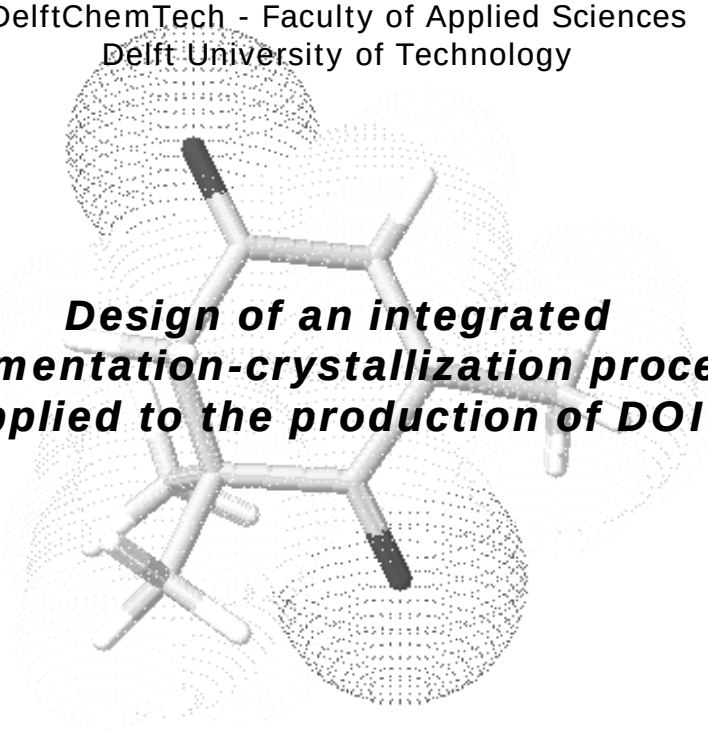
CPD nr. 3312
Conceptual Process Design

Process Systems Engineering
DelftChemTech - Faculty of Applied Sciences
Delft University of Technology



Design of an integrated fermentation-crystallization process applied to the production of DOIP

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Keywords
Fermentation, crystallization, ISPR, in situ product removal, Levodione production, (6*R*)-dihydro-oxoisophorone, DOIP

Assignment issued: 21-09-2004
Report issued: 20-12-2004
Appraisal: 11-01-2005

Preface

This report describes the design of two different processes for the production of a fine chemical using biomass. It is written to support scientific work done at the Kluyver laboratory of the TU Delft and provides an example of how in situ product removal (ISPR) compares to current biotechnological practice. To this end both an ISPR process and a comparable industrial 'Base case' were designed. It has been the design team's purpose to identify and overcome the design challenges and come to a good design.

Among those design challenges were aligning team direction and goals, the handling of uncertainties and coming up with creative and technically feasible solutions. Even though the way taken to achieve this has not always been smooth, in hindsight it can be said that the goals set at the beginning have been achieved. The design presented in this report is based on decisions, which were made carefully and are supported by every member of the design team. We hope that the work done will meet expectations and perhaps even surpass them.

During the process of working on the designs, we consulted many people of Delft University of Technology, which all helped us in our project. In special we would like to thank Evelyn Buque, the principal, and Adrie Straathof, our creativity coach, for all the information and support they gave us regarding the design. Furthermore we like to thank Dennis Sterzenbach and Mark Dressen, employees of DSM for showing us a multi purpose plant in Venlo, the Netherlands. Finally we would like to thank Johan Grievink for his insights in the process of designing a (bio)chemical plant.

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December 20th, 2004
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Summary

The design problem of CPD3312 was the comparison of the conventional batch (Base case) and the new integrated fermentation-crystallization process (In Situ Product Removal or ISPR case) in particular for the production of 2 tonnes 6*R*-dihydro-oxoisophorone (DOIP) from 4-oxo-isophorone (OIP) per year. Creativity tools were used to generate different process options for the two cases. The process is to be implemented on a multi purpose plant (MPP) and the product targets have to be achieved in 2000 hours. Basic feedback control and safety measures were implemented in the designs of both cases. Both processes were simulated using specialized software and all process equipment was designed and sized.

For the Base case a process was chosen typical for the fine-chemical industry. OIP is converted using immobilized biomass in a bubble column. DOIP is then extracted from water with ethyl acetate. DOIP is subsequently crystallized using evaporative crystallization. Filtration, washing and drying leads to an overall yield of 79% of DOIP on OIP. This process generates a significant amount of waste due to the usage of solvent and large amounts of water.

The ISPR process chosen is of the "indirect contact, external removal" type. OIP is continuously fed to the fermentor; an external loop removes the formed DOIP. The external loop consists of an ultrafilter to ensure high purity and a scraped cooling crystallizer where DOIP is crystallized. At the end of a batch, the crystals are filtered, washed and dried, leading to an overall yield of 91%. This process does not generate substantial waste streams.

The process concept used in the Base case is more likely to be found in industry. However, the ISPR case does have the best overall technical performance. It has a higher yield and produces far less waste than the Base case. The process setup of the ISPR is also much simpler as can be seen from process flow sheets and the batch cycle diagrams. So although the ISPR case is a new technology, it performs significantly better and no insurmountable technical reasons were found for not implementing the ISPR technology.

Both processes were economically evaluated and compared. It turned out that both the processes had about the same investment costs. The operating costs were however completely different for the processes. The operating costs were mainly determined by the yield of DOIP on OIP and the usage of solvent. The needed margin between the DOIP and OIP prices should be €285/kg for the ISPR case and €425/kg for the Base case. Lowering the solvent costs, for example by using an adsorber, could lower this margin for the Base case.

As stated above, the ISPR case is considered to be both technically and economically superior to the Base case. It is therefore recommended to construct the ISPR process for the production of DOIP.

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1 Introduction

In general downstream processing in the biochemical industry is requiring a lot of different operating units. Another major problem when using micro-organisms is product-inhibition. Research at the TU Delft is being done in the field of in-situ product removal (ISPR); this method can enhance the productivity of the process and decrease the number of downstream operating units [24]. Although this technique is applied in a few major biochemical bulk processes, it is not widely applied in fine chemical industry. Research is being done on applying ISPR to this industry, and one such project, 'In-situ removal of solid products during whole-cell bio catalysis', is being performed by Evelyn M. Buque-Taboada. Currently she is doing research on the production of 6*R*-dihydro-oxoisophorone (DOIP) from 4-oxo-isophorone (OIP) catalysed by baker's yeast (*Saccharomyces cerevisiae*). To determine how an ISPR process might compare to a Base case currently used in industry, the project principal Evelyn M. Buque-Taboada commissioned a design of a biochemical process that would produce 2000 kg of DOIP per year for a.o. zeaxanthin synthesis. The design problem was formulated as:

Comparison of the conventional batch and new integrated fermentation-crystallization process

The chemistry of production of DOIP from OIP with baker's yeast and the unwanted subsequent reaction of DOIP to (4*S*,6*R)*-actinol (ACT) is shown in Figure 1.1.

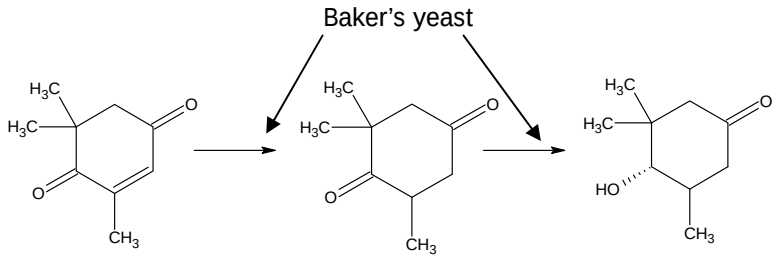


Figure 1.1: Production of DOIP from OIP and subsequent reaction of DOIP to ACT

DOIP is an intermediate in the synthesis of zeaxanthin, a cartenoid that is suspected to reduce the risk of chronic eye disease [24]. The fact that DOIP is an intermediate for a pharmaceutical product imposes requirements on crystal size, purity and enantiomeric excess (e.e.), since two enantiomeres exist (*R* and *S*).
Because DOIP is not sold on the open market and is mostly used internally as an intermediate, both producers of DOIP and zeaxanthin are listed in Table 1.1. This is done because it is likely that the zeaxanthin producers themselves produce the DOIP needed for zeaxanthin production.

Table 1.1: DOIP and zeaxanthin manufacturers

Product	Producer	Main office
DOIP	Fluka Chemie A.G. [6]	Buchs, Switzerland
	Interchim S.A. [6]	Montlucon, France
Zeaxanthin	Apin Chemical Ltd. [6]	Oxon, United Kingdom
	Eextrasyntheses S.A. [6]	Genay Cedex, France
	Indofine Chemical Company Inc. [6]	Sommerville NJ, United States
	Carl Roth Gmbh & Co. Chemische Fabrik [6]	Karlsruhe, Germany
	Sigma Chemical Company [6]	St. Louis MO, United States
	Spectrum Chemical MFG. Corp. [6]	Gardence CA, United States
	DSM [9]	Heerlen, The Netherlands

Little is known about the current production process for DOIP and current production levels, as these are industrial secrets. However, patent literature by DSM/Roche [10], one of the producers of zeaxanthin, has been found that describes a process for the production of DOIP with immobilized biomass; this is suspected to be the process used in industrial practice. The process described in the patent is changed slightly to fit our specifications, as described in paragraph 2.1.1.

As DOIP is a fine chemical intermediate that has a rather small production volume (2 tonnes/year), the process will be designed to attain production targets in approximately three months to take advantage of economy of scale. As DOIP is only used as an intermediate, no real market prices for DOIP exist. As result, a margin will be calculated based on estimated prices. Also, the processes we are to design are intended to replace the existing process. The process will therefore have no impact on the world market.

The ISPR process we are going to use was developed by the TU Delft and is currently not patented, though there are plans to patent it in the future. This process exists currently only on lab scale and is not being applied in chemical industry practice. This process is described in paragraph 2.1.2.

Physical properties and solubilities of OIP, DOIP and ACT in water can be found in chapter 4. As OIP, DOIP and ACT are uncommon substances, little is known about their solubility in organic solvents, vapour pressures and other properties critical to our process. To estimate what was unknown, properties of Isophorone (which is chemically fairly similar) and thermodynamic correlations were used to obtain the information needed. Kinetics were investigated by Buque et al. [5].

The most important design challenge is to make a product with sufficient purity. Besides this, the product we produce is solid at ambient temperature; therefore a suitable separation technique is crystallization. From experiments performed by the principal was found that with cooling crystallization a purity of 99.5 %wt is obtainable[1]. Other crystallization techniques will also be explored for both processes to see whether they are suitable for implementation.

[1] Source: conversation with principal.

2 Process, Options and Selection

In this chapter the two different design cases are technically defined. All relevant choices between process options are made and block schemes are presented.

2.1 Process concept chosen

Criteria and impact factors
One process option of ISPR is already given in the project description, since it is based on the lab scale research of the principal. Given that process, some scale up calculations were made, these calculations gave an indication of criteria that would be important in generating a successful design. The main conclusions were that the yield of DOIP on OIP is very important since the OIP is relatively expensive (see paragraph 3.4), also biomass, glucose and buffer would be a cost factor, on the other hand the cooling and heating cost seemed given the mild circumstances not that important. These conclusions were substantiated when the criteria and their weight factors were qualitatively determined (chapter12.1):

Table 2.1: Criteria and impact factors

Criterion	Impact factor
A. Purity of product (e.e.)	5
B. Yield product on OIP	4
C. Equipment costs	4
D. Complexity	3
E. Biomass costs	3
F. Number of unit operations	3
G. Waste streams	2
H. Utility costs	2
I. Safety	1

The purity of the product seemed the most important criterion, because the product would not be useful anymore if the purity requirements are not met. The product should not only be of high purity, but also be a pure enantiomere, because only the *R*-configuration of the DOIP molecule is useful for further processing. This means that for the process baker's yeast or comparable micro-organisms can be used, because this yeast is known to produce DOIP with high enantiomeric excess [4].

Both the yield and the equipment costs were also considered as crucial criteria and obtained a high impact factor. The criteria complexity and number of unit operations are a bit intertwined, but also very different. A process with just one apparatus may have a positive score on the number of unit operation, but if this one piece of equipment is used for a lot of different processes, it may be very complex and this will lead to a negative score on complexity. The safety criterion has the lowest impact, not because safety is not considered to be important, but because it seemed that for the processes considered simple measures can be taken to ensure a safe operation, so it should not be a crucial criterion in the evaluation of process options.

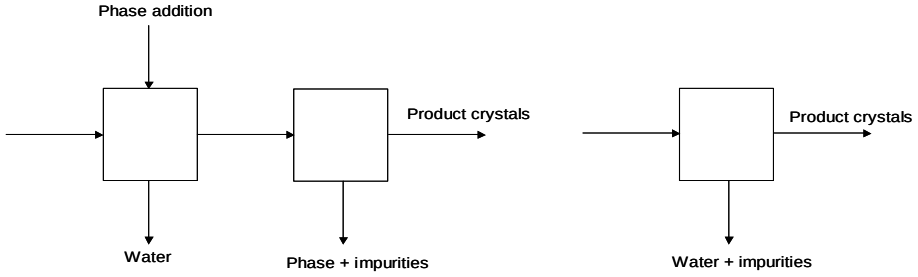
Operating time
The project description has no demands on the operating time. So the choice is whether to produce the product during the whole year in a dedicated section of the plant or to produce it in a short period in the year using multi purpose equipment and use the advantages of large-scale production. Therefore the operating time was for us considered to be a variable. A period of 3 months (2000 production hours) for the entire production of 2 tons seems reasonable.

Suspended or immobilized biomass
Immobilization of biomass is often done when the biomass used has a high volumetric productivity. When applied its advantages are lower filtration cost and the possibility of re-using the biomass for multiple batches. The disadvantages of immobilizing biomass are higher cost for the immobilization of the biomass and possible diffusion limitations. Knowing that one immobilized biomass batch can be used for a long time period (over 3 months, for example in ethanol production[2]), the advantages will weigh up the to disadvantages and therefore the option of immobilized biomass with a higher productivity will be chosen. It is however important to check the diffusion limitations within the immobilized biomass.

For both the Base case and the ISPR case a choice has to be made what kind of biomass is going to be used. There are two options available: very active but expensive biomass [10] or less active and cheap biomass [5]. When both are used as suspended biomass the activity of the expensive biomass does not weigh up to the extra cost of it. To make the expensive biomass feasible for use it has to be reusable, this can be achieved by immobilization. The downside of immobilization is that is has to be regenerated once in a while [10], this makes it unsuitable for the ISPR case, which is semi-continuous. The Base case is operated batch wise, therefore the active biomass, in an immobilized form, is the option used.

2.1.1 Base case

For the downstream processing two different processes were evaluated. The first one is based on a phase addition (adsorption or extraction), the second on a phase creation (crystallization).



A. phase addition B. Phase creation

Figure 2.1: Downstream processing

The main advantage of the first process is the possible solvent recycle and the accompanying low utilities cost. The second process has a simpler setup, but a much higher utilities cost, because a lot of water needs be to be evaporated. A general

[2] Source: Tanaka,A., Tosa,T., Kobayashi,T., Industrial Application of immobilized biocatalysts (1993)

problem in both processes is the possible evaporation of DOIP in the evaporator; this can significantly lower the yield. The first process has the advantage that the evaporated solvent can be re-used and thereby minimising the yield loss, in the water process this is more difficult because of the build-up of impurities that can influence the fermentation. Both the solvent-based and the water-based processes were judged according to the criteria mentioned in Table 2.1 and the results of this judgement can be found in Table 2.2.

Table 2.2: Solvent vs. water crystallization

Criterion	Impact factor	Solvent	Water
A. Purity of product (e.e.)	5	+ +	+
B. Yield Product on OIP	4	+	0
C. Equipment costs	4	0	+
D. Complexity	3	-	0
E. Biomass costs	3	0	0
F. Number of Unit operations	3	-	0
G. Waste Streams	2	-	0
H. Utility costs	2	0	- -
I. Safety	1	-	+
Total		5 +	6 +

The solvent and the water process received roughly the same score, with a slight advantage for the water based process. The solvent process scores better on purity, yield and utilities cost, because the crystallization in solvent generates less impurities, because for example all salts remain in the water phase. On the other hand the solvent has some inherent disadvantages on extra equipment, safety and waste streams, also the equipment costs will probably be higher. The crucial point in the water-based process is the yield loss in the crystallizer. The cost of raw materials is the most significant cost factor in the process and therefore it is a very important decision criterion. Another important thing to remember is industrial practice in which mostly solvent processes are used for recovery. With these considerations in mind we will chose to take the solvent process for the recovery of DOIP in the Base case.

In the solvent process two options are available: use of an extraction or an adsorption column. These two design cases are schematically represented in block schemes (see Appendix 2.1). Furthermore some detailed explanation about the processes will be given and finally a choice will be made for one of two for further design.

For the DOIP production with adsorption patent EP1074630 [10] is taken as a start. In this patent a process is described which produces around 500kg in 1000 hours. As the target for this project was set to 2000 kg of DOIP, with this setup it would take 4000 hours (= 0.5 year) to produce the required amount. In the basic assumptions (paragraph 3.3) it is mentioned that the total production time should be 2000 hours, thus giving a factor 2 to improve on production in this case. A simplified block scheme of this process can be seen in Appendix 2.1. Some research done on the adsorption column can be found in Appendix 1.1.

The alternative for the adsorption column in the separation unit is an extraction unit as described by Leuenberger [17], where ethyl acetate is used as a solvent during

the extraction. The reaction step is the same as in [10], however in contrast to the patent every batch is handled separately in the separation unit to minimize the size of the units. The block scheme for the extraction Base case process is given in Appendix 2.1.
For the further design of the Base case one of the two processes has to be chosen. When looking at the block schemes the only difference between the two is either the adsorption unit or the extraction unit. The main advantage of an adsorption column is less contact between the solvent and water phase and thereby a minimization of solvent loss. This results in smaller streams and operating units after adsorption. However, despite these advantages of the adsorption unit we have chosen to design the extraction unit. The main reason for this choice is the large number of unknowns in the adsorption design compared to the extraction unit. This would give a "black box" design for the adsorption unit in which a yield of DOIP and the size of the streams would be guessed. So in light of the educational value of the this project the extraction unit has the preference, for which the partition coefficients and concentrations are either measured experimentally or determined theoretically as will be seen in later chapters. As a solvent ethyl acetate will be used, as is described by Leuenberger.

2.1.2 In Situ Product Removal

For the ISPR case four different types of product removal are distinguished [24]. These types are based on the different way of removal of the product, by direct or indirect contact between phases and internal or external removal from the reactor, shown in Figure 2.2.
Various options were developed for each of the four types during creativity sessions. In Appendix 12.5 seven of these processes can be found. These processes were judged by the criteria of Table 2.1 and three of these processes, shown schematically in Figure 2.3 will be discussed in this paragraph. The processes that used direct contact were rejected, because of foreseen problems with purity and the complexity of the process.

Direct contact Internal removal	Direct contact External removal
Indirect contact Internal removal	Indirect contact External removal

Figure 2.2: Four types of ISPR

The first process that will be looked into is the ISPR process as proposed by the principal [4]; the complete layout of the process can be found in Appendix 12.5, figure A12.4, OIP is converted in the fermentor and after ultrafiltration DOIP will be crystallized by cooling. The water that still contains DOIP and unconverted OIP is fed back to the fermentor. The advantages of this process are a.o. the simplicity, the high yield and purity of the product. A disadvantage is the energy duty of the crystallizer.
The second process contains two cycles and a third piece of equipment where the mass transfer of DOIP from the fermentor to the crystallizer is located. This can be either a dialysis unit or an adsorber/solvent combination. The advantage of a dialysis system is that there is no trans-membrane pressure drop as a driving force of mass transfer and no extra filters will be needed. Fouling will be less likely to happen. Also the process control of the system is different, since the two loops can be controlled separately. A disadvantage is that this kind of equipment is not used very often and probably can be used for this process only.
The third process consists of one apparatus in which both the conversion and the crystallization occur. It has 2 compartments separated by a membrane. The OIP is

converted in the upper section and the produced DOIP diffuses to the crystallization section, which operates at a temperature of 5° C. The obvious advantage is that only one apparatus is needed. The disadvantages are the different temperatures in the compartments and complex equipment with probably the need for immobilization of the biomass.

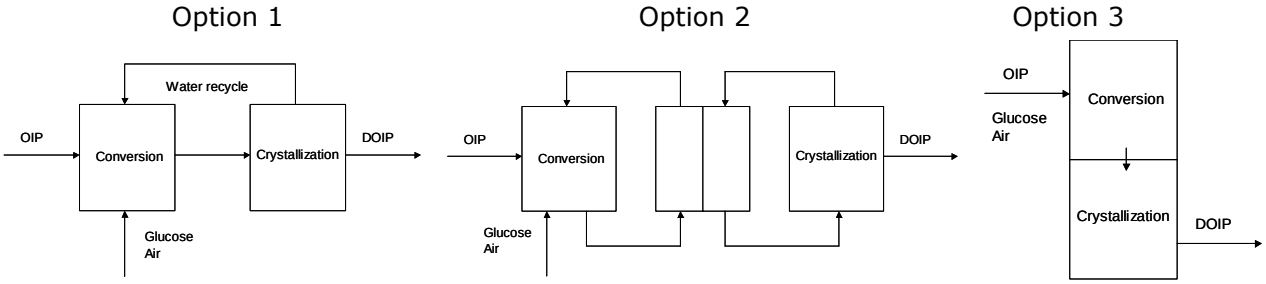


Figure 2.3: option 1: one cycle system
option 2: two cycles system
option 3: fermentation-crystallization

In Table 2.3 the three different processes are compared with each other. It is clear that the fermentor-crystallizer option is less suitable than the other two. To make a choice between the other two option both the areas of a dialysis unit and an ultrafilter were calculated: the results for the ultrafilter gave 2 times an ultrafilter of 6 m^2 and can be found in paragraph 8.2.2, the result of the dialysis unit was at its best 350 m^2 and can be found in Appendix 1.2. Since filter area is a significant cost factor we choose to use the ten times smaller ultrafilter. Also the reliability of the ultrafilter in industrial processes supports this choice.

Table 2.3: ISPR options

Criterion	Impact factor	1 cycle system	2 cycles system	Fermentor-crystallizer
A. Purity of product (e.e.)	5	0	0	0
B. Yield Product on OIP	4	0	0	0
C. Equipment costs	4	0	0	+
D. Complexity	3	+	0	-
E. Biomass costs	3	0	0	-
F. Number of unit operations	3	0	0	+ +
G. Waste Streams	2	0	0	0
H. Utility costs	2	0	+	-
I. Safety	1	0	0	0
Total		+ + +	+ +	- -

2.1.3 Conclusion

According to the project description two processes will be designed. The Base case, a batch reduction of OIP using immobilized biomass with an extraction and crystallization unit for product recovery and an ISPR process, consisting of a normal fermentor, ultrafilter and crystallizer. As the process of designing continues, several of the options rejected above will also be quantified, to ensure that the right choices were made.

3 Basis of Design

Here the Basis of Design (BOD) is presented; this will set the boundaries in which the two processes will be designed. First a short summary of the previous chapter will be given after which the Basic Assumptions and the Economic Margin are presented.

3.1 Description of design

A process for producing two tonnes of 6*R*-dihydro-oxoisophorone (DOIP) from 4-oxo-isophorone (OIP) catalysed by biomass (e.g. *Saccharomyces cerevisiae*) should be designed. To overcome the problem of product inhibition, in situ product removal (ISPR) based on work done by Buque et al. [4,5] will be applied to the ISPR case. Because DOIP is a fine chemical intermediate, there are no real market prices for DOIP. For economical comparison the ISPR process designed will be compared to a Base case based on a patent by industry [10]. One of the main challenges in designing the process are attaining a high yield as the substrate OIP is the major cost factor. Another key issue is ensuring very high product purity. Enantiomeric excess for DOIP is not a problem as baker's yeast produces DOIP with an e.e. of 98%. It is assumed that the immobilized biomass used in the Base case (*Saccharomyces rouxii*) has this same characteristic.

3.2 Process definition

In this paragraph a summary of the process concept chosen and thermodynamic properties will be given. A block scheme of the Base case and the ISPR case can be found in paragraph 3.2.2 and the list of pure compounds is shown.

3.2.1 Process Concept chosen

In chapter 2 two process concepts were chosen, one for the Base case and one for the ISPR case. For the Base case one of the choices was whether or not to use immobilized yeast. The option for immobilized biomass was preferred because of the better volumetric performance and the estimated lower cost. Downstream crystallization could take place in either a solvent or process water. The latter would have higher utility costs and also the yield would be lower due to evaporation of DOIP. For these reasons a solvent was chosen and will be used in the Base case. Finally the choice was made between extraction or adsorption unit for the solvent; here the choice was made for extraction, because of the educational value as explained in paragraph 2.1.1.
For the ISPR case a combined fermentor and crystallizer was considered and rejected, because of its complexity and higher utilities and biomass costs. Another option was to use dialysis unit instead of an ultrafilter. This has the advantage of a small transmembrane pressure drop and another type of control system. An ultrafilter is on the other hand a more reliable piece of equipment and often-used in industry. In the end the more than ten times smaller surface area of the ultrafilter was decisive.

3.2.2 Block schemes

Base case
The process flow scheme can be found in Figure 3.1; in the flow scheme the process is given schematically with the mass streams, pressures and temperatures. The overall process yield of DOIP on OIP is 79 %wt, with a production of 2.1 tonnes of DOIP in approximately 2000 hours. In Table 3.1 indications of batch times are given as well as the amount of batches per unit operation. The batch cycle diagram for the final design can be found in Appendix 5.2.

Table 3.1: Indication of operating times

Unit operation	Process time [h]	Batches
Reaction	9.5	176
Extraction	5.7	176
Crystallization	12.4	22
Filtration/drying	10.5	22

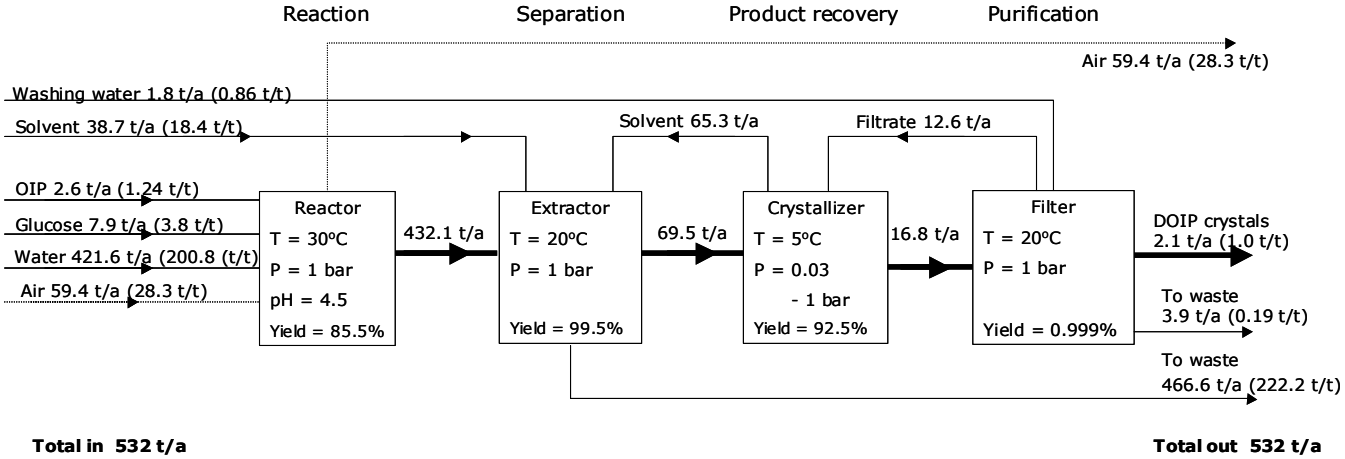


Figure 3.1:Simplified Block Scheme of Base case DOIP production process

The thicker lines show the flow of product. The numbers shown in this figure are flows per annum, where in this case an annum is 2000 hours. These figures have been used for calculation of the economic margin in paragraph 3.4. For the in- and outgoing streams the yields are given in kg/kg DOIP.

In Situ Product Removal: 1-cycle system
The simplified flowsheet of the ISPR case can be found in Figure 3.2. In this figure also the yields per step are indicated. The overall process yield of DOIP on OIP is 91%wt. A process cycle of one ISPR-batch will be around 400 hours, which results in a total of 5 batches. A detailed batch cycle diagram can be found in Appendix 5.6.

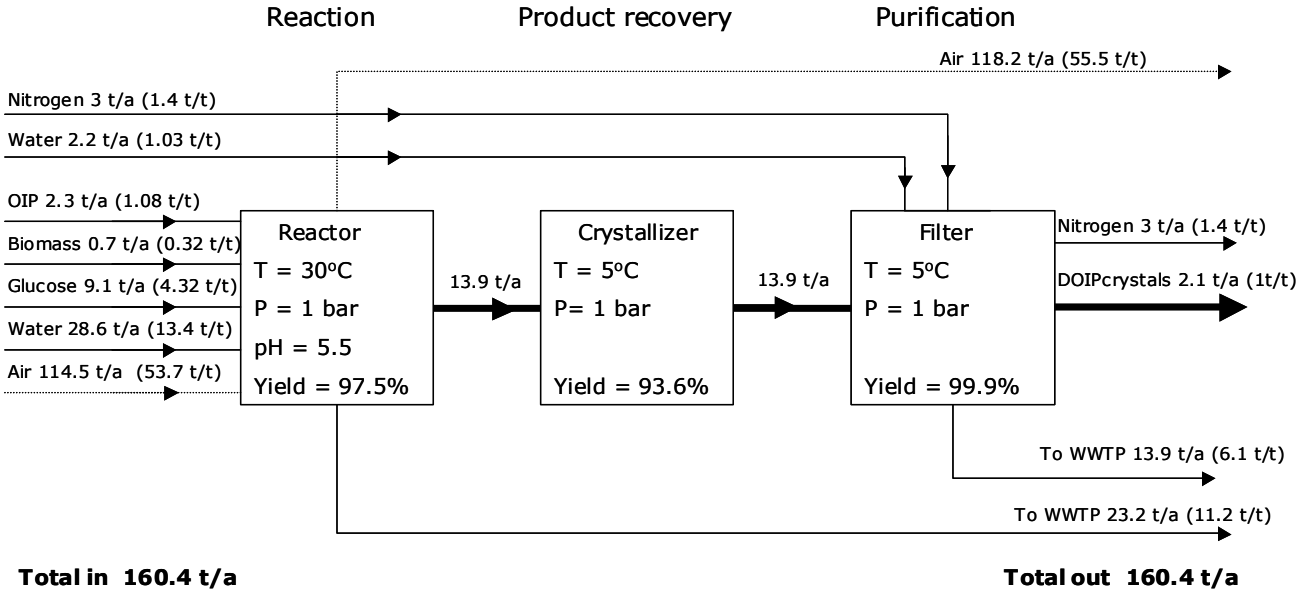


Figure 3.2 Block scheme ISPR 1-cycle system

The ISPR process has characteristics of both a continuous and a batch process, but because the process is mostly operated continuous, the streams for a continuous process were calculated.

3.2.3 Thermodynamic properties & reaction kinetics

Little was found in literature about the three main components OIP, DOIP and ACT. Therefore, as described in chapter 4, all unknown and relevant thermodynamic properties are estimated. When the reliability of the relations was mentioned in literature it is given with the estimation. Finally, when estimated properties were used in other relations the effect of the reliability of the used property was examined in paragraph 4.4. The theoretical validity of the estimated properties could not be checked, because no literature and experimental values where known. For this reason they were compared to values from similar components. The reaction kinetics are also derived in chapter 4. For the Base case the kinetics are derived from [10] and in the ISPR case this is done from [5].

3.2.4 List of Pure Component Properties

In Paragraph 3.3.4 the input-out diagram is given. From this diagram it can be seen what components are used in the two processes. The properties of the components are given in Appendix 3.1, here some extra properties of the biocatalyst, the baker's yeast cell will be given. The properties of *Saccharomyces rouxii* are supposed to be very similar.

Table 3.2: Biocatalyst properties

Properties	Quantity
Diameter (mm)	0.01
Operating temperature (^{0}C)	25-42[3]
Force needed to burst a cell (μN)	55-175 [4]
pH - range	3-8 [5]

3.3 Basic Assumptions

In this chapter the basic assumptions will be given, which form the starting point of the process design. All of these assumptions are made in consultation with the principal. An overview will be presented with regard to the production capacity, feedstock, definition of streams, the battery limit and requirements for the plant location. Particular issues are highlighted for the Base case and the ISPR case.

3.3.1 Plant capacity

For the process design of the production of DOIP a capacity of 2000 kg per year of crystals in the size range of 0.01 - 0.1 mm is assumed. The production will not be spread over the whole year, but will be performed in a time span in the order of 3 months (2000 production hours), as is already pointed out in Paragraph 2.1. The purity of the product needs to be 99.5 wt%. With respect to the e.e. of the product a purity of 98.0% is required. This requirement can be guaranteed by using baker's yeast or another similar yeast as a biocatalyst, which reduces OIP to the desired enantiomere of DOIP. The by-product ACT has no economical value due to its unfavourable enantiomeric configuration. The production capacity and the purity requirements are desired for both design cases. All detailed in- and outgoing streams can be found in the stream summaries of chapter 5.

3.3.2 Location and plant life

For the process design there are obviously considerations required with respect to the location of the production plants. This is an important issue, since it involves environmental, transportation, legislative and thus ultimately cost issues. It is already stated before, that in the case of well-known and relative standard equipment, it is desired to locate the production at a MPP. At such a plant there is a wide variety of process equipment available for processing fine chemicals batch wise. The equipment is possibly used for different batch processes during the whole year. An example of such plant is DSM's MPP situated in Venlo, the Netherlands.

[3] Source: Conversation with principal.
[4] Source: Mashmoushy,H., Zhang,Z., Thomas,C.R., Biotechnology Techniques 12, 925-929 (1998).
[5] Source: scientific staff of Kluyverlab, TU Delft.

At a MPP there is an existing infrastructure for means of communication and transportation of raw materials and product. Further, the facility is able to supply heat transfer oil at a wide temperature range, approximately between –10 to 150^{o}C and electricity. With respect to wastewater and other waste streams the MPP has facilities available to which these can be discarded. It is assumed that the DOIP process, event though it's only using 25% of the total possible production hours (2000 hours out of 8000 hours), it will use the equipment for 33% of the time per year. This will have its implication for the economic analysis of both processes.

The economical plant life for large production plants for bulk products is in general about 20 years. In contrary, fine chemicals are produced with much smaller capacities. Moreover, the market for fine chemicals is quite flexible and demands can change in a couple of years and thus the economical plant life for the design cases is assumed to be shorter than 20 years. However, there has to be made a distinction in the economical plant life for particular cases, as it is strongly dependent on what kind of equipment is designed and implemented. If usage of equipment, which is commonly available at a normal MPP, is possible, the economical plant life will be relatively longer. In the case an unconventional piece of equipment is designed, that is not available at a MPP, the economical plant life will be shorter than with common available equipment. This is due to the fact that conventional equipment can be used for other processes as well, while a new specific piece of equipment probably cannot be used for the production of other fine chemicals. From this reasoning it is assumed that conventional equipment will have an economical plant life of 15 years, and in the case of unconventional equipment an economical life of 10 years will be taken.

3.3.3 Feedstock

For the production a feedstock of OIP is required, which is reduced by the biomass to DOIP during the fermentation. The Base case process will be catalyzed by immobilized *Saccharomyces rouxii*, which has a higher reduction activity than the suspended baker's yeast, which is used for the ISPR case.

For the fermentation process there are also other fermentation chemicals required: glucose (the C-source), oxygen, buffer, acid, base and anti foaming agent. The fermentation liquid will be sterilised process water. More information about the specifications of the feedstock is presented in Appendix 3.2.

3.3.4 Battery limit

In order to make a good comparison between the Base case and the ISPR case, it is important to attain an as close as possible similar battery limit. For both design cases it is obvious that the fermentation takes place within the battery limit. In both cases a fermentor will be used.

With regard to the biomass, it will not be cultivated within the battery limit and thus acquired from outside the battery limit, which accounts for both cases. However, for the Base case the regeneration of the immobilized biomass will be implemented within the battery limit. Further, downstream equipment will be implemented within the battery limit in order to separate and purify the product. For the Base case this implies units for filtration, extraction, evaporation, crystallization and solid handling. For the ISPR case the amount of downstream devices will be limited to filters, crystallizer and the solid handling units. For both cases auxiliary equipment is desired, as storage vessels, pumps, piping, valves and process control devices.

Because for fermentation many different components are needed in small quantities, it becomes a mess showing all of them in the flowsheets. For this reason several solutions are mentioned. These solutions are for the Base case fermentation solution and reactivation solution and for the ISPR case this is the biomass suspension. The feedstock for these solutions will be acquired from outside the battery limit and subsequently mixed within the battery limit. In the report no further reference is made to the mixing, when the solutions are mentioned the solutions specified in Table 3.3 are meant.

Table 3.3: Content of the premixed solutions

	Fermentation solution	Reactivation solution	Biomass suspension
OIP (wt%)	1.24	-	0.75
Glucose (wt%)	3.70	2.00	-
Buffer (wt%)	0.54	0.54	0.54
Sterilized water (wt%)	94.52	97.46	95.41
Biomass (wt%)	-	0.10	3.30

Treatment of the waste streams of both designs cases will be done outside the battery limit. Spent baker's yeast will go with the spent process water to a wastewater treatment (WWTP). The immobilized biomass cannot be processed in a WWTP and needs to be discarded in another way at the end of the process. In the Base case there is also a solvent in use for the purification of the product. This gives an additional waste in this design, which needs to be discarded in an organic waste vessel or towards the water treatment facility.

Finally, also utilities are needed in a plant, so heating and cooling agents are necessary, just as electricity. More about utilities can be read in chapter 5 and 8. In Table 3.4 a summary is presented of the ins and outs of the battery.

Table 3.4: Definition of units/ operations in- and outside the battery limit

Base case		ISPR case	
Inside battery limits	**Outside battery limits**	**Inside battery limits**	**Outside battery limits**
Fermentor	Acquisition feedstock	Fermentor	Acquisition feedstock
Filters	Waste treatment	Filters	Waste treatment
Extractor	Cooling duties	Crystallizer	Cooling duties
Evaporator	Sterilisation of process water	Solid Handling	Sterilisation of process water
Crystallizer		Auxiliary equipment	
Solid Handling			
Auxiliary equipment			
Regeneration of biomass			

For the sake of clarity, the in- and output diagrams that visualize the entering and outgoing materials of the battery limit, are given in Figure 3.3. The specifications and additional information with concern to prices and producers of the in- and outgoing materials are given in table format in Appendix 3.2.

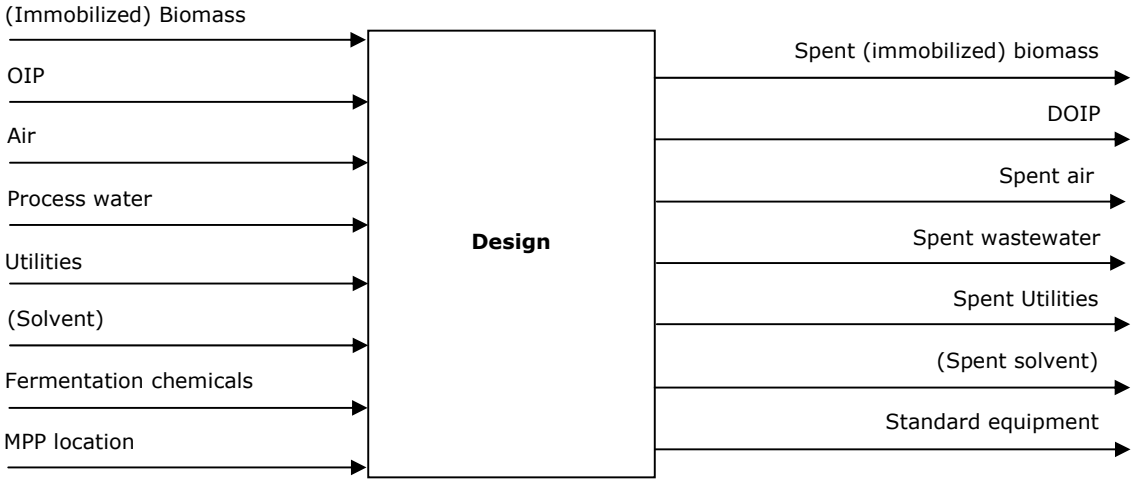


Figure 3.3: In- and output diagram of battery limit for the design cases

3.4 Economic Margin

In this paragraph the economic margin of both processes is calculated. The Net Cash Flow (NCF), given in Table 3.5, is the difference between income from sales of DOIP minus costs for feedstock and waste streams. The economic margin is the NCF divided by the total amount of product. With this margin the maximum allowable investment for the design is obtained. This is also called Net Present Value (NPV).

For the calculation of the Net Present Value the method described in Coulson&Richardson [23, p271-272] is used. The discounted cash-flow rate of return (DCFRR, r') is 10 % [11]. The life span of the plant is 15 years with the assumption that all units used are present at a normal MPP (see Chapter 3.3.2).

Previously it is chosen that the production of DOIP will last for 2000 hours per year. To be economically at the safe side it is chosen to calculate the annual NCF by taking the difference between costs and revenues for DOIP production in 2000 hours and multiply this figure by a factor 3. In this way is accounted for the time the operational units have to be modified to be able to run a different production. It is assumed that the time the MPP isn't used for DOIP production, it runs products with the same costs and revenues. In other words, the designed process for DOIP production adsorbs 33% of the plant costs and for economic evaluation it will be assumed that the plant will produce for 6000 hours per year.

Table 3.5: Economic figures Base case and ISPR

	Base case	ISPR
Margin (€/ kg DOIP)	230	290
Costs (€/2000 h)	350,000	236,000
Revenues (€/2000 h)	830,000	852,000
Net Cash Flow (€/a)	1,440,000	1,846,000
Net Present Value (€)	10,900,000	14,000,000

The complete calculations can be found in Appendix 3.4.

The differences between the Base case and ISPR case are quite significant, especially the margin per kg DOIP is bigger for the ISPR case. The reason for this is that the yield on DOIP produced for the ISPR case was bigger than for the Base case. Furthermore in the Base case a solvent is used, which causes a higher raw material costs and the amount of water/buffer used for the Base case is much higher than for the ISPR case. If one would optimize the Base case, the margin for that case would rise quite significantly.

Finally it can be said that the maximum investment of the plant, if building completely grass roots can be between 11 and 14 million euro, depending on the type of process. The fixed operating costs have not been taking into account, so the actual maximum investment should be lower.

A more comprehensive and complete economic analysis will be done in chapter 11.

4 Thermodynamic Properties and Reaction Kinetics

In literature little was found about the thermodynamic properties of the three main components OIP, DOIP and ACT. However, to be able to design the two processes a number of thermodynamic properties have to be determined, this is done with various relations from [21]. The reaction kinetics are shown in Paragraph 4.1.2, these are taken from [5].

4.1.1 Thermodynamic properties

The processes will be simulated in SuperPro Designer® v5.1 developed by Intelligen Inc. To simulate them correctly the components have to be characterised by certain thermodynamic properties, these are the ones that are derived in this paragraph. The results are presented and the reliability, where possible, is discussed. In Appendix 4 the derivation of the properties of OIP is shown. The properties of Isophorone are reported as a reference value, these are taken from the database of SuperPro Designer® v5.1.

First the enthalpy and entropy of formation will be approximated, the group-estimation method suggested by Anderson, Beyer and Watson [21] is used, this method is reasonably accurate and can be used on a wide variety of substances. In Appendix 4.1 the calculation of the enthalpy and entropy of formation of OIP can be found.

Table 4.1: Enthalpy and entropy of formation

Component	ΔH_f (kJ/mol)	ΔS_f (kJ/(mol/K))
Isophorone	-301.4	-
OIP	-365.7	0.428
DOIP	-478.0	0.430
ACT	-622.0	0.440

The critical temperature, pressure and volume are estimated with Lydersen's method [21, p12]. The method employs structural contributions to estimate T_c, P_c and V_c, the relations and the calculations for OIP are given in Appendix 4.2.

The typical error which is introduced for the critical temperature with this method is usually less than 2%, however for molecules with higher molecular weight (>100 Dalton) can go up to about 5%. For the critical pressure and volume about double these values can occur, which is about 10%.

Table 4.2: Critical temperature, pressure and volume

Component	T_c (K)	P_c (bar)	V_c (cm^3/mol)
Isophorone	715.0	33.30	-
OIP	698.9	36.09	454
DOIP	728.6	34.28	471
ACT	697.6	33.09	485

There are two other factors to determine which are important for further calculations, the critical compressibility factor and the acentric factor. These are calculated with Equation A4.4 and A4.5 given in Appendix 4.3.

Table 4.3: Critical compressibility factor (Z_c) and acentric factor (ω)

Component	Z_c (-)	ω (-)
Isophorone	0.255	0.400
OIP	0.286	0.532
DOIP	0.267	0.525
ACT	0.278	0.823

The liquid densities of the components are estimated with a correlation of Yen and Woods given in Appendix 4.4. The Yen-Woods correlation is a general correlation, which can be applied to both saturated and compressed liquids. It has been extensively tested with pure materials, both polar and nonpolar and was found to be reasonably accurate.

The obtained expression is a function of temperature and is approximately linear over small temperature ranges. When the expression is plotted for the temperature range of the process and is approximated with the linear relation A4.12, as shown in Appendix 4-4 for OIP, values for A and B can be determined. These are given in Table 4.4

Table 4.4: Constants for the liquid density

Component	A (g/l)	B (1/K)
Isophorone	1134	-0.720
OIP	1182	-0.685
DOIP	1222	-0.718
ACT	1155	-0.694

The molar liquid heat capacity is determined with the group contribution method of Chueh and Swanson, shown in Appendix 4-5. This is again a method, which adds up the contributions of the various groups that make up the component. The method is quite accurate and can be used at a wide variety of substances; the error rarely exceeds 2 to 3 percent. The results can be found in Table 4.5.

Table 4.5: Liquid molar heat capacities

Component	C_p (J/(mol.K))
Isophorone	253.5
OIP	289.9
DOIP	230.0
ACT	322.5

The ideal-gas heat capacity is a function of temperature; therefore not a fixed value is derived but four constants, which are used in the following equation.

$$C_p^o(J/(mol.K)) = A + BT + CT^2 + DT^3 \qquad 4.1$$

The method used is the one developed by Rihani and Doraiswamy, which is again a group contribution method. The errors are generally less than 2 to 3 percent. The constants A, B, C and D are determined as shown in Appendix 4.6.

Table 4.6: Constants for calculation of ideal-gas heat capacity

Component	A	B x 10^2	C x 10^4	D x 10^6
Isophorone	-72.62	108.76	-8.853	0.3028
OIP	-69.18	95.32	-5.894	0.1336
DOIP	-76.14	104.43	-6.584	0.1527
ACT	-67.79	109.49	-6.905	0.1607

The vapour pressure of the different components is estimated by the Antoine equation. The determination of the constants of this equation can be found in Appendix 4.7. However, the temperature interval over which the Antoine equation can be used is small and corresponds to a pressure interval of about 10 to 1500 mm Hg. The critical pressure is outside this range; therefore one can question the reliability of the approximation, especially because only three data points are used. However, when looking at the Antoine plot for isophorone, which goes quite reasonably through the three points taken as reference, one can justify using this approximation. The only thing that has to be kept in mind is the fact that the Antoine equation shouldn't be used outside the mentioned pressure interval.

Table 4.7: Constants for the Antoine equation

Component	A	B	C
Isophorone	7.687	2365	3.725
OIP	7.598	2035	-55.802
DOIP	7.511	2057	-65.365
ACT	7.975	2197	-81.051

E.M. Buque-Taboada determined the solubility of OIP, DOIP and ACT in water experimentally. After regression of the results of these experiments relations A4.14, A4.15 and A4.16 given in Appendix 4.9 were found.

The melting enthalpy of the DOIP, OIP and ACT is determined by using experimental data, which can be found in Appendix 4.8. From the maximum solubility the melting enthalpy was calculated by rearrangement of the equations of the Regular-Solution Theory and the Theory for Solubilities of Solids in Liquids [21 p326, p380]. Since the solubility of the ACT and OIP could not be measured and the solubility data for water is not applicable in the Regular-Solution Theory, the melt enthalpies of these components are estimated with the theory of Dannenfalser and Yalkowsky [14]. This theory resulted in ratios between the melt enthalpies of DOIP and ACT/OIP, which were used to estimate the melt enthalpy of ACT and OIP from the calculated value with the Regular-Solution Theory for DOIP. Calculations are enclosed in Appendix 4.8 and the estimated melt enthalpies are given in Table 4.8.

Table 4.8: Estimation melt enthalpy

Component	*Estimation* $\Delta H_{m,i}$ (kJ/mol)
DOIP	27.17
OIP	22.27
ACT	23.61

In order to estimate the distribution coefficients of the components in water and ethyl acetate for extraction purposes, three theories were combined. The Regular-Solution Theory and the Theory for Solubilities of Solids in Liquids were used to estimate the activity coefficient of a particular component dissolved in ethyl acetate at its maximum solubility. Since the Regular-Solution Theory only accounts for mixtures of non-polar molecules, the activity coefficient at maximum solubility of the components solved in water was estimated by combining the Theory for Solubilities of Solids in Liquids with the experimental solubility data of E.M. Buque-Taboada (see Appendix 4.9).
The obtained fixed points (at maximum solubility) were used in order to estimate the parameters of the Wilson equations [21, p300], in this way the activity coefficients for binary systems can be estimated. With these parameters a function is developed of the activity coefficient for a particular species as a function of its fraction in the binary system. The activity coefficient is chosen at half the maximum solubility of the species. Finally the distributions coefficients are calculated by dividing the obtained activity coefficients in water and ethyl acetate of a given solute. More detailed description of this approach can be reviewed in Appendix 4.10. In Table 4.9 a review is given of the estimated distribution coefficients based on molar and mass fractions.

Table 4.9: Distribution coefficients bases on molar and mass fraction of the components over water and ethyl acetate

Component	$K_{D,i}$ (-)	$m_{D,i}$ (-)
DOIP	124.805	23.471
OIP	32.884	7.017
ACT	45.093	9.291

The diffusion coefficients of substances in water at infinite dilution can be estimated according to the Hayduk-Laudi correlation [21, p573]. For this correlation an error is reported of 5.9%. The diffusion coefficients for OIP, DOIP and ACT at T = 25°C can be seen in Table 4.10. More information about the calculations done can be found in appendix A4.10.

Table 4.10: Diffusion coefficients in water at T = 25°C

Component	D (m^2/s)
DOIP	$8.0*10^{-10}$
OIP	$8.0*10^{-10}$
ACT	$7.6*10^{-10}$

The order of magnitude for the obtained diffusion coefficient is the same as found in literature. E.g. the diffusion coefficient for cyclohexane in water is $8.4*10^{-10}$ m^2/s [2].

Thermodynamic models
Selection of the thermodynamic models was done with Aspen Plus version 11.1 'Guidelines for choosing a Property Method'. Besides Aspen Plus also the possibilities of SuperPro Designer® v5.1 were explored. After evaluating these possibilities the choice was made to use the model of Soave-Redlich-Kwong for the gas phase. The model is suitable for the use with non-polar, real components and is readily available in SuperPro Designer® v5.1. For the liquid phase the case of an ideal liquid is taken, because the concentration levels are very low, so large non-ideal mixture effects aren't expected.

4.1.2 Reaction kinetics

Base case reaction kinetics
To determine the kinetics of Saccharomyces rouxii, the immobilized biomass described in patent EP1074630 [10], the data points given in figure 2 of that patent were used to determine the parameters. The kinetic model, given in [5] has been altered for the ACT production rate to better represent the kinetics at low OIP concentrations and looks as follows:

$$r_{DOIP} = q_{DOIP}^{\max} \cdot \frac{C_{OIP}}{K_{M,OIP} + C_{OIP}} \cdot \left(1 - \frac{C_{OIP}}{C_{OIP}^{*}}\right)^{n} \cdot C_x \qquad 2.2$$

$$r_{ACT} = k_1 \cdot {C_{DOIP}}^2 \cdot C_x - k_2 \cdot {C_{ACT}}^2 \cdot C_x \qquad 2.3$$

In Appendix 4.12 the derivation of the kinetic parameters is described. Below a summary is given of the important parameters,.

Table 4.11: Kinetic parameters for the kinetics model of the Base case

Constant	Value	Unit
q_{DOIP}^{max}	13.79	mmol/gdw/h
$K_{M,OIP}$	86	mM
C^{*}_{OIP}	130	mM
n	1	-
k_1	0.0031	L^2/mmol/gdw/h
k_2	0.1	L^2/mmol/gdw/h

ISPR reaction kinetics
The kinetics of the reduction of OIP to DOIP and the side-reaction of DOIP to ACT are described in [5]. It is thought that the kinetics are based on the reaction scheme in the figure below.

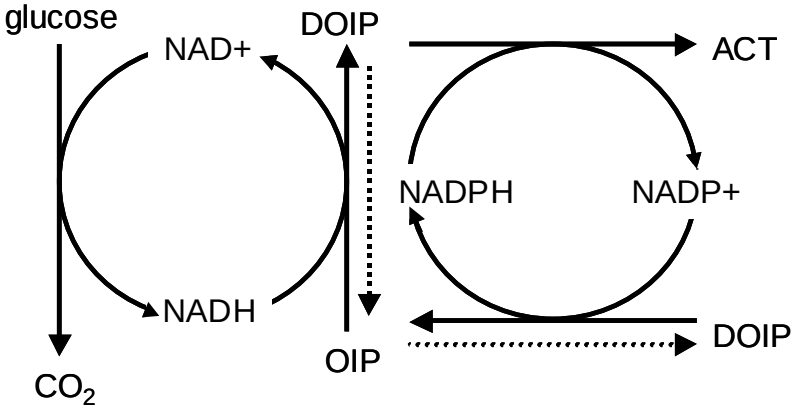


Figure 4.1 Schematic representation of reactions [5]

NADH generated by glucose oxidation drives the main reaction of OIP to DOIP. NADPH instead of NADH powers the degradation of DOIP to ACT; NADPH is generated by the oxidation of DOIP back to OIP giving a net reaction of:

2 DOIP → ACT + OIP

The reaction rate without glucose and oxygen limitation of DOIP production is given by:

$$r_{DOIP} = q_{DOIP}^{\max} \cdot \frac{C_{OIP}}{K_{M,OIP} + C_{OIP}} \cdot \left(1 - \frac{C_{OIP}}{C_{OIP}^{*}}\right)^{n} \cdot C_x \qquad 2.2$$

with:

C_{OIP}^{*} = 130 mM → The inhibition concentration of OIP [5].

n = 1 → The degree of inhibition constant [5].

$K_{M,OIP}$ = 860 mM → The half-velocity constant for substrate [5].

$q_{DOIP}^{\max}$ = 3.9 mmol/gdw/h → Maximum specific rate constant, determined with the results of [5].

The reaction rate without glucose and oxygen limitation of ACT production is given by:

$$r_{ACT} = k_1 \cdot C_{DOIP}{}^{2} \cdot C_x - k_2 \cdot C_{ACT} \cdot C_{OIP} \cdot C_x \qquad 2.3$$

with:

k_1 = 3.1 10^{-6} L^2/mmol/gdw/h → The reaction constant found at zero OIP concentration [5].

k_2 = 6.1 10^{-5} L^2/mmol/gdw/h → The reaction constant found with results of [4]. See the file "k2calculation.mcd".

4.2 Operating Window

The operating conditions in the two processes are mentioned in Table 4.12 for OIP, DOIP and ACT. The only exception is in the Base case during the evaporative crystallization were the evaporated ethyl acetate reaches a temperature of 92 ^{0}C after the vacuum pump. For ethyl acetate reliable literature values are available, therefore this temperature is not a problem during the design of the process. All the other operations in the two processes are within the mentioned operating windows and the derived thermodynamic properties are valid in these mild conditions. The validity is therefore, while keeping the data accuracy of the thermodynamic calculations in mind, guaranteed.

Table 4.12: General operating windows in the two processes

Operating condition	Range
Temperature	5 – 30 ^{0}C
Pressure	0.03 – 2 bar

4.3 Data Validation

Data validation for the thermodynamic properties mentioned is, as mentioned before, very difficult. In general no literature values were found, when they were found this is mentioned. As a reference substance isophorone is taken because of its chemical resemblance to OIP, DOIP and ACT. It is found that derived values are in reasonable correspondence with the values from isophorone.

4.4 Data Accuracy

To examine the accuracy of the thermodynamic calculations, the critical temperature, critical pressure and critical volume obtained through the Anderson, Beyer and Watson method were varied according to the accuracy of the method. The relative change of the critical compressibility factor, acentric factor, heat of vaporization, the critical density, liquid density and critical temperature and pressure used in the Antoine equation were calculated. For example, as the accuracy of the critical temperature obtained is 5 % the value of the critical temperature was set to both 95 and 105 % of the value calculated. The same was done for critical pressure and critical volume (both having an accuracy of 10%) leading to 8 calculations. The highest of relative errors (HRE) for OIP and DOIP are given in Table 4.13. As the HRE's obtained for the various parameters differed only slightly, no further calculations for ACT were performed.

Table 4.13: HRE for parameters obtained through thermodynamic calculations

Parameter	HRE for OIP	HRE for DOIP
Critical compressibility factor	0.274	0.274
Acentric factor	0.662	0.674
Heat of vaporization	0.184	0.186
Critical density	0.111	0.111
Liquid density	0.514	0.325
Critical temperature for Antoine	0.05	0.05
Critical pressure for Antoine	0.0103	0.0104

Form the results in Table 4.13 can be seen that the results vary substantially, although not in such a way that using them becomes impossible. The most important parameters are those used in the Antoine equation, and have low HRE's. Of secondary importance is the liquid density as it is used in SuperPro Designer® v5.1 for calculations. However, as OIP, DOIP and ACT are present only in small amounts in the process, it is concluded that the variance in liquid density is acceptable. Furthermore the liquid densities obtained by the estimation methods are comparable with sort like structures, thus can be considered reasonable values.

5 Process Structure & Description

In this chapter the process structures of the Base case and the ISPR case are explained. First the criteria are mentioned and a selection is made for every operation unit. The process flow schemes, batch cycle diagrams, process stream summary and the utilities are explained. Finally the yields of all the ingoing and outgoing components are presented per kg of DOIP produced. The operating conditions and further specifications of the process units can be found in chapter 8.

5.1 Process Structure & Description of Base case

In the following paragraph the process structure of the Base case will be explained.

5.1.1 Criteria (Base case)

The most important design criterion is purity, since only a product that can meet purity demands will be accepted for further processing. From an economical perspective the yield of DOIP on OIP is really important, other important factors are the equipment costs and the availability of equipment in a MPP. Also easy and logical operation schemes are considered when designing the batch process.

5.1.2 Selection (Base case)

Fermentor
A bubble column is used as fermentor in the Base case; there are several reasons for choosing this type of reactor. The first ones are the good mass and heat transfer properties in the fluid phase and the oxygen transfer between gas and liquid phase. Furthermore the fluidization of the immobilized biomass via the rising liquid and gas bubbles and thereby the lack of a need for a stirrer has a positive effect on the lifespan of the immobilized biomass. Finally there are financial reasons for the choice of a bubble column. A bubble column is less expensive than a fermentor and it has no moving parts, which can break down. The bubble column will be operated with atmospheric top pressure and a temperature of 30^{o}C. More about the operating conditions can be read in paragraph 8.1.2

To ensure that no solids, for example torn off parts of the immobilized biomass, are present in the downstream processing the fermentor liquid is filtered with a microfilter of 1 μm. The filter is placed in-line, this means that the capacity of the filter is limiting for the flow from the fermentation section to the downstream section. In principle no solids are present in the stream. Therefore the inline filter has, as seen on the PFS in Appendix 5.1, no solid stream exiting the unit. If at any time the filter should suffer from fouling it can be easily replaced

Extractor
For the extraction unit a mixer-settler setup has been chosen, for the simplicity of the units and the high efficiency. In our batch wise operation a high efficiency in few extraction steps is wanted. The simplicity of the unit needed is wanted in a MPP, because with the chosen setup a normal stirred vessel can be used, where a solvent (ethyl acetate) will be added to the filtered aqueous fermentation solution. The extraction will take place at atmospheric pressure.

The extractor was designed for an operating temperature of 20°C, because at higher temperatures the thermodynamic models used for calculation of the distribution coefficient of OIP was unreliable. Besides this, it was assumed that temperature doesn't have a big effect on extraction.

The number of stages was calculated according to a 98% extraction yield. In practice 3 stages implicates that the aqueous solution coming from the fermentor will go through 3 extraction batches in the same vessel. The solvent used for this extraction is recycled. For these three batches some fresh solvent is also needed, due to solvent loss in the raffinate and the solvent recycle purge. After 3 extraction batches the raffinate (aqueous solution) is discharged to the wastewater treatment facility.

Further elaboration about the choices made for the extraction unit can be found in chapter 8.1.2.

Evaporative crystallization
The choice has been made for evaporative crystallization because the solubility of DOIP in the solvent used is high at a crystallization temperature of 5°C (84.2 g/l), which would lead to high losses if only cooling crystallization would be used due to the DOIP remaining in solution. By evaporating the solvent the concentration is higher and crystallization will be more effective. Furthermore, the sequence of unit operations of the patent [10] has been followed by first evaporating and then crystallizing.

After approximately 6 hours the evaporation is stopped and the crystallization will be finished in the following 6 hours, leading to a total time for the evaporative crystallization of 12 hours [10]. For crystallization some seed crystals will be added, but this is not accounted for in the mass balances, because the amount will be negligible.

Multi purpose vessel (MPV)
When looking at the different operations in the downstream processing of the Base case and after having visited an existing MPP, the idea arose to use the same vessel for extraction and evaporative crystallization. With all the typical times known for each step, this option was possible, but some extra buffer vessels were necessary. This MPV (Base case vessel (S201)) should have special features to be able to be used for both unit operations; these are mentioned in the equipment specification sheets.

5.1.3 Process Flow Scheme (Base case)

In Appendix 5.1 the process flow sheets (PFS) can be found for the Base case. There are two different kinds of flow sheets in the appendix: one with stream numbers and controllers (Appendix 5.1.1), the other describes the batch operations done during the process (Appendix 5.1.2). In this paragraph the different batch operations (BO) and their functions will be described, the reference to the streams will be done via the stream numbers in the other PFS, the different batch operations will be referred to with BO1.1, e.g. fermentation section (1) batch operation 1, which can be found in the flow sheets.

In the fermentation section three different processes occur: fermentation, washing and reactivation. BO1.1 shows the filling of (R101) with fermentation solution, the composition of the fermentation solution can be found in paragraph 3.3.4, via <103>/<106>/<107>. (P102) is used to pump the fermentation solution from (T103) to (R101) and (E101) is used to heat it up to 30°C for fermentation.
BO1.2 shows the fermentation process that takes 8 hours. Here the filtered air is coming, at elevated pressure, through <108> for the aeration of (R101). The flow is controlled with a throttling valve, which adjusts the pressure to give the needed flow. The spent air is exiting (R101) through <109> and subsequently the evaporated water and other components are condensed in (E102). The condensed components are stored in (V101) and returned to (R101) via <111>, the spent air exits the process via <110>. Aqueous sodium hydroxide is added through <101>/<102> from (T101) to control the pH in (R101). The temperature of (R101) is kept at 30°C by using the jacket of (R101).
In BO1.3 (R101) is emptied via <112>/<113>/<114> and temporarily stored in (V102) until (V204) is available.
The transfer of the aqueous solution from (V102) to (V204) can be found in BO1.7 and BO2.1. There it is shown that it is transferred through <115>/<116>/<117>/<118>/<201>/<202>. The large impurities are retained in (S101), which is a dead-end microfilter of 1μm, and the temperature is decreased from 30 to 20°C in (E103). The complete transfer form (V102) to (V204) takes 1 hour.

The washing process starts on BO1.4, where (R101) is filled with water from (T104) through <104>/<106>/<107>. The temperature of the water is increased to 30°C in (E101).
The actual washing is can be found in BO1.5. The actions are the same as described for BO1.2, the only difference is the time span that for the washing process is 15 minutes. The emptying of (R101) as described in BO1.6 is the same as described in BO1.3.

The reactivation process starts on BO1.8, where (R101) is filled with reactivation solution from (T105). The composition of the reactivation solution can be found in paragraph 3.3.4. Again the temperature is increased to 30°C with (E101). The reactivation itself, as in BO1.9, is the same as the fermentation on BO1.2, only the time span is 24 hours instead of 8 hours.
After the reactivation the spent reactivation solution is pumped with (P103) to the wastewater treatment facility (WWTP), through <112>/<113>/<119>; this is described on BO1.10.

In the downstream processing three different processes occur: extraction, evaporative crystallization and filtering of the DOIP crystals. The start of the downstream section is the transfer of the aqueous solution from (V102) to (V204), this is shown in BO1.7 and BO2.1 as said before.

The first process is the extraction of the aqueous solution with ethyl acetate this is done three times. The first extraction starts by pumping the aqueous solution from (V204) with (P203) to (S201) via <203>/<204>/<205>, as shown in BO2.2. Next, in BO2.3, the ethyl acetate make-up is added from (T201) to (S201) via <209>/<210>/<211>. In BO2.4 the remaining amount of ethyl acetate is added from (V201) via <206>/<210>/<211>.
After the mixing and settling, which takes 1 hour, first the raffinate is pumped with (P202) to (V204) for temporary storage, as shown on BO2.5. Next the extract is

pumped from (S201) to (V205) via <212>/<213>/<214>/<215>/<218>, as shown in BO2.6, where it is stored until the evaporative crystallization starts after 8 extraction batches. The total time needed for the first extraction is 2 hours.
The raffinate of the first extraction is transferred from (V204) to (S201) for the second extraction cycle, as is shown in BO2.7. On BO2.8 the ethyl acetate is pumped from (V202) via <207>/<210>/<211> to (S201) after which the extraction starts.
Again the raffinate is transferred from (S201) to (V204) for temporary storage for the next extraction on BO2.9. The extract is transferred from (S201) to (V201) via <212>/<213>/<214>/<215>/<216>/<221>/<222>/<223> for use in the first extraction of the following fermentation batch on BO2.10.
The raffinate of the second extraction is transferred from (V204) to (S201) for the third extraction cycle, as is shown in BO2.11. On BO2.12 the ethyl acetate is pumped from (V203) via <208>/<210>/<211> to (S201) after which the extraction starts.
The raffinate is now transferred from (S201) via <212>/<213>/<214>/<215>/<216>/<217> to the WWTP on BO2.13. The extract is transferred from (S201) to (V202) via <212>/<213>/<214>/<215>/<216>/<221>/<222>/<224>/<225> for use in the second extraction of the following fermentation batch on BO2.14. The time for both the second and third extraction is 110 minutes.

After 7 whole extraction cycles and the first extraction of the eighth extraction cycle the content of (V205), which consists of the extract of the 7 cycles and the filtrate of the previous filtration batch, is transferred to (201) with (P204) via <219>/<220>/<205> for evaporative crystallization on BO2.15. In BO2.16 the actual evaporation is shown, were (K201) reduces the pressure in (S201) to 30 mbar, so that ethyl acetate starts to evaporate. (E201) condenses the stream coming from (K201) and the condensed liquid is stored in (V206). (P205) maintains a constant level in (V206) by continuously pumping from (V206) to (V203) via <229>/<230>/<222>/<224>/<226>. This process is shown in BO2.16, the complete evaporation of ethyl acetate and crystallization of DOIP takes 12 hours. When the crystallization is finished the slurry is pumped with (P202) from (S201) to (S202) for filtration via <121>/<213>/<214>/<231> as shown in BO2.17.

On BO2.18 the slurry is filtered in (S202) and a part of the filtrate is pumped with (P206) via <232>/<233>/<234>/<235> to (S205) where it is stored for the next evaporative crystallization batch, the rest is purged via <232>/<233>/<234>/<236>. The retained crystals in (S202) are washed with water coming from <237>. The spent wash is leaving (S202) via <232>/<233>/<238> as shown in BO2.19. The washed crystals are dried by blowing nitrogen from <239> into (S202); the spent drying gas is leaving (S202) via <240>, shown on BO2.20. On BO2.21 the crystals are recovered from (S202) via <241>.

5.1.4 Batch Cycle diagrams (Base case)

An overall batch cycle diagram of the Base case is presented in appendix 5.2. Each step in this diagram represents the total time of a particular part of the process. The batch operations of these parts are specified in additional batch cycle diagrams. Below an overview is given of the operation times of each part of the process.

Table 5.1 Operation times of processes in Base case

Process operation	Time [h]
(Re-)activation biomass / start up	24.0
Fermentation	9.5
Transfer to downstream	1.0
Extraction	5.7
Evaporation	6.3
Crystallization	6.3
Solid Handling	10.5

The cycle time of the complete process is determined by the reactivation step, which occurs every 176 hour. The make span for 16 fermentation batches is 202 hours (see Appendix 5.2, figure A5.2); this is taken from the start of activation of the immobilized biomass till the end of the solid handling.
More specifications with concern to the batch operations are tabulated in Appendix 6. The particular operations of Table 5.1 are described below.

Activation
The bubble column (R101) is filled in 30 minutes with reactivation solution. The biomass is reactivated during 23.4 hours. The spent reactivation solution is transferred to the WWTP in 18.5 minutes.

Fermentation
Filling of the fermentor with aqueous fermentation solution is processed via pump (P102) and takes 18.5 minutes. Subsequently aeration of the fermentor (R101) and addition of sodium hydroxide starts. Fermentation is done for 8 hours with recovery of water and solutes from the gas exit. After the fermentation is finished, the aqueous solution is transferred to storage (V102) in 18.5 minutes. Washing water is transferred to (R101) in 19 minutes and washing with aeration is processed for 15 minutes. Next the washing solution is transferred in 19 minutes to (V102).

Transfer aqueous solution
The content of (V102) is processed in 1 hour through the in line filter (S101) to (V204) in the downstream section. In the planning it is taken into account that (V204) needs to be available for loading with aqueous solution.

Extraction 1
The first step of the extraction is the filling of the MPV (S201) with aqueous solution which is transferred from (V204) in 15 minutes. Subsequently the ethyl acetate (EA) make up from (T201) and "medium EA" from (V201) are both transferred in 10 minutes to (S201). After that extraction is processed and the vessel content is stirred for 20 minutes after which the content settles for 40 minutes. The raffinate 1 and extract 1 are successively transferred to storage (V204) and (V205) in respectively 15 and 10 minutes.

Extraction 2
The first task is filling (S201) with raffinate 1 from (V204) and takes 15 minutes. Next "low EA" is transferred in 10 minutes from (V202) to (S201). Mixing and settling is processed successively in respectively 20 and 40 minutes. After the extraction raffinate 2 transferred to (V204) in 15 minutes and extract 2 is recycled to (V201) in 10 minutes.

Extraction 3
Successively, raffinate 2 is transferred in 15 minutes and "clean EA" in 10 minutes to (S201). Mixing and settling is processed in respectively 20 and 40 minutes. Next, the obtained raffinate of this third extraction is pumped off to the WWTP in 15 minutes. The extract is pumped to (V202) in 10 minutes.

Each 8th aqueous solution batch that goes through the downstream, the schedule of the batch operations changes slightly. The first extraction is processed regularly, but the remaining extract stays in (S201). The raffinate is transferred to (V204) and remains there for storage. The MPV is than filled with the content of (S205) and starts to operate the evaporation and crystallization. When this batch operation is finished, the obtained crystal slurry is transferred to (S202) for solid handling. (S201) is than used for two remaining extractions of the stored raffinate.

Evaporative crystallization
In the first task the content of (V205) is transferred in 10 minutes to (S201). The evaporative crystallization is designed for an operating time of 5.5 hours (see paragraph 8.1.2). A margin of 0.5 hour is taken into account for this procedure, which adds up an operating time of 6 hours for evaporation in vessel (S201). Subsequently the vessel is kept at a temperature of 5^{o}C for further crystallization of product during 6 hours. The obtained crystal slurry is transferred to (S202) for solid handling in 15 minutes.

Solid Handling
The slurry is filtered in 1 hour and the filtrate is simultaneously transferred to the purge and (V205). Next the crystals are washed with water in 1 hour and drying is processed in 7.5 hours with nitrogen. Finally, the crystals are recovered and packed in 1 hour.

5.1.5 Process Stream Summary (Base case)

In Appendix 5.3 the process stream summary for the Base case can be found. In general the process stream summary is self-explaining, here the decisions made will be explained and clarified. First the fermentation section will be explained.
In the fermentation section the presence of the buffer in the fermentation solution and reactivation solution is not mentioned in the stream summary. This is done because the buffer has no influence on the fermentation and other processes in the fermentation section, other than keeping the pH at the desired value. Therefore the choice was made to combine the buffer and the water stream in the stream summary. The actual content of the fermentation and reactivation solution are mentioned in paragraph 3.3.4.
The amount of aqueous sodium hydroxide added during the fermentation is estimated by looking at the amount added in the ISPR. The buffer contains the capacity to keep the pH for some time at the desired level. Because the fermentation batch time is much shorter compared to the ISPR case, the amount sodium hydroxide added is lowered by approximately a factor 2. The real amount is unknown, but the estimate is reasonable.
In the stream summary two different kinds of water are mentioned: 'water' and 'water*'. The difference between the two is that water is fresh water or buffer, which was neglected in the stream summary. 'Water*' is water which comes out of the fermentor after the fermentation or washing. The content of this stream is complex and unknown, because the processes that occur during the fermentation are numerous.

Washing of the fermentor is needed because 23% of the OIP, DOIP, ACT and glucose present during the fermentation - equal to the volume of the immobilized biomass in the fermentor - remains in the immobilized biomass after the fermentor is emptied.
Another important simplification made in the fermentation section is the consumption of glucose. The assumption is made that the consumed glucose goes to the water phase, in other words no carbon dioxide is produced during the fermentation. This is of course not true, but the effect of this simplification is small and again it is done to keep the stream summary comprehensive.
Now the downstream section (extraction and evaporative crystallization) will be explained. The assumption is made that next to the buffer and other salts glucose remains in the water phase and only fresh water dissolves in the ethyl acetate extract. Therefore the glucose, which is mentioned in the fermentation section, is neglected in the streams of the downstream section and the fresh water, dissolved in ethyl acetate extract streams, is placed under 'water' and not 'water*'. All the streams mentioned are calculated with the help of SuperPro Designer® v5.1.
At the evaporative crystallization section the "Content of (S201) at start of evaporation" is not a stream, but it is mentioned in the stream summary for clarity. The contents of (S201) differ from the ingoing stream, because the first extract from the 8th extraction cycle, as described in paragraph 5.1.4, remains in (S201) for the evaporation and crystallization. The evaporation and crystallization is only done once every 8 extraction batches, therefore the streams in the evaporative crystallization section are 8 times as large as in the extraction stream summary.
Finally the filtration section will be shortly discussed. Again all streams are taken from SuperPro Designer® v5.1, only the washing and drying are adjusted slightly. The adjustment during the washing is that 0.1% of the DOIP crystals dissolve in the washing stream. The needed amount of nitrogen for drying is adjusted so that the temperature within the Nutsche filter is kept at approximately ambient temperature, while adding 4 kW of heat input during the drying.

5.1.6 Utilities (Base case)

The overview of the utilities for the Base case can be found in Appendix 5.4 The assumption is made the pumps in general have no significant power consumption compared to the duty of the vacuum pump. Besides the vacuum pump only the stirrer of the MPV uses electricity.
As is mentioned in the BOD (paragraph 3.3.2) the MPP is assumed to have a heat exchange oil. But since no properties of this oil are known the calculation of the utilities are done with other common used substances.
The heating and cooling duties are also mentioned in Appendix 5.4, the cooling duties are divided in two sections: one with cooling water of 20 ^{0}C, the other with brine –10^{o}C. During fermentation and reactivation the fermentor is cooled with cooling water, during the washing the fermentor has to be heated according to the balances. However, in real life this will probably be not the case, because the temperature effect is negligible, but for completeness it is shown. The condensers of the fermentor and the MPV and the heat exchanger (E103) are cooled with brine of –10 ^{0}C. The heating duties are needed to heat the ingoing streams of the fermentor, the MPV during evaporation and the Nutsche filter during drying. This is done with warm water of 50 ^{0}C and for the Nutsche filter with electrical heating.

5.1.7 Process yields (Base case)

The yields for in- and outgoing streams per kg of DOIP were calculated. Not only the yields for components mentioned in the process stream summary will be given, but also for other components that were used like the salts for the buffer solution. Also yields of waste streams are given since they are needed for the economics. In the yield of ethyl acetate also a stock of 3500 kg is included. This 3500 kg is necessary to start up the extraction; this is 3 times 350 kg for the first extraction cycle and another 7 for the third extraction of the 7 subsequent cycles. The evaporation, at which the ethyl acetate is recovered, is done every 8 batches.

Table 5.2: Yields of the Base case process

Component	Stream number	IN kg/kg	Stream number	OUT kg/kg	Process kg/kg
DOIP crystals			<241>	1.00	1.00
OIP	<107>	1.27	<217> <236> <238>	0.01	-1.26
DOIP			<217> <236> <238>	0.09	0.09
ACT			<217> <236> <238>	0.19	0.19
Air	<108>	34.57	<110>	34.57	0.00
Water	<101> <103> <104> <105>	208.75	<217> <236> <238> <240>	209.26	0.51
Ethyl acetate	<209>	20.38	<217> <236> <238>	20.38	0.00
Glucose	<103> <105>	3.95	<118> <119>	3.42	-0.53
Biomass		29.28		29.28	0.00
Sodium hydroxide	<101>	0.39	<118> <119>	0.39	0.00
Magnesium sulphate	<103> <105>	0.06	<118> <119>	0.06	0.00
Sodium phosphate	<103> <105>	6.30	<118> <119>	6.30	0.00
Nitrogen	<239>	1.06	<240>	1.06	0.00
COD			<217> <236>	37.05	37.05

The process yields for sodium hydroxide, magnesium sulphate and sodium phosphate are set to zero, because no data were available.

5.2 Process Structure & Description of ISPR

In the following paragraph the characteristics of the ISPR case are explained.

5.2.1 Criteria (ISPR)

For the ISPR the same criteria apply as for the Base case, being purity, yield of DOIP on OIP and availability and operability of the equipment. In chapter 2 and 3 most selections for this process are already made. In this paragraph more selections will be done, although more specific choices on process parameters and specific equipment will be made in chapter 8.

5.2.2 Selections (ISPR)

In the fermentor there is a possibility of evaporation of OIP and DOIP resulting in yield loss. This will however only occur at high aeration rates; therefore the fermentor will be designed in such a way that there is high oxygenation efficiency. A measure that could help achieving this is a high stirrer speed.
The problem with the ultrafilter could be plugging of the membrane, for example by proteins of disrupted cells. A cross flow ultrafilter would have the least problems with this. If the ultrafilter however fails, the process stops, resulting in high losses, therefore two ultrafilters will be installed. If one fouls, the other one can be put online, allowing for the first one to be cleaned.
In the crystallizer cooling problems might occur, because if the wall is too cold, crystals will be formed at the wall. This makes the cooling capacity even poorer and the DOIP cannot be crystallized at a sufficient rate. The ingoing stream will therefore be pre-cooled in a heat exchanger with the outgoing stream. Also the crystallizer will have a plastic scraping mechanism. This "scraper" scrapes the formed crystals off the wall and stirs the crystallizer at the same time. In the crystallizer there will be a microfilter preventing the crystals from going back to the fermentor.

5.2.3 Process Flow Scheme (ISPR)

In Appendix 5.5 the process flow sheets (PFS) and the batch cycle diagrams can be found for the ISPR case. There are two different kinds of flow sheets in the appendix: one with stream numbers and controllers (Appendix 5.5.1), the other describes the batch operations done during the process (Appendix 5.5.2). In this paragraph the different batch operations and their functions will be described, the reference to the streams will be done via the stream numbers in the other PFS, the different batch processes will be referred to with BO1, e.g. batch operation 1.

In a year 5 batches will be done in order to meet the production target. At the start of a batch, as shown in BO1, the fermentor (R101) will be filled through <105>/<106> with the biomass suspension out of (T103). This suspension contains buffered water on pH 5.5 and 33 g/l biomass. Also the suspension contains the starting concentration of OIP.
On BO2 the biomass in the fermentor is activated for 4.5 hours, afterwards it will start converting OIP. The glucose feeding through <103>/<104> and the aeration through <111>/<112> is started. The spent air goes through <114> to the condenser (E102/V101), were the condensed water of <115> goes to the WWTP and the air in <114> is released into the atmosphere.
In BO3 the conversion process is started by the feeding of OIP to the fermentor through <101>/<102>. Also the recycle for product removal is started. This means

that fermentor liquid is fed to the ultrafilter (S101) by <113>/<117>/<118>. The retentate is going back to the fermentor by <119>/<120> and the permeate is going to the scraped and cooled crystallizer (S102) by <121>/<123>. On its way the permeate passes the heat exchanger (E101), which cools it down to 10°C with the outgoing stream of (S102) <125>/<126>/<127>. This stream goes back to the fermentor (R101), completing the recycling. After about 20 hours the concentration of DOIP in the system is high enough to start crystallizing at 5°C, therefore the crystallizer is seeded with 15 kg of DOIP crystals on BO4. After 300 hours of fermentation the OIP feed of <101>/<102> is stopped. In BO5 this closedown procedure is shown. After 70 hours the closedown period is stopped and both (R101) and (S102) are emptied in BO6. The fermentor liquid goes via <113>/<117>/<131>/<132> to the WWTP. The slurry out of the crystallizer (S102) goes through <128>/<129> to the Nutsche filter (S103). On BO7 the crystals are concentrated in (S103) for 6 hours and the filtrate <130>/<132> goes to the WWTP. On BO8 the crystals are washed with water for 6 hours <133> in (S103) and again the filtrate <130>/<132> goes to the WWTP. After that on BO9 the crystals are dried for 30 hours in (S103) with nitrogen from <135>, the humid nitrogen goes out of the system by <136>. On BO10 the crystals are ready to be packaged from (S103) to <137>. Finally the equipment (R101)/(S101)/(S102) will be cleaned and sterilized for the next batch.

5.2.4 Batch Cycle Diagram (ISPR)

In Table 5.3 the typical times of all the processes in the ISPR case are described. In chapter 8.2 the origin of these times can be found. With these times two batch cycle diagrams were made. The first one (Appendix 5.6.1) describes in detail one cycle that takes 423 h, this is also the make span. The second one (Appendix 5.6.2) describes one year of production (2019 h). Since the fermentor can be started when the filter is still working, the cycle time of the process 399 h.

Table 5.3 Operation times of processes in ISPR case

Process	time
Starting up	5 h
OIP feeding	300 h
Closedown	70 h
Filtration	6 h
Washing	6 h
Drying	30 h
Packaging	4 h
Cleaning	24 h
Total make span	**423 h**
Total cycle time	**399 h**

5.2.5 Process Stream Summary (ISPR)

In Appendix 5.7 the process stream summary for the ISPR can be found. Because the water used contains a complex of salts that do not interfere with the reaction, only the mass flows of water were described. This water with salts was described as 'water*', and if fresh water was used or formed this was described as water without the '*'.

5.2.6 Utilities (ISPR)

In Appendix 5.8 the overview of utilities of the ISPR is given. It was assumed that feed pumps and pumps that operate a short time have no significant power consumption. The pump duties of continually operating pumps (P106) and (P107) were however calculated, but also turned out to be low. The stirring of the fermentor and the scraping of the crystallizer were the main power consuming tasks.
As is explained in paragraph 5.1.6, a closed circuit of special heating oil will be used, but the utility duties will be calculated with common used substances.
No heating duties are necessary and the cooling duty is divided in two categories; cooling duty that can use ordinary cooling water of 20° C and cooling duty that needs brine of –10° C. The fermentor can be cooled with normal cooling water. The condenser and the crystallizer will be cooled with brine.
The total electrical power consumption is higher than the combined cooling duties. Because the cost per kilowatt-hour of electricity is higher than that of the cooling agents, the main utilities cost consists of the electricity costs of the scraper and the stirrer.

5.2.7 Process yields (ISPR)

The yields for in- and outgoing streams per kg of DOIP were calculated. Not only the yields for components mentioned in the process stream summary will be given, but also for other components that were used like the salts for the buffer solution. Also yields of waste streams are given since they are also needed for the economics.

Component	Stream number	IN kg/kg	Stream number	OUT kg/kg	Process kg/kg
DOIP crystals	<124>	0.04	<137>	1.04	1.00
OIP	<101><105>	1.08	<131><130>	0.01	-1.07
DOIP			<131><130>	0.07	0.07
ACT			<131><130>	0.02	0.02
Air	<111>	53.74	<116>	55.47	1.74
Water	<103><105> <107><133>	14.48	<131><130> <115><136>	17.14	2.66
Glucose	<103>	4.28			-4.28
Biomass	<105>	0.32	<131>	0.32	0.00
Sodium hydroxide	<107>	0.86			-0.86
Magnesium sulphate	<105>	0.01			-0.01
Sodium phosphate	<105>	0.05			-0.05
Nitrogen	<135>	1.41	<136>	1.41	0.00
COD			<130><131>	0.56	0.56

6 Process Control

Both the Base case and ISPR case work optimally under a certain set of process conditions and control is needed to make sure these conditions are maintained. For this various controllers are necessary. In this chapter the placement of controllers and the reasoning behind their placement will be discussed, not only for the control of process variables but also for product quality control. Controllers placed for safety purposes are discussed in paragraph 10.1.3 and 10.2.3. Only basic control will be designed, as advanced control was beyond the scope of the project.

First, all parameters (such as flow, temperature and level) to be controlled were determined for both cases and this was the main consideration for controller placement. With this in mind, as little flow controllers as possible were placed, so preferably after piping converges and before piping splits. This was especially important in the separation section of the Base case. Also, it should not occur that two controllers control the same flow to avoid any undesired interaction between controllers.

Please note that like the process, the controllers are within a MPP, so it should be easy to change the set point on controllers. This could, for example, be achieved by installing a centralised process control computer network. Under such a system, it should also be able to control other aspects of the process, such as opening and closing valves.

6.1 Process control (Base case)

The process flow sheet containing the controllers can be found in Appendix 5.1.1.

6.1.1 Fermentation section process control

Flow control was placed as economically as possible, so preferably, as said before, after piping converges and before piping splits. Flow control was placed on stream <106> and after pump (P103). Temperature controllers control the temperature of stream <106> and fermentor (R101).

The pH of the fermentor is kept constant by adding base (and in rare instances acid) through stream <101> (and <102>), so a pH controller YC1 controls the base addition. The airflow through the fermentor <108> is controlled with a set point provided by the dissolved oxygen tension controller YC2. To make sure only condensed water re-enters the fermentor, a level controller that manipulates stream <111> is placed on vessel (V101).

The outgoing air stream <110> was not controlled as the rate is fixed by the control of stream <108>. Stream <115>/<116>/<117>/<118> is controlled by a flow controller in the separation section on <201>. As the condenser (E102) is over-designed, control of stream <109> was not considered necessary. The temperature in (E102) is controlled with a temperature controller, which controls the flow of the cooling agent.

6.1.2 Separation section process control

Flow controllers were placed on <201>, <205>, <211>, <213>, <230>, <233>, <237> and <239>. The only instance of "double" control is during washing, where both <233> and <237> are controlled. However, as the washing water is sprayed on the product in (S202), <233> and <237> are not directly linked because the washing water doesn't go straight through the crystals. Temperature control is placed on the MPV (S201) to control the evaporation and crystallization. To make sure the ethyl acetate evaporated from (S201) is fully condensed a pressure controller, controlling the cooling duty in condenser (E201) is placed. A level controller on (V206) makes sure only liquid ethyl acetate leaves (V206). The same applies to the permeate of Nutsche filter (S202) exiting (S202) through stream <232>/<233>.

6.2 Process control (ISPR)

The process flow sheet containing the controllers can be found in Appendix 5.5.1. The flows of OIP, glucose and the biomass suspension need to be controlled, so flow controllers were placed on flows <102>, <104> and <106>. Similar arguments hold for the flow controllers present on streams <129>, <131>, <133> and <135>. Temperature controllers control the coolant flows for the fermentor (R101), crystallizer (S102) and condenser (E102). The level in the condenser (V101) and the level of the permeate of the Nutsche filter (S103) are controlled to make sure the only liquid exits through streams <115> and <130> respectively. This is done for the same reasons mentioned in the previous paragraph for (V102) and (S202)

The pH of the fermentor (R101) is kept constant at 5.5 by adding base through stream <108>, so a pH controller (YC1) controls the base addition. A similar approach is used for controlling the addition of support chemicals, such as acid and anti-foam. As their streams are lumped on the flow sheet under <110>, so have the controls of those streams been lumped under YC3. The airflow through the fermentor <112> is controlled with a setpoint provided by the dissolved oxygen tension controller YC2. To make sure there is sufficient flow through filter (S101), even when partial clogging occurs, manipulating the flow through stream <119> controls the flow on stream <121>. If the flow through the filter <121> decreases, the valve on stream <119> is adjusted and pressure on the reactor side of the filter increases. This causes an increased flow through the filter. When the valve on stream <119> is adjusted too much, flow will be rerouted through the back-up filter for (S101).

To make sure volume accumulation takes place in (S102) (and not in (R101)), a level controller is placed on (R101) providing a set point for the flow controller on stream <127>. Another possibility would have been to use the level controller provide a set point for the flow controller on <121>, but there are several advantages to the control setup chosen. Firstly, the control system around (S101) is already fairly complicated. Secondly, allowing the level controller to set the flow <121> would introduce disturbances in operating (S101). Having the level controller set the flow controller for stream <121> does have the advantage that relative changes in stream <121> would be smaller as stream <121> will be increased instead of <127> decreased. However, this advantage is not considered to weigh up against the advantages of the setup chosen.

Finally, streams <114> and <117> are left uncontrolled as these streams are fixed by <112> and the combination of <119> and <121>, respectively.

6.3 Quality control

Because the process is a batch process, for steps of the process such as crystallization, it is also necessary to check their progress to make sure the processes have been completed. To check this, measures need to be available; these measures are discussed below.

The extraction step needs to be monitored carefully during two stages. The settling step needs to be monitored to make sure ethyl acetate and water have separated and when draining the water phase to make sure the separation attained in the settling step is retained. Both these steps can be monitored with a conductivity measurement or by having an operator visually check the progress[6].

In the Base case the concentrations of OIP and ACT rise significantly in the MPV (S201) during the evaporative crystallization step. To make sure concentrations of these components remain low enough after evaporation and do not crystallize into the product, samples should be taken out of (V205) to determine the actual OIP and ACT concentrations. The maximum amount of solvent that can be evaporated during crystallization without lowering product quality can then be determined.

The progress of the crystallization step, for both the Base and the ISPR case, can be checked online by using a laser to measure the percentage of solids. For the ISPR case, it might also be possible to measure the amount of solids online through a conductivity measurement.

[6] Source: Plant visit to DSM Venlo with D. Sterzenbach and M. Driessen

7 Mass and Heat Balances

The mass and heat balances in this chapter are derived from the process flow sheets in paragraph 5.1.3 and 5.2.3 and the process stream summaries in 5.1.5 and 5.2.5. So in this chapter no new information is introduced. The purpose of the chapter is to check if all the information given in previous chapters is consistent.

7.1 Mass and heat balances (Base case)

The mass and heat balances for the Base case can be found in Appendices 7.1 and 7.2. For the fermentation, washing and reactivation section the total and operating unit mass and heat balances were set up for one cycle of the different sections. This means that, for the fermentation and washing section, a mass and heat balance was set up over a cycle of 8 hours and for the reactivation section this is 24 hours.
In the downstream section the mass and heat balance were set up slightly different. The reason for this is the planning of the downstream section. For the units in the downstream section the mass and heat balances were set up for one cycle of the unit. For the complete downstream process the mass and heat streams of the evaporative crystallization and filtering where divided by 8, this is done because for every 8 extraction batches 1 evaporative crystallization and filtering batch is performed. The conclusion from these balances is that no mass and heat is lost in the system, for both the complete system and every single operating unit.

The component balances can be found in Appendix 7.3 These are slightly more complicated, because now reactions in the fermentation section play a role and are simplified as components are converted. First the component balances for OIP, DOIP and ACT are checked. For the individual component balances the ingoing mass does not equal the outgoing mass, but the total number of moles OIP+DOIP+ACT remains the same. The increase of mass can be explained by the hydrogen atoms, which are added to the OIP and DOIP atoms during the reaction. The amount of increase of mass at the OIP, DOIP and ACT balances is the reason for a decrease in the water balance. In the water balance all the dissolved components, like buffer, base, salts etc. are included, this is the reason for the above-described shift in mass from water to OIP, DOIP and ACT.

7.2 Mass and heat balances (ISPR)

The mass and heat balances over the system boundary for one cycle of the ISPR case were performed and can be found in Appendix 7.4. Since these balances combine a lot of information from all kind of different sources and design files, some inconsistencies showed up. However all these inconsistencies are below 1% of the total mass or heat stream involved.
In order to see where these inconsistencies are located also balances were made over all the equipment involved in the ISPR case, the results can be found in Table 7.1. The balances over the ultrafilter (S101), heat exchanger (E101) and the Nutsche filter (S103) were consistent. The heat balance over the condenser (V101) was not entirely consistent because the spreadsheet uses a simple thermodynamic model.
The overall inconsistencies were traced to the fermentor and the crystallizer.

Table 7.1 Results of mass and heat balances

	mass	heat	mass	heat
	kg/batch	MJ/batch	%	%
R101	-131	-539	-0.03	-0.09
V101	0	-48	0.00	-0.50
S101	0	0	0.00	0.00
E101	0	-8	0.00	0.00
S102	189	365	0.12	0.20
S103	0	0	0.00	0.01
Total	58	-229	0.18	-0.38

In order to find the components involved also component balances were made (Appendix 7.5). First the balance over OIP, DOIP and ACT was made. It turned out that all the moles of these components that came into the system, also came out.
The balances over nitrogen and biomass turned out to be consistent. Next the balance over glucose was made. It was assumed that all glucose would be consumed according to the following reaction.

$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O$$

Now the mass balances over water and air were made and the production of CO_2 and water was taken into account. The air balance was consistent within 0.05%. The water balance differed 0.65%, so the inconsistencies in the mass balances are due to water. This is not a major problem since it means that a little bit more water comes out of the system, which does not have a great an effect on the economics.

8 Process and Equipment Design

This chapter will continue in the design process where chapter 5 has stopped. All operating units will be designed in more detail. The detailed specifications of the units can also be found in the equipment specification sheets in Appendices 8.6-8.9. First the Base case is discussed, followed by the ISPR case.

8.1 Process and Equipment Design (Base case)

Here the unit operations of the Base case will be further discussed.

8.1.1 Integration by Process Simulation (Base case)

The downstream of the Base case is modelled in SuperPro Designer® v5.1 developed by Intelligen Inc. First the downstream was modelled for the recovery of product from one aqueous fermentation batch. This model does not represent the actual performances and scheduling of the equipment, but simulates the in- and outputs of all equipment in a steady state situation. This way of simulation is chosen, since there is a significant number of recycles present in the design. Further the knowledge from our side and the TU Delft about this software was not sufficient to simulate the sequential downstream of the 176 batches. Besides the general model a smaller one is developed in order to simulate the final stage of the downstream when 8 extracted batches after storage are crystallized and the solids are handled. The file "Downstream_base_case.spf" of both models can be reviewed from the CD-ROM.

In prior of the development of the downstream model the distribution coefficients of the relevant components over water and ethyl acetate were estimated, which can be reviewed in Chapter 4. In the model it was assumed that the distribution coefficients of the components are not influenced by the presence of other solutes. Further the presence of dissolved salts in the aqueous feed from the fermentor is neglected, as the concentrations are rather small and moreover these components tend to stay in the aqueous phase during the extraction. In order to prevent an accumulation of ACT and OIP in the downstream a purge is implemented in the filtrate recycle stream. This will also contribute to a removal of any salts present in the ethyl acetate stream. Together this implies that salts will not contribute to any product impurity.

The model integrates the downstream procedures of extraction, evaporation, crystallization and finally the filtration and solid handling of the product. Through the integration of the procedures the model is able to calculate all the mass and volumetric streams of the downstream and their composition at steady state, which is achieved after several batches. With the model the downstream recovery of DOIP for the steady state situation is determined.

In the development of the downstream model some design criteria were taken into consideration. The number of extraction stages and ethyl acetate utility are set (see paragraph 5.1). Second, due to the large process time of the crystallization, it is desired to process an as large as possible number of extracted batches in the evaporation and crystallization procedure. An important restriction during the evaporation is that, according to [20], a working volume of at least 12.5% of the vessel volume is needed in order to be able to stir the content. Finally, the overall downstream yield needs to be maximized.

The general model simulates, as said before, the downstream of one particular aqueous fermentor feed. The extraction of DOIP is implemented in the model with a mixer-settler unit procedure. Each aqueous fermentor feed is extracted three times in order to remove more product from the aqueous phase. The first extract is relative highly loaded with DOIP and proceeds in the downstream to the evaporative crystallization procedure. The other two extracts are recycled in the downstream and used in the extraction of sub sequential aqueous batches. The second extract is used as the organic phase in the first extraction of the sequential aqueous batch extraction, while the third extract is used in the second extraction. For each third extraction recovered ethyl acetate from the evaporative crystallization is used.

The evaporative crystallization is simulated in one unit procedure. For the settings of the relative mass evaporation it is assumed that ethyl acetate and water evaporate likely, while the other components tend to stay in the liquid phase. This estimation appeared to be well chosen, since a simulation in a thin film evaporator proved comparable distributions of the components.

With respect to evaporative crystallization several variables were introduced or adjusted from the simulation data in order to meet the design criteria. During the evaporation and crystallization procedure, the concentration factor of the working vessel volume was finally set at 5, so a reasonable super saturation is achieved. In the filtrate that is recycled for crystallization a purge of approximately 9% is introduced in order to prevent the accumulation of ACT in the downstream. Through these two measures, the evaporation and crystallization is modelled to yield DOIP crystals, but simultaneously the formation of ACT crystals is prevented. According to the thermodynamic relations (see Appendix 4.10) the solubility of ACT in the organic solvent at 5^{o}C is about 240 g/L. In order to have a reasonable margin the maximum allowable concentration of ACT in the concentrated stream is set at 200 g/L, for this reason the purge is introduced (see Appendix 4.8). The remaining DOIP is dissolved in the concentrated stream at its maximum solubility of 84,2 g/L at 5^{o}C.

With these criteria the simulation data of the general model gave a feed of the evaporative crystallization with a volume of 511 L at steady state. The evaporative crystallization will be performed in the same vessel as the extraction, because in the Batch Cycle Diagram was seen that this was possible. The volume of the vessel was adjusted to be as large as possible, because of the design criteria that as many extracted batches at once have to be crystallized. But the size also has to be economically attractive, therefore a volume of 4,5 m^3 is chosen, because than the needed extraction volume and the starting volume of the evaporative crystallization are as similar as possible. Introducing buffer vessels for the aqueous and extracted phases is needed to perform both operations in the same unit. 7 extraction batches and the recycle of the filtration have to be stored in the buffer vessel for the extracted phase. Considering the volume of 435 L of one extraction batch and the volume of 610 L of the recycle a buffer vessel of 4 m^3 is installed. When the first extraction of the eighth aqueous batch is finished, the raffinate is pumped off to the aqueous storage vessel while the extract remains in the vessel. At this point the procedure of the MPV is evaporative crystallization. The content of the buffer vessel, which is seven extraction batches and the recycle of the filtration, is transferred to the MPV and evaporation (at vacuum conditions) of ethyl acetate and crystallization (at 5 ^{o}C) is performed. It is assumed that the volume is concentrated in 6 hours and for the sequential 6 hours further crystallization is processed at normal pressure (1 bara). In the latter case, no more heat is added to the MPV via the jacket, but cooling medium keeps the temperature at 5 ^{o}C. In order to simulate the evaporative

crystallization of 8 batches a smaller model is set up for this last part of the downstream with ingoing data retrieved from the general model. In the smaller model the settings for purge, evaporation and crystallization are kept equal. This model gives a final working volume during the crystallization of 815 L, which meets the requirement of the ability of stirring the slurry. An elaboration of the evaporative crystallization with regard to the required heating and cooling duty at vacuum conditions is given paragraph 8.1.3.

After the crystallization the solids need to be treated in solid handling procedures. The slurry stream with crystals is processed in a Nutsche filter. In this unit three procedures are modelled. First the filtration is processed, which yields a cake with a dryness of 30%. Sequentially, the cake of crystals is washed with water and dried. The model finally calculates a yield of 92.0 % for the total downstream.

In the entire downstream ethyl acetate is lost through the purge and the raffinate, which is discarded to the wastewater treatment after three extractions of the aqueous stream from the fermentor. For this reason a make up of ethyl acetate is introduced. According the model the required make up is 220 L, which is fed to the first extraction of each aqueous fermentation batch.

8.1.2 Equipment Selection and Design (Base case)

Fermentor and inline filter
As described in paragraph 5.1.2 the choice is made for a bubble column fermentor. In a patent [10] fermentation with immobilized *Saccharomyces rouxii* is described, which will be used as a blue print for the fermentation. The kinetics associated with the fermentation were determined in paragraph 4.1.2 and are used for the scale-up of the fermentor (R101). The mass transfer limitations of OIP are checked in Appendix 8.1.1 and the effectiveness was found to be 0.92, so the assumption is made that the mass transfer is not a limitation during the fermentation.

First the volume of fermentor was determined using the kinetic model described in paragraph 4.1.2 and the minimum production requirement of 12.35 kg/batch [see Appendix 8.2], the minimum volume is 1.5 m^3, which gives a production of a little more than 2000 kg/annum. Next the oxygen transfer was calculated and was found to be sufficient at an aeration rate of 0.6 Nm^3/h. Finally the heat production was calculated and the required cooling water flow rate is 0.56 m^3/h.

All operating conditions for the fermentor are shown in Table 8.1.

Table 8.1: Operating conditions fermentor

Parameter	Value
Temperature	30 ^0C
Pressure at the top	1 bara
Fermentation time	8 hours
Volume	1.5 m^3
Aeration rate	0.6 Nm^3/h
Cooling water rate	0.56 m^3/h

In order to recover the water, which evaporates because of the aeration, a condenser is designed for the gas exit on top of (R101). The required cooling duty is relatively small and since at a MPP it is assumed that condensers can deliver much

larger duties, the condenser which is used in practice would be over designed for this particular purpose. Nevertheless this condenser (E102) is designed for the actual cooling duty (see "Design E102 (Base case).mcd").

The inline filter (S101) is implemented to retain solid particles coming from the bubble column. In principle no solids are present in the stream, but e.g. the immobilized biomass can suffer from attrition. If at any time the filter should suffer from fouling it can easily be replaced to ensure the retaining of particles. The capacity of the in-line filter is designed to be able to filter the entire volume of a fermentation batch and washing batch in one hour, the calculations can be found in the file "Inlinefilter.mcd". The characteristics for the filter as given in Table 8.2 were determined.

Table 8.2: Characteristics of the in-line microfilter

Characteristic	Value
Pore size	1 μm
Area	0.071 m^2
Pressure drop	1 bar
Flux	49.22 $m^3/m^2.h$

In the downstream a MPV (S201) is designed as was already stated in paragraph 5.1.2. First the extraction is processed in this vessel with its sequential steps of mixing and settling. Introducing storage vessels and adjusting the schedule puts this piece of equipment also into service for the evaporative crystallization. These downstream operations are more detailed described below.

Extraction
The number of stages necessary for extraction depends on the desired yield in the extraction step, which on its turn depends on the amount of solvent used per extraction. The complete set of decisions taken has been done in 1 turn. The relationship between the theoretical yield and the amount of solvent added is shown in figure A8.5 of Appendix 8.3.1.

A theoretical extractor yield of 98% was chosen, which leads to 350 kg of solvent per batch and 3 equilibrium stages for the extractor. If 2 stages are chosen for 98% theoretical yield a significant increase of used solvent is needed. If 4 stages are used scheduling problems occur when operating the process.

The figures are obtained, using a counter current extraction operation. Because a mixer uses a regime, which is in between a cross-, and counter-current regime, it should be taken into account that the values obtained with this model are the lower limit, as for cross-current operations the yields will be higher. If the process will be designed in practice this has to be taken into account.

Mixing and settling
For liquid-liquid mixing normally 1-1.5 KW/m^3 is needed for stirring [23, p471]. Since the mixing volume will be around 3 m^3 - a total power P of around 4.5 kW is needed for good agitation in the mixing vessel.

During the mixing the Power number (Po) is chosen to be 3, which leads to an impeller frequency of 270 rpm, which is a reasonable figure, as it indicates a tip velocity of the impeller of 6.3 m/s. Literature reports that this value should be

between 3-15 m/s [7, p.603]. All these data result in a turbulent mixing regime with the Reynolds number being $1.3*10^6$.

Because in every extraction step a different amount of DOIP is transferred from the aqueous solution to the solvent, this has to be taken into account for calculation of time needed for stirring. This mixing time can be calculated by dividing the total DOIP transferred by the mass transfer flow. The mixing times for the different steps can be found in Table 8.3. An explanation of the calculations done can be found in Appendix 8.3.1.

Table 8.3: Overview mixing data

Extraction step	Δc [kg/m^3]	Mass transfer flow [kg/s]	DOIP transferred [kg]	Mixing time [min]
1	27.7	0.0350	9.50	4.6
2	6.3	0.0078	2.43	5.2
3	2.0	0.0025	0.66	4.4

The mixing times calculated are rough estimations, since the driving force (Δc) is an estimate. It does give results in the right order of magnitude, because in the industry mixing times of 15-30 minutes are taken [20]. In our process, to be on the safe side and because first the ethyl acetate droplets need to be formed (which also takes time), a mixing time of 20 minutes is used for the batch cycle diagram. If required also the stirring speed can be increased for getting smaller ethyl acetate droplets to achieve the necessary DOIP transfer. In industry practices a settling time of 30-60 minutes is used [20]. For this process a settling time of 40 minutes is taken.

The final operating conditions of the extraction are given in Table 8.4.

Table 8.4: Operating conditions extraction

Parameter	Units
Temperature	20 ^oC
Pressure	1 bar
Number of stages	3
Liquid Volume	3 m^3
Power needed	4.5 kW
Mixing time	20 min
Settling time	40 min

Evaporative crystallisation
The evaporation of solvent, which is operated in the MPV (S201), has been split into two sequential parts:

1) Evaporation without extra heat input, using the heat capacity of the liquid
2) Evaporation with heat input through a jacket

In the first part only a small portion of solvent evaporates by putting the vessel under vacuum (30 mbar, which is below the vapour pressure of the solvent at 5 ^oC). The heat needed for evaporation is delivered by the heating of the solvent in the vessel, for which ideal mixing is assumed.

The second part has been modelled with Matlab®, because the volume solvent in the vessel is diminishing during the vaporization, resulting in a smaller heat transfer area

over time. During this second part also crystallization will take place, when the concentration rises above the maximum solubility.
With a heat transfer coefficient of 300 W/m^2K, which is an estimate for heat transfer oil to solvent in a jacket[7] [23 p 638] and a temperature difference of 40 ^oC between the heat transfer oil and the solvent, evaporation can take place within 5.5 hours towards the final needed volume for crystallization, which is 1/5 of the initial volume (see paragraph 8.1.1). The model actually simulates that a larger amount of solvent will evaporate in the 5.5 hours. However a process time of 5.5 hours is taken into account in order to have a reasonable margin. More details about the evaporation can be found in Appendix 8.3.2.

In order to recover the evaporated ethyl acetate during the evaporative crystallisation a condenser (E102) is designed on top of the MPV. The evaporation rate is not constant during this procedure, so for designing the condenser the maximum required cooling duty is used as a starting point. The maximum evaporation rate is established at the beginning of this process. Consequently for the overall procedure the condenser is over designed. Calculations can be reviewed from the CD-ROM in file "Design K201 and E201.mcd". Specifications are enclosed in Appendix 8.8.

To crystallize the remaining DOIP crystallization will be continued during the next 6 hours. For this operation the heat transfer oil will have a temperature below 5^oC, because during crystallization heat is produced when crystals are formed, but this is negligible compared to the heat of evaporation and thus is omitted in the heat balances. For this reason the cooling jacket should have the possibility to use the same heat transfer oil at different temperatures. The power input needed for keeping the crystals in suspension is negligible, since the volume is even smaller than in the ISPR-case, see description of ISPR crystallizer , paragraph 8.2.2.

Solid Handling
At the start of the solid handling step, the contents of the MPV (S201) is pumped by pump (P202) into the Nutsche filter (S202) and the liquid is allowed to drain through the filter. The liquid permeate from filtration is partially recycled for the next evaporative crystallization batch and the rest is used as a purge for the extraction section to prevent OIP and ACT accumulation. The crystals are then washed with a cold-water volume equal to the volume of solids present. The used washing liquid is sent to the WWTP. The cake is then dried using nitrogen and by heating the wall and stirrer. After drying, the product is packaged using an "endless bag", reducing the chance of a dust explosion and/or inhalation by operators.

The highest throughput in the Base case is approximately 95 kilograms of DOIP in 76 hours (see Appendix 5.3, stream <241>), so time management of the filter equipment is not especially critical. However, note that the filtration step and washing step will be fast compared to the drying step.

Pumps
Most of the pumps in the Base case will be one-step centrifugal pumps. The pump at the bottom of the MPV (P202) will also have to pump slurry, besides aqueous solution and solvent. Furthermore the pump (P204) feeding the solvent to the evaporative-crystallization step will have a higher capacity, because the MPV needs

[7] Confirmed by DSM

to be filled in a short time (see Appendix 5.2). The pump in front of the micro filter should have a higher pressure drop, to overcome the pressure loss in the filter.
In general the pumps will supply an overpressure of 1 bara, giving room for pumping water over a 10m height difference, which should be enough when doing the final layout of the plant. The pressure in all vessels is 1 bara.
The pumps, which will supply the base and acid towards the fermentor, will be peristaltic pumps, because the quantities added are very small.

An example for characterisation of centrifugal pumps (P101) can be found in Appendix 8.8. From this sheet it can be seen that the utilities of these pumps can be neglected, because the power consumption is 0.1 kW.

A vacuum pump (K201) is required for the evaporative crystallisation, which is operated at 30 mbar. For this vacuum pump a liquid-ring single stage pump has been selected from the product catalogue of US vacuum pumps[8]. This pump can reduce the pressure to a minimum of 27 mbar vacuum, which is below the required 30 mbar. The required energy input is of 20 hp (15 kW). Design calculations are given in the MathCad file "Design K201 and E201 (Base case).mcd" on the CD-ROM.

Vessels
Since the Base case is operated batch wise and moreover a MPV is introduced in which the main part of the downstream is processed, storage vessels are inevitably needed in the design. Also the aspect of recycling extracts in the downstream, forces to implement these equipment units.
In the fermentation section a storage vessel (V102) is introduced for the finished aqueous solution from the fermentation and washing. The liquid is stored in this vessel until the downstream section (V204) is ready to receive the content.
In the downstream section three vessels ((V201), (V202) and (V203)) are introduced to either store extracts of two processed extractions of each aqueous solution batch or the evaporated ethyl acetate from the evaporative crystallization. These organic batches are used in the sub sequential downstream processing of the next aqueous solution batch and so need to be stored for a time.
Since a MPV (S201) is used in the design, two more vessels are required for storage of the first extracts of each aqueous solution batch and for storage of the aqueous phase. In the vessel (V205) seven first extracts and the recycled filtrate are stored before they are processed to (S201) for evaporative crystallization. Vessel (V204) is used as storage for the first and second raffinate of the extractions. These raffinates are fed again to the following extraction procedure. When the second raffinate is processed to (S201), (V204) is available to receive new aqueous solution from the storage (V102) from the fermentation section. The third raffinate is pumped to the WWTP. In Table 8.5 an overview is given of the capacities of the storage vessels.

[8] http://www.usvacuumpumps.com/2004CondensedCatalog.pdf, visited 7-12-2004.

Table 8.5: Overview vessels Base case

Storage Vessel	Capacity [m^3]
V102	3.0
V201	0.5
V202	0.5
V203	4.0
V204	3.0
V205	4.0

Heat exchangers
The contents of the storage tanks are at ambient temperature (±15°C). Since, the fermentation is processed at 30°C it is required to heat up the fermentation solution, the washing water and the reactivation solution, when these are transferred to (R101). A heat exchanger (E101) for this purpose is designed with a required exchange area of 3 m^2.
When aqueous solution is transferred from (V102) to the downstream section a heat exchanger (E103) is introduced to cool down this stream, as the operating temperature in the downstream is 20 °C. For this heat exchanger a required heat exchange area of about 1 m^2 is calculated. The design calculations of these heat exchangers are given on the CD-ROM respectively in the MathCad files "Design HE E101 (Base case).mcd" and "Design HE E103 (Base case).mcd" and specifications are presented in the equipment data sheets in Appendix 8.8.

8.2 Process and Equipment Design (ISPR)

Here the unit operations of the Base case will be further discussed.

8.2.1 Integration by Process Simulation (ISPR)

Modelling the ISPR case in Matlab®
First mass balances were setup for OIP, DOIP and ACT in order to model the behaviour of the system. Important assumptions are a constant volume in the fermentor and changing volume in the crystallizer, so all mass build up is in the crystallizer. A liquid build-up in the fermentor would dilute the biomass and the fermentor would be less productive. Also no evaporation of OIP, DOIP and ACT is assumed. These balances were used to make a model in Matlab® and can be found in Appendix 8.4.1. The scripts of this model can be found in on the CD-ROM. The script "ISPR.m" calculates with the input variables like starting concentrations, volume of the fermentor, mass build-up in the system and flows between the two vessels, yields of DOIP, DOIP-crystals and by-product formation. This model could be used to evaluate the best setup using economic and operability trade-offs.

The model shows the dynamic behaviour of all concentrations, the liquid volume of the crystallizer and the total amount of DOIP crystals formed. First the model was used to simulate the experiment done by the principal. The resulting graph can be found in Appendix 8.4.2. In both situations a pseudo-steady-state is reached after about 80 hours and the concentration levels are approximately equal. To get these results however, the recycle stream between the crystallizer and the fermentor had to be tripled compared to the paper otherwise the DOIP concentration would have been above the one mentioned for the fermentor. It was assumed that this was correct, since it is theoretically impossible to remove DOIP at the rate given in the paper [5].

As the model seemed to predict the experimental situation pretty well, it then was used to model the large scale. The first parameter that was changed was the operation time. It was thought that the biomass could be used longer than 180 hours, so the batch time was prolonged to 370 hours[9]. The yield of DOIP crystals on OIP went up from 60% to 72%, because the loss of DOIP is mainly dependent on the total amount of liquid volume in the system. Because the OIP and DOIP concentration in the fermentor is rather high at the end, a closedown procedure was used: at 70 hours before the end of the batch time the feed of OIP was stopped, letting the system consume all OIP and form more DOIP crystals. The yield now went up to 80%. The system was scaled up to 4.1 m^3, because per batch approximately 400 kg of DOIP crystals is needed. This did not affect the yield, but set the end volume of the crystallizer to 7600 litres. It was then recognized that this volume is rather high and that if it could be decreased, the yield would also go up, because less product would be dissolved in the water at the end of the batch.

The liquid build-up in the crystallizer is equal to the total mass build-up in the system; if that build-up could be lowered also the yield would go up. First all the mass streams were analyzed, also using the scale up calculations of Appendix 8.5. The results are in Table 8.6 and the accumulation is already lower than the previously shown 20.5 kg/h, which was determined by rough scaling up of the fermentor mentioned in the paper. The accumulation of 17.83 kg/h gives a yield of 84.9%.

Table 8.6: Mass accumulation, calculated values

IN			**OUT**		
Air	61.16	kg/h	Air	64.73	kg/h
OIP	1.36	kg/h			
Glucose	4.87	kg/h			
Glucose-H2O	7.43	kg/h	**ACCUMULATON**		
Acid/Base	6.15	kg/h		17.83	kg/h
Condensed water	1.59	kg/h			

Four cumulative measures were considered to lower the mass build up in the system.
Step 1: Remove the condensed water stream back to the fermentor.
Step 2: Half acid-base addition by doubling concentrations. NaOH is normally used at 4M now at 8M.
Step 3: Use glucose solution of 80 wt% instead of 30%.
Step 4: Add solid glucose without water.

Another important parameter is the recycling rate or in other words the flows between the crystallizer and the fermentor. More recycling leads to a lower concentration of DOIP in the fermentor and a better yield. On the other hand more recycling means more cooling in the crystallizer and more ultrafilter area. These effects may reduce the profits gained by a better yield.
In order to investigate the effects "ISPR.m" was turned in a functionfile, "ISPRfun.m", a file that returns the yield of DOIP-crystals at given recycling rate and mass build-up in the system. In the file "optimizeISPR.m" the results were transferred into a simple economical model, which uses the prices of OIP and DOIP and a simple economical factor based on filter-area associated with a recycling rate.

[9] Discussed with Adrie Straathof

For all measures the optimal recycling rate was calculated and the associated yield was given.

Table 8.7: Results of ISPR optimization

Step	Description	Accumulation [kg/h]	Yield [%]	Crystallizer volume [m^3]
No measures	-	17.83	84.9	6.4
Step 1	No condensed water reflux	16.24	85.9	5.9
Step 2	Stronger base	13.17	87.7	5
Step 3	80 wt% glucose	6.91	91.3	2.8
Step 4	Solid glucose	5.74	91.7	2.2

The results shown in Table 8.7 and in graph A8.9 in appendix 8.4.2 indicate a maximum yield of 85% with no measures and of 92% in the case of all measures taken. The first 3 measures can be taken fairly easy and will be used in the process, the addition of solid glucose will not be done since solid glucose has a higher price and solid addition is more complicated; this will not weigh up to the increase in yield, which is just 0.4%.

So the yield has now increased to 91% and the crystallizer volume is at the end of the batch 2.8 m^3. The recycling rate is now 415 l/h versus 276 l/h at the initial model. The system now produces during one batch 404 kg of DOIP-crystals. This amount can be increase further by increasing the feed of OIP a little to a maximum of 435 kg DOIP can be reduced; this barely affects the yield that stays around 91%.

After a batch of the ISPR, a yield of DOIP crystals of 91% is obtained, however the yield of total DOIP is even higher 97.5 %. This means that still 27.6 kg of DOIP is still in the process water. This represents a value of € 5500,- per batch or an annual €27600,-, the cost of recovering this DOIP will now be evaluated. The Base case downstream processing yields and costs will be used in order to see whether it makes sense to do this.

It was estimated that for 1 year approximately 1500 l ethyl acetate would be needed. Including waste costs this would cost about €7500,-. Also extra equipment like a vacuum pump is needed, the extra revenues are now negligible compared with the costs for these complex operations.

8.2.2 Equipment Selection and Design (ISPR)

Fermentor
For the design of the fermentor in the ISPR case the experimental results of [4] were used as a starting point for the scale up. Through a dimensional analysis the relevant dimensionless numbers for the process were derived.

The scale up of the fermentor is approached in a way by scaling the working volume of the small-scale experiments. This scaling factor (k_V) is determined by mass balance calculations in order to meet the demand of DOIP production in the assumed time span (see paragraph 3.3). From the k_V the corresponding scaling factors for the dimensions of the fermentor are determined.

The oxygen transfer rate (OTR) is an important criterion in the scale up since it determines the oxygen uptake of the baker's yeast and ultimately the production rate of DOIP. So in order to meet the required productivity of the baker's yeast the OTR, based on the working volume, is kept constant in the scale up.

The k_La is a very important factor that highly determines the OTR. An expression for this dependency is given in equation A8.16 in Appendix 8.5. According to Winkler et al [28] this coefficient is also dependent on several dimensionless numbers. From this expression (given in equation A8.15 in Appendix 8.5) it becomes clear that the k_La is strongly dependent on the impeller speed, impeller diameter and the superficial gas velocity, which is in fact determined by the airflow, because of the fixed diameter of the fermentor.

These two equations can be rearranged for the OTR as a function of several quantities. Setting the impeller diameter and the physical properties gives ultimately an expression (equation A8.17 in Appendix 8.5) for the OTR as a function of the impeller speed and the superficial gas velocity. So the OTR can be tuned by these two quantities. In order to reduce the power dissipation of the agitator it is desired to keep the stirrer speed as low as possible.
Further considerations, which are taken into account for the scale up, are related to the gas circulation in the fermentor and the mixing of the liquid phase. A total gas circulation is desired to provide the whole fermentor with sufficient oxygen and to ultimately have an optimal productivity of the baker's yeast throughout the fermentor. The gas circulation is determined by the regimes of the Froude number (Fr) and the Gas throughput number (Fl_G) [13]. Both numbers are related to the stirrer speed and the latter also to the airflow. Complete liquid mixing also contributes to an optimal production throughout the whole fermentor. This is achieved in the case that the characteristic time for the oxygen transfer exceeds the mixing time of the liquid [28].

From the above reasoning it can be concluded that the airflow (and so the superficial gas velocity) and the impeller speed need to be chosen at the large scale in such way that we meet the following criteria are met:

- Keeping the OTR at the same level as in the small case.
- Keeping Froude number (Fr) Gas throughput number (Fl_G) in the regime of total gas circulation.
- Total mixing of the liquid phase.
- Keeping the impeller speed as low as possible.

From the scale up the required agitation, aeration power and cooling duty is calculated. The scale up and heat balance calculations are presented on the CD-ROM (ISPR_fermentor_design.mcd). A short overview is given below and more details are tabulated in Table A8.13, Appendix 8.5.

Table 8.8: Fermentor ISPR specifications

Quantity	Large scale
Fermentor volume	6.0 m^3
Fermentor diameter	1.86 m
Work liquid volume fermentor	4.1 m^3
Gas hold up	4.72 %
Air flow	52.5 m^3/h
Impeller diameter	0.8 m
Impeller speed	135 rpm
OTR	1.28 kg m^{-3} h^{-1}
CTR	1.77 kg m^{-3} h^{-1}
k_La	0.179 s^{-1}
Power aeration	0.216 kW
Power dissipation agitator	15.2 kW
Cooling duty fermentor	32.4 kW

Like in the Base case, a condenser is designed for the gas exit on top of (R101) in order to recover the water, which evaporates because of aeration. The required cooling duty is relatively small and since at a MPP it is assumed that condensers can deliver much larger duties, the condenser which is used in practice would be over designed for this particular purpose. Nevertheless this condenser (E102) is designed for the actual cooling duty (see equipment data sheet in Appendix 8.9 and "Design E102 (ISPR case).mcd").

Crystallizer

The scraped cooling crystallizer (S102) continuously receives filtrate obtained from ultrafilter (S101). To reduce the cooling duty in the crystallizer, the filtrate from the ultrafilter is pre-cooled to 10 °C in the tube side of heat exchanger (E101). In the crystallizer the incoming flow is cooled to the crystallization temperature of 5 °C. The content of the crystallizer is pumped back through the shell side of the heat exchanger to fermentor (R101). The stream exiting the crystallizer is slightly smaller then the stream entering the crystallizer; this is to accumulate in the crystallizer any volume added to the system by addition of DOIP, glucose and acid or base to the fermentor.

To accommodate the gradually increasing volume in the crystallizer, the crystallizer should have a size of at least 3 m^3. The crystallizer is outfitted with a cooling jacket and a scraper for scraping the wall and bottom of the crystallizer. According to [16], it is necessary to scrape the crystallizer because heat transfer is between 200 and 1000 W/m^2 because crystallisation on the cooling surface leads to significant loss in heat transfer. The heat exchanger was used to make sure the cooling capacity did not exceed 1000 W/m^2. If a crystallizer without scraper was to be used as crystallizer, additional heat exchange capacity in the heat exchanger would be needed and the stream exiting the heat exchanger would have a relative super saturation of 0.9 (see "Crystallizer calculations.mcd"). It was expected that at a relative super saturation 0.9, heterogeneous crystallisation on heat exchanger and pipe walls would become a serious problem. Therefore, the temperature of the stream exiting the heat exchanger was not lowered below 10 °C, which means that the relative super saturation is around 0.6; this was considered acceptable. The heat exchanger should have a heat exchange area of slightly under 2 m^2 (see also "Crystallizer calculations.mcd").

Inside the crystallizer also a microfilter will be installed in order to retain the crystals and only recycle the water back to the fermentor. In the MathCad-file "DarcyMF.mcd", this filter is designed using Darcy's law for laminar flux through pores. The microfilter will have pores of 1 µm so crystals from that size on will be retained. Even smaller crystals that will go through the pores will dissolve again in the fermentor and won't form severe problems. The microfilter has cylindrical form and about 0.05 m^2 of surface area. The trans-membrane pressure needed to ensure the flow is 0.15 bar.

Table 8.9: Characteristics of microfilter

Characteristic	Value
Pore size	1 µm
Area	0.05 m^2
Pressure drop	0.15 bara
Flux	6.04 $m^3/m^2.h$

Ultrafilter

The ultrafilter is a very important unit for the ISPR, not only because it has to retain the biomass in the fermentor, but also for the purity of the end product. The fermentation broth is very likely to contain small amounts of macromolecules like proteins, DNA and other product from cell debris. If these macromolecules would end up in the crystallizer they are very likely to precipitate on, for example, the DOIP crystals. The ultrafilter has a molecular weight cut off of 500 kDa, meaning it can retain molecules larger then 500 kDa. Experiments [4] have shown that using such a membrane gives a product meeting the required quality specifications of 99.5 wt% purity.

The largest problem using membranes is fouling. Although the concentration of cell debris is considered to be low, it might go up at the end of the process, requiring higher trans-membrane pressures and possible blocking of the complete flow. In order to by-pass this problem it was already in chapter 5 discussed that two ultrafilters would be used. One ultrafilter will be online, the other will be cleaned and ready to take over, if the fouling is severe.

From the brochure of Amersham Biosciences a cross-flow ultrafilter was chosen that could meet the required flow (415 l/h). This filter (UFP-500-C-75) was further designed in the file "DarcyUF.mcd". First the clean-water-flux was calculated using Darcy's law for flow through laminar pores. This resulted in the membrane resistance. Then the fouling of yeast particles was calculated, resulting in a cake resistance, which was modest. The combined resistances led to the operating pressure for our desired flow. The characteristics are given in Table 8.10.

This unit has no utilities of its own; since the energy will provided by pump (P106).

Table 8.10 Characteristics of the ISPR ultrafilter

UFP-500-C-75	Value
Pore size	50 nm
Area	6 m^2
Transmembrane pressure	0.73 bara
Shear rate	6000 s^{-1}
Feed flow rate	1200 L/h
Permeate flow	415 L/h
Retentate flow	785 L/h
Flux	69 $L/m^2.h$

Solid Handling
At the start of the solid handling step, the content of the crystallizer is pumped by pump (P108) into Nutsche filter (S103) and the liquid is allowed to drain through the filter. All liquid permeate from filtration is then sent to the WWTP. The crystals are then washed with a cold-water volume equal to the volume of solids present. The washing liquid permeating the filter is also sent to the WWTP. The cake is then dried using nitrogen and by electrical heating the wall and stirrer. After drying, the product is packaged using an "endless bag", like in the Base case

The highest throughput in the ISPR is 400 kilograms of DOIP in 380 hours (see Appendix 5.7 stream <128>), so, like in the Base case, time management of the filter equipment is not especially critical. Considering the size of the filter, a solid handling time of 48 hours per batch is estimated.

Pumps
For the pumping between the fermentor and the crystallizer ((P106) and (P107)) one step centrifugal pumps will be used, just as for filling the fermentor with the initial biomass suspension. The pump before the ultrafilter (P106) will have to supply, besides the normal 1 bara, an extra pressure of 1 bara, to obtain the right flow towards the crystallizer. These two pumps will be considered in the calculation of the utilities, since they are used continuously. All other pumps that are treated below are neglected in utility calculations.

For feeding of the substances in the ISPR fermentor a peristaltic pump will be used. This type of pump is used a lot in biochemistry processes and can handle up to 20 l/s. It is supposed that all substances can be pumped with these pumps, including 8M NaOH and 80 wt% glucose solution. For the pumping of the slurry after crystallization a diaphragm pump will be used. This pump is often used for pumping of slurries to filter presses.

9 Wastes

In this chapter wastes generated by both cases and how each of these waste streams are disposed will be examined. The effect of design decisions on waste generated will be examined and both cases will be compared.

9.1 Wastes (Base Case)

The wastes generated are listed in Table 9.1 (a full inventory of the waste streams can be found in Appendix 9.1). All of these wastes will need to be treated and shall be discussed briefly. However, as the WWTP is a slightly more complex treatment option, the WWTP shall be look at in more depth.

Table 9.1: Waste generated by Base case

Waste	Description	Origin	Possible effect	Disposal method
Spent air	Air exiting fermentor that might contain biomass (by-)products	<110>	Bad odour	Filter if odorous
Spent reactivation solution	Solution used to reactivate the biomass	<112>/<113> <119>	Pollution of ground water	To WWTP
Spent Base case biomass	Biomass immobilized in Calcium Alginate and resin	(R101)	Odour, littering	To external solid waste burner
Spent raffinate	Water containing a high load of ethyl acetate and traces of OIP, DOIP and ACT	<212>-<217>	Pollution of ground water	To WWTP
Ethyl acetate purge	Ethyl acetate containing OIP, DOIP and ACT	<236>	Pollution of ground water, fire hazard	To burning facility
Spent washing water	Water containing OIP, DOIP, ACT and ethyl acetate	<232>/<233> <238>	Pollution of ground water	To WWTP
Spent nitrogen	Nitrogen used in drying containing evaporated water	<240>	None	Release to environment
Packaging materials	Packaging materials for raw materials	N.A.	Obstruction, littering	Domestic waste

The spent air should be filtered to reduce odour to an acceptable level. The spent ethyl acetate should be burned; this can be done internally if facilities are present. Spent nitrogen can freely be vented into the surroundings if care is taken to release at sufficient altitude. Packaging materials can be disposed of as domestic waste as quantities of raw materials (and thus packaging) used are low.

The aqueous streams will have to be treated by the WWTP on site before they can leave the perimeter. All these components will be removed by a standard WWTP.
From the content of the streams the chemical oxygen demand (COD) can also be calculated. This is done by calculating the amount of oxygen that needs to be added in order to completely oxidise the contaminations. The COD value for ethyl acetate is 1.8 kg/kg, for OIP, DOIP and ACT it is 2.3 kg/kg and for glucose it is 1.1 kg/kg. These values can be used to calculate the load of the aqueous waste streams, which is an annual 76800 kg of COD. As one population equivalent (the amount of COD per capita per year) is about 11 kg, this means a waste of 7000 population equivalents is produced. Also the COD per volume of waste is rather high, about 165 gCOD/L. As Table 9.2 shows this high COD load is mainly due to the ethyl acetate. In the mixer settler step ethyl acetate is going partly to the water phase, because the solubility is 80 g/l. A way to prevent this expensive waste is using another solvent and/or an adsorber.

Table 9.2: COD load Base case

Component	**COD kg/kg**	**COD kg/ year**
Ethyl Acetate	1.8	68500
OIP/DOIP/ACT	2.3	700
Glucose	1.1	7600
Total		**76800**

The waste generated by the fermentation section has low treatment requirements, but the solvent used in the separation step is cause for a fair amount of waste. The solvent purge also contributes significantly to the waste produced and the solvent also contaminates the water used for washing the crystals. The waste produced in solid handling contains solvent, but the presence of solvent should mainly be attributed to the extraction-crystallisation step and not solid handling itself. Solid handling wastes are minimal compared to the wastes generated by the extraction-crystallisation step.

9.2 Wastes (ISPR)

The wastes generated are listed in Table 9.3 and a full listing of the stream can be found in Appendix 9.2. The considerations for disposal of the various waste streams are similar as those for the Base case.

Table 9.3: Waste generated by ISPR case

Waste	Description	Origin	Possible effect	Disposal method
Condensed water	Water condensed from the air stream exiting fermentor	<115>	Might contain OIP, DOIP or ACT	To WWTP
Spent air	Air exiting fermentor that might contain biomass (by-)products	<116>	Bad odour	Filter if odorous
Spent Nitrogen	Nitrogen used in drying containing evaporated water	<136>	None	Release to environment
Filtrate & washing water	Aqueous waste from the crystallizer that is obtained during solid handling	<130>/<132>	Pollution of ground water	To WWTP
Spent fermentor contents	Same as filtrate (132), but also contains biomass	<113>/<117> <131>/<132>	Pollution of ground water	To WWTP
Packaging materials	Packaging materials for raw materials	N.A.	Obstruction and littering	Domestic waste

Wastes generated in the ISPR case have low waste treatment requirements, because all wastes are limited to solubility of OIP, DOIP and ACT. The biomass is the main pollutant, but in total it is a small waste of about 100 population equivalents. The COD concentration is only 33 g COD/l.

Table 9.4: COD load ISPR case

Component	COD kg/kg	COD kg/ year
OIP/DOIP/ACT	2.3	475
Biomass	1.1	720
Total		**1195**

9.3 Comparison of wastes

The Base case generates more waste than the ISPR case and this is mainly caused by the solvent loss, both as purge and dissolved in the spent washing water. The total mass stream of water for the Base Case is also 10 times larger than for the ISPR. Furthermore, the biomass waste is more difficult to process in the Base Case than in the ISPR case, because of the immobilization. Other wastes inherent to the processes are roughly the same.

10 Process Safety

Any chemical process should be safe. There are several reasons for this, such as the reputation of the chemical industry and the environmental and financial impact on the environment. To integrate safety into a design, it is important to consider safety during every step of the design. A thorough safety evaluation has to be made after the conceptual design is finished. To do this two tools are used to examine both cases: the DOW fire and explosion index (F&EI) and a hazard and operability study (HAZOP). The purpose of this chapter is to perform these analyses on both processes and use the conclusions to improve the safety of operating personnel.

The DOW F&EI is applied widely in industry, as it is a quick method that provides a significant insight into process safety. Not only can it be used for identifying the process sections that generate the most risk, it also allows for estimation of the economic loss in case of an accident. In the interest of time, only one F&EI will be performed per process. This will be applied to the phase and part of the process that is considered the most hazardous, as a worst case scenario for a possible accident. The results obtained should be carefully examined as the DOW F&EI is intended for larger processes then the two being reviewed.

A HAZOP is an open-ended method that uses guide words, such as 'no', 'more' and 'as well as', in combination with process parameters, such as 'pressure', 'mixing' and 'reaction' to analyse the process in a brainstorm session. The advantage of this open-ended method is that it can also reveal interactions between hazards. A short HAZOP was performed on both processes.

10.1 Process safety (Base case)

The flow sheet analysed for the Base case can be found in Appendix 5.1.

10.1.1 DOW F&EI study (Base Case)

For the Base case, evaporative crystallisation in (S201) was identified as the most hazardous BO for the separation section, so analysis was performed on operation during the aforementioned BO. The results of the F&EI for the separation section can be found in Appendix 10.1. The evaporation crystallization phase was categorised as a moderately hazardous process. Please note that there are also risks associated with extraction, ethyl acetate storage and solid handling. Extraction and storage will be less hazardous than the evaporative crystallization because of the atmospheric operating pressure. The solid handling hazard will be very similar to the solid handling hazard in the ISPR case.

10.1.2 HAZOP study (Base case)

A HAZOP was performed on the Base Case and results can be found in Appendix 10.2. Ethyl acetate-air explosion, the possibility of vessel failure due to high pressure and a dust cloud explosion in the solid handling section were considered to be the key safety issues. Measures are easily taken to mitigate these risks and a full list of proposed measures can be found in the HAZOP results. The most important of these is preventing ethyl acetate explosions by installing protections against over-pressure in vessels containing ethyl acetate and installing detectors for the presence of ethyl acetate in the process area. Also, making sure that a possible dust explosion is detected early is very important. An oxygen detector should therefore be placed inside (S201) and (S202).

10.1.3 Measures proposed (Base case)

Based on threats identified, several safety features are proposed for the Base case. These measures should only be seen as a preliminary evaluation, as design of a complete set of safety measures is best left to safety experts. It should be noted that training of operating staff cannot be substituted by any process feature.

First, some general measures are proposed. A sprinkler system would be effective for fighting fires. Also, spark prevention is useful to reduce explosion and fire risk. Furthermore, eye showers and first aid equipment on site should also be present. Secondly we will look at ethyl acetate, as using ethyl acetate also brings risks. Appropriate measures like installing level controllers, over-pressure seals and a dump-vessel on vessels containing ethyl acetate will mitigate risks. Lower explosion limit (LEL) detectors in the process area will also help to prevent a possible explosion. Thirdly, constantly padding the Nutsche filter with nitrogen (at a alight over-pressure) and installing oxygen detectors inside the filter can significantly improve the safety of the solid handling section.

10.2 Process safety (ISPR)

The flow sheet for the ISPR case can be found in Appendix 5.5.

10.2.1 DOW study for F&EI (ISPR)

For the ISPR case, solid drying was considered the most dangerous operation, so this is the stage on which the analysis was performed. The results of the F&EI can be found in Appendix 10.3. The hazard for solid handling falls into the 'Moderate' category.

10.2.2 HAZOP study (ISPR)

A HAZOP was performed on the ISPR Case and results can be found in Appendix 10.4. Coolant leakage and a dust cloud explosion in the solid handling section were considered to be the key safety issues. However, these risks are easily mitigated. These measures can be found in the HAZOP results. Most important is detecting any possible leak in (S103).

10.2.3 Measures proposed (ISPR)

All measures suggested for fermentation and solid handling in the Base case were also suggested for the ISPR case. Therefore, only the measures suggested shall be given and the reasoning behind them can be found in 10.1.3. It is proposed to install a sprinkler system and spark prevention, to have continuous padding of the solid handling with nitrogen and to install oxygen detectors in (S103).

10.3 Comparison of Base case and ISPR

With the knowledge obtained from F&EI and HAZOP performed, the safety of Base case and ISPR case con be compared. Looking at both F&EI's performed, it can be seen that the fire and explosion risks estimated are fairly similar. Both have almost the same F&EI number, although the explosion causes more damage for the solid handling as the damage factor is higher for the dust explosion due to a higher base material factor. However, it should be remembered that a Nutsche filter very similar to the one present in the ISPR case and therefore the risk found for the ISPR case also applies to the Base case. Also, the risks of extraction and ethyl acetate storage have not been evaluated with a DOW F&EI, but these also need to be taken into consideration. The HAZOP give a similar impression, because any hazards present in the ISPR case are almost all present in the Base case, with the base case having the additional hazards of extraction and crystallization.

In conclusion we can safely say that the ISPR process is inherently safer than the Base Case. The ISPR process has only one moderate F&EI, as opposed to at least two in the Base Case, and less process hazards were identified during the HAZOP performed.

11 Economy

In this chapter the economics of both the Base case as the ISPR case are discussed and in the end a comparison will be made to see which case is economically more attractive. The economic analysis has been done with the help of Harrison [12, paragraph 11.5], Coulson&Richardson [23, chapter 6] and Douglas [8, chapter 2]. For conversion between US Dollars ($) and Euros (€), the average ratio of 2004 according to www.dft.nl has been taken, 1.25 $/€.

In the BOD (paragraph 3.4) it is said that the production will be in 2000 hours. For the calculations of the economic figures this has been modified in the following way.
In practice all figures are given per year; for this reason it is assumed that the production time and quantity used for the economic calculation will be threefold of the designed time and quantity. In this way it is assumed that the possible other processes, operated with the equipment designed for our processes, have exactly the same economic figures and values as our processes. A threefold increase has been taken, to be on the safe side, not assuming 100% equipment use.

The price of OIP has been estimated at €100/kg, which is the price per kg of 5 kg OIP divided by 3[10]. The price of DOIP has been estimated at €400/kg, based on a ratio DOIP/OIP of 4 given by the principal.

11.1 Economic calculations

In this paragraph it is explained which economic figures are calculated for both the ISPR case and the Base case. The results of these calculation can be found in Appendix 11.1 (Base case) and Appendix 11.2 (ISPR case).

First the equipment costs (PCE) for each process were determined. Then with the Lang Method the once-off investment has been calculated. The Lang factors used have been taken from Harrison [12, p 335], where a range was given for these factors. The average Lang factors mentioned there are normally used for relative large biochemical plants for medium to high value products (E.g. an Insulin production plant of 1800 kg/ year). The DOIP production of 2000 kg/year has been considered to be in the same range.

The operating costs have been calculated according to Coulson&Richardson[23, p 266]. The major difference in the calculation of the operating costs is the amount of operators. Because the Base case has more units and more unit batch operations than the ISPR case, 2 operators are necessary for this process, while the ISPR case only needs 1 operator.
The annual income only depends only on the amount of DOIP produced, all other outgoing streams are considered to be waste. The Net Cash Flow is the difference between the Income and the Operating Costs.

[10] www.fluka.com, visited 17-10-2004

To make a comparison the following economic criteria are determined:

Table 11.1: Explanation of economic criteria used

Criterion	Explanation
Rate of Return (ROR)	Figure of the performance of the capital invested
Pay-back time (POT)	Time required after the start of the project to pay off the initial investment from income
Discounted cash-flow Rate of Return (DCFRR)	Interest rate at which the present worth of the plant at the end of the project is zero and thus is the maximum rate the project could still break even at the end of project life
Return on Investment (ROI)	Profitability measure and is often used in within companies

11.2 Adsorber (Base case)

In a previous stadium the adsorber was rejected for educational purposes, but it is used in the economic comparison, with very rough estimates, to show its economic potential. Using an adsorber may lower the utility costs of the solvent, because less make up solvent is needed and less waste is generated. Also a cheaper solvent can be used; methanol of € 0.25/kg instead of ethyl acetate of € 1.19/kg. For the economic comparison the economic spreadsheet of the Base case was used and the effects of using an adsorber were incorporated. All those changes will now be explained.
For the investments an extra € 5000,- for a column was added (see appendix 1.1). The adsorber beads were also added to the consumables, according appendix 1.1. In the utilities the amount of solvent was brought down from 40000 to 5000 kg, because the solvent is not directly contacted with the water phase anymore. Also the price of solvent was changed to the price of methanol. At last the COD load of the waste was lowered from 76800 kg COD to 5% of the original load, which results in 3480 kg. With these numbers we can get a feeling how a successfully designed adsorber influences the economic data for the Base case. Since the adsorber is not actually designed in the process, it should be emphasized that these numbers are only rough estimates. The detailed results for the adsorber can be found in Appendix 11.4, the general results in paragraph 11.3.

11.3 Economic comparison

When looking at the economic values for both cases, some of those values had to be changed to be able to make a good comparison between the cases. This was done because the Lang method was unfair for some of the direct costs. Because the ISPR has higher equipment costs, also all direct costs were higher, while it would be for example unlikely that the piping for the ISPR is more expensive than for the Base case because the latter has many more units and thus more piping is necessary. The complete set of changes made can be read in Appendix 11.3

The final results of these changes can be found in Table 11.2 and Table 11.3. Also the adsorber Base case is included. As can be seen these figures differ from the numbers in Appendices 11.1 and 11.2.

Table 11.2: Final economic figures all cases (1 year)

	ISPR [k€]	Base case [k€]	Adsorber [k€]
Purchased Equipment Costs (PCE)	907	661	666
Investment Costs			
Direct Costs (DC)	1,620	1,740	1,750
Indirect Costs (IC)	970	1,040	1,050
Direct Fixed Capital (DFC)	2,970	3,160	3,220
Total Investment costs (IT)	3,720	4,000	4,030
Operating Costs			
Fixed Costs (FC)	580	860	860
Variable Costs (VC)	760	1,080	900
Other costs	85	120	120
Annual Production Costs (APC)	1,415	2,020	1,880
Income			
Revenues	2,560	2,490	2,490
Net Cash Flow	1,130	420	600
Net Cash Flow (3 months)	377	140	200
DOIP produced (1 year) (kg)	6393	6222	6222

The costs per kg of DOIP can be found in the table below. As can be seen has the ISPR case the lowest Annual Production Costs and thus the highest Net Cash Flow, since all processes produce almost the same amount of DOIP.

Table 11.3: Main economic figures per kg DOIP

	ISPR [€/kg]	Base case [€/kg]	Adsorber [€/kg]
Annual Production Costs (APC)	221	324	302
Margin (NCF/kg DOIP)	177	68	96
Margin (from paragraph 3.4)	290	230	-

The difference in the margin, calculated in the Basis of Design (paragraph 3.4) and the margin obtained by doing the complete analysis occurs, because the latter includes the fixed operating costs and other operating costs (see Table 11.2), which are not included in the BOD calculation. It can be seen that the margin obtained in the basis of design is 1,5-2,5 times higher than the final margin. When applying this factor to the total investment costs in Table 11.2 it results in values close to the maximum amount of investment calculated in paragraph 3.4.

With the economic figures the economic criteria are determined, which can be found in Table 11.4.

Table 11.4: Economic criteria all cases (1 year)

Criterion	ISPR	Base case	Adsorber
Rate of Return	31%	11%	15%
Pay-back time	4.3 years	10.5 years	7.8 years
DCFRR	26.1%	6.4%	11.4%
Return on Investment	17%	2%	5%

The following plot shows the project cash flow diagram of all cases. The explanation of this diagram can be found in Appendix 11.1.

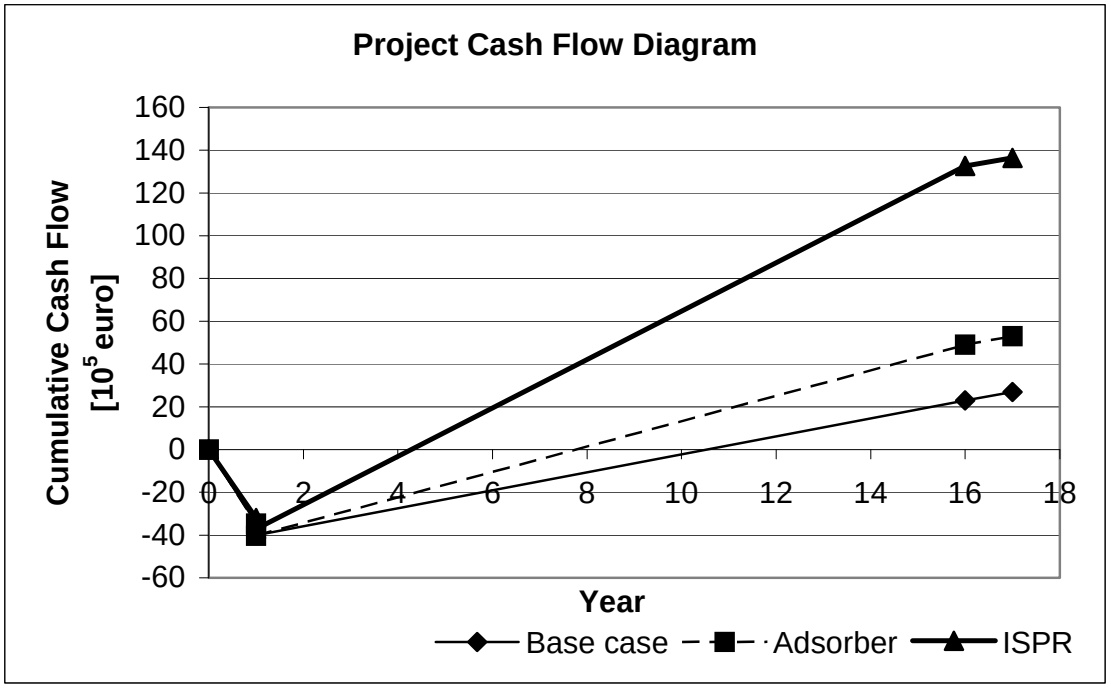


Figure 11.1: Project Cash Flow for all cases

From the above tables and plot it can be seen that the ISPR has the highest economic potential, scoring better on all economic criteria. This is mostly because no solvent is used. As can be seen for the other two cases, solvent use resulted in higher utility costs and higher waste costs, which are both in variable costs. This can also be seen when looking at the figures for the adsorber, where less and cheaper solvent (methanol) is used. Although the equipment costs (PCE) of the ISPR are higher, the final total investment made is the same for all processes. The higher PCE for the ISPR depend mostly on the high price of the ISPR fermentor.

As was mentioned at the beginning of this chapter, is the price of OIP an estimated value. The price ratio DOIP/OIP was set to 4 after consultation with the principal. When taking a closer look at the difference between DOIP and OIP price an analysis has been done by changing the DOIP price for a set of OIP prices. The combination of both process had to comply with a target for the Return on Investment of 15%, a figure, which is common in industry. The OIP price was set because the market will have determined this price and because OIP has to be obtained from the market. DOIP however will be used for further processing within the same producer.

When doing this for the both cases it could be said that the difference in price between DOIP and OIP should be €285/kg for the ISPR case and €425/kg for the Base case.

11.4 Possible economic improvements

Possible economic improvements for the Base case could be the usage of another solvent which is either cheaper or is less soluble in water, so that the utilities costs are lowered as will be the waste costs, because the COD demand will be lower when less solvent is lost. The adsorber case shows the trend of this impact.
Another issue that could be improved is the yield DOIP on OIP for the Base case, so that more DOIP is produced per kg of OIP, increasing the Net Cash Flow. The last improvement for the Base case could be to reduce the amount of used process water, which will reduce the amount of solvent loss and thus the will save on utilities and wastes.

For the ISPR case no large savings can be made. It might be possible to save on electricity costs or on fermentor costs, because the fermentor takes up half of the equipment costs.

12 Creativity and Group Process Tools

Creativity is an important aspect in designing a new plant and often necessary to get a competitive set-up. Therefore in this chapter is explained how creativity is implemented in our design process. Also a plant visit to the MPP of DSM in Venlo is described, giving us new insights and more creative ideas in the design of the process.

12.1 General creativity

It started with each person reading a few articles on creativity, both technical and non-technical. From these articles the following points were used in our creativity process:

- Usage of a mix between verbally, visual and objectual brainstorming
- Association with other processes
- Exploration and discussion of all parameters
- Work from the input to the output and vice versa
- Imagine yourself to be component in system and describe what happens/you need
- Keep creativity session in creative rooms

From the start some basic rules for brainstorming were set. These included no negative thinking or disapprovals during ideas generating, commitment of all team members to participate in some new methods and acceptance of the creativity leader's plan. With the latter is meant that one team member prepared each meeting and that person led the group through the meeting. An overview of all meetings held can be found in the group activity book, Appendix 12.1.

Besides specific creativity sessions every team member carried a small notebook to write down his/her ideas during the day, so that the ideas wouldn't get lost. Furthermore twice a meeting was held with our creativity coach, to evaluate some of our methods and results. An informal team get-together was organized twice to also enjoy non-project related activities together.

Three explicit creativity sessions have been held, each focussing on different things, which are explained below.

Potential improvements of processes

Before the kick-off meeting a brainstorm session was held about the weaknesses and potential improvements of the two processes given to us by the principal. Each team member wrote down his/her initial ideas and this was used as a start for the group brainstorm to generate more ideas. From this a total of 25 ideas for each case was generated. These ideas were then filtered to those, which we considered worthy to investigate further. This gave the following list of ideas:

Table 12.1: Possible improvements after first brainstorm

Base case	ISPR case
1. Evaporation of OIP & DOIP in the fermentor 2. Crystallization in the fermentor / difficult separation of biomass 3. Many waste streams / loss of product 4. Many operating units 5. Evaporation & crystallization 6. Filters and biomass separation	1. Evaporation of OIP & DOIP in the fermentor 2. Cold recycle stream issue 3. Crystallizer & end-of-batch 4. Biomass separation

The complete, more detailed lists can be found in Appendices 12.2 and 12.3.
After the kick-off meeting these ideas were distributed amongst the team members and some preliminary calculations and reasoning for these cases were done in the second week after the kick off meeting. These assumptions and calculations will be used during the project.

Component Imagination session

Because we felt we had started too soon with such detailed calculations it was decided to do a more general creative session to get more feeling with the process. For this session we went the building of Industrial Design, to be in a different and e creative environment. We imagined ourselves to be a component and described what we saw and felt throughout the process. This was done in such a way that two components were chosen, being the baker's yeast cell and the OIP/DOIP molecule in three different physical-chemical steps of the process: Reaction, Concentration and Purification

For each step of the process our imaginative observations and feelings were written down. These results can be found in Appendix 12.4.
The most interesting things are given below:

- Biomass is much bigger than the other molecules, so this feature can be used in different ways in separation techniques.
- There is a need of quick DOIP removal
- Conditions of the operation units should be as constant as possible
- The biomass catalyses a non-specific reduction
- The purification of the crystals is unknown

ISPR visual brainstorming

The last creative session was done in the third week after the kick-off meeting and consisted of a drawing brainstorming session, for different ISPR settings. First the different concepts were explained and a list had been made of all different separation techniques [22, p. 6]:

- Putting up a barrier
- Phase addition
- Phase creation
- Solid agent addition
- Making a force field gradient

Before starting the brainstorming of the processes conceptual schemes were made how the process should look like.

The ISPR figure was used as a starting point. All possible set-ups for in situ product removal were drawn individually and collected. They were stuck to a wall and each team member had to decide which process layout in each of the 4 groups seemed best. When this was done the best processes were evaluated and briefly discussed. The rejected ideas were put on a different sheet of paper, so that the ideas wouldn't get lost. To quantify the final decision it was decided to write down all different aspects that were important for making the choice.

The judging started with making a list of 14 important criteria, important for the choice between processes. Their importance was judged by comparing two aspects wit each other and saying which one we considered more important. If two criteria were compared, and one criterion was considered to be more important, this was given 2 points, the less important criterion was given 0 points. If the two criteria had the same importance, both were given 1 point. This is the first step of the so-called value benefit analysis developed by C. Zangenmeister[11].

Table 12.2: Criteria matrix

No		1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
	Criterion															
1	Yield Product on substrate	x	2	2	1	2	1	2	2	0	1	2	1	2	2	20
2	Glucose consumption	0	x	0	0	0	0	0	1	0	0	0	0	1	1	3
3	Biomass costs	0	2	x	1	0	0	2	1	0	0	1	1	1	2	11
4	Equipment costs	1	2	1	x	2	0	1	2	0	0	1	1	2	1	14
5	Equipment availability	0	2	2	0	x	0	0	1	0	0	1	0	1	0	7
6	Reliability	1	2	2	2	2	x	2	2	1	1	1	1	1	2	20
7	Waste Streams	0	2	0	1	2	0	x	2	0	1	0	1	2	2	13
8	Utility costs	0	1	1	0	1	0	0	X	0	0	0	1	1	1	6
9	Purity of product	2	2	2	2	2	0	2	2	x	2	2	1	2	2	23
10	Safety	1	2	2	2	2	1	1	2	0	x	1	1	2	2	19
11	Operability	0	2	1	1	1	1	2	2	0	1	x	1	2	1	15
12	Environment	1	2	1	1	2	1	1	1	1	1	1	x	2	2	17
13	Proven Technology	0	1	1	0	1	1	0	1	0	0	0	0	x	0	5
14	Number of Unit operations	0	1	0	1	2	0	0	1	0	0	1	0	0	x	6

With the obtained total amount of points for each criterion, a ranking was made and evaluated. Some criteria were put together and formed a new criterion, because the original three were too similar. In this case "reliability of the process", "operability" (ease of operation) and the use of "proven technology" are put together in the criterion "complexity of the process".
From the initial 14 criteria nine were kept. Besides the above "glucose consumption" was omitted because it was considered not important as glucose consumption is almost the same for all processes. Furthermore "environment" was left out because at this point it is not quantifiable. "Waste streams" instead are quantifiable, and in such a way that the amount of waste streams and the concentrations of its content can be analysed quickly.

[11] Used by Schott Glass Malaysia

The final 9 criteria were given an impact factor, after a short discussion with the results from the above table in mind. One exception made was for the number of units operations, which we considered more important than the outcome of the first step showed. This was because one of the main advantages of ISPR is the reduction of number of process units, which are all capital costs. Another exception that has been made is that "safety" was awarded a low impact factor in general, because the process that will be designed will be safe, otherwise it will not be used.

The below table gives the impact factors which are used to weigh the different processes (see Paragraph 2.1)

Table 12.3: Importance factor of the selection criteria

Criterion	Impact factor
Purity of product (e.e.)	5
Yield Product on substrate	4
Equipment costs	4
Complexity	3
Biomass costs	3
Number of unit operations	3
Waste streams	2
Utility costs	2
Safety	1

It can be said that purity of the product, including enantiomeric excess, is a knockout criterion for this process. If a process gives a low ranking of this, even though it still has a high total score, it will not be used.

For the different processes, which can be found in Appendix 12.5, a rating was made by giving values of ++, +, 0, - or - - for each criterion, ++ being very positive. The ISPR processes have been evaluated separately for the base case processes. Finally this rating has also been used for a fermentor and an immobilized bed reactor, comparing the two reactors.
Each of the team members has done this, giving the basis for the final results given in Paragraph 2.1. The complete list can be found in Appendix 12.6.

Although each of the team members used his own subjective way of rating the processes in the end something can be said about the results of this rating methods, because every team member did the rating consistently. The difference in total points per process tells us something about the future possibilities of using this process.
As can be seen in paragraph 2.1 three processes for ISPR were selected to have potential. Furthermore it can be said that the fermentor seems more favourable to use than immobilized baker's yeast, but a more detailed investigation is necessary.

12.2 Plant visit to DSM

Here the plant visit to DSM Venlo is also described because it gave a new and practical insight in a MPP.
During the visit at DSM we had at first a 30 minutes discussion with a process engineer and a chemist about the possibilities of running our process in a MPP.
Here they explained that at the DSM Venlo site, they used at the T6 MPP a train system, meaning that all vessels had the same capacity. E.g. a 4 m^3 reactor, with a 4 m^3 extractor a 4 m^3 crystallizer and a 4 m^3 filter press. They normally have a "train" of vessels, which have the same size. If a unit operation from another train is needed, this would implicate that this whole train couldn't be used. At the DSM T6 plant 3 trains existed: two 4m^3 and one 10 m^3 train. Besides the trains some technical parameters of units were discussed and compared what was used at the DSM site.

During the plant visit it was seen that these train are operated downwards, meaning that the reactor would be at a higher level then the crystallizer, using gravity as much as possible as a driving force for flow. The final packaging would be on the ground level. The visit gave a clear understanding about how a process is actually operated and some good ideas about sizes and operating conditions of unit operations.

The information gathered during this visit can be read in Appendix 12.7, where it is present point wise.

12.3 Evaluation of plant visit

During the evaluation session of the plant visit to DSM a method was used where the process of DSM was evaluated bottoms-up, starting with the exit streams and then going backwards in the process. In the DSM plant the exit streams were placed on ground level and the incoming streams were at the top floor of the building. During this session, the idea came up to use one vessel for multiple unit operations, because the conditions of each unit operation weren't that far apart. Also it was discussed that if all unit operations had to be placed vertically above each other the plant would be quite high, having 5 to 6 levels, while the DSM plant only had 3 levels.

One of the other things that were changed after this visit was the usage of equally sized units in the Base case as much as possible. Another thing that gave thoughts was the amount of Base case batches in the reactor (being around 176), which would implicate many handling steps in the 3 months of running the process and thus would require extra operators.

13 Conclusions and Recommendations

In this last chapter the conclusions on the design of both cases will first be presented separately. Recommendations to improve the design and lower the uncertainties will be made for both cases. Then both processes will be compared and the main differences will be presented. This will lead to a general recommendation for the production of DOIP.

13.1 Conclusions Base case

Strengths and weaknesses
An obvious strength of the Base case is that the design makes use of proven technology. There is much know-how and the processes are widely applied in large-scale operations in industry. This all together makes the Base case a reliable process with respect to the individual operations of the equipment.
Since the process times of the batches are relatively small, the design has the ability for dealing with batch failures. For example, the fermentation batches are relatively short, so when one batch fails the impact on production will not be disastrous. This ability of the process is considered to be a strength of the Base case, as a batch failure has fewer consequences on the overall performance and ultimately the revenues. The consequence of this feature and the complicated sequence of batches is that the overall operability of the process is not straightforward and that there is a significant chance that errors or fouling could occur during and between batch operations. Consequently, more operators are required in order to monitor and troubleshoot problems when necessary, this complexity is a weakness of the design.
A further weakness of the design is the relative large amount of waste. In the procedure of extraction a significant amount of solvent dissolves in the aqueous solution, which finally needs to be disposed to the WWTP. Also a purge has to be installed to prevent ACT from crystallizing, which has a considerable contribution to the overall waste stream. Overall the usage of solvent is a major cost factor in the Base case with its accompanying waste stream.

Evaluation on choices
The choice for the implementation of immobilized biomass, as the biocatalyst in the Base case is a well-considered one. The high volumetric productivity and the short batch process time is a very attractive feature for the fermentation, as it reduces the equipment size. Further the immobilized biomass implies that filtration with an ultrafilter is not required in the downstream.
As stated earlier in this report, separation in the downstream with adsorption is from an economical point of view more interesting than solvent extraction. The design is based on the latter option, because of educational value of the CPD project. Implementation of adsorption in the downstream would give lower utility costs, as there is less solvent loss. However, an additional vessel in comparison with the extraction case would be required.
The choice for ethyl acetate as a solvent in the extraction was based on the article of Leuenberger [17]. No decent selection of solvent was possible, because of the lack of information and time to determine solubilities for other solvents and ultimately distribution coefficients of the relevant reaction components. The choice for ethyl acetate appeared not to be desirable, since the solubility of this solvent in water is quite high giving ultimately significant wastes. On the other hand, this choice implies that the design is reliable and leaves some room for improvement.
In the downstream the different processes are integrated by the introduction of the Multi-Purpose Vessel. This piece of equipment is able to execute a large part of the

processes in the downstream, because of the times and the scheduling of the batch operations. This process integration implies that the investment in equipment is reduced. On the other hand it leads to an increased complexity and therefore reduced operability. From an economical point of view the process integration outweighs the increase of complexity.

13.2 Recommendations Base case

Improvements
There is some room for improvements in the designed Base case with extraction. Firstly, the downstream can be improved by selecting a different organic solvent. Ethyl acetate appeared to be unfavourable due to its high solubility in water. Further research may point out a solvent with more favourable properties, as a lower solubility in water and a higher solubility of DOIP in this particular solvent. Both properties would improve the yield of the downstream.
Improvements on yield are also possible in the fermentation section. The implementation of a different biocatalyst with better reaction kinetics, could give a higher productivity and ultimately a higher yield. Also on this matter further research is required.
Finally, a reduction of the usage of process water can improve the design. Washing of the bubble column after each fermentation batch may be redundant, as less frequent washing could also recover the product from the bubble column without changing the reaction kinetics. However, this needs further investigation with respect to the amount of reaction components that remain in the column after a fermentation batch, as it may influence the reaction kinetics of the subsequent batches.
Processing extraction in the downstream of the Base case is, as said before, from an economical point of view not the most attractive option, implementation of adsorption improves the design considerably. In the procedure of adsorption there is no contact between the aqueous phase and the organic phase, so no considerations are required in the solvent selection with respect to the solubility in water. This implies that a cheaper solvent, such as methanol, can be used. Consequently this reduces the solvent loss significantly, which leads to savings on waste. Since there is little information on the mass transfers of the relevant components during the adsorption, further research is desired on this matter in order to have a reliable design.

Uncertainties
In the design of the Base case a few uncertainties are encountered. In the first place there was no data available about the kinetics of crystallization of DOIP in ethyl acetate. From the literature a crystallization time of 12 hours is taken in the design. Research on the crystallization would give a more accurate design.
Furthermore, there was no data available on the solubilities of the components DOIP, OIP and ACT in an organic solvent. Measurements of the solubility of DOIP in ethyl acetate were done, with which the solubilities of OIP and ACT in ethyl acetate were estimated. Subsequently the distribution coefficients between ethyl acetate and water were calculated for the components. However, it is strongly recommended to do more measurements on the relevant properties in order to improve the reliability of solubilities and distribution coefficients and thereby the extraction design.
The downstream of the Base case is simulated in SuperPro Designer® v5.1 for a steady state situation. This does not represent the actual processing, since there is a start up in the downstream with fresh solvent and it takes a number of batches to approach steady state. In order to simulate the succeeding batches more accurately,

sufficient experience and knowledge is needed about this software. Nevertheless, the steady state approach is a reasonable approximation of the real situation.

13.3 Conclusions ISPR

A full-scale production system of the ISPR was successfully designed. The design is both technical and economical feasible.

Strengths and weaknesses
As OIP is an expensive raw material, prevention of yield loss is very important. With an overall yield of 91% on OIP, the ISPR system performs very well. Therefore the major strength of the ISPR process is the high yield of DOIP on OIP. Main reasons for this high yield are operation at the following conditions: inhibition of the production of actinol, a long batch time and prevention of water build-up in the system. The ISPR also produces only small amounts of waste and the process can even be called clean, since only air and a very limited amount of water that is easily treated come out of the system. Another strong point of the ISPR is the inherently advantage of in-situ product removal, the small amount of operating units in the process. Only two vessels and three filters are needed. There is no need for intermediate storage and no complicated purification of the crystals is needed.
One of the problems for the ISPR case is that it is a new technique and that it is not that often used in the fine chemical industry. The technique has not been proven to work on full scale. Implementing this technique means therefore taking a risk, even though it has high benefits. Also a weakness in the design is the fermentor, it is quite large and costly compared to the other units. The installation cost and the stirring cost of this fermentor are both relatively high.

Evaluation on choices
Most choices on the ISPR have worked out fine. The ultrafilter instead of a membrane does not lead to high costs; the fermentor does not lead to yield losses of DOIP into the air. Cooling crystallization as such also worked out fine, only the choice for a scraper is considered to be not optimal. The scraper uses a lot of energy and leads to extra investments. More data on the meta-stability of the DOIP solution could lead to a better crystallizer without the need of scraper.

13.4 Recommendations ISPR

Improvements
The ISPR can still be improved further in several ways. Firstly, by finding a way to crystallize without using a scraper of which one is mentioned above. Also it is interesting to look whether the fermentation can be improved. This can be done by improving the active biomass, for example the usage of the yeast of the Base case (Saccharomyces rouxii), which is more active, but also more expensive. For now however it is not known whether this yeast would work also in the ISPR setting. Using another type of reactor like a bubble column or an airlift reactor could also lower the cost of fermentation. Controls of the stirrer with an oxygen sensor can minimize the electricity needed for stirring.
It could still be sensible to try to improve the yield of DOIP on OIP even further, for example by looking for easy methods of getting the remaining DOIP at the end of the batch out of the water.

Uncertainties
The design is based on a lot of different sources of information. In most cases adequate information is given, but the reliability of the information needs to be increased in order to construct the process. Another thing that needs to be improved is the model for crystallization; now a really simple model was assumed, due to the lack of more detailed information. Also the ultrafilter should be tested for its behaviour at higher fluxes.
In terms of the operation conditions, it was suspected that the ISPR could function for about 370 hours. There is however no experimental data to support this choice other than common practice, so it should be investigated how long the ISPR can operate without losing activity. This number is essential for the yield and the economic evaluation.

13.5 General conclusions

The problem statement of our conceptual process design was: *The comparison of the conventional batch and new integrated fermentation-crystallization process.* As both processes were successfully designed, their performance can be compared economically and technically.

Technical comparison
From a technical perspective it can be seen that the Base case uses a more conventional and thus more proven technique. The process concept used in the Base case is more likely to be found in industry and industry has for this reason probably a preference for using this kind of technique. However, the ISPR does have the best overall technical performance, it has a higher yield and produces far less waste than the Base case. The process setup of the ISPR is also much simpler as can be seen from flow sheets and the batch cycle diagrams. So although ISPR is a new technique, it performs significantly better and no insurmountable technical reasons were found for not implementing ISPR technique.

Economic comparison
For the economical comparison first grass-roots calculations were made for both processes, then all numbers were critically reviewed and reconsidered. A third process, the Base case with an adsorber was also economically evaluated.
It turned out that all the processes had about the same investment costs. The operating costs were however completely different for the three processes. The operating costs were mainly determined by the yield of DOIP on OIP and the usage of solvents. Since the ISPR had the highest yield and it uses no solvent, it had the lowest operating costs and the best overall economic performance. The Base case with adsorber then had the lowest operating costs. This has multiple reasons. The adsorber uses cheap methanol instead of more expensive ethyl acetate, also it uses less solvent, lowering the costs of fresh solvent and also the costs of waste treatment.

13.6 General recommendations

As stated above, the ISPR is considered both technically and economically superior to the Base case. It is therefore recommended to construct an ISPR process for the production of DOIP. Of course it is in that case also recommended to carefully look at the recommendation for the ISPR giv en in paragraph 13.4. Because in order to successfully implement this process more experiments need to be done.

List of Symbols

Symbol	Description	unit
A,B	Constants for liquid density	[g/l], [1/K]
A, B, C, D	thermodynamic constants	Not applicable
a,b,c,d	thermodynamic constants	Not applicable
A	surface area	m^2
A	Area of dialysis unit	m^2
A_{GS}	empirical coefficient	-
A_H	empirical coefficient	-
C	concentration	mmol/L; kg/m^3
C^*	inhibition concentration	mmol/L
c	cohesive energy density	J/m^3
Δc_{lm}	log mean driving force	mmol/L
C_P	specific heat constant	J/(mol K)
D	diffusion coefficient	m^2/s
d	diameter	m
D_{bc}	bubble column diameter	m
D_c	diffusion coefficient in water	m^2/s
d_c	coil pipe thickness	mm
$D_{e,i}$	effective diffusivity	m^2/s
d_h	Hydrolic diameter	m
d_m	Molecular diameter	m
d_p	Pore diameter	m
F	Raffinate weight	kg
Fl_G	gas throughput number	-
Fr	Froude number	-
H	height	m
h	heat transfer coefficient	$W/(m^2 K)$
ΔH_f	enthalpy of formation	kJ/mol
ΔH_m	enthalpy of melting	kJ/mol
K	partition coefficient	-
K	overall mass transfer resistance	m/s
k	reaction constant	$L^2/(mmol\ gdw\ h)$
k	scaling factor	-
k_i	mass transfer coefficient	m/s
K_D	molar based distribution coefficient	-
kL	Mass transfer coefficient	dm/h
k_La	mass transfer coefficient times specific area	1/s
K_M	the half-velocity constant, Michaelis-Menten constant	mmol/L
$K_{r,i}$	restrictive factor	-
L	length	m
ℓ_{ij}	binary parameter binary mixtures	-
l_m	wet thickness	
m_D	mass based distribution coefficient	-
M,m	mass	kg
M_W	molecular weight	g/mol

Symbol	Description	unit
N	impeller speed at large scale ISPR fermentor	1/s
N	number of stages	-
n	molar flow	mmol/h
n	number of years	year
n	impeller speed at small scale ISPR fermentor	1/s
n	order of substrate inhibition	-
N_{AS}	aeration number	-
N_{GF}	gas flow number	-
Nu	Nusselt number	-
P	pressure	bar
P	power added	J/s
P_c	critical pressure	bar
$P_{m,i}$	solute permeability	m^2/s
Po	Power number	-
Pr	Prandtl numer	-
Q	heat	W
q^{max}	maximum specific rate constant	mmol/(gdw h)
r	volumetric reaction rate	mmol/(L h)
r_v	volumetric reaction rate	mmol/(L h)
r'	DCFRR	%
R	gas constant	J/(mol K)
R_Y	numerical coefficient	-
Re	Reynolds number	-
RING	number of rings in molecule	-
S	Solvent weight	kg
Sc	Schmidt number	-
ΔS_f	entropy of formation	kJ/(mol K)
$\Delta S_m{}^{tot}$	total entropy of melting	kJ/(mol K)
Sh_a	Sherwood number based on k_La	-
SP2	number of non-ring sp^2 configurations in molecule	-
SP3	number of non-ring sp^3 configurations in molecule	-
T	temperature	K, °C
T	time	s
T_c	temperature cooling medium	K
T_m	melting temperature	K
U	Overall heat transfer coefficient	$W/(m^2 K)$
U	Energy	J
ΔU	energy isothermal evaporization liquid	J/mol
u_t	superficial velocity cooling medium	m/s
V	volume	m^3
V_c	critical volume	m^3/mol
V^L	liquid molar volume	m^3/mol
V_m	liquid molar volume	$cm^3/g\text{-}mol$
v_r	characteristic rise velocity	m/s
v_s	superficial gas velocity	m/s
We	Weber	-
x	molecular fraction	-
x	empirical coefficient	-
y	empirical coefficient	-

Symbol	Description	unit
%wt	weight percentage	%
z	coordination number	-
Z_c	critical compressibility factor	-
Greek		
β	proportionality factor	-
γ	activity coefficient	-
Δ	increment contribution	-
Δ	impeller diameter at large scale ISPR	m
δ	impeller diameter at small scale ISPR	m
ε	Extraction factor	-
ε	gas hold up	%
ε	porosity	-
ϕ	molecular flexibility number	-
ϕ	flow	m^3/h, kg/h
θ	ratio boiling and critical temperature	-
Λ	total energy parameter	-
λ	energy parameter interaction molecules	-
λ	thermal conductivity	W/(m K)
μ	viscosity	Pa*s
Π	Simplex	-
ρ	density	g/l
σ	rotational symmetry number	-
σ	surface tension	N/m
φ	Thiele-modulus	-
τ	number of torsional angles	-
τ	Tortuosity	-
Φ	volume fraction	-
Φ	Weisz Prater number	-
Φ_m	mass flow	kg/h
Φ_V	volumetric flow	m^3/h
η	viscosity	Pa.s
η	effectivity	-
ω	acentric factor	-

Table 0.1: Subscript list

Subscript	Description
a	ambient
ACT	(4S, 6R)-actinol
aeration	aeration
air	air
agitator	agitator
ave	average
b	boiling point
b	bubble
bc	bubble column
bottom	bottom of the vessel
c	critical
coil	cooling coil

Subscript	Description
cool	cooling medium
crys	crystallizer
crystall	crystallizer
crystals	crystals
crystalliser	crystalliser
DOIP	(6R)-dihydro-oxo-isophorone
EA	ethyl acetate
eff	effective
evap	evaporization
f	fermentor
f	filtrate
feed	feed
ferm	fermentor
i	specie
i	inner coil pipe diameter
i	internal
l, L	liquid
LEL	Lower explosion limit
liq	liquid
m	mass
m	mixing
max	maximum
met	metabolic
metabolic	metabolic
o	oxygen
OIP	4-oxo-isophorone
out	outlet
p	permeate
p	pressure
r	reduced
recycle	recycle
T	temperature
tot	total
uf	ultrafilter
v	vessel
v	volume
v	volumetric
w	water
w	working
wall	wall
x	biomass
0	auxiliary
*	saturation

List of abbreviations

Abbreviation	Description
ACT	(4S,6R)-actinol
APC	Annual production cost
(aq)	dissolved in water
BO	batch operation
BOD	basis of design
(c)	crystal
COD	Chemical oxygen demand
CPD	conceptual process design
CTR	carbon dioxide transfer rate
DC	Direct costs
DCFRR	discounted cash-flow rate of return
DFC	Direct fixed capital
DOIP	(6R)-dihydro-oxo-isophorone
DOT	Dissolved oxygen tension
DSMZ	Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH
EA	ethyl acetate
e.e.	enantiomeric excess
FC	Fixed costs
F&EI	fire and explosion index
HAZOP	hazard and operability study
HRE	Highest relative error
IC	Indirect costs
ISO	International Organization for Standardization
ISPR	in situ product removal
IT	Total investment costs
LEL	lower explosion limit
(m)	dissolved in methanol
MPP	multi purpose plant
MPV	multi purpose vessel
NCF	Net cash flow
NPV	net present value
OIP	4-oxo-isophorone
OTR	oxygen transfer rate
PCE	Purchased equipment costs
PEG	polyethylene glycol
PFS	process flow sheet
POT	Pay-back time
PPG	polypropylene glycol
ROI	return on investment
ROR	rate of return
SHE	safety, health & environment
TPC	Total Plant Costs
VC	Variable costs
WWTP	Wastewater treatment plant

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