heat loss through the fermentor wall is:

\[ r_{HW} = 10 * 206.1 * (25 - 20) = 10.3 \text{ kW} \] \hspace{1cm} (6.66)

Ad 5. The energy dissipated by the expanding rising bubbles is equal to the heat absorbed by the gas isothermal compression. The net heat effect is zero. The air is compressed adiabatically resulting in a significant increase in temperature."
Ad 6. Contributions of heat production with respect to feed flows, pH control or antifoam administration are small and will therefore not be considered.

The overall heat production \( (r_{HT}) \) at the end of the fermentation then adds up to:

\[
\begin{align*}
    r_{HT} &= r_{HS} + r_{HM} - r_{HE} + r_{HW} + r_{HA} \\
    &= 554.2 + 912.6 - 100.9 + 10.3 + 0 \\
    &\approx 1400 \text{ kW} \tag{6.69}
\end{align*}
\]
6.7. Calculation of broth cooling

The broth can be cooled with the aid of a cooling coil and/or jacket. Because the heat transfer capacity of a cooling coil, with respect to heat transfer coefficient and cooling surface, is superior to a jacket type of cooling (see Appendix B) we remove the heat with a cooling coil.

Calculation of overall heat transfer coefficient of cooling coil ($U_c$).

The overall heat transfer coefficient can be estimated according to:

$$\frac{1}{U_c} = \frac{1}{\alpha_{bc}} + \frac{d_c}{\theta_c} + \frac{1}{\alpha_c} + \frac{1}{R_{cb}} + \frac{1}{R_c}$$  \hspace{1cm} (6.70)

with:
- $U_c$ overall heat transfer coefficient ($\text{W/m}^2/\text{°C}$)
- $\alpha_{bc}$ heat transfer coefficient of broth on the outside of cooling coil ($\text{W/m}^2/\text{°C}$)
- $\alpha_c$ heat transfer coefficient on the inside of cooling coil ($\text{W/m}^2/\text{°C}$)
- $d_c$ thickness of cooling coil ($\text{m}$)
- $\theta_c$ thermal conductivity of cooling coil ($\text{W/m/°C}$)
- $R_{cb}$ fouling resistance on outside surface of cooling coil ($\text{W/m}^2/\text{°C}$)
- $R_c$ fouling resistance on inside surface of cooling coil ($\text{W/m}^2/\text{°C}$)

6.7.1. Estimation of $\alpha_{bc}$

Experimental investigations by Edney$^{19}$ showed that heat transfer from agitated non-Newtonian fluids to a helical cooling coil, using a six-bladed turbine impeller, can be described by:

$$Nu_c = 0.067 \times Re^{0.607} \times Pr^{0.345} \times Vi^{-0.2}$$  \hspace{1cm} (6.71)

where:
- $Nu_c = \frac{\alpha_{bc} \times D_c}{\theta^b}$  \hspace{1cm} (6.72)

- $Re_{1} = \frac{\mu_b \times N_s \times D_s}{\mu_a} = \frac{1037 \times 2 \times 1.8^2}{0.57} = 1.1789 \times 10^4$  \hspace{1cm} (6.73)
\[ Pr_t = \frac{C_{p,b} \times \mu_b}{\theta_b} = \frac{4.2 \times 10^3 \times 0.57}{0.6} = 3990 \quad (6.74) \]

\[ Vi = \frac{K}{K_w} = 1.06 \quad (6.75) \]

with:
- \( \theta_b \) thermal conductivity of broth \( (\text{W/m}^2/\text{°C}) \)
- \( K \) consistency index \( (\text{Pa.s}^n) \)
- \( K_w \) consistency index at mean temperature of heat transfer surface \( (\text{Pa.s}^n) \)
- \( C_{p,b} \) specific heat of broth \( (\text{J/kg/°C}) \)

The value of the thermal conductivity \( (\theta_b) \) and the specific heat \( (C_{p,b}) \) of the broth are estimated to be equal to the values for water:

\[ \theta_b \approx 0.6 \text{ W/m}^2/\text{°C} \quad (6.76) \]
\[ C_{p,b} \approx 4.2 \times 10^3 \text{ J/kg/°C} \quad (6.77) \]

The dimensions of the cooling coil are:
- \( D_h \) helix diameter = 4.75 m
- \( D_e \) outside diameter of coil = 0.16 m
- \( D_i \) inside diameter of coil = 0.15 m
- \( n_c \) number of coils = 25

This all leads to:

\[ Nu_c = 0.0675 \times 296.1 \times 17.47 \times 0.988 = 345.0 \quad (6.78) \]

It follows:

\[ \alpha_{bc} = \frac{\theta_b}{D_c} \times Nu = \frac{0.6}{0.16} \times 345 = 1294 \text{ W/m}^2/\text{°C} \quad (6.79) \]

6.7.2. Calculation of coil heat resistance

With a cooling coil made of stainless steel with a thickness of 0.01 m:

\[ \frac{\theta_b}{d_c} = \frac{50}{0.01} = 5000 \text{ W/m}^2/\text{°C} \quad (6.80) \]
6.7.3. Calculation of $\alpha_c$

The heat to be removed by the cooling coil is:

$$\Phi_{hc} = r_{HT} - \Phi_{Hj} = 1400 - 120 = 1280 \text{ kW} \quad (6.81)$$

Assuming an incoming temperature of the cooling water of $10^\circ C$ and an outgoing temperature of $18^\circ C$, the velocity of the cooling liquid in the coil can be calculated as follows:

$$v = \frac{\Phi_{hc}}{\mu_w \cdot 0.25 \cdot \pi \cdot D_i^2 \cdot C_p \cdot T} = \frac{1280 \cdot 10^3}{1000 \cdot 0.25 \cdot \pi \cdot 0.15^2 \cdot 4.2 \cdot 10^3 \cdot 8} = 2.16 \text{ m/s} \quad (6.82)$$

Iterative calculation showed the required velocity of the cooling water towards the end of the fermentation is:

$$v = 2.55 \text{ m/s} \quad (6.83)$$

Temperature of the outgoing cooling water now is:

$$T = 16.8^\circ C \quad (6.84)$$

The Reynolds number now becomes:

$$Re = \frac{\mu_w \cdot v \cdot D_i}{\mu_w} = \frac{1000 \cdot 2.55 \cdot 0.15}{10^{-3}} = 382,500 \quad (6.85)$$

and Prandtl:

$$Pr = \frac{C_p \cdot \mu_w}{\theta_w} = \frac{4.2 \cdot 10^3 \cdot 10^{-3}}{0.6} = 7 \quad (6.86)$$
Now we can calculate the Nusselt number according to\textsuperscript{33}:

\[
\text{Nu} = \frac{X/8 \ast (\text{Re} - 1000) \ast \text{Pr}}{1 + 12.7 \ast X/8 \ast (\text{Pr}^{2/3} - 1)} \quad (6.87)
\]

with:

\[
X = (1.82 \ast \log \text{Re} - 1.64)^2 \quad (6.88)
\]

Nu becomes:

\[
\text{Nu} = 4345.5
\]

Therefore:

\[
\alpha_c = \frac{\theta_w}{D_i} \ast \text{Nu} = \frac{0.6}{0.15} \ast 4345.5 \approx 17382 \text{ W/m}^2/\degree \text{C} \quad (6.89)
\]

\textbf{6.7.4 Fouling resistances}

The fouling resistance on the process side of the coil (R\textsubscript{eb}) is assumed to be\textsuperscript{21}:

\[
R_{eb} = 2275 \text{ W/m}^2/\degree \text{C} \quad (6.90)
\]

The fouling resistance on the inside of the cooling coil (R\textsubscript{c}) can be estimated as\textsuperscript{21}:

\[
R_c = 5680 \text{ W/m}^2/\degree \text{C} \quad (6.91)
\]
The overall heat transfer coefficient of the cooling coil \( (U_c) \) becomes:

\[
U_c = \frac{1}{\alpha_{bc}} + \frac{\theta_c}{d_c} + \frac{1}{\alpha_c} + \frac{1}{R_{cb}} + \frac{1}{R_c} \quad (6.92)
\]

\[
= \frac{1}{1294} + \frac{1}{5000} + \frac{1}{17382} + \frac{1}{2275} + \frac{1}{5680} \quad \text{-} 1
\]

\[
= 607.6 \text{ W/m}^2/\text{°C}
\]

The heat removed by the cooling coil can now be calculated as:

\[
\phi_{HC} = U_c \times A_c \times T_{ln}
\]

(6.93)

with \( A_c \) the surface of the cooling coil (m²). The surface \( A_c \) can be calculated as:

\[
A_c = \pi^2 \times D_c \times D_h \times n_c
\]

\[
= \pi^2 \times 0.16 \times 4.75 \times 25 = 187.5 \text{ m}^2
\]

Therefore:

\[
\phi_{HC} = 607.6 \times 187.5 \times 11.3 \approx 1290 \text{ kW}
\]

(6.95)

The cooling capacity of the cooling coil is sufficient to keep the broth temperature at a constant value of 25°C during the 200 hours of fermentation.
7. Filtration of the fermentor broth

7.1. Introduction

Because of the poor thermal conductivity of the fermentation broth, it is decided to cool the fermentation liquid and not the broth as whole. Therefore it is necessary to filtrate the broth. Studies of filtration of fermentation broths of penicillin showed that these kind of broths can be filtered with a vacuum filter. Because of its continuous operation and its somewhat lower costs than for example a belt filter, we decided to filter the broth with a rotating vacuum drum filter (RVDF).

7.2. Filter Theory

In a RVDF there are three processes to be discerned:

1) filtering
2) cake washing
3) cake drying

These three processes all take place during one rotation of the drum, so their operation time can be expressed in terms of rotation time.

7.2.1. Filtering

If we express the filterability of the broth in the permeability of the filter cake \( K \) we can derive the filter equation from D'Arcy's Law:

\[
V_{11} = \left( 2 \times A^2 \times \Delta P \times K \times C_f \times t_f / \mu \right)^{1/2}
\]

\( V_{11} \) amount of filtrate \( m^3 \)
\( A \) filter surface \( m^2 \)
\( \Delta P \) pressure drop cake \( Pa \)
\( K \) permeability cake \( m^2 \)
\( C_f \) filter coefficient --
\( t_f \) filter time \( s \)
\( \mu \) viscosity \( Pa.s \)

If we express the filter time \( t_f \) as a part of the rotation time \( t_c \):

\[
t_f = \alpha \times t_c
\]
Then the filtrate flow \((Q_{11})\) becomes:

\[ Q_{11} = V_{11} / t_c \]  
(7.3)

Substituting these parameters in (1):

\[ Q_{11} = (2 * A^2 * \Delta p * K * Cf * \alpha / t_c / \mu)^{1/2} \]  
(7.4)

With \(Cf\) being the volume ratio between filtrate and cake:

\[ Cf = V_{11} / V_{12} \]  
(7.5)

We now have an expression for calculating the filtrate flow. By choosing either the pressure drop over the cake \((p)\) or the rotation time \((t_c)\) the filter equation can be solved.

7.2.2. Cake washing

After filtering, the cake has to be washed in order to recover the products that are present in the saturated cake. The ratio between the washwater and the liquid in the cake is given by:

\[ N = 0.5 * \beta * C \]  
(7.6)

\[ \beta = t_w / t_f \]  
(7.7)

\[ C = Cf / \epsilon \]  
(7.8)

\[ \epsilon = \text{voidage of cake} \]  
(7.9)

7.2.3. Drying

There are no good theories relating drying time \((t_d)\) and saturation of the cake. Therefore we choose the saturation of the cake. A good experimental figure seems to be 0.15 %.

7.3. Operating times

If we consider the washing and drying of the cake to be purely plugflow than the relation between the filtration, washing and drying time is given by:

\[ t_f : t_w : t_d = 1 : 2/C : 1/C \]  
(7.10)

\[ C = Cf / \epsilon \]  
(7.11)
7.4. Designing the vacuum filter

We calculated that a flow of 59.45 m$^3$/hr leaves the fermentor every ten hours during three hours. This flow contains:

$$0.162 \text{ m}^3 \text{ mycelium/ m}^3 \text{ fermentation broth}$$

The mycelial flow then becomes.

$$Q_m = 9.63 \text{ m}^3/\text{hr}$$

If we set the cake voidage $\epsilon$ at $\epsilon=0.375$ then this results in:

$$0.26 \text{ m}^3 \text{ cake / m}^3 \text{ fermentation broth}$$

This results in a cake flow ($Q_c$) and an initial filtrate flow of:

$$Q_c = 15.46 \text{ m}^3 \text{ m/hr}$$

$$Q_{f,i} = 44 \text{ m}^3/\text{hr}$$

The filtration coefficient is defined as:

$$C_f = V_{filtrate} / V_{cake} = 0.725/0.27 = 2.85$$  \hspace{1cm} (7.12)

The relation between the different process times is given by:

$$t_f : t_w : t_d = 1 : 2/C : 1/C$$  \hspace{1cm} (7.13)

with:

$$C = C_f/\epsilon = 7.6$$  \hspace{1cm} (7.14)

Because

$$t_c = t_f + t_d + t_w$$  \hspace{1cm} (7.15)

We can define the different process times as a fraction of the rotation time of the filter:

$$t_f/t_c = 0.7$$
$$t_w/t_c = 0.2$$
$$t_d/t_c = 0.1$$

The relation presented above is based on a plugflow model of cake washing and cake drying. This means that the two processes are performed ideal. Because this is not true we suggest that the washing and drying time should be $0.45t_c$, this results in:

$$t_f/t_c = 0.55$$  \hspace{1cm} (7.16)
$$t_w/t_c = 0.30$$  \hspace{1cm} (7.17)
$$t_d/t_c = 0.15$$  \hspace{1cm} (7.18)
The filter equation was defined as:

\[ Q_{11} = \sqrt{\frac{2A^2 \Delta p K C_f \alpha}{\mu t_c}} \]  

(7.19)

With the parameter values:

- \( \Delta p = 0.95 \) bar
- \( K = 5 \times 10^{-12} \) m²
- \( C_f = 2.85 \)
- \( \alpha = 0.55 \) (=\( t_f / t_c \))
- \( \mu = 0.57 \) Pa.s
- \( Q_{11} = 1.22 \times 10^{-2} \) m³/s (with \( Q_{11} \) being equal to \( Q_{f,i} \))

this results in:

\[ A = 7.55 \times \sqrt{t_c} \]

If the filter surface is set at 150 m² then the rotation time (\( t_c \)) becomes 395s. Which means that the rotation speed of the filter drum becomes 9.16rph.

The cake height then becomes:

\[ H_{cake} = \frac{V_{cake}}{A} = \frac{Q_{c} \times t_{c}}{A} / 3600 \]

\[ H_{cake} = 15.46 \text{ m}^3 / \text{hr} / 9.16 \text{ RPH} / 150 \text{ m}^2 \]

(7.20)

\[ H_{cake} = 11.3 \text{ mm} \]

After filtering the cake has to be washed. The wash ratio is calculated as:

\[ N = 0.5 \times \beta \times C \]  

(7.21)

with:

\[ \beta = \frac{t_w}{t_f} = 0.55 \]  

(7.22)

this results in:

\[ N = 0.5 \times 0.55 \times 7.6 \]

\[ = 2.1 \]

The cake contains 15.46 m³/hr * \( \epsilon \) = 5.8 m³/hr fermentation liquid. Therefore the washwater flow (\( Q_w \)) becomes 12.2 m³/hr.

After the cake is washed, the cake is dried. We stated that the liquid content of the dried cake is about 15%. The total amount of washwater in the cake then becomes 1.445 m³/hr washwater. The total flow coming from the filter \( Q_{f,tot} \) then becomes:

\[ Q_{f,tot} = Q_{f,i} + (Q_{w} - Q_m) + (Q_w - 0.15 \times Q_m) \]

\[ = 44 + 5.80 + 10.7 \]

\[ = 60.5 \text{ m}^3 / \text{hr} \]
7.5. Calculation of density of filtrate

The fermentation broth of 59.5 m³/hr has a density of 1037 kg/m³. The massflow then results in 61.6 ton/hr.

The density of the mycelium is 1125 kg/m³, with \( Q_m \) being 9.63 m³/hr this results in an mycelial massflow of 10.83 ton/hr.

To the filtrate 10.8 m³/hr washwater is added. We now have all the data to calculate the density of the total filtrate flow \( \mu_{f, tot} \):

\[
\mu_{f, tot} = \frac{\Sigma m}{\Sigma V} \tag{7.23}
\]

\[
= \frac{(61.6 - 10.83 + 10.8)}{60.5} = 1018 \text{ kg/m}^3
\]

The filter surface was set at 150 m², this can well be three filters of 50m² each.

Cake discharge can be performed by knife scraping of the cake.
8. Cooling the filtrate

8.1. Introduction

After the filtration, the filtrate has to be cooled to prevent further thermal degradation of the penicillin. Because the fermentor is emptied in three hours, and every ten hours a fermentation is ended, this means that the cooling device has to be operated discontinuously. We decide to cool the filtrate in a U-tube heat exchanger with Freon-12 as refrigerant. We suppose that the discontinuous operation will not be a problem and that the seven hours of operation stop can be used for cleaning.

8.2. Determining the cooling capacity

As we already calculated, the flow resulting from the filter is 61.6 ton/hr. The temperature is 298 K and we want to cool it to 278 K. If we suppose that the specific heat is about equal to that of water, then the heat to be exchanged (Q) becomes:

\[ Q = 20 \times 4.2 \times 61600 \times 1014 \times 3600 = 1437 \text{ kW} \quad (8.1) \]

The refrigerant we have chosen was Freon-12. It is being vaporized at 266.23 K and 2.46 bar. Some thermodynamic properties are described in appendix H.

8.3. Determining the cooling surface

In order to determine the cooling surface we have to determine the overall heat transfer coefficient \( U \), which is defined as:

\[ \frac{1}{U} = \frac{1}{\alpha_u} + \frac{1}{\alpha_i} + Ru + Ri \quad (8.2) \]

Determining \( \alpha_u \):

\[ \alpha_u = 3.755 \times 10^{-5} \times P_c^{-0.9} \times Q_{\text{max}}^{0.7} \times \left(1.8\frac{(p/p_c)^{1.7}}{(p/p_c)^{1.2}} + 4\frac{(p/p_c)^{1.2}}{(p/p_c)^{1.0}}\right) \quad (8.3) \]

\[ Q_{\text{max}} = 0.054 \times r_g^{-0.5} \times (\sigma \times (r_l - r_g) \times g) \quad (8.4) \]

\[ Q_{\text{max}} = 138.5 \text{ kW/m}^2 \]

this results in:

\[ \alpha_u = 6868.34 \text{ W/m}^2/\text{K} \]

A good first estimation for \( \alpha_i \) is 4000 W/m\(^2\)/K. The fouling resistances are both set at 1.76 \times 10^{-4} \text{ m}^2/\text{K/W}

40
This results in:

\[ U = 1338 \text{ W/m}^2/\text{K} \]

If we determine \( T_{\text{ln}} \) we can calculate the surface needed to cool the filtrate:

\[ \Delta T_{\text{ln}} = \left( \Delta T_g - \Delta T_k \right) / \ln \left( \frac{T_g}{T_k} \right) \]  
\[ \Delta T_{\text{ln}} = 20.1 \text{ K} \]

Resulting in a cooling surface of:

\[ A = \frac{Q}{\Delta T_{\text{ln}}} / U = 53.4 \text{ m}^2 \]  

(8.6)

8.4. Designing the heat exchanger

With the surface known, we can choose a heat exchanger. A heat exchanger with the needed surface and an allowable pressure drop is:

- 8-pass U-tube
- number of tubes 190
- \( D_i \) 25 inch
- \( d_u \) 25 mm
- \( d_l \) 21 mm
- pitch 1.25 inch
- configuration triangle
- \( L_{\text{eff}} \) 7.16 m

With these data we can calculate the velocity through the tubes:

\[ v_{tu} = 4 * \Phi_m * N / \mu_l / \pi / d_i^2 / z \]  
\[ v_{tu} = 2.05 \text{ m/s} \]  

(8.7)

Reynolds then becomes:

\[ Re = 1018 * 2.05 * 0.021 / 1*10^{-3} = 43825 \]  

(8.8)

The friction factor is \( f=0.027 \). Therefore the pressure drop becomes:

\[ \Delta p = N * ( f*1/d_i +1.5 ) * 1/2 * r_l * v_{tu}^2 \]  
\[ \Delta p = 0.45*10^5 \text{ Pa} \]  

(8.9)

This pressure drop is acceptable.

We can make a better calculation of the overall heat transfer coefficient. The \( \alpha_i \), the \( Ru \) and the \( Ri \) remain the same. We can now however make a better estimation of \( \alpha_i \).
Prandtl is defined as:
\[ \text{Pr} = \frac{C_p \cdot \mu}{\lambda} = 7 \]  
(8.10)

With Reynolds we can now calculate Nusselt:
\[ \text{Nu} = 221 \]  
(8.11)

Then \( \alpha_i \) becomes:
\[ \alpha_i = 6320 \text{ W/m}^2/\text{K} \]

And \( U \) becomes:
\[ U = 1318 \text{ W/m}^2/\text{K} \]

Therefore \( A \) becomes:
\[ A = 55 \text{ m}^2 \]

This is about the same as we already calculated. We add about 15% to compensate for any in- and outflow phenomena eddy's:
\[ A = 63 \text{ m}^2 \]

and \( L_{\text{eff}} \) becomes 8.22 m.
9. **Extraction section**\textsuperscript{34,35,36,37}.

9.1. *Extraction of penicillin*

In order to concentrate the penicillin before crystallization and achieve partial purification of the penicillin, it is extracted. The extraction is usually performed by absorption in an organic phase. Depending on the concentration wanted and the phase in which crystallisation has to take place, the penicillin is reextracted to the aqueous phase. Sometimes even a third extraction is performed, of course the penicillin losses increase with increasing number of extractions.

This extraction is based upon physical absorption of the penicillin in an organic phase, such as butyl acetate. The problem with physical absorption of penicillin is the necessity of low pH values to obtain a high distribution. Physical absorption only concerns the associated penicillin acid therefore the pH value has to be as low as possible to obtain as high as possible concentrations of the associated penicillin acid. However with low pH values the degradation of penicillin increases severely. This consequently leads to the design of extractors with extreme short contact times, meaning expensive extractors.

This is the reason why we choose to examine the extraction of penicillin by means of reactive extraction, which is based on the chemical reaction between a carrier molecule, mostly dissolved in the organic phase, and the penicillin in the aqueous phase. The complete mechanism is described below. The main advantage of reactive extraction is the better performance at higher pH values (pH = 5). At this value penicillin is fairly stable. The overall reaction of the reactive extraction model as we used it is:

\[ \text{Ca}_{\text{org}} + \text{Cp}^- + \text{Ch}^+ \rightleftharpoons \text{Cah}_{\text{org}} \]  \hspace{1cm} (9.1)

Of course the physical absorption also has to be taken into account.

Because the carrier Amberlite-LA2 is dissolved in the organic phase crystallization from this phase is avoided. This means that the penicillin has to be reextracted into the aqueous phase. This can be achieved by a pH-shift. From the definition of the equilibrium constant of the reactive extraction (9.6), it can be understood that an increase of the proton concentration, therefore a decrease of the pH, forces the reaction in (9.1) to the right. Lowering the proton concentration forces the equilibrium to the left.

This is the reason why we use an absorber operating at a rather low pH value (pH=5), and a desorber operating at a rather high pH value (pH=9). The organic phase with the carrier is being recycled from the absorber to the desorber and sent back to the absorber again. Because the recovery in the desorber will not be complete, the returning organic phase will still contain some penicillin.
The carrier will not only react with the penicillin-ion but also with other ions present, for example the acid-ion of the precursor, used to obtain the penicillin-G. Phenylacetic acid is toxic therefore its extraction has to be dealt with in a quantitative way.

Not only the phenylacetic acid is unwantedly extracted, also various other ions will be either strongly or weakly bound by the carrier. Some ions may be bound so strongly to the carrier that they will not sufficiently desorb in the desorber. In time the carrier will become fouled with those ions. This is the reason why every once in a while the carrier has to be regenerated. For continuous operation however, the recycle flow can be regenerated continuously. Regeneration can be realized for example by desorption at very high pH value. There will still be some ions that will irreversibly bind to the carrier, therefore eventually the whole carrier has to be renewed.

The main objective of an absorber-desorber section is concentrating the penicillin at a minimum of loss. The penicillin loss of an extraction section is determined by the performance of the absorber and the desorber. If the efficiency of the penicillin recovery in the absorber is too low, the penicillin will be lost in the waste water. If the efficiency of the penicillin recovery in the desorber is too low, the penicillin will be lost in the regeneration section of the carrier. Below is described which parameters influence the performance of the extraction section.

In order to calculate the penicillin recovery of an extraction section, a simulation model was developed. The quantitative extraction of the phenylacetic acid was also taken into account. Below is described how the simulation model calculates the extraction section. In the next paragraph will be described how one theoretical stage can be calculated for a two ion extraction.

9.2. Calculations for one theoretical stage (T.S.)

\[
\begin{array}{cccc}
\text{C}_{\text{ahp}}, & \text{C}_{\text{ahf}}, & \text{C}_{\text{ahp}}, & \text{C}_{\text{ahf}} \\
\text{Ch}_{p}, & \text{Ch}_{f}, & \text{Ch}_{p}, & \text{Ch}_{f} \\
\text{Ca} & \text{org}_{\text{out}} & \text{org}_{\text{in}} & \text{Ca} \\
N-1 & \text{absorber} & \text{N}^{\text{th}} \text{T.S.} & N+1 \\
\text{water}_{\text{i}n} & \text{water}_{\text{o}ut} & \text{C}_{p}, & \text{Ch}_{p} \\
\text{C}_{f}, & \text{Ch}_{f} & \text{C}_{f}, & \text{Ch}_{f} \\
\end{array}
\]

If we want to determine the extraction of two components in one theoretical stage, we first have to determine the number of variables and the number of relations. In one theoretical stage we can define 20 variables, being:
We have got 20 variables. If we determine the number of relations we know how many variables have to be set in order to solve the system. For every component we have two equilibrium relations, one of the reactive extraction and one of the physical absorption. This makes four equilibrium equations together. For the two components in the aqueous phase we have for both the in- and outgoing flow a relation between the associated and the dissociated acid, this results in a total number of four acid relations. We can define three mass balances one for penicillin one for phenylacetic acid and one for the carrier. Because we chose the pH value and the ratio of the organic and aqueous phase (E/R) in advance, we have a total of 13 relations. This means that 7 concentrations have to be chosen or set.
When we start calculating an absorber we usually start at one end, the bottom or the top. In our case we calculate from bottom to the top. This means that, if we concern the aqueous phase, we have to choose or know how much penicillin and phenylacetic acid will not be recovered. If we concern the organic phase we need to know what the concentration of the components in this flow is. Initially we suppose all the concentrations of the ingoing organic phase to be 0, except for the free carrier concentration, which is equal to the total carrier concentration. Later we shall see that this assumption is not correct because the organic flow returns from the desorber and will still be containing some penicillin and phenylacetic acid.

We have now determined five concentrations in the organic phase, and we have chosen two extra relations for the aqueous phase, this includes that we can now solve the theoretical stage. The next theoretical stage can be solved by using the data of the previous theoretical stage.

We will now describe the calculations that are necessary to determine one theoretical stage, if two ions are being extracted by reactive extraction and physical absorption.

In the aqueous phase the penicillin is present as the associated acid and the dissociated acid:

\[
HP \rightleftharpoons H^+ + P^- \tag{9.2}
\]

the equilibrium is defined by:

\[
K_{z_p} = \frac{Ch_p}{Ch^+ \cdot Cp^-} \tag{9.3}
\]

For phenylacetic acid we can define the same relation:

\[
HF \rightleftharpoons H^+ + F^- \tag{9.4}
\]

\[
K_{z_f} = \frac{Ch_f}{Ch^+ \cdot Cf^-} \tag{9.5}
\]

In the above we stated that if we calculate an absorber from bottom to top, we know the concentrations in the outgoing aqueous phase of the theoretical stage. In a theoretical stage the two outgoing flows are at equilibrium. Therefore the outgoing organic phase is at equilibrium with the outgoing aqueous phase. The equilibrium constant for the reactive extraction is defined as:

\[
K_{re_p} = \frac{Ca_{hp,org}}{10^{-pH} \cdot Cp^- \cdot w \cdot Ca_{org}} \tag{9.6}
\]

\[
K_{re_f} = \frac{Ca_{hf,org}}{10^{-pH} \cdot Cf^- \cdot w \cdot Ca_{org}} \tag{9.7}
\]
Ca is the concentration of the unreacted carrier. This concentration can be substituted by:

\[
Ca = Ca_{ot} - Ca_{hp} - Ca_{hf}
\]  

(9.8)

Rewritten this becomes:

\[
Ca = Ca_{ot} / (1 - K_{rep} * 10^{-pH} * Cp^- - K_{ref} * 10^{-pH} * Cf^-)
\]  

(9.9)

This is substituted in (9.6) and (9.7):

\[
Ca_{hp} = K_{rep} * 10^{-pH} * Cp^- * Ca_{ot} / (1 - 10^{-pH} *(K_{rep} * Cp^- + K_{ref} * Cf^-))
\]  

(9.10)

\[
Ca_{hf} = K_{ref} * 10^{-pH} * Cf^- * Ca_{ot} / (1 - 10^{-pH} *(K_{ref} * Cf^- + K_{rep} * Cp^-))
\]  

(9.11)

The concentration of P^- and of F^- are known, if these values are respectively substituted in (9.10) and (9.11), this will result in the amount of P^- and F^- that have reacted with the carrier. Not only reactive extraction occurs but also physical absorption. The physical distribution coefficients are defined as:

\[
\alpha_p = Ch_{org}/Ch_w
\]  

(9.12)

\[
\alpha_f = Ch_{org}/Ch_w
\]  

(9.13)

Because we know HPw and HFw we can calculate the amount of penicillin and phenylactic acid that are physically absorbed. We have calculated the total amount of penicillin and phenylactic acid that will be extracted. So we have determined the outgoing organic phase of the theoretical stage. Because we now have determined three flows, we can determine the fourth by solving the mass balances for penicillin and phenylactic acid. The mass balance for penicillin is defined as:

\[
C_{penw_{in}} * \Phi_v + C_{pen_{org_{in}}} * \Phi_v * E/R = C_{penw_{out}} * \Phi_v + C_{pen_{org_{out}}} * \Phi_v * E/R
\]  

(9.14)

\[
C_{pen_{org_{in}}} \text{: total concentration of penicillin in the organic phase in}
\]

\[
C_{pen_{w_{out}}} \text{: total concentration of penicillin in the aqueous phase out}
\]

\[
C_{pen_{org_{out}}} \text{: total concentration of penicillin in the organic phase out}
\]

\[
C_{penw_{in}} \text{: total concentration of penicillin in the aqueous phase in}
\]

\[
E/R \text{: ratio between extract and raffinate in this case between organic and aqueous phase}
\]
For phenylacetic acid we can define an analogous relation:

\[
C_{fen\text{in}} \times \phi_v + C_{fen_{\text{org}\text{in}}} \times \phi_v \times E/R = C_{fen\text{out}} \times \phi_v + C_{fen_{\text{org}\text{out}}} \times \phi_v \times E/R
\]

(9.15)

Therefore by solving the mass balances we know the values of \( C_{pen\text{in}} \) and \( C_{fen\text{in}} \).

With the acid constants we then can determine the percentage of acid ions.

Because we now have determined all the values of the concentrations in one theoretical stage. We can now go to the next theoretical stage. If we calculate from the bottom to top this will be the \( N-1\)th stage.

9.3. Penicillin loss

There are two ways of loosing penicillin in the extraction section. The first is the penicillin that is not extracted in the absorber and will be lost in the wastewater treatment. The second way of loosing the penicillin is in the desorber. The recovery of the penicillin in the desorber is not 100\%, this means that some of the penicillin is returned to the absorber in the organic phase. The loss does not occur by recycling the organic phase but by the partial regeneration of the organic phase. In the next section we shall look at the different variables that are important to the absorber and desorber performances.

9.3.1. Regenerated recycle flow

Studies of reactive extraction of penicillin stated that every four passes the organic phase containing the carrier was regenerated. Because we want a continuous regeneration, in order to maintain stationary performance of the absorber and the desorber, we decided to regenerate 25\% of the total recycle stream continuously.

In our simulation model this means that 25\% of the penicillin, that is not recovered in the desorber, is lost. If we decrease the part of the total recycle-flow that is regenerated, the total penicillin loss decreases too, according to the simulation model. In a real system however the total penicillin recovery may be decreased by the decreased regeneration flow. The reason for this is that the carrier becomes fouled, which will lead to a decreasing performance of the absorber.

Therefore the part of the recycle flow that is being regenerated definitelty influences the total penicillin recovery. In the simulation model however we will not consider fouling effects. We consider the organic phase returning from the regeneration section as being clean.
Fig. 9.1 Penicillin recovery (%) as a function of the number of absorber stages

<table>
<thead>
<tr>
<th>parameters</th>
<th>value</th>
<th>unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/R-abs</td>
<td>0.167</td>
<td></td>
</tr>
<tr>
<td>pH-abs</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>T.S.abs</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>R/E-des</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>pH-des</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>T.S.des</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>conc. carrier</td>
<td>0.326</td>
<td>mol/l</td>
</tr>
</tbody>
</table>
Fig. 9.3 Penicillin recovery (%) as a function of the dimensionless carrier concentration

<table>
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</thead>
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<tr>
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<td></td>
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<tr>
<td>R/E-des</td>
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</tr>
<tr>
<td>pH -des</td>
<td>9.0</td>
<td></td>
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<tr>
<td>T.S.des</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>conc. carrier</td>
<td>variable mol/l</td>
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</tbody>
</table>
Fig. 9.2 Penicillin recovery (%) as a function of the number of desorber stages

<table>
<thead>
<tr>
<th>parameters</th>
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<tr>
<td>pH-abs</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>T.S.abs</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>R/E-des</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>pH-des</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>T.S.des</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>conc. carrier</td>
<td>0.326</td>
<td>mol/l</td>
</tr>
</tbody>
</table>

9.3.2. pH values

It can be seen from the definition of the equilibrium constant that a low pH value will lead to higher penicillin recoveries in the absorber. A high pH value in the desorber will lead to higher recoveries of penicillin in the desorber.

Both the pH value of the absorber and the desorber are limited by the stability of penicillin. It is found that in the range of pH=5 to pH=9 the penicillin is fairly stable. That is why we choose pH=5 for the absorber and pH=9 for the desorber.

9.3.3. Number of theoretical stages (T.S.)

Of course the efficiency of the absorber as well as that of desorber increases with the increasing number of theoretical stages. From fig. 9.1 and fig. 9.2 it can be derived that above three theoretical stages not much extra penicillin recovery is achieved in the absorber and the desorber. This is the reason why we set the number of theoretical stages for both the absorber and desorber at three.

9.3.4. Carrier concentration

From fig. 9.3 it can be derived that there is an optimum in the penicillin recovery at different carrier amounts. This can be explained as follows. If there is more penicillin present than carrier it is impossible to recover all the penicillin in the absorber. This means that the penicillin recovery of the absorber increases with increasing carrier amount. This implies that desorption will be more difficult at high carrier concentrations, as also can be seen from the definition of the equilibrium-constant. Therefore penicillin recovery of the desorber decreases with increasing carrier amount. These effects lead to a maximum in the penicillin recovery at a certain carrier amount. This amount is slightly more than one time the amount of penicillin present, and is influenced by the presence of phenylacetic acid.
**Fig. 9.4** Penicillin recovery as a function of the concentration factor

<table>
<thead>
<tr>
<th>parameters</th>
<th>value</th>
<th>unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/R-abs</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>pH-abs</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>T.S.abs</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>R/E-des</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>pH-des</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>T.S.des</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>conc. carrier</td>
<td>0.326</td>
<td>mol/l</td>
</tr>
</tbody>
</table>

**Fig. 9.5** Phenylacetic acid recovery (%) as a function of the concentration factor

<table>
<thead>
<tr>
<th>parameters</th>
<th>value</th>
<th>unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/R-abs</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>pH-abs</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>T.S.abs</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>R/E-des</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>pH-des</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>T.S.des</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>conc. carrier</td>
<td>0.326</td>
<td>mol/l</td>
</tr>
</tbody>
</table>
9.3.5. Ratio organic aqueous phase

For the absorber we define the ratio:

\[ E/R-\text{abs} = \text{Extract}/\text{Raffinate} \]  \hspace{1cm} (9.16)

as the ratio between the organic and the aqueous phase. For the desorber we define the ratio:

\[ R/E-\text{des} = \text{Raffinate}/\text{Extract} \]  \hspace{1cm} (9.17)

as the ratio of the organic and the aqueous phase. The concentration factor (CON) is defined as:

\[ \text{CON} = \frac{R/E-\text{des}}{E/R-\text{abs}} \]  \hspace{1cm} (9.18)

As we would expect, the penicillin loss increases with increasing concentration factor. As can be seen from fig.9.4, the lines of equal concentration factor have a slightly upward directed slope towards a higher R/E desorber. The differences however are only marginal.

The penicillin recovery is well over 99%. It can also be seen (fig.9.5) that there is hardly any selectivity between penicillin extraction and phenylacetic acid extraction. This means that almost all the phenylacetic acid has to be absorbed by the coal absorption section, or be lost in the crystallization section.

The solubility of penicillin acid in water at high pH values is high. We decided to concentrate the penicillin to a factor 36, six times in the absorber and six times in the desorber. The E/R-abs then becomes 0.167, the R/E-des then becomes 6.

9.4. Simulation model

The objective of the simulation model is to make a quantitative calculation of the penicillin and the phenylacetic acid recovery of an extraction section. Above we described how to calculate one theoretical stage. In this paragraph we shall describe how we can calculate an absorber and desorber section by using these equations.

We shall now have a closer look at the simulation model.

First of all we know the amount of penicillin and phenylacetic acid in the aqueous phase leaving the storage tank and entering the absorber. These are our reference values. As we already stated we have to know the amount of penicillin and phenylacetic acid leaving the absorber. In the simulation model this is realized by choosing a certain penicillin and phenylacetic acid recovery, \( N_p \) and \( N_f \) respectively. Therefore the amounts leaving the absorber become:
Fig. 9.7 Flowsheet simulation model of extraction.

1. Set all data

2. Input pen & fen in

3. Set Npabs & Nfabs

4. Desorber data known?
   y
   5. Start values org-phase desorb.
   6. Org. clean

7. Calculate Nth stage

6. N=1?
   y
   9. Calculate all other stages.

10. Have all been calc.?
    y
    13. Change Np

11. Np correct?
    y
    14. Change Nf

12. Nf correct?
    y

15. Choose start Np & Nf

16. Start values desorber

17. Calculate first stage desorber

18. N=1?
   y
   19. Calculate other stages desorber

20. All stages been calc.?
    y
    23. Change Np

21. Np des. correct?
    y
    24. Change Nf

22. Nf des. correct?
    y

25. System stationary?
    y

26. OUTPUT
The objective is to choose the exact efficiencies that will lead to the same values of \(C\text{pen}_w,\text{out}\) and \(C\text{fen}_w,\text{out}\) as in the flow leaving the storage tank. If this is not accomplished the efficiencies have to be chosen again and the calculations are repeated. We start the calculations at the bottom of the absorber. And stage by stage we calculate our way to the top of the absorber.

After we have calculated the top theoretical stage of the absorber we have determined the concentrations of the ingoing aqueous phase of that theoretical stage. If these values are equal to our reference values, the absorber is finished and the desorber can be calculated.

Explanation of the simulation model with the flowsheet. (fig.9.7).

ad.1 Set all data.

In this part of the program all data necessary to calculate the extraction are set or read-in by key-board.

ad.2 Input Penicillin\(_{in}\) and Phenylacetic acid\(_{in}\).

Defining the reference values.

ad.3 Set \(N_{p,abs}\) and \(N_{f,abs}\).

Setting the efficiencies for the penicillin and phenylacetic acid recoveries.

ad.4 Are desorption data known?

If this is the first calculation of the absorber of this determination of the extraction section, then there will be no information about the organic phase coming from the desorber.

ad.5 Start values of the organic phase of the desorber.

If the question in ad.4 is answered with YES. Then the model uses the outgoing organic phase of the desorber as the ingoing organic phase of the absorber.

ad.6 Start values organic phase; organic phase is clean.

If the question in ad.4 is answered with NO, then the ingoing organic phase of the absorber is supposed to be clean.
ad.7 Calculate $N^{th}$ stage absorber

The $N^{th}$ stage, being the last stage, is being calculated according to the equations derived in the previous section.

ad.8 $N=1$ ?

Is the number of theoretical stages one?

ad.9 and 10 calculate absorber

If the answer to ad.8 is NO, then all the other stages are being calculated.

ad.11 Is $N_{\text{abs}}$ correct?

All stages have now been calculated and the model has calculated what the amount of penicillin and phenylacetic acid entering the absorber in the aqueous phase are. The value of penicillin is being checked and if it is within a certain range of the reference value the program continues, if the value is outside the range the penicillin efficiency it is adjusted and the program is repeated from ad.4 onwards.

ad.12 Is $N_{\text{abs}}$ correct?

The model checks if the phenylacetic acid efficiencies are correct. If this is not true then the efficiency is adjusted and the program is repeated from ad.4 onwards. If the phenylacetic acid efficiency is correct then the absorber is finished and the desorber can be calculated.

Calculating the desorber.

The desorber is calculated in the same way as the absorber (No. 15 to 24). The only differences are that the desorber is calculated from the top to the bottom. And that the reference values now become the clean aqueous phase which enters the desorber at the bottom. The amount of penicillin and phenylacetic acid in this flow are zero.

When the desorber has been calculated analogously to the absorber and the efficiencies of the penicillin and the phenylacetic acid recovery have been calculated, then the model will check if the extraction section is stationary (No. 25). The system is stationary if the mass balance over the whole extraction section for both penicillin and phenylacetic acid are correct.

If this is not true then the whole program is repeated from ad.3 onwards.

A detailed description of the necessary calculations has been presented above.
Fig. 9.6 Molar flows of penicillin and phenylacetic acid in absorber and desorber.

**ABSORBER**

- 18.15 m³/h WATERPHASEout
- 3E-4 mol/h PENout
- 15E-4 mol/h FENout
- 3.03 m³/h ORG. des->abs
- 61E-4 mol/h PEN
- 0 mol/h FEN

75 % direct to abs.  25 % to regeneration

**DESORBER**

- 18.15 m³/h WATERPHASEout
- 94E-3 mol/h PENin
- 83E-4 mol/h FENin
- 5E-3 m³/h ORG. abs->des
- 946E-4 mol/h PEN
- 82E-4 mol/h FEN
- 0.51 m³/h WATERPHASEin
- 0 mol/h PENin
- 0 mol/h FENin
9.4.1. Results simulation model

In the previous paragraphs we described some of the parameters that influence the performance of the absorber and the desorber. In fig. 9.6 can be seen what the molar flows of penicillin and phenylacetic acid become when the model is processed with the above described values. The operation conditions are listed in table 9.1. From fig. 9.1 it can be derived that the overall penicillin recovery is well over 99%. It can also be seen that there is no selectivity between penicillin extraction and phenylacetic acid extraction.

Table 9.1: operating parameters simulation model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>value</th>
<th>unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph absorber</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ph desorber</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Number of T.S. abs.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Number of T.S. des.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>E/R abs.</td>
<td>0.167</td>
<td></td>
</tr>
<tr>
<td>R/E des.</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>carrier concentration</td>
<td>0.326</td>
<td>mol/l</td>
</tr>
<tr>
<td>Waterflow entering abs.</td>
<td>18.15</td>
<td>m³/hr</td>
</tr>
<tr>
<td>Penicillin conc.</td>
<td>0.0518</td>
<td>mol/l</td>
</tr>
<tr>
<td>Phenylacetic acid conc.</td>
<td>0.0046</td>
<td>mol/l</td>
</tr>
</tbody>
</table>

| criterion for efficiencies | 0.5 | % |
| criterion for stationary sys | 0.25 | % |

9.5. Regeneration of organic phase

The organic phase becomes fouled with apolar molecules, and the carrier will also react with ions present, other than penicillin and phenylacetic acid. This is the reason why the organic phase has to be regenerated. M. Reschke and K Schügerl\textsuperscript{37} stated that the organic phase has to be regenerated every 4 times. Because we want a stationary performance of the extraction section we propose a continuous regeneration of the organic phase. The organic phase leaving the desorber is for 25% regenerated and for 75% directly returned to the absorber.

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The part of the organic phase that is being regenerated is treated with acid to achieve precipitation of the proteins present. The precipitated proteins are then filtered off by a discontinuous pressure filter. The mixture of the acid and the organic phase are then being separated in a phase separator.

The organic phase is treated with lye to achieve a maximum desorption of the ions that are bound to the carrier. In the next phase separator the lye and organic phase are being separated.

The carrier is now sufficiently clean to be sent back to the absorber. Of course the butyl acetate is still fouled with apolair molecules like all kind of mycelium waste products. The butyl acetate however plays a minor role in the absorption and desorption, the major part is exerted by the carrier. And as long as the polair molecules in the butylacetate do not interfere with the mechanism of reactive extraction there are no problems with those molecules being present.

In time however the concentrations of those molecules in the butyl acetate may rise to a too high degree. There will also always be ions that are very strongly bound by the carrier and will consequently not desorb, even at high pH value treatment. This means that every now and then the whole organic phase has to be refreshed.
10. **Extractor**

The original commercial process for the recovery of penicillin from fermentation broths was based upon the adsorption of the product on activated carbon. However as higher quantities of penicillin were produced this approach became impractical because of the increased carbon requirements.

Modern processes are based upon solvent extraction; penicillin G being a strong acid and being readily soluble in many organic solvents as amyl acetate or butyl acetate at low pH (2.5-3.0). But because the product degrades under acidic conditions the contact time between the two phases should be as short as possible.

This can be attained using countercurrent centrifugal extractors, in which the emulsification and separation of the two phases can be achieved quickly and efficiently in a single step. With two extractors in series the overall recovery of extractable penicillin amounts to 98-99%.

Two frequently used extractors are the Podbielniak D-36 and the Alfa-Laval ABE 216. The flow of the liquid phases is radial and countercurrent; the heavy phase flows outwards from the centre of the apparatus while the light phase moves inwards from the periphery.

We will now introduce a centrifugal extractor with an axial countercurrent flow of the liquid phases. The advantages of this type of extractor compared to the centrifugal extractors with radial flows are:

- lower investment costs in material, control circuits etc.
- less maintenance
- easier to clean
- uniform hydrodynamic behaviour
- behaviour of mixing and settling can be adjusted separately
- lower rotational speeds

Because the extractor has only been operated under pilot plant conditions \(^{22,23,24}\) we designed a scaled up version.

10.1. **Description of extractor**

The apparatus is a tubular centrifuge consisting of a centrally placed shaft with agitators and a shell. The agitators are separated by plate arrays connected to the column wall. The shaft and the shell are driven separately by electronically controlled motors.

The two liquid phases are injected tangentially at the column ends and form two concentric layers along the wall of the extractor. Depending on the difference in rotational speed between shaft and shell either the heavy phase or the light phase will become dispersed.
Fig. 10.1 Schematic view of the flow of heavy (H) and light (L) phase in the extractor.
When the speed of the shaft is greater than the speed of the shell the agitators divert the light phase to the periphery and disperse it in the heavy phase. On the other hand when the speed of the shell is greater than that of the shaft the liquids are retarded along the agitators resulting in a dispersion of the heavy phase in the light phase layer.

Because the shaft and the shell are being driven separately it is possible to regulate the droplet size of the dispersed phase and the settling of the dispersed phase independently. For, the droplet size is determined by the relative revolution speed of shaft and shell, while the settling as such is determined by the absolute rotational speed of the shell.

In between two mixing zones is a settling zone where the dispersed phase is separated from the continuous phase by centrifugal forces. To improve this process special calming elements, attached to the column wall, are used. These elements consist of wide axial channels made of layers of corrugated sheet. Their function is to enhance coalescence of the dispersed droplets and transport the liquid countercurrently in the axial direction.

At both ends of the centrifuge circular weirs are placed. One for the light phase the other for the heavy phase. The light phase is removed from the calming chamber by a fixed scoop. The heavy phase on the other hand is removed by a scoop the position of which can be regulated. Both the scoop of the light phase and the heavy phase are placed behind the weir.

By adjusting the position of the scoop of the heavy phase the flow leaving the centrifuge can be regulated and therefore the relative amount of both phases in the column. The total amount of both phases is determined by the height of the weir for the light phase.

Compared to the existing centrifugal extractors with radial countercurrent flows the hydrodynamic conditions along the axis remain constant, because there is an uniform centrifugal acceleration along the whole length of the extractor. Therefore the number of achievable theoretical stages increases linearly with the length of the extractor\(^2^2\).

Technical advantages of the tubular extractor are that the liquids do not come into contact with the bearings of the axis and shell. So no special (i.e. expensive) seals are necessary.

10.2. Number of transfer units

A schematic view of the flow of the heavy (H) and light (L) phase is given in fig.10.1.\(^2^8\) In the mixing zone the dispersion is formed, part of which leaves in the direction of the heavy phase, the other part leaving in the direction of the light phase. Therefore, light phase is being transported with the heavy phase and vice versa, resulting in recirculation flows of both phases.
The fraction of dispersion flowing in the direction of the light phase is called $\alpha$:

$$\alpha = \frac{L + H'}{H + H' + L + L'}$$ (10.1)

The value of $\alpha$ influences the holdup ($h$). In case of the heavy phase being the dispersed phase the holdup is defined as:

$$h = \frac{H + H'}{H + H' + L + L'}$$ (10.2)

Even so the holdup can be written as:

$$h = \frac{H'}{H' + L}$$ (10.3)

or:

$$h = \frac{H}{L' + H}$$ (10.4)

Combination of the above equations leads to:

$$h = \frac{H/L}{H/L + (1 - \alpha)/\alpha}$$ (10.5)

The overall efficiency of a mixer with reference to the dispersed phase ($R_{o,d}$) can be estimated as $^2$:

$$R_{o,d} = \frac{N_{tu,d}}{1 + N_{tu,d}}$$ (10.6)

with $N_{tu,d}$ the number of transfer units related to the dispersed phase.
The number of transfer units \( (N_{tu,d}) \) is given by:

\[
N_{tu,d} = \frac{K_{o,d} \ast a \ast V_m}{Q_d} \tag{10.7}
\]

with:
- \( K_{o,d} \) overall mass transfer coefficient of dispersed phase \((m/s)\)
- \( a \) specific area \((m^2/m^3)\)
- \( V_m \) mixing volume \((m^3)\)
- \( Q_d \) volumetric flow of dispersed phase \((m^3/s)\)

We shall now have a closer look at these parameters.

1. \( K_{o,d} \)

The overall mass transfer coefficient \( (K_{o,d}) \) can be calculated with the following equation:

\[
K_{o,d} = \frac{1}{k_d} + \frac{1}{K_{eq} \ast k_c} \tag{10.8}
\]

with:
- \( k_d \) mass transfer coefficient of dispersed phase \((m/s)\)
- \( k_c \) mass transfer coefficient of continuous phase \((m/s)\)
- \( K_{eq} \) distribution coefficient (-)

The mass transfer coefficients of the dispersed phase \( (k_d) \) and continuous phase \( (k_c) \) are given by \(^2\):

\[
k_d = \frac{10 \ast D_d}{d_{3.2}} \tag{10.9}
\]

and:

\[
k_c = \frac{D_c}{D_w} \ast \left[ 2 + 0.47 \ast \frac{d_{3.2} \ast 4/3 \ast \epsilon^{1/3}}{\mu_c} \ast \frac{0.62}{\mu_c} \ast \frac{D_s}{D_w} \ast \frac{\mu_c}{\mu_c \ast D_c} \right] \tag{10.10}
\]
where:
- \( D_c \) diffusion coefficient of penicillin in continuous phase \( (m^2/s) \)
- \( D_d \) diffusion coefficient of penicillin in dispersed phase \( (m^2/s) \)
- \( d_{3.2} \) Sauter diameter \( (m) \)
- \( \varepsilon \) power input per unit mass \( (W/kg) \)
- \( \rho_c \) density of continuous phase \( (kg/m^3) \)
- \( D_s \) diameter of agitator \( (m) \)
- \( D_w \) height of blades of agitator \( (m) \)
- \( \mu_c \) viscosity of continuous phase \( (Pa.s) \)

The Sauter diameter \( (d_{3.2}) \) is estimated as:

\[
d_{3.2} = 0.11 \times \frac{\sigma^{0.46}}{\varepsilon^{0.4} \rho_c^{0.6}} \times h^{0.5} \times \frac{\mu_d^{0.25}}{\mu_c} \quad (10.11)
\]

with:
- \( \sigma \) surface tension dispersed/continuous phase \( (kg/s^2) \)
- \( \mu_d \) viscosity of dispersed phase \( (Pa.s) \)

The power input per unit mass \( (\varepsilon) \) can be calculated as:

\[
\varepsilon = \frac{P_0 \times N_s^3 \times D_s^5}{V_m} \quad (10.12)
\]

with:
- \( P_0 \) Power number \( (-) \)
- \( V_m \) mixing volume \( (m^3) \)

2. The mixing volume \( V_m \).

The mixing volume is given by:

\[
V_m = L_m \times \pi \times (r_5^2 - r_1^2) \quad (10.13)
\]

with:
- \( L_m \) length of mixing zone \( (m) \)
- \( r_5 \) inside radius of extractor \( (m) \)
- \( r_1 \) distance between axis and light phase \( (m) \)

The length of the mixing zone \( (L_m) \) is estimated as:

\[
L_m \approx 3 \times D_w \quad (10.14)
\]
The Power number \( (P_0) \) for a four bladed impeller, with \( Re > 6700 \), is given by\(^{28}\):

\[
P_0 = 6 \times \frac{D_w}{D_s} \quad (10.15)
\]

3. The specific area \( a \).

\[
a = \frac{6 \times h}{d_{1.2}} \quad (10.16)
\]

4. The volumetric flow of the dispersed phase \( Q_d \).

\[
Q_d = H \times \frac{1}{(1 - \alpha)} \quad (10.17)
\]

The above presented calculation of \( N_{tu,d} \) was used in the computer design of the extractor. With the overall stage efficiency \( (R_{o,d})^6 \) known the needed number of mixers per theoretical stage \( (N_{m,s}) \) is calculated as:

\[
N_{m,s} = \frac{N_{tu,d}}{R_{o,d}} \quad (10.18)
\]

As has already been shown the number of theoretical stages for both the absorber and the desorber amounts to three. Therefore, the total number of mixers \( (N_{m,t}) \) is calculated by adding the needed number of mixers for each of the three theoretical stages and rounded off upwards:

\[
N_{m,t} = \text{ENT} \left( \sum_{s=1}^{3} N_{m,s} + 0.5 \right) \quad (10.19)
\]
(a) Construction of extractor: 1-Drive shell, 2-Drive shaft, 3-Weir light phase, 4-Weir heavy phase, 5-phase Accelerator, 6-Agitator, 7-Stage separation, 8-Scoop.

Fig. 10.2 Schematic view of the extractor (a) and its dimensions (b).

\[ r_1 \] - Distance between shaft and weir of light phase
\[ r_2 \] - Distance between shaft and weir of heavy phase
\[ r_3 \] - Distance between shaft and liquid liquid interface
\[ r_4 \] - radius of agitator
\[ r_5 \] - inside radius of extractor
10.3. Designing the extractor

10.3.1. Introduction

Several criteria are used in scaling up the pilot plant designed by Steiner, Gebauer and Hartland.

Because we wanted to increase the throughput of both phases the diameter of the extractor was enlarged with a factor "p". The total throughput of both phases however is limited by the following boundary values:

1. the cross sectional area of the extractor occupied by the liquid amounts to 67% of the total cross sectional area.
2. the maximum axial liquid velocity does not exceed $50 \times 10^{-3}$ m/s.

Another criterion is the power input per unit mass. This is taken to be about 60 W/kg, the same value as in the pilot plant.

With these data given the dimensions of the extractor can now be calculated (fig.10.2).

10.3.2. Dimensions

The parameters involving the specific dimensions of the extractor are:

- $r_s$ radius extractor
- $A_t$ cross sectional area
- $A_f$ flown through area
- $r_1$ height of the weir of the light phase
- $r_3$ height of liquid liquid interface
- $r_4$ radius of the impeller
- $D_w$ width of the impeller blades.

We shall now determine some relations for these parameters.

The diameter of the extractor.

The diameter of the pilot plant extractor is multiplied by a factor $p$. Therewith the inside radius of the scaled up extractor ($r_s)$ now becomes (22,24):

$$ r_s = p \times 47 \times 10^{-3} \text{ m} \quad \text{(10.20)} $$

The cross sectional area ($A_t$).

The total cross sectional area of the extractor ($A_t$) is given by:

$$ A_t = \pi \times r_s^2 \text{ m}^2 \quad \text{(10.21)} $$

The flown through area ($A_f$).

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The maximum cross sectional area flown through \((A_f)\) amounts to 67\% of the total cross sectional area:

\[
A_f = 0.67 \times A_t = 0.67 \times \pi \times r_5^2 \quad (m^2)
\]

The flown through area \((A_f)\) determines the height of the weir \((r_1)\) of the light phase:

\[
A_f = \pi \times (r_5^2 - r_1^2) = 0.67 \times \pi \times r_5^2 \quad (m^2) \quad (10.23)
\]

Height of the weir of the light phase \((r_1)\).

It follows for the height of the weir of the light phase:

\[
r_1 = r_5 \times \sqrt{1 - 0.67} \quad (m) \quad (10.24)
\]

Height of the liquid liquid interface \((r_3)\)

The position of the liquid liquid interface \((r_3)\) is determined by the ratio of both phases \((H/L = a)\):

\[
r_3 = \sqrt{(r_5^2 + a \times r_1^2) / (a + 1)} \quad (m) \quad (10.25)
\]

Radius of the impeller \((r_4)\)

Taking the tip of the agitator being positioned just beyond the liquid liquid interface \((r_3)\) the radius of the impeller \((r_4)\) becomes:

\[
r_4 = (r_3 + 0.001) \quad (m) \quad (10.26)
\]

Width of the impeller blades \((D_w)\).

The width of the impeller blades \(D_w\) is estimated as:

\[
D_w = \frac{1}{12} \times D_s \quad (m) \quad (10.27)
\]

with \(D_s\) being diameter of the impeller, therefore \(D_s = 2 \times r_4\)

10.4. Rotational speed of shaft and shell
Because the dimensions of the extractor are determined it is necessary to determine the speed of revolution of the agitator and the shell, and see if the conditions in the mixing and settling zone will meet the requirements for achieving a small enough droplet size and a good separation respectively.

In order to obtain a certain droplet size in the mixing zone it is necessary that the residence time \( t_r \) of both phases in the mixing volume \( V_m \) is greater than the needed time for mixing \( t_m \).

The residence time \( t_r \) is given by:

\[
 t_r = \frac{V_m}{Q_d + Q_c} = \frac{V_m}{H/(1-\alpha) + L/\alpha} \quad (10.28)
\]

and the mixing time \( t_m \) is estimated as four times the circulation time \( t_c \)\(^{18} \):

\[
 t_m = 4 \times t_c = 4 \times \frac{V_m}{\Phi_c} = \frac{4 \times V_m}{\Delta N \times \pi^2 \times D_s^2 \times D_w} \quad (10.29)
\]

where: \(- \Delta N\) difference in rotational speed between agitator and shell \( (s^{-1}) \)

On the condition that the residence time \( t_r \) of both phases being greater than the mixing time \( t_m \), this results in the following relation:

\[
 \Delta N > \frac{48 \times (H/(1-\alpha) + L/\alpha)}{\pi^2 \times D_s^3} \quad (s^{-1}) \quad (10.30)
\]

The maximum difference in speed of revolution between agitator and shell amounts 30\%. In order to calculate the absolute speed of revolution of the agitator \( N_s \) we revert on the condition of a power input per unit mass of 60 W/kg.
With this the rotational speed of the agitator can be estimated as:

\[ N_s = \frac{\varepsilon \cdot V_m}{P_0 \cdot D_s^5} \]  
(10.31) 

From equations (10.13, 10.14, 10.26) it follows:

\[ N_s = \frac{\varepsilon \cdot \pi \cdot (r_s^2 - r_1^2)}{4 \cdot P_0 \cdot D_s^5} \]  
(10.32) 

Now the rotational speed of the shell can be calculated with the above obtained information:

\[ N_{shell} = N_s + \Delta N \]  
(10.33) 

10.5. Length of the settler

In order to check whether the length of the settling zone \( L_s \) is adequate to fulfill the requirements of the settling time \( t_b \) being smaller than the residence time of the continuous phase in the settling zone \( t_s \), the following calculation is made.

The sedimentation velocity \( v_b \) of a droplet in a centrifugal field is given by:

\[ v_b = \frac{\Omega^2 \cdot R \cdot d_{3.2} \cdot \Delta \rho}{18 \cdot \mu_c} \]  
(m/s)  
(10.34) 

where:
- \( \Omega \) angular speed of shell \( (s^{-1}) \)
- \( R \) distance between droplet and axis \( (m) \)
- \( \Delta \rho \) difference in density between continuous and dispersed phase \( (kg/m^3) \)

The sedimentation time \( t_b \) follows from:

\[ t_b = \int \frac{dt}{v_b} = \int \frac{dR}{v_b} = \int \frac{r_3}{r_1} \frac{18c \cdot \mu_c}{\Omega^2 \cdot d_{3.2}^2 \cdot \Delta \rho} \frac{dR}{R} \]  
(10.35) 

or:

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The residence time of the continuous phase in the settling zone \( t_s \) is given as:

\[
t_s = \frac{L_s \cdot A_s}{Q_c}
\]  
(10.37)

with:
- \( A_s \) cross sectional area of continuous phase \( (m^2) \)
- \( Q_c \) volumetric flow rate of continuous phase \( (m^3/s) \)

The cross sectional area \( (A_s) \) of the continuous phase is given by:

\[
A_s = \pi \cdot (r_3^2 - r_1^2)
\]  
(10.38)

and the volumetric flow of continuous phase \( (Q_c) \):

\[
Q_c = \frac{L}{\alpha}
\]  
(10.39)

The minimum length of the settling zone \( L_s \) now follows from the stipulation:

\[
t_b < t_s
\]  
(10.40)

and with the above equations can be deduced to be:

\[
L_s > \frac{18 \cdot \mu_c}{\Omega^2 \cdot d_{3.2}^2 \cdot \mu} \cdot ln \frac{r_3}{r_1}
\]  
(10.41)
The minimal length of the extractor \((L_{t, \text{min}})\) can be calculated as:

\[
L_{t, \text{min}} = N_{m,t} \cdot L_m + (N_{m,t} + 1) \cdot L_s \tag{10.42}
\]

Because the phases leaving the extractor at both ends should be separated from each other the number of needed settlers is given by the number of needed mixers plus one.

The calculated dimensions of the extractor have been assembled in table 10.1. If we consider the absorber than we can see that the rotational speed of the agitator is greater than the speed of the shell. This indicates that the light phase is being dispersed in the heavy phase. In case of the desorber the situation is vice versa.

Table 10.1: the minimal needed dimensions of the extractor in order to fulfill all requirements (for explanation see text).

<table>
<thead>
<tr>
<th></th>
<th>Absorber</th>
<th>Desorber</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N_s) ((s^{-1}))</td>
<td>982</td>
<td>921</td>
</tr>
<tr>
<td>(N_{\text{shell}}) ((s^{-1}))</td>
<td>687</td>
<td>1197</td>
</tr>
<tr>
<td>(D_s) ((m))</td>
<td>0.546</td>
<td>0.282</td>
</tr>
<tr>
<td>(L_m) ((m))</td>
<td>0.093</td>
<td>0.068</td>
</tr>
<tr>
<td>(L_s) ((m))</td>
<td>0.271</td>
<td>0.203</td>
</tr>
<tr>
<td>(L_{t, \text{min}}) ((m))</td>
<td>1.363</td>
<td>1.016</td>
</tr>
</tbody>
</table>

The absorber and desorber have been scaled up with different factors, this because the ratio length of mixer to length of settler \((L_m/L_s)\) has to be three to four. In the case of the absorber this results in a length of the mixer of 0.093 m and of the settler of 0.20 m. In case of the desorber the respective values are \(L_m = 0.068\) m and \(L_s = 0.203\) m.

The ratio of heavy and light phase being different in absorber and desorber leads to different positions of the liquid liquid interface and so to a varying diameter of the agitator. The diameter of the agitator in the absorber amounts to 0.370 m and in the desorber to 0.270 m.
However, these values are the minimal necessary values in order to fulfill all the requirements mentioned above. Therefore, to the final dimensions 10% is added:

\[ L_t = L_{t, \text{min}} \times 1.1 \]  

(10.43)

The final dimensions of absorber and desorber are given in table 10.2. The conditions under which both are operated are summarized in table 10.3. The rotational speeds have been rounded off in such a way that both the mixing, determined by the difference in speed of revolution between agitator and shell, as well as the sedimentation, determined by the speed of revolution of the shell, improves.

Table 10.2: the final dimensions of absorber and desorber.

<table>
<thead>
<tr>
<th></th>
<th>Absorber</th>
<th>Desorber</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_t ) (m)</td>
<td>1.50</td>
<td>1.12</td>
</tr>
<tr>
<td>( D_r ) (m)</td>
<td>0.564</td>
<td>0.282</td>
</tr>
<tr>
<td>( D_s ) (m)</td>
<td>0.370</td>
<td>0.270</td>
</tr>
</tbody>
</table>

Table 10.3: operational conditions of absorber and desorber.

<table>
<thead>
<tr>
<th></th>
<th>Absorber</th>
<th>Desorber</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_s ) (s(^{-1}))</td>
<td>980</td>
<td>920</td>
</tr>
<tr>
<td>( N_{\text{shell}} ) (s(^{-1}))</td>
<td>690</td>
<td>1200</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>
11. Crystallization

In order to crystallize the penicillin a vast number of methods is available\(^1\)\(^7\). First of all the choice to be made depends on the type of penicillin-G to be crystallized; different salts have different therapeutic applications. Secondly, in which phase should the actual precipitation take place, the organic or the aqueous phase? In the following an example of both is given.

Crystallization from the aqueous phase.

Crystalline sodium penicillin-G is obtained by adding an excess amount of n-butyl alcohol to the aqueous phase. The water is then completely removed by distillation and upon further concentration the penicillin crystallizes out.

Crystallization from the organic phase.

The penicillin, in its associated form, is extracted into butyl acetate. The organic phase is dried with MgSO\(_4\) or Na\(_2\)SO\(_4\). Further purification can now be achieved by using active coal in order to absorb most of the remaining impurities like pigments and pyrogens.

To the dewatered butyl acetate phase is now added an organic base, for example N-ethyl piperidin, resulting in crystallization of the penicillin-G salt of the concerned base. The crystals are being separated by filtration or centrifugation and are being vacuum dried after washing with aceton or ether.

The purity of the crystals can be improved by adding aceton as a second solvent to the butyl acetate. The aceton functions as a solvent for the salts of the impurities.
Fig. 12.1 Integrated power consumption (J) of air compressor (AIRI) and stirring (ROERV) in time.
12. **Costs of the plant**

Before we determine the total costs of our penicillin production plant, it is necessary to define some specific costs. According to "the Chemical Plant" we define:

\[ C_t \text{ total costs, is the sum of:} \]

- \( C_p \) production costs
- \( C_l \) semi-variable costs, like wages, maintenance.
- \( C_i \) investment costs
- \( C_o \) plant overhead costs, like estate, fire dept. etc.
- \( C_g \) general costs, like administration, marketing etc.

We will now have a closer look at the specific costs.

12.1. **Production costs**

Those costs concern raw materials, electricity, cooling water, steam etc. The costs are calculated for 876 fermentations per year.

The overall electricity costs can be determined from fig.12.1. If we set the efficiency of the electromotors for stirring and compressing at 95%, then the overall electricity consumption becomes:

- **stirring**: \( 72.389 \text{ kWh/ferm.} \)
- **compress**: \( 40.906 \text{ kWh/ferm.} \)

**total**: \( 113.295 \text{ kWh/ferm.} \)

Raw materials:

In appendix J a list of the used prices of the raw materials is presented.

In appendix I we stated that the solubility of the butyl acetate in water at 5°C is about 1%, this results in an annual loss of 1600 ton.

The annual carrier losses mount up to 9.3 ton/hr. This is based on the fact that the concentration of the carrier in the butyl acetate phase is 0.326 mol/1, and the efficiency of the wastewater stripping being 90%.
<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>39.607 kg/ferm</td>
<td>f 52.000.000,00</td>
</tr>
<tr>
<td>NH₃</td>
<td>1.604 kg/ferm</td>
<td>f 760.000,00</td>
</tr>
<tr>
<td>Phacetic</td>
<td>1.531 kg/ferm</td>
<td>f 3.300.000,00</td>
</tr>
<tr>
<td>H₂SO₄</td>
<td>1.306 kg/ferm</td>
<td>f 980.000,00</td>
</tr>
<tr>
<td>Buacetate</td>
<td>1600 ton/y</td>
<td>f 2.500.000,00</td>
</tr>
<tr>
<td>Amberlite</td>
<td>9.3 ton/y</td>
<td>f 1.400.000,00</td>
</tr>
<tr>
<td>Nutrients</td>
<td></td>
<td>f 1.500.000,00</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td><strong>f 62.440.000,00</strong></td>
</tr>
<tr>
<td>electricity</td>
<td>113 MWh/ferm</td>
<td>f 9.898.800,00</td>
</tr>
<tr>
<td>Cooling water</td>
<td>2500 m³/ferm</td>
<td>f 525.660,00</td>
</tr>
<tr>
<td>Other utilities</td>
<td></td>
<td>f 8.760.000,00</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td><strong>f 19.184.400,00</strong></td>
</tr>
</tbody>
</table>

**Production costs total**  f 81.624.400,00

2. **Semivariabel costs**

For the semivariabel costs we consider the labour costs and the maintenance costs.

For the labour costs we have to make an estimation of the number of labourers needed to operate the plant. We need about 39 labourers per shift to operate the plant. Because this is a full continuous plant five shifts are needed. This means that a total of 195 are needed to keep the plant in process continuously.

The maintenance costs are about 4% of the total investment costs (see below).

<table>
<thead>
<tr>
<th>Cost Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour cost</td>
<td>f 11.700.000,00</td>
</tr>
<tr>
<td>Maintenance</td>
<td>f 1.113.616,36</td>
</tr>
<tr>
<td><strong>Semivariabel costs</strong></td>
<td>f 12.813.616,36</td>
</tr>
</tbody>
</table>
12.3. Investment costs

In order to determine the investment costs, we have to make a stock taking of all the apparatus in the plant and determine their cost. Because of continuous operation and hygienical reasons, the extraction section and the storage tank are installed in twofold.

Apparatus

<table>
<thead>
<tr>
<th>Item</th>
<th>Capacity/Size</th>
<th>Cost (f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 fermentors</td>
<td>250 m³ stir. &amp; cool.</td>
<td>30,000,000,00</td>
</tr>
<tr>
<td>30 air compressors</td>
<td>300 kW</td>
<td>15,000,000,00</td>
</tr>
<tr>
<td>3 vacuum filters</td>
<td>50 m² each</td>
<td>750,000,00</td>
</tr>
<tr>
<td>1 washwater tank</td>
<td>10 m³</td>
<td>24,000,00</td>
</tr>
<tr>
<td>1 filtrate tank</td>
<td>5 m³</td>
<td>16,000,00</td>
</tr>
<tr>
<td>2 storage tanks</td>
<td>200 m³</td>
<td>600,000,00</td>
</tr>
<tr>
<td>1 acid tank</td>
<td>1 m³</td>
<td>10,000,00</td>
</tr>
<tr>
<td>2 absorber/desorber sections</td>
<td></td>
<td>1,500,000,00</td>
</tr>
<tr>
<td>2 lye tanks</td>
<td>5 m³</td>
<td>32,000,00</td>
</tr>
<tr>
<td>1 acid tank</td>
<td>5 m³</td>
<td>16,000,00</td>
</tr>
<tr>
<td>2 disc. filters</td>
<td>2 m²</td>
<td>60,000,00</td>
</tr>
<tr>
<td>2 stirring tanks</td>
<td>5 m³</td>
<td>100,000,00</td>
</tr>
<tr>
<td>2 fase separators</td>
<td></td>
<td>50,000,00</td>
</tr>
<tr>
<td>2 coalbed absorbers</td>
<td></td>
<td>70,000,00</td>
</tr>
<tr>
<td>1 cooler</td>
<td>60 m²</td>
<td>60,000,00</td>
</tr>
<tr>
<td>2 condensors</td>
<td></td>
<td>50,000,00</td>
</tr>
<tr>
<td>2 pumps</td>
<td>37.5 kW</td>
<td>48,000,00</td>
</tr>
<tr>
<td>1 pump</td>
<td>22 kW</td>
<td>21,000,00</td>
</tr>
<tr>
<td>1 pump</td>
<td>5 kW</td>
<td>15,000,00</td>
</tr>
<tr>
<td>8 pumps</td>
<td>2 kW</td>
<td>40,000,00</td>
</tr>
</tbody>
</table>

Subtotal                                      |               | 47,962,000,00 |

This stock taking only concerns the apparatus described on the flowsheet, there are however four parts of the plant which are not described.

- 1. Seed developing section.
- 3. Crystallization.
- 4. Air filtering.

ad 1.

This section involves some smaller fermentors (30 m³). Because the duration of this fermentation is about 20 hr., we only need three such fermentors.

ad 2.

This section contains as a main part the extraction section for the carrier, a distillation tower for butyl acetate and some coalbed adsorbers.

ad 3.
The crystallization section contains, depending on the method chosen, one or more crystallizers.

ad. 4

Air filtering involves heating and filtering devices.

A rough estimation of the investment costs are

1. seed developing section $f\ 1,000,000,00$
2. waste water treatment $f\ 2,000,000,00$
3. crystallization $f\ 2,000,000,00$
4. air filtering $f\ 2,000,000,00$

subtotal $f\ 7,000,000,00$

As a result the total stock taking of the plant adds up to:

$\text{total} f\ 47,962,000,00$

$\text{total} f\ 7,000,000,00$

$\text{total} f\ 54,962,000,00$

With Lang's method we can calculate the total investment. Lang states that this is 3.63 times the apparatus costs.

total investments $f\ 199,512,206,00$

The apparatus are depreciated in about 10 years. This results in an annual investment cost of:

$\text{interest} f\ 7,889,188,43$

Another cost is the loss of interest over the invested capital. If we calculate the loss of interest over half of the invested capital at a rate of 6% per year over ten years,

Therefore the total investment costs become

depreciation $f\ 19,951,220,60$

interest $f\ 7,889,188,43$

Investment costs $f\ 27,840,409,03$
12.4. **Plant overhead costs**

For the plant overhead costs several estimations can be made on basis of the investment costs and labour costs. We propose to use 1.5% of the total investment and 45% of the labour costs.

So the plant overhead costs become

\[ f 6,089,430,00 \]

12.5. **General costs**

The general costs are mostly 5% of the turnover. We can now make a list of the total costs.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Production costs</td>
<td>( f \ 81,624,400,00 )</td>
</tr>
<tr>
<td>Semi variable costs</td>
<td>( f \ 12,813,616,36 )</td>
</tr>
<tr>
<td>Investment costs</td>
<td>( f \ 27,840,409,03 )</td>
</tr>
<tr>
<td>Plant overhead</td>
<td>( f \ 6,089,430,00 )</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>( f \ 128,367,855,00 )</td>
</tr>
<tr>
<td>Turn over</td>
<td>( f \ 6,418,392,75 )</td>
</tr>
<tr>
<td>General costs</td>
<td>( f \ 128,367,855,00 )</td>
</tr>
<tr>
<td><strong>Total annual cost</strong></td>
<td>( f \ 134,786,247,80 )</td>
</tr>
</tbody>
</table>

We already stated that we perform 876 fermentations per year. One fermentation produces 9972.5 mol of penicillin. This equals to:

\[ 3113478.3 \text{ kg of Na-penicillin-G} \]

The cost of the penicillin is \( f \ 43,30 \) per kg. The efficiency of the plant being 92% the price of penicillin becomes:

\( f \ 47,06 \) per kg
12.6. Conclusions

From the above presented calculation it can be derived that about 30% of the price of penicillin is determined by the price of glucose. It can also be seen that the fermentation section amounts to about 80% of the total investment costs and that this section practically consumes the major part of all power consumed.

Therefore it is concluded that the price of penicillin is determined by the costs of the fermentation section. The extraction section is both investment and raw material wise of minor importance.
Literature


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27. Cooney, Healthcare Products


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41. A.G. Montfoort, College dictaat St44 "De chemische fabriek deel 2", TU Delft 1986


List of symbols

Symbols of Fermentor

Concerning geometry:

- **B** Baffle width (m)
- **C** Height of first agitator with reference to bottom of fermentor (m)
- **C'** Height of second agitator with reference to bottom of fermentor (m)
- **D_c** Diameter of outside coil (m)
- **D_i** Diameter of inside coil (m)
- **D_h** Diameter of helix of coil (m)
- **D_s** Diameter of the agitator (m)
- **D_f** Diameter of the fermentor (m)
- **D_w** Height of blade of agitator (m)
- **H_f** Height of the fermentor (m)
- **M_d_w** Total dry weight (kg)
- **M_b** Total mass of broth per fermentor (kg)
- **n_c** Number of coils
- **µ_b** Broth density (kg/m³)
- **µ_m** Medium density (kg/m³)
- **µ_p** Dry mycelium density (kg/m³)

Concerning the kinetic model:

- **s_c** Concentration vector of the elements (g. atom/m³)
- **s_s** Substrate concentration in broth (mol/kg)
- **s_x** Biomass concentration in broth (mol/kg)
- **E** Elementary matrix
- **h** Vector of molar enthalpies
- **G** Total mass of broth (kg)
- **k** First order rate constant (h⁻¹)
- **K_s** Michaelis constant for substrate uptake rate (mol/molDM/hr)
- **m_s** Maintenance constant (mol/molDM/hr)
- **q_p, max** Maximum specific penicillin synthesis rate (mol/molDM/hr)
- **q_s, max** Maximum specific sugar uptake rate (mol/molDM/hr)
- **t** Time (s)
- **r_e** Vector of conversion rates
- **r_c** Net rate of carbon dioxide conversion (mol/hr)
- **r_h** Net rate of metabolic heat production (mol/hr)
- **r_n** Net rate of ammonia conversion (mol/hr)
- **r_o** Net rate of oxygen conversion (mol/hr)
- **r_p** Net rate of penicillin conversion (mol/hr)
- **r_p_a** Net rate of phenylacetic acid conversion (mol/hr)
- **r_p_h** Net rate of orthophosphoric acid conversion (mol/hr)
- **r_p_o** Net rate of penicilloic acid conversion (mol/hr)
- **r_s** Net rate of glucose conversion (mol/hr)
- **r_s_u** Net rate of sulphuric acid conversion (mol/hr)
- **r_x** Net rate of biomass conversion (mol/hr)
- **Y_s x** True yield for biomass on substrate (mol/mol)
- **Y_p s** True yield for penicillin on substrate (mol/mol)
Greek symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>Stoichiometric matrix</td>
<td></td>
</tr>
<tr>
<td>( \mu )</td>
<td>Specific growth rate</td>
<td>h(^{-1})</td>
</tr>
<tr>
<td>( H_{cr} )</td>
<td>Critical specific growth rate</td>
<td>h(^{-1})</td>
</tr>
<tr>
<td>( \phi_0 )</td>
<td>Vector of exchange</td>
<td></td>
</tr>
<tr>
<td>( \phi_i )</td>
<td>Flow of component i in to system</td>
<td>mol/hr</td>
</tr>
<tr>
<td>( \phi_s )</td>
<td>Flow of glucose in to system</td>
<td>mol/hr</td>
</tr>
</tbody>
</table>

Symbols of viscosity

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_n )</td>
<td>Biomass concentration</td>
<td>kgDM/m(^3)</td>
</tr>
<tr>
<td>( K )</td>
<td>Consistency index</td>
<td>Pa.s(^n)</td>
</tr>
<tr>
<td>( K_1 )</td>
<td>Casson constant</td>
<td>Pa.s (^b)</td>
</tr>
<tr>
<td>( K_2 )</td>
<td>Constant in equation</td>
<td></td>
</tr>
<tr>
<td>( L_n )</td>
<td>Dimensionless hyphal length</td>
<td>m</td>
</tr>
<tr>
<td>( L_{gu} )</td>
<td>Length of the hyphal growth unit</td>
<td>m</td>
</tr>
<tr>
<td>( n )</td>
<td>Flow behavior index</td>
<td></td>
</tr>
<tr>
<td>( N_s )</td>
<td>Impeller speed</td>
<td>s(^{-1})</td>
</tr>
</tbody>
</table>

Greek symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau )</td>
<td>Shear rate</td>
<td>s(^{-1})</td>
</tr>
<tr>
<td>( \tau_{bulk} )</td>
<td>Mean bulk shear rate</td>
<td>s(^{-1})</td>
</tr>
<tr>
<td>( \tau_{av} )</td>
<td>Average shear rate</td>
<td>s(^{-1})</td>
</tr>
<tr>
<td>( \tau_0 )</td>
<td>Shear rate at defined impeller speed</td>
<td>s(^{-1})</td>
</tr>
<tr>
<td>( \mu_a )</td>
<td>Apparent viscosity</td>
<td>Pa.s</td>
</tr>
<tr>
<td>( \tau' )</td>
<td>Shear stress</td>
<td>Pa</td>
</tr>
<tr>
<td>( \tau_0 )</td>
<td>Yield stress</td>
<td>Pa</td>
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Symbols of filtration.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A )</td>
<td>Filter surface</td>
<td>m(^2)</td>
</tr>
<tr>
<td>( C )</td>
<td>Filtercoefficient</td>
<td></td>
</tr>
<tr>
<td>( C_f )</td>
<td>Filtercoefficient</td>
<td></td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>Voids of cake</td>
<td></td>
</tr>
<tr>
<td>( K )</td>
<td>Permeability of cake</td>
<td>m(^2)</td>
</tr>
<tr>
<td>( N )</td>
<td>Wash ratio</td>
<td></td>
</tr>
<tr>
<td>( \Delta p )</td>
<td>Pressure drop over cake</td>
<td>Pa</td>
</tr>
<tr>
<td>( Q_{1,1} )</td>
<td>Flow of filtrate</td>
<td>m(^3)/s</td>
</tr>
<tr>
<td>( Q_m )</td>
<td>Mycelial flow</td>
<td>m(^3)/hr</td>
</tr>
<tr>
<td>( Q_s )</td>
<td>Cake flow</td>
<td>m(^3)/hr</td>
</tr>
<tr>
<td>( Q_{r,i} )</td>
<td>Initial filtrate flow (no washwater)</td>
<td>m(^3)/hr</td>
</tr>
<tr>
<td>( Q_{r,\text{tot}} )</td>
<td>Total filtrate flow</td>
<td>m(^3)/hr</td>
</tr>
<tr>
<td>( t )</td>
<td>Time</td>
<td>s</td>
</tr>
<tr>
<td>( V_{1,1} )</td>
<td>Amount of filtrate</td>
<td>m(^3)</td>
</tr>
</tbody>
</table>
Greek symbols

$\alpha$ Ratio $t_f/t_c$

$\beta$ Ratio $t_u/t_f$

$\mu$ Viscosity

Subscripts

c Rotation
d Drying
f Filtering
w Washing

Symbols of cooling

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cooling surface</td>
<td>m²</td>
</tr>
<tr>
<td>$C_p$</td>
<td>Specific heat capacity of water</td>
<td>kJ/kg/K</td>
</tr>
<tr>
<td>$D_i$</td>
<td>Inner diameter of heat exchanger shell</td>
<td>inch</td>
</tr>
<tr>
<td>$d_i$</td>
<td>Inner diameter of heat exchanger tubes</td>
<td>mm</td>
</tr>
<tr>
<td>$d_o$</td>
<td>Outer diameter of heat exchanger tubes</td>
<td>mm</td>
</tr>
<tr>
<td>$f$</td>
<td>Friction factor</td>
<td></td>
</tr>
<tr>
<td>$g$</td>
<td>Gravity acceleration</td>
<td>m/s²</td>
</tr>
<tr>
<td>$l$</td>
<td>Length of tube of one passage</td>
<td>m</td>
</tr>
<tr>
<td>$l_{eff}$</td>
<td>Effective length of heat exchanger</td>
<td>m</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Thermal conductivity of water</td>
<td>W/m/K</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of passages</td>
<td></td>
</tr>
<tr>
<td>Nu</td>
<td>Nusselt</td>
<td></td>
</tr>
<tr>
<td>$P_c$</td>
<td>Critical pressure Freon-12</td>
<td>Pa</td>
</tr>
<tr>
<td>Pr</td>
<td>Prandtl</td>
<td></td>
</tr>
<tr>
<td>$\Delta p$</td>
<td>Pressure drop over tubes</td>
<td>Pa</td>
</tr>
<tr>
<td>$Q$</td>
<td>Heatflow to be exchanged</td>
<td>kW</td>
</tr>
<tr>
<td>$Q_{max}$</td>
<td>Maximum heat flux at boiling</td>
<td>kW/m²</td>
</tr>
<tr>
<td>$Q_{vap}$</td>
<td>heat of vaporization of Freon</td>
<td>kW/kg</td>
</tr>
<tr>
<td>$\rho_g$</td>
<td>Density of Freon gas</td>
<td>kg/m³</td>
</tr>
<tr>
<td>$\rho_l$</td>
<td>Density of Freon liquid</td>
<td>kg/m³</td>
</tr>
<tr>
<td>Re</td>
<td>Reynolds</td>
<td></td>
</tr>
<tr>
<td>$R_u$</td>
<td>Heat resistance refrigerant</td>
<td>m²/K/W</td>
</tr>
<tr>
<td>$R_i$</td>
<td>Heat resistance filtrate</td>
<td>m²/K/W</td>
</tr>
<tr>
<td>$\Delta T_{ln}$</td>
<td>Logarithmical temperature difference</td>
<td>K</td>
</tr>
<tr>
<td>$\Delta T_g$</td>
<td>Greatest temperature difference between</td>
<td>K</td>
</tr>
<tr>
<td>filtrate and refrigerant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta T_k$</td>
<td>Smallest temperature difference between</td>
<td>K</td>
</tr>
<tr>
<td>filtrate and refrigerant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U$</td>
<td>Overall heat transfer coefficient</td>
<td>W/m²/K</td>
</tr>
<tr>
<td>$V_{tu}$</td>
<td>Velocity in the tube</td>
<td>m/s</td>
</tr>
<tr>
<td>z</td>
<td>Number of tubes</td>
<td></td>
</tr>
</tbody>
</table>

Greek Symbols

$\alpha_i$ Heat transfer coefficient in tube

$\alpha_u$ Heat transfer coefficient shell side

$\Phi_m$ Mass flow filtrate

$\mu$ Viscosity of filtrate

$\sigma$ Surface tension of Freon

Pa.s

m²

kJ/kg/K

inch

mm

mm

W/m²

kJ/kg

kg/m³

kg/m³

m²/K/W

m²/K/W

K

K

W/m²/K

m/s

N/m
### Symbols of extraction

- $C_a$: Carrier concentration \( \text{mol/l} \)
- $C_{a_{\text{tot}}}$: Concentration of total free carrier \( \text{mol/l} \)
- $C_{a_{\text{HP}}}$: Concentration of penicillin bound to the carrier \( \text{mol/l} \)
- $C_{a_{\text{HF}}}$: Concentration of phenylacetic acid bound to the carrier \( \text{mol/l} \)
- $C_{\text{pen}}$: Total penicillin concentration \( \text{mol/l} \)
- $C_{\text{fen}}$: Total phenylacetic acid concentration \( \text{mol/l} \)
- $C_{\text{hp}}$: Concentration of the associated penicillin acid \( \text{mol/l} \)
- $C_{\text{hf}}$: Concentration of the associated phenylacetic acid \( \text{mol/l} \)
- $C_{p^{-}}$: Concentration of penicillin acid ion \( \text{mol/l} \)
- $C_{f^{-}}$: Concentration of phenylacetic acid ion \( \text{mol/l} \)
- $C_{h^{+}}$: Concentration of protons \( \text{mol/l} \)
- $K$: Acid constant
- $K_{\text{r}}$: Equilibrium constant of reactive extraction
- $K_{\text{p}}$: Penicillin acid
- $K_{\text{f}}$: Phenylacetic acid
- $K_{\text{a}}$: Proton
- $P^{-}$: Penicillin acid ion
- $F^{-}$: Phenylacetic acid ion
- $E/R$: Ratio between extract and raffinate
- $R/E$: Ratio between raffinate and extract
- $\text{CON}$: Concentrating factor
- $N$: Number of theoretical stages
- $N_{p}$: Efficiency of penicillin recovery
- $N_{f}$: Efficiency of phenylacetic acid recovery

### Greek symbols

- $\alpha$: Physical distribution between organic and aqueous phase
- $\phi$: Volume flow \( \text{m}^3/\text{hr} \)

### Indices

- $p$: Penicillin
- $f$: Phenylacetic acid
- $\text{org}$: Organic phase
- $w$: Aqueous phase
- $\text{abs}$: Absorber
- $\text{des}$: Desorber
- $\text{in}$: Entering
- $\text{out}$: Leaving
Symbols of extractor

\( A_t \) Flown through cross sectional area of extractor \( m^2 \)
\( A_s \) Cross sectional area of continuous phase \( m^2 \)
\( A_r \) Total cross sectional area of extractor \( m^2 \)
\( a \) Specific area \( m^2 \)
\( D_c \) Diffusion coefficient of penicillin in continuous phase \( m^2/s \)
\( D_d \) Diffusion coefficient of penicillin in dispersed phase \( m^2/s \)
\( D_s \) Diameter of agitator \( m \)
\( D_w \) Width of blades of agitator \( m \)
\( d_{s,2} \) Sauter diameter \( m \)
\( h \) Holdup of dispersed phase \( m \)
\( H \) Main volumetric flow of heavy phase \( m^3/s \)
\( H' \) Recirculating flow of heavy phase \( m^3/s \)
\( k_c \) Mass transfer coefficient of continuous phase \( m/s \)
\( k_d \) Mass transfer coefficient of dispersed phase \( m/s \)
\( K_{eq} \) Distribution coefficient \( m^3/s \)
\( L \) Main volumetric flow of light phase \( m^3/s \)
\( L' \) Recirculating flow of light phase \( m^3/s \)
\( L_m \) Length of mixing zone \( m \)
\( L_s \) Length of settling zone \( m \)
\( N_{m,s} \) Number of mixers per theoretical stage \( m \)
\( N_{m,t} \) Total number of mixers \( m \)
\( N_{t,u,d} \) Number of transfer units related to dispersed phase \( m \)
\( p \) Factor of scaling up \( m/s \)
\( K_{o,d} \) Overall mass transfer coefficient of dispersed phase \( m/s \)
\( \Delta N \) Difference in rotational speed between shaft and shell \( s^{-1} \)
\( N_s \) Speed of revolution of shaft \( s^{-1} \)
\( N_{sh,ell} \) Speed of revolution of shell \( s^{-1} \)
\( P_0 \) Power number \( m^3/s \)
\( Q_c \) Volumetric flow of continuous phase entering mixing zone \( m^3/s \)
\( Q_d \) Volumetric flow of dispersed phase entering mixing zone \( m^3/s \)
\( \Delta \rho \) Difference in density between continuous and dispersed phase \( kg/m^3 \)
\( R \) Distance between droplet and axis \( m \)
\( r_1 \) Distance between shaft and weir of light phase \( m \)
\( r_2 \) Distance between shaft and weir of heavy phase \( m \)
\( r_3 \) Distance between shaft and liquid liquid interface \( m \)
\( r_4 \) Radius of agitator \( m \)
\( r_5 \) Inside radius of extractor \( m \)
\( t_b \) Sedimentation time \( s \)
\( t_c \) Circulation time \( s \)
\( t_m \) Mixing time \( s \)
\( t_r \) Residence time of droplets in mixing zone \( s \)
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_s$</td>
<td>Residence time of continuous phase in settling zone</td>
<td>s</td>
</tr>
<tr>
<td>$v_b$</td>
<td>Sedimentation velocity</td>
<td>m/s</td>
</tr>
<tr>
<td>$V_m$</td>
<td>Mixing volume</td>
<td>m$^3$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Fraction of dispersion flowing in the direction of light phase</td>
<td></td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Power input per unit mass</td>
<td>W/ kg</td>
</tr>
<tr>
<td>$\rho_c$</td>
<td>Density of continuous phase</td>
<td>kg/m$^3$</td>
</tr>
<tr>
<td>$\rho_d$</td>
<td>Density of dispersed phase</td>
<td>kg/m$^3$</td>
</tr>
<tr>
<td>$\mu_c$</td>
<td>Viscosity of continuous phase</td>
<td>Pa.s</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>Viscosity of dispersed phase</td>
<td>Pa.s</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Surface tension</td>
<td>kg/s$^2$</td>
</tr>
<tr>
<td>$\Phi_c$</td>
<td>Circulation flow</td>
<td>m$^3$/s</td>
</tr>
<tr>
<td>$\Omega$</td>
<td>Angular speed of shell</td>
<td>s$^{-1}$</td>
</tr>
</tbody>
</table>
Appendix A

Broth density

The total broth mass per fermentor \( (M_t) \) amounts to:

\[
M_t = 184,884 \text{ kg}
\]

with a dry weight \( (M_{b,w}) \) of:

\[
M_{b,w} = 11,330 \text{ kg}
\]

According to J.C. van Suijdam\textsuperscript{3} the density of dry mycelium \( (\rho_s) \) and of the medium \( (\rho_m) \) can be assessed as:

\[
\rho_s \approx 1400 \text{ kg/m}^3 \\
\rho_m \approx 1020 \text{ kg/m}^3
\]

The volume of mycelial mass in the fermentor is:

\[
\frac{11,330}{1400} = 8.09 \text{ m}^3
\]

The volume of liquid in the fermentor is:

\[
\frac{184,884 - 11,330}{1020} = 170.15 \text{ m}^3
\]

With this the broth density \( (\rho_b) \) becomes:

\[
\rho_b = \frac{184,884}{8.09 + 170.15} = 1037 \text{ kg/m}^3
\]
Appendix B

Ratio Gassed to Ungassed Power Input

According to Nagata et al.\textsuperscript{13} the ratio of gassed to ungassed power can be approximated by:

$$\log \frac{P_g}{P_0} = -192 \times \frac{D_s^{4.38}}{D_l} \times \frac{D_s^2 \times N_s \times \mu_b}{\mu_a} \times \frac{D_s \times N_s^2}{g} \times \frac{196 D_s / D_l^{1.15}}{N_s \times D_s}$$

To correct for the non-Newtonian behaviour of the liquid Calderbank et al.\textsuperscript{7} suggest an adjustment of the Re-number:

$$\frac{D_s^2 \times N_s \times \mu_b}{\mu_a} = \frac{D_s^2 \times N_s^{2-n} \times \mu_b}{0.1 \times K} \times \frac{n}{6n + 2}$$

where \(n\) and \(K\) are the power index and flow behaviour index respectively.

Kossen\textsuperscript{18} uses the following equation to estimate the power input under aerated conditions:

$$\frac{P_g}{P_0} = 0.10 \times \frac{\phi_g}{N_s \times V} \times \frac{N_s^2 \times D_s^4}{g \times D_w \times V^{1/3}}$$

The results are assembled in table 1. As can be seen the ratio of gassed to ungassed power input varies strongly among the different authors. Additional information comes from Bauer\textsuperscript{8} who states that the energy transfer for turbine stirrers in presence of a gas is reduced by about 40%.

We concluded the gassed power input to be about half of the ungassed power input.
**Table 1:** ratio gassed/ungassed power input \( (P_g/P_0) \) according to different authors.

<table>
<thead>
<tr>
<th>Author</th>
<th>( P_g/P_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagata</td>
<td>0.15</td>
</tr>
<tr>
<td>Bauer</td>
<td>0.60</td>
</tr>
<tr>
<td>Calderbank</td>
<td>0.78</td>
</tr>
<tr>
<td>Kossen</td>
<td>0.82</td>
</tr>
</tbody>
</table>
APPENDIX C

Air compression

The air that is required for the aerobe growth has to be compressed before entering the fermentor. The back pressure at the top of the fermentor is 10 psi, which is equal to 0.7 bar.

At the end of the fermentation the liquid height in the fermentor above the sparger is 6.9m. Which is equal to 7.14 m water column. Therefore the air entering the fermentor has to be compressed to 2.41 bar.

Assuming adiabatic compression:

\[ c_p = 1000 \text{ J/kg/K} \]
\[ c_v = 714 \text{ J/kg/K} \]

The compressibility factor \( k \) becomes:

\[ k = 1.4 \]

The relation between pressure and volume is given by:

\[ p_1 V_1^k = p_2 V_2^k \]

with the pressures substituted:

\[ V_1 = 1.874 \times V_2 \]

With the relation:

\[ pV = RT \]

we can determine the temperature of the compressed air:

\[ T = 345 \text{ K} = 72 \text{ °C} \]

We shall now have a look at the power input, at maximum requirements, that is towards the end of the fermentation. The volumetric air flow at \( p_1 \) and \( T_1 \) is:

\[ \phi_1 = 2.57 \text{ m}^3/\text{s} \]

The power input necessary to compress the air is given by:

\[ \int \phi_1 \, dp = k/(k-1) \times p_1 \times V_1 \times (1 - T_2/T_1) = 178 \text{ kW} \]

If we take friction losses and the electrical efficiency into account then the total power input at the end of the fermentation becomes: 87
\( P = 222.5 \text{ kW}. \)

The temperature rise of the air after the compression is about 60°C. Because of the difficulties of heat transfer in the fermentor, the air is cooled again to 25°C before entering the fermentor.
APPENDIX D

Carbon dioxide leaving the fermentor

Because too high a concentration of carbon dioxide in the liquid will inhibit the mycelial growth, the carbon dioxide must be removed by the throughflowing air. According to Cooney⁶ the percentage of CO₂ in the air leaving the fermentor should be kept under 4%.

Towards the end of the fermentation the amount of carbon dioxide produced is (see fig.6.4):

\[ r_c = 2920 \text{ mol/hr} \]

With an airflow of 50 Nm³/ton/hr, a broth weight of about 185 tons and a molar volume of 13.3 l/mol, the increase of the CO₂ percentage in the air leaving the fermentor, is given by:

\[ \%CO_2 = \frac{2990 \times 13.3 \times 10^{-3}}{50 \times 185} \times 100\% = 0.42\% \]
APPENDIX E

Jacket cooling

The Nusselt number for the jacket (Nu\textsubscript{j}) can now be calculated:

\[
\text{Nu}_j = 0.215 \times 127.4 \times 31.3 \times 0.99 \\
= 848.8
\]

Therefore:

\[
\alpha_{bj} = \frac{\Theta_b}{D_f} \times \text{Nu}_j = \frac{0.6}{5.4} \times 848.8 = 94.3 \text{ W/m}^2/\text{°C}
\]

However the used formula of Gluz may not be applied when \( \text{Re} < 4\times10^5 \), as in our case. But because there are no suitable equations to predict the heat transfer coefficient of the broth in case of a jacket type of cooling the above calculated value (\( \alpha_{bj} \)) is used as an estimate.

Calculation of jacket resistance

Because the thickness of the fermentor wall increases from 0.01m at the top to 0.02m at the bottom of the fermentor, an average thickness of 0.015m is taken. Thermal conductivity of stainless steel is:

\[
\Theta_j = 50 \text{ W/m/°C}
\]

So:

\[
\frac{\Theta_j}{\alpha_j} = \frac{50}{0.015} \approx 3335 \text{ W/m}^2/\text{°C}
\]

Heat transfer coefficient of water on the inside of the jacket (\( \alpha_j \))

According to Perry\textsuperscript{21} \( \alpha_j \) can be estimated as:

\[
\alpha_j = 750 \text{ W/m}^2/\text{°C}
\]
Fouling resistances

The fouling resistance on the broth side of the jacket \( (R_{jb}) \) is estimated as:

\[
R_{jb} = 2275 \text{ W/m}^2/\text{°C}
\]

and the fouling resistance on the inside of the jacket \( (R_j) \):

\[
R_j = 2840 \text{ W/m}^2/\text{°C}
\]

Now, all the relevant data are known. This leads to an overall heat transfer coefficient of the jacket \( (U_j) \):

\[
U_j = \frac{1}{94.3} + \frac{1}{3335} + \frac{1}{750} + \frac{1}{2275} + \frac{1}{2840}
\]

\[
= 76.8 \text{ W/m}^2/\text{°C}
\]

With a temperature of the incoming cooling liquid of 10°C and an outgoing temperature of 18°C and a cooling surface \( (A_f) \) of about 146.6m², the heat removed by the jacket amounts to:

\[
\Phi_{nj} = U_j \cdot A_f \cdot T_{ln}
\]

\[
= 76.8 \cdot 146.6 \cdot 10.5
\]

\[
\approx 120 \text{ kW}
\]

As can be seen the cooling capacity of the jacket compared to that of the cooling coil is less then 10% and is therefore not taken into account as an additional cooling device.
Empty time

Why the fermentor is emptied in 3 hours.

Because the penicillin is not very stable at 25°C it has to be cooled to about 5°C. Every 10 hours one fermentation is finished, so the maximum empty time is 10 hours. It can be easily understood that there will be a minimum in costs somewhere between an empty time of 0 hours and 10 hours.

In 10 hours the penicillin losses will be very high. But at very short empty times the filter surface and heat exchange surface become very large.

We will make a prediction of the empty time at minimum cost.

2. Degradation of penicillin in time.

The penicillin balance over the fermentor is:

\[ \text{OUT} = \text{IN} - \text{CONV} - \text{HOLDUP} \]
\[ \phi_v \cdot c = 0 - k \cdot c \cdot V - \frac{dN}{dt} \]
\[ \frac{dN}{dt} = V \cdot \frac{dc}{dt} + c \cdot \frac{dV}{dt} \]
\[ V = V_0 - \phi \cdot t \]
\[ \frac{dV}{dt} = -\phi_v \]

This results in:
\[ \frac{dc}{dt} = -k \cdot c \]

So the total amount of penicillin coming out of the fermentor is:
\[ \int \phi_v \cdot c \cdot dt = \phi_v \cdot c_0 \cdot \exp(-kt) \cdot dt \]

resulting in:
\[ P_{tot} = \phi_v \cdot c_0 / k \cdot (1 - \exp(-kt_e)) \]
\[ \phi_v = V_0 / t_e \]

The loss of penicillin is \( P_{tot_0} - P_{tot} \). So we now know the loss of penicillin as a function of the empty time \( t_e \).
Fig. 1 Process costs as a function of the empty time of the fermentor
3. The cost of processing with increasing process time.

For the filter we can derive the following relation for the surface as a function of $t_e$:

\[ A = \frac{500}{t_e} \]

And for the heat exchanger:

\[ A_h = \frac{200}{t_e} \]

When we determine the cost of the filter surface per $m^2$, the costs of the heat exchanger surface per $m^2$ and the price of penicillin, we can determine the empty time at minimum cost.

In fig. 1 the cost as a function of the empty time is given. From the graph can be seen that the empty time at minimum cost is at about three hours.

In this calculation we negociated a lot of things, for example the increasing costs because the filter and the heat exchanger cannot be operated continuously (after every three hours there is a seven hours stop). We suppose that these effects are of minor importance.
APPENDIX H

Freon-12

For cooling the filtrate we used Freon-12 (Mwt. 121.9) as a refrigerant. We shall now present some properties of Freon-12. The operating pressure and temperature at which the Freon is vaporized are:

\[
T = -6.77 \, ^\circ\text{C} \\
p = 2.43 \, \text{atm.}
\]

At this pressure and temperature the density of the liquid and gas become:

\[
\rho_l = 1412.7 \, \text{kg/m}^3 \\
\rho_g = 14.2 \, \text{kg/m}^3
\]

The heat of vaporization becomes

\[Q_{l,g} = 157.9 \, \text{kJ/kg}\]

We estimated the surface tension of Freon-12 at:

\[\sigma = 25\times 10^{-3} \, \text{Nm}\]
APPENDIX I

Wastewater treatment

The loss of carrier is dependent on the solubility of butyl acetate in water. At 25°C the solubility of butyl acetate in water amounts to 2.3%.$^{44}$ The solubility of butyl acetate in water at 5°C is estimated as 1%.

This means that the aqueous phase leaving the absorber will contain 181.5 l/hr of butyl acetate. Because the butyl acetate contains 0.326 mol carrier/l, we lose 22.2 kg carrier/hr. With the price of amberlite-LA2 being $ 76 /kg, this would mean an annual loss of $14,770,000.00. This is the reason why the wastewater is treated to recover the carrier.

We suggest that the aqueous phase is stripped with clean butyl acetate, this way we recover the carrier. The carrier in the butyl acetate can be, if necessary, concentrated by destilling of the butyl acetate. This organic phase can be sent to the regeneration section of the organic phase leaving the desorber.
APPENDIX J

Prices

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APPENDIX K

Physical-Chemical parameters

Estimations of diffusion coefficients of penicillin in an aqueous phase and in butyl acetate phase had to be made because no values could be found in literature.

According to Wilke-Chang\textsuperscript{21} the diffusion coefficient of component A in phase B can be estimated as:

\[ D_{A,B} = 7.4 \times 10^{-8} \times \frac{(\Phi \times M_B)^{1/2} \times T}{\mu_B \times V_A^{0.6}} \]

where:
- \( D_{A,B} \) diffusion coefficient of component A in phase B (cm\(^2\)/s)
- \( \Phi \) constant related to phase
- \( V_A \) molar volume of component A (cm\(^3\)/mol)
- \( \mu_B \) viscosity of phase B (cP)
- \( M_B \) molweight of solvent (g/mol)

The following values have been used:
(\( \text{BA} = \text{butyl acetate}; \text{pen} = \text{penicillin}; \text{pa} = \text{phenyl acetic acid} \))

\[
\begin{align*}
\Phi_H2O &= 2.6 \\
\Phi_{BA} &= 1.0 \\
V_{pen} &\approx \frac{M_{pen}}{\mu_{pen}} = 335/1.35 \text{ (cm}^3\text{/mol)} \\
V_{pa} &\approx \frac{M_{pa}}{\mu_{pa}} = 136.1/1.09 \text{ (cm}^3\text{/mol)} \\
M_{H2O} &= 18 \\
M_{BA} &= 116.16 \\
T &= 298 \text{ (K)} \\
\mu_{H2O} &= 1.519 \text{ (cP)} \\
\mu_{BA} &= 0.88 \text{ (cP)}
\end{align*}
\]

This results in:

\[
\begin{align*}
D_{\text{pen},H2O} &= 3.73 \times 10^{-11} \text{ m}^2/\text{s} \\
D_{\text{pen},BA} &= 1.02 \times 10^{-10} \text{ m}^2/\text{s} \\
D_{\text{pa},H2O} &= 7.42 \times 10^{-11} \text{ m}^2/\text{s} \\
D_{\text{pa},BA} &= 2.02 \times 10^{-10} \text{ m}^2/\text{s}
\end{align*}
\]

Other parameters are given below:
(\( \text{LA} = \text{Amberlite LA-2} \))

\[
\begin{align*}
\sigma_{BA/H2O} \text{ (5}^\circ\text{C)} &= 53 \times 10^{-3} \text{ (N/m)} \\
M_{\text{LA}} &= 375 \\
M_{\text{NaPenG}} &= 356.38 \\
\mu_{BA} \text{ (20}^\circ\text{C)} &= 882.5 \text{ (kg/m}^3\text{)} \\
\mu_{\text{pen}} &= 1350 \text{ (kg/m}^3\text{)}
\end{align*}
\]
APPENDIX L

Overall efficiency

The following efficiency estimations for the different process steps have been assumed:

1. loss of penicillin during filtration: 0.5%
2. loss of penicillin during hold up, being the time between emptying the fermentor and leaving the buffer tank towards the heat exchanger: 1.5%
3. loss of penicillin during extraction: 0.5%
4. loss of penicillin during crystallization: <5%

Therewith the overall efficiency becomes 92.5%.
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## APPENDIX N

### Table with flow numbers

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Apparatenlijst voor pompen, blowers, kompressoren

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* aangeven wat bedoeld wordt