CPD NR 3272
Conceptual Process Design

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

Subject
Process route selection and process design for antidepressant manufacture

Authors	***Telephone***
J.W.H. Briët	06-24936659
S. Driessen	06-14899351
W.P.A. van Houten	06-28559435
M.H. Moonen	-----

Keywords
Antidepressant, Prozac®, fluoxetine, enantiomers, batch, catalysis, tablets, pharmaceutical, patent, generic, market.

Assignment issued: 29-10-01
Report issued : 13-02-02
Appraisal : 05-03-02

Content

Literature

1. David Wong, Frank Bymaster, Eric Engleman, *Prozac, the first selective serotonin uptake inhibitor and an antidepressant drug: 20 years since its first publication*, Life Sciences, Vol. 57, No. 5, pp 411-441, 1995.

2. Business Communications Co., Inc, *RB-130 The Expanding Market for Psychotherapeutic Drugs*, Norwalk, 2000.

3. Molley et al., A*rloxyphenylpropylaminese*, US patent 4314081, 1982.

4. Paul Stark, *Use of fluoxetine as an anti-anxiety agent*, UK patent 2137496A, 1983.

5. Chenevert et al, *Asymmetric synthesis of both enantiomers of fluoxetine via microbiological reduction of ethyl benzoylacetate*, Tetrahedron, Vol. 48, pp 6769-6776, 1992.

6. Scheider, Goergens, *An efficient route to enantiomerically pure antidepressants: tomoxetine, nisoxetine and fluoxetine*, Tetrahedron: Asymmerty, Vol. 3, pp 525-528, 1992

7. W. Miles, E. Fialcowitz, E. Halstead, *Enantioselective synthesis of (S)- and (R)-fluoxetine hydrochloride*, Tetrahedron, Vol. 57, pp 9925-9929, 2001.

8. Mitchell, Koenig, *Synthesis of R- and S-fluoxetine, norfluoxetine and related compounds from styrene oxide*, Synthetic Comm., Vol. 25, pp1231-1238, 1995.

9. J. Young, J. Baberich, *Method for treating migraine headaches using optically pure (S)-fluoxetine*, US patent 5589511, 1996.

10. Instructions for use of Prozac® by Eli Lilly.

11. J. Douglas, *Conceptual Design of Chemical Processes*, pp 107-110, 1995.

12. www.acros.be

13. www.sigma-aldrich.com

14. *Life after Prozac*, www.imsglobal.com/insight/news_story/0009/news_story_000925.htm

15. S. Rose, *Fluoxetine pharmaceutical formulationsi*, US patent 5747068, 1998.

16. www.fda.com

17. Sarnyai-Z; Sibille-EL; Pavlides-C; Fenster-RJ; McEwen-BS; Toth-M, *Impaired hippocampal-dependent learning and functional abnormalities in the hippocampus in mice lacking serotonin (1A) receptors,* Proceedings of the national academy of science of the USA, pp 14731-14736, 2000.

18. Den-Boer-JA, *Social anxiety disorder/social phobia: Epidemiology, diagnosis, neurobiology, and treatment,* Comprehensive Psychiatry, pp 405-415, 2000.

19. R. Weinekotter, H. Gericke, *Mixing of solids,* pp 63-85, 2000.

20. J. Boekema, M. Broekhof, *Basisboek Marketing*, pp 53-72, 2000.

21. American Home Products Corp., Imines. British Pat. No. 702,985, Jan. 27, 1954; C.A. 49: 5515g (1955).

22. Dr. J. Froelich, *Johnson & Matthey* U.S.A.

23. Dr. U. Hanenfeld, *Organic Chemistry* TU-Delft.

24. Perry and Chilton, Chemical engineering handbook.

25. Chemical Health & Safety, Vol. 3, pp 19-23, 1996.

26. CRC Handbook

Preface

As a part of the chemical technology education at the University of Technology Delft the course Conceptual Product/Process Design has been completed. The authors would like to take this opportunity to thank everyone who has helped with the completion of this project. Special thanks go to:

Dr. Corbeij for providing the starting information regarding the Prozac® medication and application,

Prof. Dr. Sheldon for information on synthesis routes, catalysts and production methods,

Prod Dr. ir. Moulijn for information on catalysts, yield and equipment,

Prof Dr. ir. Vromans for information on industrial applications, drug product formulation and for showing the production and research facilities at Organon Oss,

Ir. Meesters for information on solid mixing,

Drs. Vermaas for help and feedback on the synthesis route and production equipment,

Dr. Hanefeld for information on synthesis routes,

Dr. ir. Gerritsen for information on equipment design,

Dr. ir. De Loos for information about the thermodynamic background,

Drs. Grunwald for help on group psychology.

Furthermore the authors would like to thank all sales representatives of the contacted companies for price quotations of raw chemicals and equipment.

Last but not least the authors would like to thank principal Prof. Dr. ir. Frens, coach Dr. Goosens and Ir. Swinkels for coaching and guidance to help complete the project.

Summary

The goal for the design project is to take advantage of the expiring patent on the production and use of fluoxetine as an antidepressant, which is marketed as Prozac® by Eli Lilly. To accomplish this goal the weaknesses of Prozac® have been analysed. These weaknesses are:

- Many and severe side effects
- No dedication to all end users

The Prozac® antidepressant market can be split into two market segments; an occasional user market for patients suffering from Pre Menstrual Syndrome, Social anxiety disorder etc., and a chronical user market for patients suffering from a chronical depression disease.

The drug substance in Prozac® is racemic fluoxetine. The difference in half-life times of the two enantiomers and the presence of an active metabolite of S-fluoxetine, S-norfluoxetine, suggests the following use of drug substances.

R-fluoxetine is used as the drug substance for the occasional “mood brightening” tablet and S-norfluoxetine is used as the drug substance for the chronical antidepressant tablet. The use of the drug substances mentioned above make the designed products more dedicated to the end user. A major advantage of the designed products over Prozac® is the lower amount and lower severity of the present side effects. Both drug products are presented in a dispersible tablet, which makes it applicable even for patient having problem with swallowing solids. The drug products are packed such that an easy to use and hard to forget product is achieved. Therefore patients will finish their treatment more often, which makes to product more successful.

The production of S-norfluoxetine and R-fluoxetine are based on a high-grade chemical, respectively optical pure R- and S-styrene oxide. The use of these chemicals enables the production of optical pure R-fluoxetine and S-norfluoxetine without the difficulties of optical purification. To total yield of the chosen production method is 77 % for R-fluoxetine and 81 % for S-norfluoxetine. The chosen formulation of the dispersible tablets enables direct compression of the components into a tablet.

Both products are sold at a price of € 1.50 per tablet, which is significantly lower than the Prozac® price and lower than the expected generic fluoxetine price. Assuming a market share of 5% of the current Prozac® market, a sales and production of 250 million tablets is expected. The expected sales result in an after tax profit of € 194 million per year.

The designed product is medically superior to Prozac®, has lower amounts and lower severity of side effect, it is cheaper than Prozac® and it is easier to use. Therefore ultimately the designed product will conquer the Prozac® market.

1. Introduction

Depressive disorders are common, affecting millions of people world wide each year. These disorders are associated with significant personal and social burden. Treatments for depressive disorders have dramatically changed over the past decades, and the ease and effectiveness of the Selective Serotonin Re-uptake Inhibitors (SSRI's) have made medication the preferred treatment for many, especially those treated in primary care systems. It is generally agreed that SSRI's are as efficacious as tricyclic antidepressants (TCA's) in terms of treating the acute-phase symptoms of depressive disorders while avoiding many of the side effects that result in poor outcomes attendant upon premature discontinuation of medication. [1]

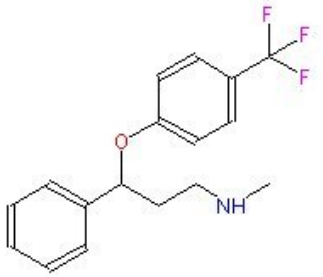


Figure 1.1 Molecular structure of fluoxetine

Fluoxetine (Figure 1.1) is a SSRI, which is marketed under the name Prozac® by Eli Lilly. The patent for this chemical used as antidepressant is expiring in 2003. The leading company in the psychotherapeutic drug sector is Eli Lilly, which holds about 30% of the market with two products - the antidepressant Prozac® and the antipsychotic Zyprexa. Other leading competitors in the market are Pfizer, SmithKline Beecham, Novartis, Johnson & Johnson and Pharmacia & Upjohn.

The market for psychotherapeutic drugs represents the third largest therapeutic category in terms of worldwide sales and is estimated at just under €21 billion in 2000. This market is expected to grow at an AAGR (average annual growth rate) of 13% during the 5-year forecast period to reach nearly €38 billion by 2005. [2]

The object of this project was to design a product that can compete with the current anti-depressant Prozac® marketed by Eli Lilly. This was done by analyzing the weaknesses of Prozac®. Two major disadvantages of Prozac® were found. The different types of depression are all treated with only one product. Furthermore Prozac® has a rather large amount of side effects. The designed products attempt to better serve the different depression-types and, although hard to predict, has less side effects.

2. Process and Product options and selection

Each member of the group has individually come up with an alternative and a production process for this alternative. The alternatives will be compared with each other and the current situation. The best aspects from the different alternatives will be combined. This results into the basis of design.

2.1 Alternatives

Current Situation: Prozac® by Eli Lilly

Currently Eli Lilly markets Prozac® as a racemic mixture of R- and S-fluoxetine [4]. This formula has been very successful in the past decade.

Production method

Beta-dimethylaminopropiophenone hydrochloride is reacted with NaOH to give the free base. Beta-dimethylaminopropiophenone is then reacted in two steps with diborane to give N,N-dimethyl-3-phenyl-3 hydroxypropylamine, which takes 24 hours. This is then reacted with thionylchloride at reflux conditions for 5 hours to give N,N-dimethyl-3-phenyl-3-chloropropylamine. This is then reacted with trifluoro-p-cresol in a NaOH and methanol solution for 5 days to give fluoxetine. [3] The most costly base chemicals are:

Beta-dimethylaminopropiophenone hydrochloride: = € 250,-/mol
Trifluoro-p-cresol: = € 150,-/mol

Summary

Table 2.1 Summary Prozac® method

Number of reaction steps	5
Tbatch	120 hrs
Chemical cost	€ 400/mol
Yield	61%
Flexibility	0
Estimated variables	0

2.1.1 Alternative 1: R-fluoxetine J.W. Briët

R-fluoxetine will be marketed as a better less damaging antidepressant to compete with the R/S-fluoxetine of Prozac®.

The two major differences between R-fluoxetine and S-fluoxetine are:

1. The major metabolite of R-fluoxetine, R-norfluoxetine is a 20-fold less active SSRI than R-fluoxetine. Whereas the major metabolite of S-fluoxetine, S-norfluoxetine, is an equal active SSRI as S-fluoxetine.
2. The half-life time of R-fluoxetine (1-4 days) is 4-fold smaller than the half-life time of S-fluoxetine (4-16 days).

The use of R-fluoxetine as the active component of an antidepressant pill may offer considerable therapeutic flexibility. Such a pill might be more useful for treating the elderly. The treatment of short-term depression like premenstrual syndrome (PMS) might be more effective with a R-fluoxetine based antidepressant.

Production method

The production method used to produce R-fluoxetine is based on the reaction route reported by Chenevert.[5]

The enzyme used is Beauveria sulferescens. After that reduction with $LiAlH_4$, the formed diol is then treated with methanesulfonyl chloride in the presence of triethylamine, leading to the monomesylate. This reacted under Mitsunobu conditions triphenylphosphine, diethyl azodicarboxylate) with trifluoro-p-cresol. This is treated with an excess of 40% aqueous methylamine in THF in a pressure tube at 70 C followed by acidification with HCl to give R-fluoxetine. The most costly base chemicals are:

Ethyl Benzoylacetate = € 100,- /mol
Trifluoro-p-cresol = € 150,-/mol

Summary

Table 2.2 Summary alternative1

Number of reaction steps	5
Tbatch	120 hrs
Chemical cost	€ 250/mol
Yield	33%
Flexibility	2
Estimated variables	0

2.1.2 Alternative 2: R- and S-fluoxetine Pure W.P.A. van Houten

Both R-fluoxetine and S-fluoxetine will be marketed. A R-fluoxetine based pill for the short-term user and a S-fluoxetine based pill for the chronical user.

This idea is based on the following aspects:

1. R-fluoxetine and S-fluoxetine are equally active SSRI's.
2. The major metabolite of R-fluoxetine, R-norfluoxetine, is 20-fold less active than the mother drug. Whereas the major metabolite of S-fluoxetine, S-norfluoxetine, is equally active as the mother drug.
3. R-fluoxetine has a 4-fold smaller half-life time than S-fluoxetine has.

Therefore a R-fluoxetine based antidepressant can be used for short-term use. Less complications and side effects can be expected because of the lower amount of drug substance in one antidepressant pill.

A S-fluoxetine based antidepressant can be used for chronical use. Less drug substance can be used because of the longer half-life time of S-fluoxetine. Because of this, fewer side effects can be expected. Only one enantiomer is used, therefore only a half of the metabolites are present in the body. This also leads to the expectation of fewer side effects.

Production method

The production method to produce both R-fluoxetine and S-fluoxetine is based on the reaction route reported by Schneider and Goergens [6].

3-Chloro-1-phenyl-1-propanone is first reduced to form the corresponding alcohol. R/S 1-phenyl, 3-chloropropanol is then converted into its corresponding chloroacetate. This is selectively converted in the presence of the lipase of *Pseudomonas fluorescence* into R-1-phenyl, 3-chloropropanol. This reaction terminates after 50% conversion (all R enantiomer of the chloroacetate). The resulting mixture is easily separated due to substantial differences in boiling point. The remaining S-enantiomer is converted into S-1-phenyl, 3-chloropropanol by saponification (K_2CO_3/MeOH). No further purification was required. The R- and S- enantiomers were at 97.3% and >99% purity respectively.

R- and S- 1-phenyl, 3-chloropropanol are converted into the corresponding amino alcohol by reaction with aqueous methylamine via NaI assisted nucleophilic substitution. Yield approximately 95%. The amino alcohol is converted into the alkoxide (NaH/DMA) followed by reaction with 4-chlorotrifuoromethylbenzene produces chiral pure fluoxetine as free base. The reaction with gaseous HCL followed by recrystallisation in hexane/ethyl acetate results in chiral pure fluoxetine hydrochloride.

The most costly base chemicals are:

1-phenyl,-3-chloropropanol = € 205,-/mol

Summary

Table 2.3 Summary of alternative 2

Number of reaction steps	8
Tbatch	1-5 days
Chemical cost	€ 205/mol
Yield	44%-74%
Flexibility	2
Estimated variables	5 (10)

2.1.3 Alternative 3: Production of (S)- and (R)-fluoxetine S. Driessen

Both R-fluoxetine and S-fluoxetine will be marketed. A R-fluoxetine based pill for the short-term user and a S-fluoxetine based pill for the chronical user.

For the chronic users of antidepressants the (S)-enantiomer can be used, due to its lengthy half-life time. This can result in less frequent use of the antidepressant. For the short-term users of antidepressant the (R)-enantiomers would be more qualified. This enantiomer has a shorter half-life and a less potent metabolite. This product can create a new market for occasional antidepressant user, as a quick mental booster.

Production method

The production method for the production of both S-fluoxetine and R-fluoxetine was based on the reaction route reported by Miles, Fialcowitz and Halstead.[7]

The synthesis of (S)-fluoxetine hydrochloride begins with the asymmetric carbonyl-ene reaction of benzaldehyde with 3-methylene-2,3-dihydrofuran catalyzed by $Ti[OCH(CH_3)_2]_4$/(S)-BINOL to give (S)-2-(3-furyl)-1-phenl-1-ethanol (2) in 90% yield and 95% ee. In five steps, alcohol 2 was converted into (S)-fluoxetine hydrochloride (97% ee and 56% overall yield from benzaldehyde). (R)-fluoxetine hydrochloride was prepared by the same sequence except that $Ti[OCH(CH_3)_2]_4$/(R)-BINOL was used in the first reaction to give the enantiomer of 2. This production method makes use of 4 Å sieves, which makes it difficult industrial applicable. The most costly base chemicals are:

3-methylene-2,3-dihydrofuran = € 500,-/mol
Trifluoro-p-cresol = € 150,-/mol

Summary

Table 2.4 Summary of alternative 3

Number of reaction steps	6
Tbatch	21 hrs
Chemical cost	€ 400 - 650,-/mol
Yield	56%
Flexibility	2
Estimated variables	1 (9)

This production method is difficult applicable on industrial scale due to use of 4 Å sieves.

2.1.4 Alternative 4: Styrene oxide to fluoxetine M.H. Moonen

R-fluoxetine and S-fluoxetine will be marketed. R-fluoxetine will be used for the short-term user and S-fluoxetine for the chronical user.

The choice for these products are based on the following arguments:

1. S-fluoxetine is equally active as R-fluoxetine.
2. R-fluoxetine has a 4-fold smaller half-life time than S-fluoxetine.
3. The major metabolite of R-fluoxetine, R-norfluoxetine, is 20-fold less active than the major metabolite of S-fluoxetine, S-norfluoxetine.

R-fluoxetine is best suitable for the production of a short-term antidepressant pill. The expected fewer side effects can be explained by the shorter residence time in the body and the lower amount of drug substance.

S-fluoxetine is best suitable for use in a long-term antidepressant pill. Fewer side effects can be expected because of the use of only S-fluoxetine. This combined with the lower amount of drug substance needed for a certain performance leads to a more user-friendly antidepressant pill.

Production method

The production mechanism used is based on the reaction mechanism reported by Mitchell and Koenig [8]

Starting with (R)-styrene oxide (S)-fluoxetine⊙HCl is produced and starting with S-styrene oxide (R)-fluoxetine⊙HCl is produced. First 3-phenyl-3-hydroxypropanenitrile is formed by treating (R)-Styrene oxide with acetone cyanohydrine in the presence of triethylamine in THF. Reduction of the formed nitrile with borane-methyl sulphide complex provides primary amine. (S)-fluoxetine is prepared by alkoxide formation with sodium hydride in DMSO and arylation with 4-chlorobenzotrifluoride. Methylation of (S)-norfluoxetine after first forming the methyl carbamate followed by subsequent

reduction with LAH. Treatment with gaseous HCl affords the salt. Starting with (S)-styrene oxide (R)-norfluoxetine◌HCl is formed. Methylation of (R)-norfluoxetine after first forming the methyl carbamate followed by subsequent reduction with LAH. Treatment with gaseous HCl affords the salt. The most costly base chemicals are:

R- and S-styrene oxide = € 650,-

Summary

Table 2.5 Summary alternative 4

Number of reaction steps	4
Tbatch	20 hrs
Chemical cost	€ 650/mol
Yield	73%[1], 81%[2]
Flexibility	4
Estimated variables	1 (6)

1 = fluoxetine, 2 = norfluoxetine

2.2 Choice of product and chemical synthesis route

The above listed alternatives have been compared. Multiple selection criteria have been used to select the best combination of alternatives. The first choice that hade to be made was whether to produce both enantiomers of fluoxetine or only one.

2.2.1 Product choice

The current "Prozac®" market can be split into two segments.

- The occasional depression market with illnesses like Pre Menstrual Syndrome (PMS).
- The chronical depression market.

Both segments of the market can be better served with a specific enantiomer of fluoxetine than with Prozac®, which has a racemic mixture of fluoxetine.

Both enantiomers of fluoxetine have antidepressant potency, but have different characteristics. These differences are listed in the following table.

Table 2.6 Characteristics of R- and S-fluoxetine

	R-fluoxetine	S-fluoxetine
Half-life time	1-4 days	4-16 days
Active metabolite	No	Yes
Possible side effects	More	Less

The occasional market is better served with a short residence time of fluoxetine in the subject body. The major metabolite of R-fluoxetine, R-norfluoxetine, has a neglectable antidepressant potency. Therefore the amount of drug substance in the subject body can be better controlled.

The chronical market is better served with a long residence time of fluoxetine in the subject body. The major metabolite of S-fluoxetine, S-norfluoxetine has equal antidepressant potency to its mother drug. This results in a less frequent intake of an antidepressant pill. The use of only S-fluoxetine probably reduces the amount and severity of side effects [9]. As explained in the process choice S-fluoxetine is replaced by S-norfluoxetine.

Therefore a R-fluoxetine based antidepressant pill can better be used for the occasional depression market, and a S-norfluoxetine based antidepressant pill can better be used for the chronical depression market.

2.2.2 Chemical synthesis route

Each alternative provides a different production process for fluoxetine. Each production method has been evaluated on the following:

- Equipment cost ratio, estimated by the number of steps multiplied by the batch cycle time. The cheapest alternative has a ratio of one.
- Base chemical cost ratio, estimated by the base chemical costs divided by the yield. The cheapest alternative has a ratio of one.
- Reagents cost ratio, estimated by the number of reaction steps. The cheapest alternative has a ratio of one.
- Flexibility, the amount chiral pure products that can be produced.
- Accuracy, A reality number of 100% indicates no variables are estimated.

Each of the following criteria has an equal importance.

Table 2.7 Multi criteria analysis of process choice

	Eli Lilly	Alt 1	Alt 2	Alt 3*	Alt 4
Equipment cost	7	7,5	2,5-19	1,5	1
Base chemical cost	1	3,1	1,1-1,8	2,9-4,4	3,1[1]-3,6[2]
Reagents cost	1,25	1,25	2	1,5	1
Flexibility	0	2	2	2	4
Accuracy	100%	100%	50%	89%	95%

* Difficult applicable on industrial scale.
[1] = norfluoxetine, [2] = fluoxetine

Alternative 1 has a yield of only 33%, so alternative 1 is discarded. Alternative 3 is difficult applicable on industrial scale and has high base chemical costs, so alternative 3 is discarded. From the two alternatives left alternative 4 is chosen as the best alternative. The only disadvantage of alternative 4 over alternative 2 is the higher base chemical cost. The lower equipment cost, the lower reagents cost, the higher flexibility and the lower amount of estimated variables make alternative the best choice.

Comparing the chosen alternative to the current production process of Eli Lilly it is concluded that the higher base chemical costs are compensated by the production of a chiral pure product. Furthermore the number of reaction steps, batch cycle time and flexibility are superior to the Eli Lilly process.

While examining this production route it was noted that S-norfluoxetine was an intermediate of S-fluoxetine. The production of S-norfluoxetine requires one reaction step less than the production of S-fluoxetine, which makes it cheaper to produce. S-norfluoxetine is the only active metabolite and has equal antidepressant potency to S-fluoxetine. Furthermore it has less metabolite than S-fluoxetine and thus will probably have fewer side effects. Therefore the decision was made to produce S-norfluoxetine instead of S-fluoxetine.

3. Basis of Design

3.1 Project Definition

The objective of this CPD project is to take advantage of the expiring patent on fluoxetine (Prozac®) by entering the market of antidepressants with a fluoxetine based antidepressant. The designed product must therefore be able to compete with the current already in the market place accepted Prozac® and other generic racemic based fluoxetine antidepressant.

Being able to compete with Prozac® and its generic deratives is the main demand for the newly designed product. This demand automatically includes the following aspects:

- The product must have an antidepressant effect
- The product must comply with medicine legislation

The following wishes apply to the newly designed product:

- The highest possible quality per tablet
- The lowest amount/severity of side effects
- The lowest possible price/performance ratio
- Easiest possible use for end user

3.2. Product and process definition

3.2.1 Specified Product Description

Current product (Prozac®)

Ingredients

The ingredients of the current Prozac® tablet [10] are:

- 20 mg fluoxetine
- Microcrystalline cellulose
- Saccharinenatrium
- Mannitol
- Sorbitol
- Mint Flavoring
- Colloidal Silicon oxide
- Starch
- Natriumstearylfuramate
- Cross-povidon

Presentation

PROZAC® 20 capsules are presented as size 3, green/cream capsules bearing the identicode "Lilly 3105" printed in black ink on both the capsule cap and base. Each capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine. PROZAC® 20 Dispersible tablets are white uncoated elongated scored tablets with an imprint. Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

Dosage

20 mg per day (1 tablet) is the recommended initial dose.

Side effects

Fluoxetine as with most antidepressants can cause nausea, headaches, anxiety, insomnia, drowsiness, and loss of appetite. Fluoxetine has been implicated in serious skin rashes and vasculitis. Increased blood pressure can occur and should be monitored. Seizures have been reported. Life-threatening interactions can occur in combination with MAO inhibitors, such as nardil and parnate. MAO inhibitors and fluoxetine should not be taken together and a waiting period of 14 days between taking these two classes of medications is strongly advised.

Designed Products

The design of the antidepressant is based on two different products. Firstly a short-term R-fluoxetine based antidepressant tablet, and secondly a S-norfluoxetine based long-term antidepressant tablet. These products will separately be described in this chapter.

R-fluoxetine based tablet

Ingredients

The ingredients of the R-fluoxetine based antidepressant tablet are listed below.

- 10 mg R-fluoxetine
- Microcrystalline cellulose
- Saccharinenatrium
- Mannitol
- Sorbitol
- Mint Flavoring
- Colloidal Silicon oxide
- Starch
- Natriumstearylfuramate
- Cross-povidon

Presentation

These ingredients are pressed into a tablet. The tablet will have a white colour, since this is the most accepted tablet color by customers for occasional use.

The tablets must be taken orally and swallowed without chewing on the tablet. They can be dispersed in a fluid, but not necessarily. The tablets can be taken independent of meals.

Dosage

One tablet per day should be sufficient for most patients to have a satisfying responds. Up to two tablets can be taken at once. More tablets should be spread over the day.

Side effects

Special caution should be taken when liver/kidney dysfunction has previously been noted.

Fluoxetine does not have a negative influence on the motoric skills of patients. Nevertheless other side effects of fluoxetine might have an indirect effect on the subject, so caution is required when operating machinery or driving cars.

Fluoxetine should not be used in combination with any MAO blocker. Given the long half-life time of fluoxetine, these MAO blockers should not be used shortly after termination of fluoxetine use.

Advantages

This tablet contains half of the fluoxetine used in Prozac®, because only the wanted enatiomer is used. This makes the tablet cheaper to produce and the possible side effects will also less severe. The half-life time of the R-fluoxetine is shorter than that of S-fluoxetine therefore the drug substance will have a shorter residence time in the body, which also will reduces the side-effects.

S-norfluoxetine base tablet

The S-norfluoxetine based tablet has the same ingredients, dosage and presentation of the R-fluoxetine based tablet, except for some minor changes.

- Instead of the R-fluoxetine this tablets contains 10 mg S-norfluoxetine.
- The tablet will have a blue color, to make a clear distinction between the two different tablets.

Advantages

This tablet contains half of the fluoxetine used in Prozac®, because only the wanted enantiomer is used. This makes the tablet cheaper to produce and the possible side effects will also less severe. In addition the S-enantiomer has less side effects than the R-enantiomer. The concentration of norfluoxetine in the subject body can be better controlled because of the uniformity of half-life times of the drug substance.

Both tablets can be used in combination to achieve the wanted drug substance concentration in the subject body. For example one S-norfluoxetine based tablet a day in combination with the R-fluoxetine based tablet when needed.

3.2.2 Specified process description

The factors that favor fluoxetine production to be a batch operation [11]:

1. Production rate
   - Usually batch if less than $5 \cdot 10^4$ kg/yr
   - Multi-products plants
2. Market forces
   - Short product lifetime
3. Scale-up problems
   - Very long reaction times

Advantages of batch:
- Amenable to direct scale-up from laboratory
- Allow product integrity (each product can be clearly identified)

Batch cycle

The production method can be described by a gantt chart. When each process is performed in a seperate reactor and only one batch cycle is performed at a time, each reactor will have a large idle time. Several methods can be used to minimize the apparatus idle times. The following assumptions have been made.

- Filling, emptying and cleaning of reactor and separator takes 0,5 hours.
- Reaction steps 2-4 can be performed in the same reactor, so R1=R2=R3.
- Separation steps 1-4 can be performed in the same separator, So S1=S2=S3=S4.

Table 3.1 Reactor Times

		Reaction Time (hrs)	Filling, Emptying & Cleaning (hrs)
Reactor 1	R1	18	0.5
Reactor 2	R2	2.5	0.5
Reactor 3	R3	1.5	0.5
Reactor 4	R4	1.5	0.5
Separator 1	S1	1	0.5
Separator 2	S2	1	0.5
Separator 3	S3	1	0.5
Separator 4	S4	1	0.5
Storage Tank	T	*	0.5

* Storage time as long as necessary.

Minimizing the idle time the sequence of batches is as follows.

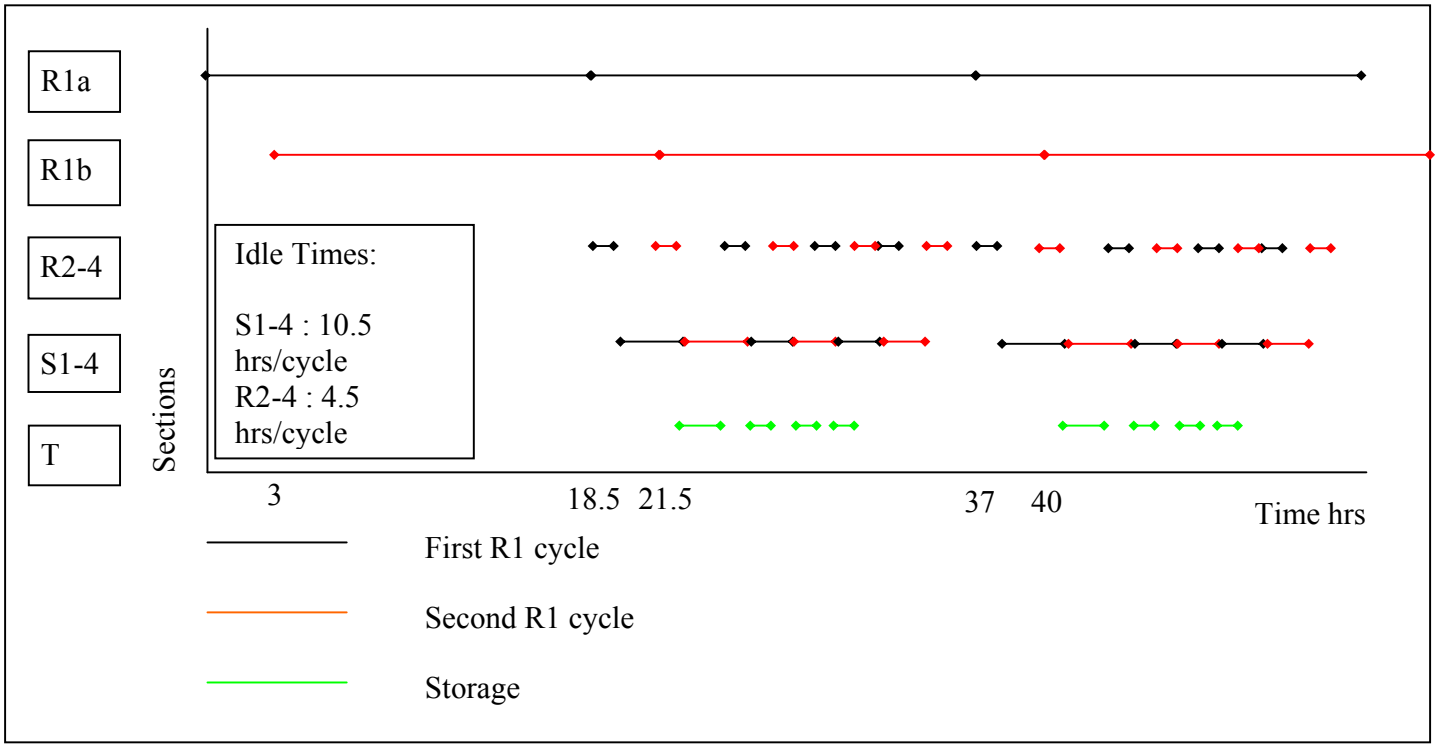
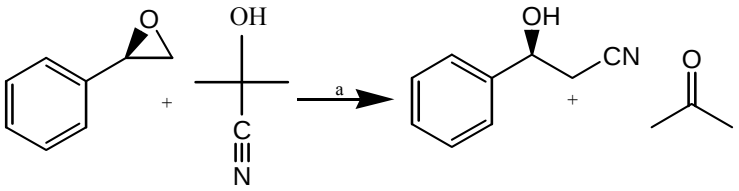


Figure 3.1 Gantt chart

As can be seen in this batch cycle diagram for an optimal use of the process two reactors are being used. These are the reactors for the first reaction step. The other reactions can be done in one in a separate reactor. The separations can be done in one separation unit.

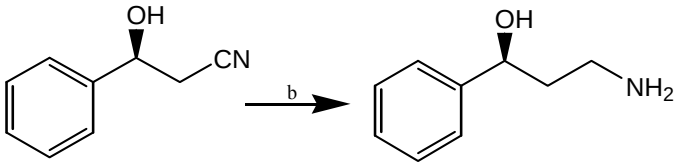
Reaction steps

The chosen synthesis route is reported by Koenig and Mitchell[5] and is shown below.



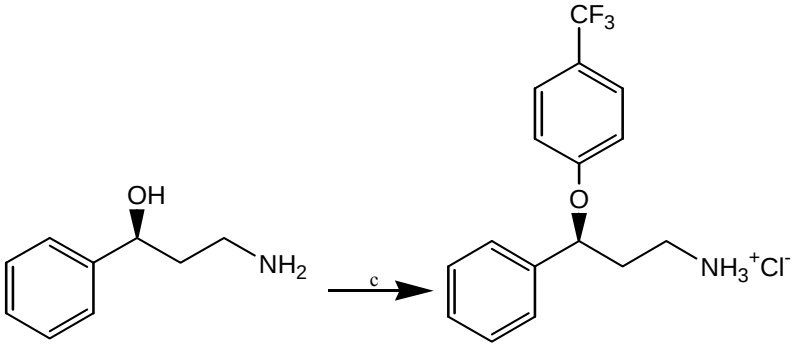
Eq 3.1

a) Step 1: Mixture is refluxed in THF with Et_3N; at 1 atm. and 339 K.



Eq 3.2

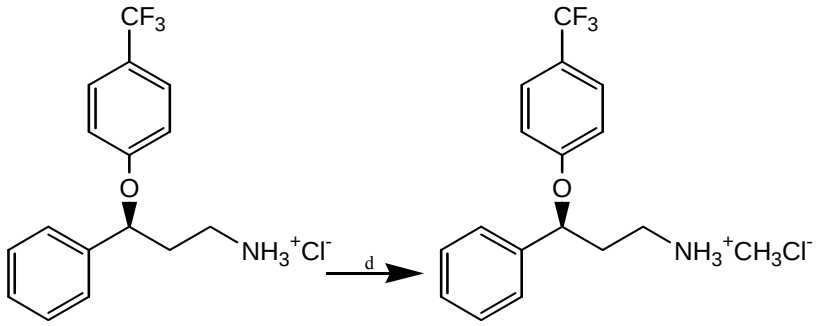
b) Step 2: Mixture is refluxed in Ethanol with 1 wt% catalyst loading of a 5% Pd/C slurry catalyst and 1 or 2 eq HCl; at 4 bar and 328 K.



Eq 3.3

c) Step 3: Mixture is stirred in DMSO with 4-$CLC_6H_4CF_3$ and HCl; at 1 atm.

[5] Mitchell and Koenig (1995), Synthetic Comm., 25(8), 1231-1238



Eq 3.4

d) Step 4: Mixture is refluxed in ethanol with 1 wt% catalyst loading of a 5% Pd/C slurry catalyst and 2 eq formaldehyde; at 4 bar and 323 K.

The complete reaction mechanism is described in appendix I.

Block schemes

The process can be divided into 4 batch processes consisting of a reaction and separation part. The block scheme can be found in appendix II. The incoming streams are coming out of drums and are 298 K and 1 atm.

List of pure components

The list of pure components and properties BOD can be found in appendix III.
Prices were retrieved form Acros [12] and Sigma-Aldrich [13]. Most of the components properties are also retrieved form Acros and Sigma-Aldrich.

Process stream summary

The process stream summary can be found appendix IV.

3.3 Basic Assumptions

3.3.1 Definition of streams

In the figure below al the in- and outgoing streams of the plant are shown.

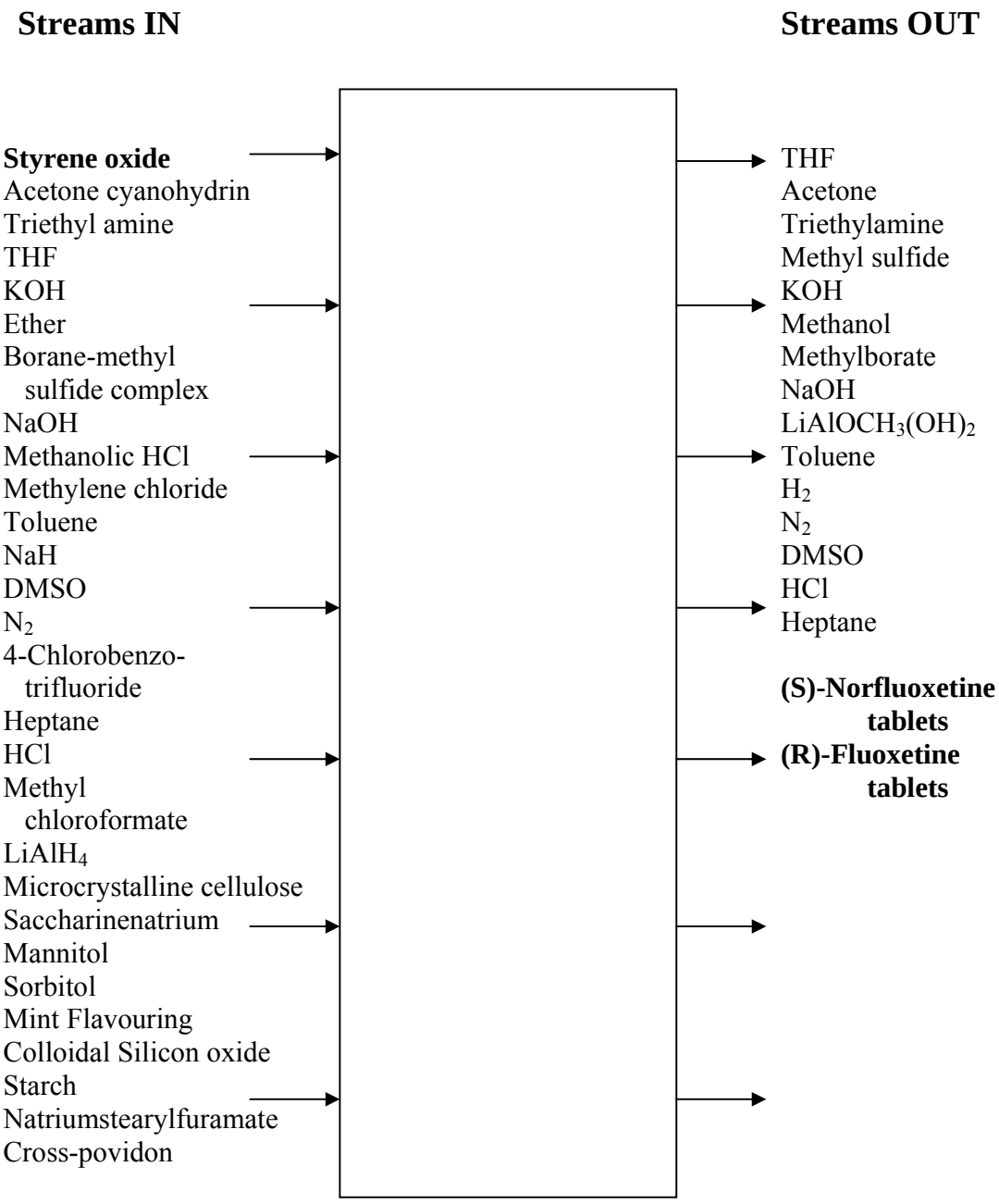


Figure 3. In- and outgoing streams

As seen in the figure several streams are in- and outgoing and can therefore be recycled. This figure can be seen as the battery limit. All the streams in come from outside the factory, and the streams out are either recycled within the battery limit or will be regarded as waste outside the battery limit.

3.3.2 Plant capacity

The plant is designed to produce 2500 kg fluoxetine per year; 1250 kg (S)-norfluoxetine and 1250 kg (R)-fluoxetine. This means 125 million (S)-norfluoxetine tablets and 125 million (R)-fluoxetine tablets.

3.3.3 Plant location

The plant will be placed in Mexico, while North America is the leading market for antidepressants, accounting for 74.6 percent of sales and a 19 percent growth rate. Costs made for transport and distributions are reduced by choosing this location. Labor prices are low in Mexico and legislation is less strict.

3.3.4 Plant Equipment

The plant consists of the following main equipment.

Table 3.2 Equipment summary

Equipment	Number
Reactors	3
Separation units	1
Storage Tank	1

3.4 Economic consideration

As physicians and patients are presented with a choice between generic and brand for the first time, what are the market drivers that will come into play?

According to IMS HEALTH's, the generics market is being positively influenced by the following events:

- Generics are the key cost containment mechanism for multisource drugs in pharmaceutical benefit plans, and the move of patients to a managed care environment is driving generic growth
- Reimbursement and dispensing fees for pharmacists are structured so that it is in the pharmacists' interests to provide a generic product. A number of states oblige pharmacists by law to dispense a generic
- Higher co-payment or reimbursement differentials between generics and brands will increase the rate of generic uptake by patients.

Most doctors are now comfortable with the quality and role of generics in keeping costs down, and accept generic substitution. Patients are also becoming increasingly willing to be given generics, especially in view of co-payment differentials. However, around 10% of patients continue to insist on a branded product.

Based on the world population, percentage of users and daily doses, the world market for fluoxetine can be estimated at 50000 kg per year. Achieving a market share of 5% is the primary goal, which means a production of 1250 kg R-fluoxetine and 1250 kg S-norfluoxetine per year. This will result in approximately 125 million tablets based on R-fluoxetine and 125 million tablets based on S-norfluoxetine.

3.4.1 Margin estimation

The current price for Prozac® is about €2,50 per tablet. To compete with this product the price of the tablets will be around € 2,00 per tablet. With a 50% margin, which is a common margin for the pharmaceutical industry, the costs per tablet are € 1,33. The costs for the base chemicals are around 1/4 of this price; the rest consists of costs for distribution, marketing, etc. This concludes that the maximum cost for base chemicals is € 0,33. The maximum costs for fluoxetine are about 1/3 of the total base chemical costs per tablet. This means that 10 mg fluoxetine has a maximum cost of € 0,10. The production costs per kg fluoxetine should not exceed € 10.000,-, which is about € 3.000,- per mol fluoxetine.

The costs for the base chemicals for the production of fluoxetine are listed below in table 10.

Table 3.3 Prices base chemicals

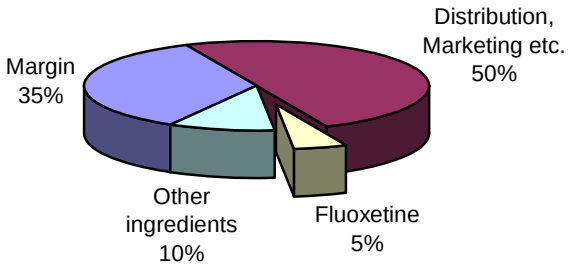
Chemicals	**Price/mol produced fluoxetine (€)**
Enantiopure Styrene oxide	910,00
Acetone cyanohydride	3,35
Triethylamine	3,80
Borane methyl sulfide complex	132,10
Sodiumhydride	3,00
4-chlorobenzotrifluoride	21,40
Lithium aluminum hydride	32,35
Methyl chloroformate	3,50
Total:	1109,50

This concludes that the costs for labour, equipment, packaging, etc. should not exceed € 1900,- per mol fluoxetine produced. This is a reasonable estimation (if not overestimated), therefore the process should be economical feasible.

3.4.2 Competing aspects

Figure 4.1 shows the tablet price build-up for an anti-depressant based tablet.

Figure 3.3 Tablet Price Build-up



As can be seen in this figure fluoxetine only accounts for only 5% of the total price. This means that a cost-reduction of 50% on the production of fluoxetine, the total price for the

tablet will be reduced by only 2.5%. Competing only on price will be insufficient to achieve a market share of about 5%. Other major differences with the current Prozac® will be necessary. One of the main competing aspects of the designed product is therefore not the price but the lower amount severity of the side effects. In addition each of the design products serves its target market better than the current anti-depressant Prozac®.

4. Detailed process design

In this chapter the process route of the BOD is worked out in more detail. Aspects as yield, waste and utilities are also discussed.

4.1 Thermodynamic Properties

For the manufacture of pharmaceuticals, in this case (R)- norfluoxetine and (S)-fluoxetine, there is no experimental data available for the starting material, key intermediates and drug substances. This means that the thermodynamic properties of styrene-oxide, 3-phenyl-3-hydroxy-propanenitrile, 2-phenyl-3-hydroxy-propylamine, norfluoxetine and fluoxetine have to be estimated.

In the design of the way of production of (R)-norfluoxetine and (S)-fluoxetine the following processes are of thermodynamic interest:

- Reaction (Units 1, 3, 4, 6, 8 and 10)
- Extraction (Units 2 and 5)
- Evaporation/Condensation (Units 1, 2, 3, 7 and 9)
- Solution (Units 1, 2, 3, 7 and 9)

Because of the fact we are unable to find enthalpies and entropies of solution for the aforementioned substances, especially since more than 2 substances are involved in every solution, it is impossible to model the mixing behavior of our process steps.

The standard enthalpies and entropies of formation (1 bar, 298 K) and the heat capacities (1 bar, 300K and 400K) in the ideal gas state are modeled by the method of Benson's group addition (Appendix IV). But the reactions take place in solution, while the equilibrium state, and therefore the minimal Gibbs energy and thus the enthalpy and entropy are different. There is no possibility of estimating the equilibrium conversion based on thermodynamics.

Based on communication with Dr. ir. De Loos it is impossible to use UNIFAQ to estimate the activity-coefficients for the extraction, due to the fact that electrolytes are present, that presses -as it were- the 3-phenyl-3-hydroxy-propanenitrile and norfluoxetine molecules into the apolar phase. Since no dedicated material was found in a literature search, there is no way of modeling the extraction.

So basically what is left is simple enthalpy estimation based on:

- Heat of formation and heat capacities for liquid or gas at 298 K out of literature [26].
- Heat of formation (1 bar, 298 K) and heat capacities (1 bar, 300 K, 400 K) for ideal gas state, calculated using Benson's group addition (See App IV).
- Trouton's rule: $\Delta_{vap}H = 21 * T_b$ ($\Delta_{vap}H$ in kcal, T_b in K)
- The simple estimation that $C_{p,gas}/C_{p,liquid} \approx 0.59$ at 298 K, 1 bar.

4.2 Process Structure & Properties

Design criteria, unit operations/equipment selection, PFS, BTD, PSS.

4.2.1 Criteria and Selections.

Design criteria:

- Assessment of a design for producing 1875 kg R-fluoxetine and 1200 kg S-nor-fluoxetine in 8000 hours in one year.
- Usability of the designed products as drug substance for the drug product, which implies a FDA approval, which implies following of the Good Manufacture Practice (GMP) guidelines.
- Efforts to increase the overall yield by improving the process route.
- Implementation of 'clean chemistry' not only by starting with a high grade starting material, but also by eliminating hazardous chemicals by improving the process route.
- Priority of authority arguments (specialists of industry and university) and pharmaceutical practice (pharmacists and industry) over theoretical models, due to lack of validation of the latter by material constants or experimental data.
- The methodology adhered is the unfolding of a criterion, within the limits imposed by the other criteria.

Process selection + block scheme:
Oxide => nitrile => amine => nor => fluoxetine

Unit 1. Guide words: reactor/heating, reflux/distillation, feed/discharge.

- Well-mixed batch reactor with electric heating. Based on Douglas [11] the scaling-up of a well-stirred batch reactor from lab scale is straight forward, only limited by heat transfer. Based on the selected article for the production of (nor)fluoxetine [8] the reactor has to be heated to and kept at reflux temperature (66 ºC). Due to the boiling of THF the reactor can be considered well mixed. Due to the size of the reactor electric heating is favored over steam, this conclusion was drawn based on communication with Organon Oss.
- Glass double tube condenser/cooler, with 15 ºC water as cooling fluid. Due to the corrosive nature of the substances condensed, glass is to be favored as heat exchanger material. Similar in size and form as those encountered when skulking inside the chemist laboratories. The difference between reflux and distillation operation is the positioning of a three-way control valve.
- Based on Organon industrial practice the pumps are eliminated. They are replaced by the appliance of pressure difference between origin and goal of fluids, established by the pressure utilities (nitrogen and vacuum). The hoses are made of teflon with a stainless steel weave. From the barrel the substances are pressed into mobile vessels on scales, from where it is sucked into the reactor. Flasks are to be added manually. Discharge form distillation and reactor is due to gravity into mobile vessels.

Unit 2. Guidewords: extraction, concentration/evaporation/condensation.

- Based on the article KOH (2M) as the heavy phase is extracted twice with ethylether as the light phase. Based on Organon industrial practice we designed a glass vessel, with a three-way control-valve. When the phase boundary passes the eye the valve changes position.
- Concentration of the light phase is done in an electrically heated vessel, followed by condensation of the ethylether vapor in a similar heat exchanger as in unit 1.

Unit 3. Guidewords: Borane methyl sulfide complex/Pd/C catalyst, pressurized reactor, filter, recrystallization/evaporation/condensation.

- Based on the article the reaction from nitrile to amine was done using borane methyl sulfide. This is toxic and expensive and easily substituted by a far more and superior method. Being a generic manufacturer Prof. Sheldon recommended performing the hydrogenation with a 5% Pd/C catalyst from Johnson & Matthey. Based on communication with Joe Froelich [22] from this company we adapted the following process conditions: Ethanol with HCl, 55 ºC, 4 bar H_2, 1 wt % catalyst loading of a 5 % Pd/C slurry catalyst. The design conversion was chosen to be 98 %. This conversion is based on literature [21] and verified by personal communication with Prof Moulijn. This also is a big advantage over the other method.
- The well-mixed pressurized batch reactor is filled and discharged like in Unit 1. Mixing is accomplished with a stirrer. Before the reactor is started its content is first stripped with nitrogen. All gas leaving the reactor is first run through a gas changer (a vessel filled with a solvent that turns the gas into an environmentally save gas).
- The reaction mixture is discharged to the filter and run through it by gravity. The holes in the filter cloth have a diameter of 10 micron [22]. The catalyst is returned to Johnson & Matthey and reactivated. The other filter cloth at the end for the filtration of the amine has holes with max 100 micron diameter.
- Evaporation and condensation were performed just like in Unit 2. To make sure we'll get rid of all impurities (like 2-phenyl-3-hydroxy propanenitrile and 3-phenyl-3-hydroxy propanenitrile) in this stage of the process the amine is recrystallized from toluene. After the evaporation of the ethanol the residue is still 78 °C. This heat is used to dissolve the slurry in toluene, after one hour the toluene is cooled down and the amine is recrystallized.

Unit 4. Guidewords: reactor/heating, feed/discharge.

- The feed and discharge of the reactor are operated like in Unit 1.
- The reaction is scaled up from literature [8]. There has to be noted that there are two reactions: **1** the deprotonation of the hydroxide by NaH and **2** the addition of the benzotrifluoride group. Therefor in this case it is also necessary to strip the

reactor content with nitrogen. The gas leaving the reactor is again just like in the previous step run through a gas changer. The mixture is mixed with a stirrer.

Unit 5. Guidewords: Extraction

- The extraction is performed like in Unit 2 only now toluene is the light phase and NaOH (2N) the heavy one. Again the extraction is scaled up from literature.

Unit 6. Key words: Salt-formation/Mineral-HCl/Toluene-Heptane, Filter.

- Based on the article one equivalent of mineral HCl is used to bubble through a toluene/heptane mixture containing S-norfluoxetine, forming the HCl-salt in solid state. The vessel is cooled with water. Hereafter the vessel-content is discharged through a filter, (a stainless steel perforated plate covered with filter-cloth in the middle of a mobile vessel), after which the salt is dried and brought to unit 11, the mixer, tablet- and packaging-machine.

Unit 7. Key words: Solvent swap/concentration /condensation.

- Due to the change in reaction route for the methylation of R-norfluoxetine (see unit 8) another solvent for R-norfluoxetine is needed. Toluene is evaporated and consecutively condensed, where after the reactor content is dissolved in ethanol. The vessel content is discharged in a mobile vessel and brought to unit 8.

Unit 8. Guidewords: Lithium aluminum hydride/Pd/C catalyst, pressurized reactor/heating, filters.

- The reasons for our choice to implement a catalyst in this unit are similar to the ones used for Unit 3. Furthermore in this step it saves us from the problem of a large salt formation, which makes the reaction difficult to perform on large scale. Again Prof. Sheldon recommended using a catalyst for this reductive amination. And based on the communication with Joe Froelich [22] the following facts where found: Ethanol with excess formaldehyde, 55 ºC, 4 bar H_2, 1 wt % catalyst loading of a 5 % Pd/C slurry catalyst.
- All other conditions and operations are exactly the same like in Unit 3.

Unit 9. Key words: Reverse of unit 7.

- Because of the salt-formation in unit 10 ethanol is swapped for toluene. First the ethanol/methanol/formaldehyde/water mixture is evaporated and condensed, where after the reactor content is dissolved in ethanol. The vessel content is discharged in a mobile vessel and brought to unit 10.

Unit 10. Key words: Identical to unit 6.

- Identical to the way S-norfluoxetine.HCl is formed in unit 6, in unit 10 R-fluoxetine.HCl is formed, filtered, dried and brought to unit 11, the mixer, tablet- and packaging machine.

4.2.2 Process Flow Scheme

The PFS can be found in Appendix V. It consists of 11 small units, which are described in detail. For a basic overview an overall combined flow sheet was added at the last page (Appendix XVI). In this section, the PFS is explained in detail. Flow rates are given in the PSS, which can be found in Appendix VI. Control of the process is also given in the PFS; a detailed description is given in paragraph 4.3. More information about the equipment properties is discussed in paragraph 4.5.

The THF barrel (T101) is linked to a nitrogen pressure pump that can be inserted into the barrel and is itself attached to a Teflon hose <101>, which runs to the mobile vessel (V101). This vessel is filled to the exactly needed amount using a scale (X101). By creating a low pressure inside the reactor (R101) the THF is sucked into it <102>. Then styrene oxide (F101) triethylamine (F102) and acetone cyanohydride (F103) are added manually <103> through a funnel. The reactor is refluxed at 66 ºC for 18 hours. After refluxing the mixture is concentrated to a residue. The THF and acetone <104> are removed by opening the three-way valve <105> to the mobile vessel (V103). KOH (2N) (T102) is added <106/107> just like it was done previously with THF. The same scale is used. Then the reactor content is discharged into another mobile vessel (V104) using gravity.

This vessel (V104) is transported to Unit 2 where it is sucked into the extractor (S201), ethylether (T201) is added twice for extraction <202/203>. After the first time the heavy phase <204> returns to (V104) using gravity at the phase change the three-way control valve is switched and the light phase <205> runs into (V202). The second run is operated identical apart from the fact that (V104) is now emptied into the waste tank. The light phase <206> is again sucked into the evaporator (S203) where its solvent is removed as a gas <207> and after the condenser (E201) the liquid <208> transported by gravity runs into (V205). The concentrated oily liquid <209> is discharged in a mobile vessel (V205).

This is sucked into the hydrogenating reactor (R301). Ethanol <302/303> and the catalyst are added. The reactor is stripped 5 times with N_2 to get rid of all the O_2. Then HCl gas <304> is added and the reactor is pressurized with H2 <305/306>. After 2 hours the reaction is finished. The gas <307> is removed to the gas changer and the mixture <308/309> discharged through a filter (S301) and taken up in a mobile vessel (V303). The filtrate is washed with water to deactivate it. The mixture <311> is sucked into the evaporator (S302) where ethanol <312/313> is removed as a gas and condensed (E301). Toluene is added in order to recrystallize the residue. After 2 hours the mixture <318> is discharged over a filter and the solid pure amine is dried and bagged (B302). The liquid <317> is wasted.

DMSO <401/402> is added. The bagged amine (B302) and NaH (B401) are manually inserted into in the substitution reactor (R401). During deprotonation H_2 gas <406> escapes through a gas changer to the waste. After 30 minutes the 4-chlorobenzotrifluoride (F401) is added manually <405>. The reactor is heated and kept at 90 for ºC one hour. Its content (mainly DMSO/norfluoxetine) <407> is discharged into a mobile vessel (V402).

This mobile vessel moved to unit 5 and sucked into the extractor (S501). NaOH (T501) is added and the mixture is twice extracted with toluene (T502). This all happens exactly the same as in the beginning of unit 2.

The mobile vessel (V503) containing toluene/S-norfluoxetine <601> is emptied into (S601). Heptane (T601) is added <602.603> and HCl <604/605> is run through the mixture. The mixture is discharged over a filter. The liquid is wasted < 608>. The solid <607> is dried and bagged (B601).

The mobile vessel (V503) filled with toluene/R-norfluoxetine is sucked into the evaporator (S701). The toluene is removed as a gas <702> at 110.6 ºC and condensed (E701) to a liquid <703> that is wasted. Ethanol (T701) is added to the residue. And the mixture <706> is discharged into a mobile vessel (V702).

The mobile vessel (V702) is sucked <801> into the reductive amination reactor (R801). The catalyst <802> is added and the reactor is stripped 5 times with N_2. Then formaldehyde is added and the reactor is pressurized with H_2. The mixture is stirred and reacts for 2 hours at 55 ºC. The discharge is operated identical to unit 3.

The content of the mobile vessel (V801) is ethanol/R-fluoxetine. Unit 9 swaps the ethanol for toluene, it is operated like unit 7 only now evaporation at 100 ºC.

Unit 10 is identical to unit 6 only now with R-fluoxetine.

The operation of unit 11 is explained in more detail in chapter 5.3.5.

4.2.3 Batch Cycle Diagram.

The batch cycle diagrams are given in Appendix VII.

4.2.4 Process Stream Summary

The complete process stream summary is specified in Appendix VI.

4.2.5 Utilities

The summary of the utilities is given in Appendix VIII.

Apart from the utilities necessary for heating, cooling and stirring, there also has to be taken account for the transport system utilities. All mobile vessels are taken up into the units through pressure differences. Every reactor or separator can be hooked to a vacuum line. This line is connected to a mobile vacuum pump, with a capacity of up to 10 mbar. Before this can be done the vessels first have to be filled. The device used, consists of a long stainless steel tube, which reaches up until the bottom of the barrels. It can be screwed upon the barrel and when connected, the top layer is pressurized with nitrogen gas. This way the liquid leaves the barrel through the tube to the teflon hoses into the mobile vessel.

4.2.6 Yields

The yields are summarized in the following table.

Table 4.1 Unit yields

Unit	**Yield**
Unit 1	0.98
Unit 2	0.95
Unit 3 reaction	0.98
Unit 3 recrystallization	0.95
Unit 4	1.00
Unit 5/6	0.93
Unit 8	0.98
Unit 10	0.98

The yield for unit 1, 2, 3_{rec}, 4, 5 and 6 are directly from the lab report. Prof Moulijn gave the yields for the catalytic reactions, 3 and 8, they could be higher but then the reaction time would increase severely. In unit 4 there is an excess of 4-chlorobenzotrifluoride, which will react until there are no more deprotonated hydroxides left. The only loss of product will occur in the separation after this reaction in unit 5. In unit 1 the ring opening of the epoxide is performed. Through various discussions with an organic chemist [23] it was estimated that this reaction also forms a byproduct in which the ring opening occurs from the other side. Since there is a large excess of cyanide there won't be any left over styrene oxide.

4.3 Process Control

Because the process design contains manual actions and therefore human presence, the control system is made as simple as possible, so that manual override is in no way a disturbance of a complex control system.

Every control unit is comprised out of a controller, a control valve and an uplink.

There are 4 basic control units:

- A temperature control of an electricity control valve limiting the vessel temperature. (Equipment numbers R101, S203, R301, S302, R401, S701, R801 and S901.)
- A level control of a 3-way control valve limiting the outflow of heavy phase and changing the path of outflow of the light phase. (Equipment numbers S201and S501.)
- A pressure control of a pressure-reducing valve reducing the cylinder pressure to vessel pressure.
- A pressure control of a control valve venting reactor gas when the pressure is above specified. (Equipment numbers R301, R401and R801.)

The process control is integrated in the PFS. (See appendix V).

4.4 Mass and Heat Balances

See Appendix IX.

4.5 Process and equipment design

4.5.1 Process simulation

During this design only two computer programs have been used: Microsoft Excel (Appendix XII) and Visio (Appendix V). There was looked into the use of Aspen + but because of the lack of thermodynamic data for most of the base chemicals this program wasn't suitable. A simple program like excel evidently was the solution.

4.5.2 Equipment selection and design

All reactors are well stirred batch tank reactors. They have been sized according to 200 % of the needed volume content. This rather conservative sizing has two grounds. First future capacity expansion is facilitated. Second since the batch reactors are a scale up from the lab, a broad safety margin is applicable.

The condensers were developed and calculated in Appendix XIII.

The heating jackets have an efficiency of 80 %. 20 % of the energy is lost to the environment.

There are two kinds of mobile vessels 25 and 50 liter vessels.

The scales can bare a weight of max. 250 kg.

The filters have a diameter of 25 cm and the filter cloth a maximal diameter of 10 micron for the catalyst filters and 100 micron for the other filters.

Equipment data summary and specification sheets are given in Appendix X. The calculations are given in Appendix XI.

4.6 Waste

The production of S-norfluoxetine and R-fluoxetine results in the production of waste. Due to high GMP standards none of the waste streams are recycled so all must be disposed. The waste streams are divided into two categories, hydrocarbon waste streams and watery waste streams. Table 4.2 shows the amount of each category. The exact waste stream compositions are listed in appendix XI. A waste disposal company will process the waste streams.

Table 4.2 Waste amounts per category

Category	**Amount (kg/year)**
Hydrocarbon	84470
Watery	33583

The costs for the waste disposal by a waste disposal company are calculated in chapter Cost calculation.

4.7 Safety

4.7.1 HAZOP

In designing a process, of course safety aspects should be taken into account. To see what a designer can do to reduce the safety risks towards operating personnel two tools can assist. In this paragraph a HAZOP (Hazard and Operability study) [11] and a Dow FE&I (Fire and explosion index) [11] analysis have been carried out.

HAZOP is essentially a qualitative procedure in which a small team examines a proposed design by generating questions about it in a systematic manner. A limited HAZOP study is carried out here. During the HAZOP each team member tried to imagine every possible hazard or risk that may arise while operating the process. The HAZOP analysis was carried out for the reflux-reactor (R101), the high pressure hydrogenating reactors (R301/R801) and the addition reactor (R401). During the brainstorming the following guidewords were used: Not or no, more, less, as well as, part off, reversed and other than.

Table 4.3 HAZOP analysis for the reflux-reactor (R101

Guide word	Deviation	Possible causes	Consequences	Action required
Not or No	Feed	Leakage	Spill of feed No reaction	Spare parts Available
		Utility loss	No reaction	Control Unit
	Heating	Power Failure	Idem	Emergency Generators
		Temp Control Failure	Idem	Regular Check-up
		Jacket leakage	Idem	Idem
	Containment	Leakage reactor	Spill of content	Idem
		Explosion	Idem	Pressure control
	Stirring	Power Failure	No homogeneity	Stirrer control
		Mechanical breakdown	Idem	Idem
More	Feed	Weighing error	Lower yield	Regular Check-up
	Heating	Temp Control Failure	Explosion Side reactions	Idem
As well as	Reflux and V103 fill	Control Valve Failure	Lower yield	Idem

Table 4.4 R301/801

Guide word	Deviation	Possible causes	Consequences	Action required
Not or No	See table R101	See table R101	See table R101	See table R101
	Stripping	Wrong medium Outlet blocked	Explosion	Control
	Hydrogen Pressure	Leakage	No reaction	Regular check-up
	Active catalyst	No hydrogen Poisoning	Idem	Catalyst validation
More	Oxygen partial Pressure	No stripping	Explosion	Control
	Hydrogen Pressure	Control valve failure	Explosion	Regular check-up
	Heating	Control failure	Polymerization	Idem
	HCl	Control valve failure	Decomposition Explosion	Idem

Table 4.5 R401

Guide word	Deviation	Possible causes	Consequences	Action required
Not or No	See table R101	See table R101	See table R101	See table R101
	Stripping	Wrong medium	Rigorous reaction	Control
More	Nitrogen partial Pressure	Outlet blocked	Explosion	Control
	Heating	Control failure	Polymerization	Idem
	NaH	Human Error	Decomposition Explosion	Idem Logbook
Reversed	NaH before stripping	Human error Control failure	Deactivation of NaH, no reaction	Idem

Table 4.6 S301

Guide word	Deviation	Possible causes	Consequences	Action required
Not or No	Washing	Human error	Active catalyst, dangerous	Control logbook

4.7.2 Fire and Explosion index

A Fire & Explosion Index (F&EI) assessment, according to the Dow Guide has been completed. The F&EI calculation is a tool to help determine the areas of the greatest loss potential in a particular process. It also enables the prediction of the physical damage and business interruption that would occur in the event of an incident. The higher the F&EI, the more hazardous the process is.

The first step is to determine which process units should be studied. Important factors for selecting pertinent process units include:

- Chemical energy potential (Material Factor)
- Quantity of hazardous material in the process unit
- Capital density (dollars per square foot)
- Process pressure and temperature
- Past history of problems that resulted in a fire and explosion incident
- Units critical to plant operation

The most dangerous unit operation is reactor R301; compared to this reactor all other equipment can be regarded as safe. Therefore the fire and explosion index is calculated for this reactor. The F&EI for R301 is 745, which makes it severe hazard unit operation. Due to the small amount of chemicals the damage resulting from an incident will not be has high as with larger chemical plants.

The calculation for the fire and explosion index can be found in Appendix XIV.

5. Detailed Product design

In this chapter the basis of design will be further detailed into an integrated product concept. In this paragraph the basis of design is worked out to a more detailed design, such as tablet composition, raw chemicals and FDA approval

5.1. Integrated product concept

5.1.1 Application and comparison

The produced fluoxetine will be used for two products; a tablet for occasional use and a tablet for chronical use. This makes the designed product competable with the current racemic fluoxetine-based anti-depressant Prozac®.

The current anti-depressant Prozac® consist of R- and S-fluoxetine. These different enantiomers have different half-life times. The half-life time of R-fluoxetine is 1-4 days, whereas the half-life of S-fluoxetine is 4-16 days.

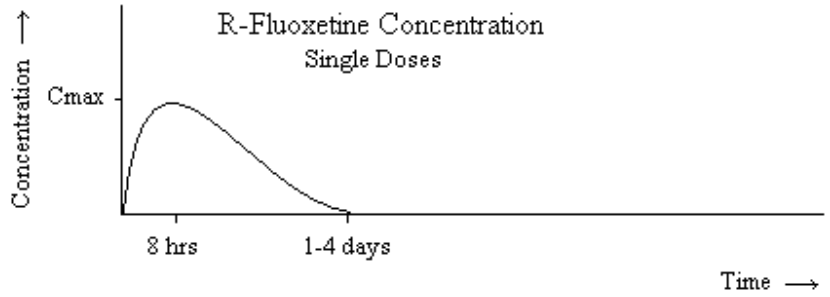


Figure 5.1 Single dose active R-fluoxetine concentration in blood plasma

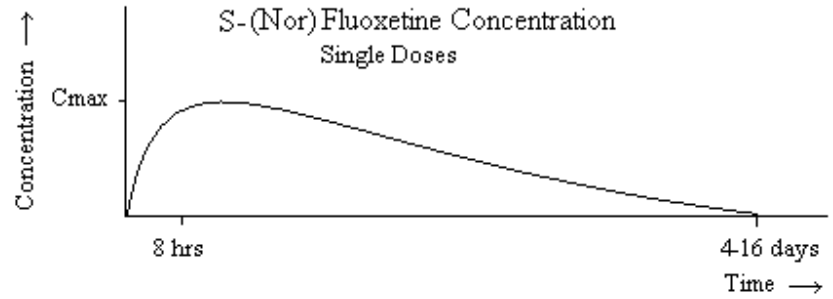


Figure 5.2 Single dose active S- (nor)fluoxetine concentration in blood plasma

Fluoxetine is converted in the human liver into norfluoxetine. S-norfluoxetine is as potent as both R- and S-fluoxetine, however the metabolite of R-fluoxetine R-norfluoxetine is not potent as anti-depressant. This explains the longer active half-life time of S-norfluoxetine.

Prozac® is composed of both R- and S-fluoxetine. The active fluoxetine concentration in the blood plasma after a single dose is shown in figure 4.3

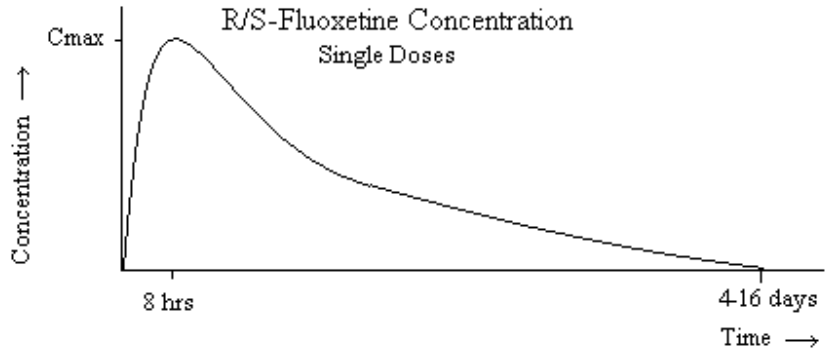


Figure 5.3 Single dose Prozac® active fluoxetine in blood plasma

The daily use of Prozac® results in an unstable concentration of fluoxetine is the blood plasma. This is shown in the following figure.

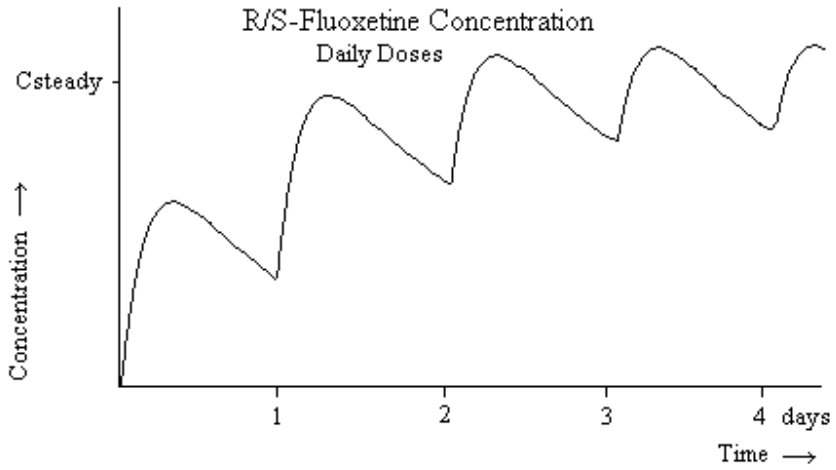


Figure 5.4 Daily dose fluoxetine concentration in blood plasma

Chronical

The designed product for treatment of patients suffering from chronical depression is based on S-norfluoxetine. The use of this enantiomer has three major advantages over Prozac®.

1. The use of only S-norfluoxetine enables the use of less fluoxetine. The chronical user benefits most of the S-fluoxetine in Prozac®, so R-fluoxetine is not useful for this purpose. Less drug substance results in a lower product cost.

2. Due to the longer half-life time the concentration of the active fluoxetine decrease slower than R-fluoxetine. This results in a more stable concentration of the drug substances in the blood plasma. This is show in figure 4.5.

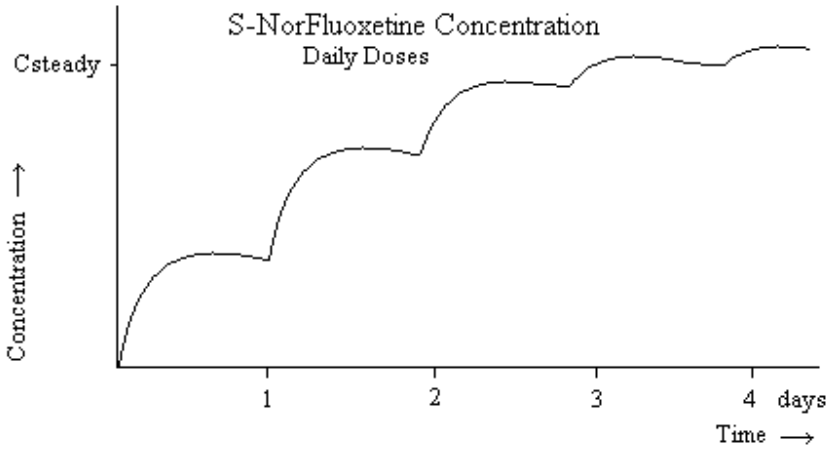


Figure 5.5 Daily dose S-norfluoxetine concentration in blood plasma

3. Due to the fact that norfluoxetine is the major active metabolite of fluoxetine, other metabolite will not be present in the patients system. In the figure bellow a scheme of the metabolites is shown.

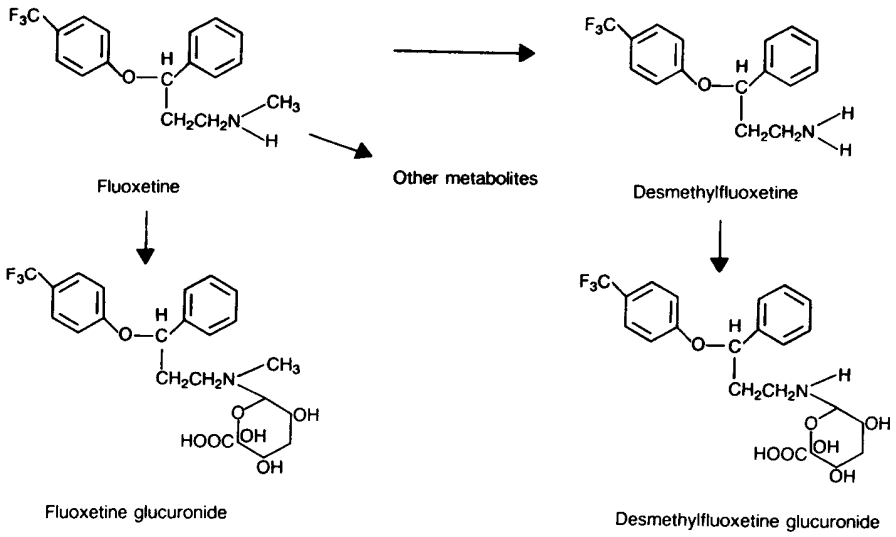


Figure 5.6 Fluoxetine and its metabolites

To allocate a side effect to a specific metabolite is medically very hard if not impossible. Significantly lower amount and concentrations of metabolites makes it reasonable to expect fewer and/or less severe side effects.

Occasional

This tablet is designed to for the treatment of occasional depression. Patients who suffer from depression influences by external factor e.g. winter depression, premenstrual syndrome (PMS), work related, etc. benefit most from this tablet. This tablet has two major advantages over Prozac®.

1. The use of only R-fluoxetine enables the use of less fluoxetine. The occasional user benefits most of the R-fluoxetine in Prozac®, so S-fluoxetine is not useful for this purpose. Less drug substance results in a lower product cost.

2. Less fluoxetine in the tablet result in lower severity of the side effects. Furthermore the absence of the S-enantiomer probably results in fewer side effects.

Both tablets can also be used simultaneously to create an optimal treatment program for different patients. For example a mild chronically depressed patients suffering from occasional deep depressions.

In conclusion these designed products serve the different anti-depressant market-segments better than the current Prozac®. Each specific patient can be served with a different type of tablet or even a combination of both. Furthermore both tablets profit from the lower dose of drug substance and fewer metabolites. Therefore will suffer less from the major disadvantage of Prozac®: the large amount of side effects.

5.1.2 Tablet composition

The designed tablets have the same composition, except for the drug substance. The drug product for chronical use also has a colorant to produce a light blue color. This color provides a clear distinction between the two different products. The ingredients are shown in table 5.1[15].

The amount of drug substance is chosen such that the desired blood plasma concentration can be achieved.

Table 5.1 Tablet composition

	Occasional Tablet	**mg**	**%**	**Chronical Tablet**	**mg**	**%**
Drug substance	R-Fluoxetine	15	8%	S-Norfluoxetine	10	5%
Thinning	Microcrystalline Cellulose	95	48%	Microcrystalline Cellulose	95	48%
Binding	Starch	46	24%	Starch	49	25%
Disintegrant	PolyVinylPyrrolidone	20	10%	PolyVinylPyrrolidone	20	10%
AntiAdherant	Colloidal Siliconoxide	3	2%	Colloidal Siliconoxide	3	2%
Colorant				Indigotine	2	1%
Lubricant	Magnesiumstearate	1	0.5%	Magnesiumstearate	1	0.5%
Sweetener	Manitol	20	10%	Manitol	20	10%
Total		200	100%		200	100%

The antidepressant will be presented in a dispersible tablet. Dispersible tablets containing fluoxetine are solid, intended for oral use, of uniform appearance, and with sufficient mechanical strength to bear possible damage from storage and transport. The active ingredient is distributed evenly in the pharmaceutical form and the disintegration rate in water is high.

The use of dispersible tablets presents a series of benefits over other forms of administration of fluoxetine (capsules and solution) including the following:

- They are suitable to treat patients with difficulties for ingesting solid forms.
- They may be used by diabetic patients since they do not contain saccharose as sweetener.
- Dosage is flexible and reasonably accurate following dissolution in the volume of water desired by the patient.
- Their solutions are of suitable organoleptic characteristics, acceptable to patients.
- Their shape size and reduced volume allow them to be presented in blister form, which is a benefit to the patient, enhancing ease of handling and carrying, to ensure that the patient completes the therapy and so raising the efficacy of the treatment.

5.1.3 Raw chemicals

The chemicals used in the drug product are all purchased, except for the drug substances S-norfluoxetine and R-fluoxetine. The drug substances are produced in the plant. The chemicals needed for the production are also purchased. In the table below the chemicals purchased are listed with company purchased from.

Table 5.2 Chemicals for production

Raw Chemical	**Manufacturer**	**Amount (t/a)**
R-styrene oxide	BASF	0.51
S-styrene oxide	BASF	0.51
Acetone cyanohydrin	Hampshire Chemical	0.90
Tetrahydrofuran	BASF	7.25
Triethtylamine	AtoFina	1.08
Diethyl ether	Condea Chemie Gmbh	16.61
Potassium hydroxide	North Industrial Chem.	11.63
Ethanol	Condea Industrial Gmbh	8.46
Hydrochloric acid	North Industrial Chem.	4.51
Pd/C catalyst	Johnson & Mathews	4.23
Sodium hydride	Rohm and Haas	0.48
Dimethylsulfoxide	AtoFina	3.99
p-Chlorobenzotrifluoride	FinChimica	2.21
Sodium hydroxide	North Industrial Chem.	12.08
Toluene	Dow Benelux	8.31
Heptane	ExxonMobil	9.04
Microcrystalline cellulose	FMC Biopolymers	25.0
Dry flowing starch	National Starch & Chemical	14.0
Colloidal silicone oxide	Nissan Chemicals	0.75
Sorbitol	Lonza Inc.	5.0
Indigotine	BASF	0.25
Polyvinylpyrrolidon	BASF	5.00
Magnesiumstearate	Akzo Nobel	0.13

5.1.4 Marketing

The market for the product can be dived into two parts. First the established market where Prozac® is already widely used, and the growing market where Prozac® not yet has an established market position.

Established markets

The markets where Prozac® has already been established are markets as the United States, Europe and Japan. These are the main markets of interest for the designed products. The majority of the patients using Prozac® can be found in these regions. The competitive aspects of the designed product will enable it to conquer a part of the market.

The intended market share of 5% will be established via different marketing techniques. Commercials on television and in magazines will alert the potential users of the product.

The drug products for occasional use will be marketed as ‘mood brighteners’. Whereas the drug products for chronical use, will be marketed as an anti-depressant, with less side effects.
In the United States the sale of pharmaceuticals via the internet is permitted. In cooperation with an established internet pharmaceutical company the designed products will be sold on the internet. Via internet other markets over the world can also be provided.

A sales representative will visit hospitals and family doctors to alert the medical world on the existence of the product. This is the main marketing method for countries where medication is only available on description by doctors.

Growing markets

The main growing markets are markets where the anti-depressants are not commonly used. Expected is that these countries will develop a growing demand for anti-depressants as their economies develop further. Examples of such countries are China, India and the Middle East.

The introduction of the designed product in this region will be done in cooperation with local pharmaceutical company. Introducing a new medicine in such countries in a difficult operation for foreign companies. Cooperation with local pharmaceuticals ensures the cooperation of local governments and makes it easier for the population to except a new medicine. Marketing methods will be developed in cooperation with the local pharmaceutical companies while they posses the knowledge on new medicine introduction.

5.1.5 Distribution

Marketing and licensing agreements will be established with pharmaceuticals companies and distributors throughout the world. In the figure below the different distributors are shown.

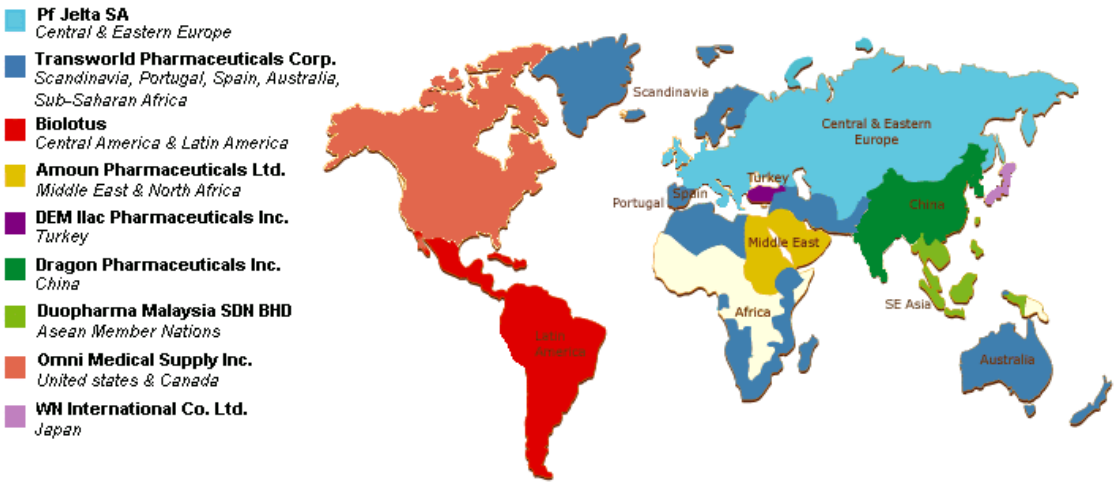


Figure 5.7 Product Distributors

These companies will distribute the product to local hospitals, pharmacies and other sellers of the product. The transport from the production facility to the distributor will be arranged by the distributors.

5.1.6 FDA approval

Before bringing a new pharmaceutical on the market an approval from the FDA (Food and Drug Administration) is required for the United States. [16]

Innovative Drug

There are essentially four phases in the development process as defined by FDA regulations in the United States. The first phase – pre-clinical research – involves laboratory and animal testing of the compound that is primarily aimed at establishing safety and efficacy. If successful, the innovator can then file an Investigational New Drug Application (IND) with the FDA, seeking approval to move the compound into a three-phase process of human testing.

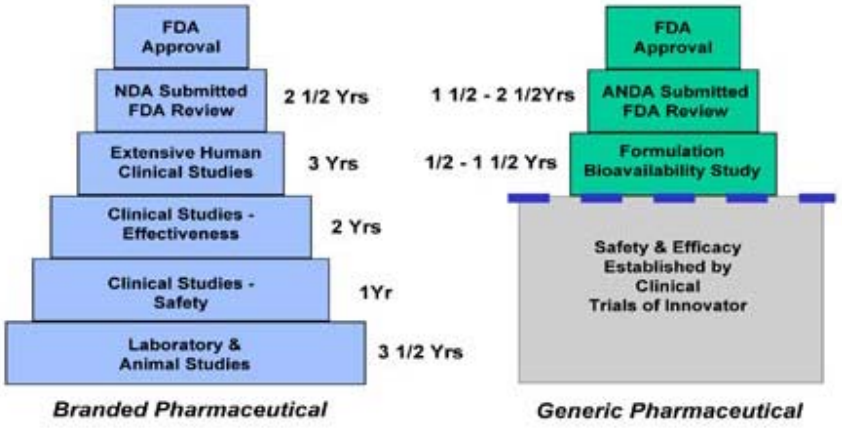


Figure 5.8 Branded vs. generic product development

At the successful completion of lengthy human clinical trials, the innovator files a New Drug Application (NDA) submission with the FDA seeking to bring the new compound to market. The process required establishing safety and efficacy could take as long as 10-12 years, and cost in excess of € 500 million. In order to recapture this investment, the innovator is typically granted a period of market exclusivity.

Generic Drug

The generic pharmaceutical company, seeking to market an equivalent to an innovator's product (once the market exclusivity on the innovator's product has expired), uses a significantly less costly and faster process, the Abbreviated New Drug Application (ANDA) process. Under this process, the generic manufacturer relies on the safety and efficacy data supplied by the innovator, and only has to prove to the FDA that its product is equivalent to the branded product. When processing an ANDA, the FDA waives the requirement for conducting complete clinical studies as the innovator company has already established safety and efficacy. However, it usually requires the generic manufacturer to conduct bioavailability and/or bioequivalence studies of its version of the branded drug.

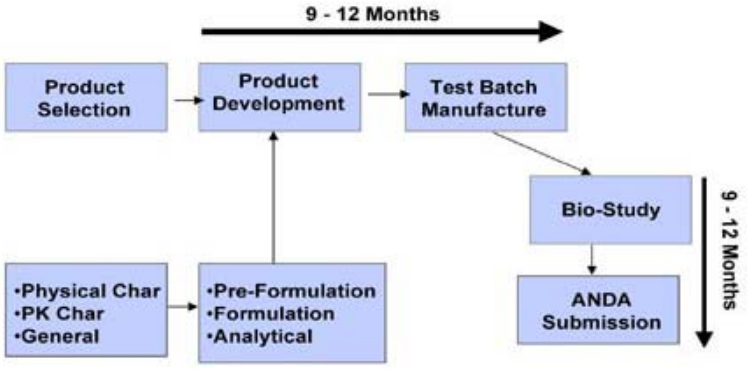


Figure 5.9 Product development process

Bioavailability studies assess the rate and extent of absorption and levels of concentration of a drug in the blood stream needed to produce a therapeutic effect. Bioequivalence studies compare the bioavailability of one drug product with another, in this case the innovator's product. When bioequivalence is established, it indicates that the rate of absorption and the levels of concentration of a generic product are substantially equivalent to the branded product. The ANDA process eliminates the lengthy and costly clinical research phase of development. As a result, generic pharmaceutical product development takes approximately 3 years.

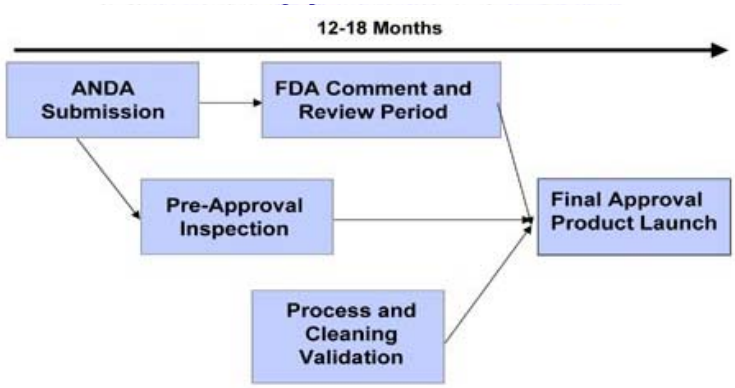


Figure 5.10 ANDA approval process

The FDA also requires that a company's manufacturing methods conform to current good manufacturing practices (cGMP), as defined in the U.S. Code of Federal Regulations. The company must follow the cGMPs in all phases of the manufacturing process, and must continually monitor compliance and measure quality control.

5.2 Target Specifications

The main target specification of the designed product is to be able to compete with Prozac®. To this purpose the designed product must have an antidepressant effect and must comply with legislation.

To compete with Prozac®, the designed product must have a significant advantage over Prozac®. Prozac® suffers from two major drawbacks.

- Prozac® is not a dedicated formulation; one formulation is used for both the chronical user and the occasional user (see IPC).
- Both types of users suffer from tremendous amounts of side effects when using Prozac®.

The advantage of the designed product over Prozac® is two fold.

- The Prozac® market is split into two segments. Each segment will be served with dedicated formulation and presentation. The occasional user will be provided with a R-fluoxetine based dispersible "mood brightening" tablet in an easy to use, quickly accessible presentation. The chronical market will be provided with a dispersible S-norfluoxetine based antidepressant tablet in an easy to use, hard to forget presentation.
- Both formulations will suffer significantly less from side effect than Prozac®.

All the information above can be summarized into the following target specifications. The designed product must:

1. Compete with Prozac®

This is the main target specification. This automatically includes the second target specification.

2. Comply with legislation

The following four target specifications describe how the designed product will be competable with Prozac®.

- Medically be superior on both market segments
- Have less/less severe side effects
- Be dedicated to both market segment users
- Price € 1.50 per tablet

5.3 Technical Feasibility

The anti depressant market can be split up into two specific extreme user groups. On one side the occasional user, on the other side the chronical user. The mood profiles of these users are significantly different and can schematically be visualized as shown in figure 5.11.

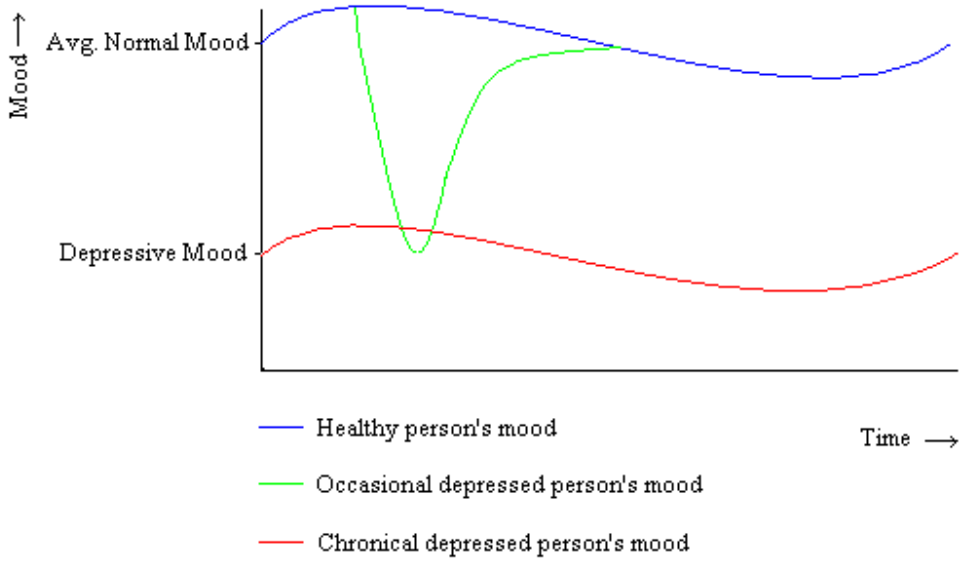


Figure 5.11 Schematic representation of mood profile

In the following paragraphs the unique properties of the designed product will be explained.

5.3.1 Medical superiority

An average healthy person has his/her natural mood swings. A person who suffers from, so called, occasional depression has an occasional mood fall. These people can best be served by a mood brightener, which has an opposite antidepressant concentration profile. The result of the use of such a mood brightener is such that the mood level of the user is only elevated from the depression level when needed.

A R-fluoxetine based mood brightening tablet is the best solution for this purpose. Its low half-life time and the absence of an active metabolite make it the perfect drug substance.

An anti-depressant for chronically depressed patients will have effect after two weeks. This is caused by the selectively down-regulates the serotonin receptors [17], which must by up-regulated. Occasional depressed patient do not have this two-week lag time because the selective down-regulation has not occurred [18]. Therefore the SSRI R-fluoxetine is suitable for this purpose.

A person suffering from chronical depression has a lower average mood, possibly caused by genetic or medical deviations. These people can best be served by an antidepressant that elevates the mood to a normal average. A constant antidepressant substance in the subject body would by ideal.

A S-norfluoxetine based antidepressant tablet is the best solution for this purpose. Its long half-life time and the active metabolite make it the perfect drug substance. The use of such a tablet results in the better control of the steady state blood plasma

5.3.2 Side effects

The mood-brightening tablet is expected to have less and less severe side effect than Prozac®. This is explained by the presence of only the R-fluoxetine. Side effects caused by S-fluoxetine and its metabolites will not occur when using this tablet. Furthermore this tablet is loaded with 15 mg R-fluoxetine. Therefore less drug substances are present in the subject body. Side effects related to the drug substance or its metabolites will be less severe.

The anti-depressant tablet is also expected to have less and less severe side effects. This is firstly explained by the presence of only S-norfluoxetine. Side effects caused by R-fluoxetine, its metabolites and S-fluoxetine will not occur when using this tablet. Furthermore only 10 mg norfluoxetine is present. Therefore less drug substances are present in the subject body. Side effects related to the drug substance or its metabolites will be less severe.

5.3.3 Tablet ingredients and presentation

All the target specifications, explained above, will be satisfied with tablets comprised of the following ingredients and presentation.

Table 5.3 Ingredients of Mood Brightener and Antidepressant tablet and presentation

Mood Brightener		Chronical Antidepressant	
Ingredients	**Amount (mg)**	Ingredients	**Amount (mg)**
R-Fluoxetine HCl	15	S-Norfluoxetine HCl	10
Microcrystalline cellulose	95	Microcrystalline cellulose	97
Free flowing starch	46	Free flowing Starch	47
Polyvinylpyrrolidon	20	Polyvinylpyrrolidon	20
Colloidal siliconoxide	3	Colloidal siliconoxide	3
Sorbitol	20	Sorbitol	20
		Indigotine	2
Magnesiumstearate	1	Magnesiumstearate	1
Total	200	Total	200
Presentation		**Presentation**	
Smiley Face Imprinted white tablet		Light blue tablet	

Packaging	**Packaging**
12 tablets containing blisters 3 carton packed blisters in a box	28 tablets containing blisters 3 blisters in a box

The occasional mood brightening tablet user needs access to the tablet any time of the day. The patient needs to be able to administer a tablet whenever he/she feels a depression coming. Therefore the mood brightening tablets will be packed in, chewing gum like, 12 tablets containing blisters, which can be carried in the trouser pocket. The tablet itself will have a happy look; it will have a "smiley face" imprint. This will help lift the mood of the tablet user.

The chronical antidepressant tablet user administers the tablet on a daily base. Therefore the tablets will be packed in 28 tablets containing blister. The blister will have a day indication, so that administration is easily remembered. Furthermore the tablets will have a light blue color to distinct them for the mood-brightening tablet.

5.3.4 Account for ingredients

R-fluoxetine and S-norfluoxetine are the drug substances, which have antidepressant potency. For the chronical tablet the explanation of the amount of drug substance is relatively easy. It contains the same amount of S-norfluoxetine as Prozac® contains S-fluoxetine. The explanation for the amount of drug substance in the occasional tablet is somewhat more difficult. The desired effect is a blood plasma drug substance concentration peak comparable to the peak generated by Prozac®.

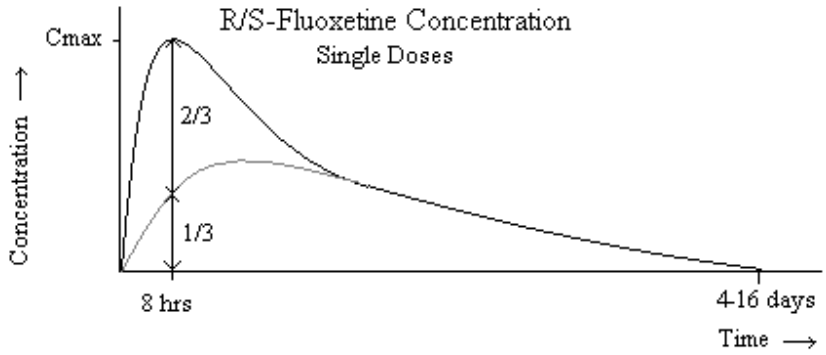


Figure 5.12 Contribution of R and S-fluoxetine to blood plasma concentration peak.

Figure 5.12 shows that the contribution of R-fluoxetine to the blood plasma concentration peak is about two third, S-fluoxetine only contributes one third. Therefore the use of 10 mg R-fluoxetine would result in a peak only two thirds of the Prozac® peak. The use of 15 mg (10/0.667) results in a peak equal to the Prozac® peak.

Microcrystalline cellulose and free flowing starch are used as both dilution and binding material. The used amounts ensure a comparable particle size distribution of the tablet bulk compounds and the drug substance. Therefore de-mixing of the tablet components does not occur. These compounds also have excellent compactability behavior.
Polyvinylpyrrolidon is used as a disintegrant, which ensures rapid tablet disintegration in water.
Colloidal siliconoxide is added as a powder flow regulator to ensure free flow ability of the powder mixture. It also acts as a adsorbent, capturing humidity which would be taken up be the (nor)fluoxetine, so slowing the degradation of the drug substance by hydrolysis.
Sorbitol is added as a sweetener. (Nor)Fluoxetine hydrochloride has a very bitter unpleasant taste. This must be masked for dissolved oral administration, so that the tablet is acceptable for the patient.
Magnesiumstearate is added as a lubricant without which tablet pressing cannot be performed.

5.3.5 Drug substance to drug product

This paragraph explains the procedure to make the active drug out of the drug substance. The production of the tablet containing the fluoxetine is worked out.

Mixing materials

The drug substance, which is a dry free-flowing solid, has to be mixed homogeneously with the other components (see table 4.2) of the tablet before they can be compressed into a tablet. Three batches of fluoxetine will be produced a day. These will be mixed in a batch mixer three times a day.

It is not yet possible to forecast mixing times for solids and therefore these have to be ascertained by dint of experiments. The traditional method of determining mixing times is sampling followed by off line analysis. Sample variance will decrease over mixing time to a stationary final condition. The mixing time, after which the sample variance does not further decreases, is the ideal mixing time. Figure 5.12 illustrates the ideal mixing time. In practice this means a mixing time around 5 minutes. [17]

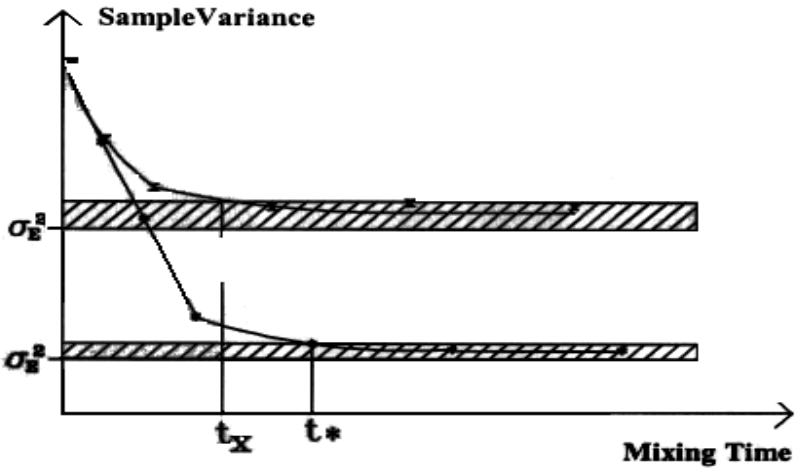


Figure 5.12 Mixing time determination by sample concentration variance

Mixing is stopped when a stationary fluoxetine concentration is reached. The acquired mixture is a dry free flowing mixture, which is suitable for direct compression [15]. The mixture is then fed into a hopper from which it is fed into the tablet press.

The tablet components are chosen such that particle size distribution of the fluoxetine (avg. 100 μm) is comparable to the particle size distribution of the tablet bulk components

Mixing Procedure

1. Weighing raw material into mixer
2. Mixing raw materials until homogeneity
3. Weighing R-fluoxetine/S-norfluoxetine into mixer
4. Mixing until homogeneity
5. Weighing magnesiumstearate
6. Mixing until homogeneity
7. Emptying mixer into mixed powder hopper

Amounts per mixing-batch

The amounts that are used per mixing batch are shown in table 5.4.

Table 5.4 Amounts per mixing batch

	Amount (kg)		Amount (kg)
R-Fluoxetine	3.75	S-Norfluoxetine	3.75
Microcrystalline cellulose	25.00	Microcrystalline cellulose	37.50
Starch	10.25	Starch	16.50
Polyvinylpyrrolidon	5.00	Polyvinylpyrrolidon	7.50
Colloidal siliconoxide	0.75	Colloidal siliconoxide	1.13
		Indigotine	0.75
Sorbitol	5.00	Sorbitol	7.50
Magnesiumstearate	0.25	Magnesiumstearate	0.38
Total	50.00		75.00

Tablet Pressing

The hopper, which is used to store the mixed powder, is also a buffer to allow the continuously pressing of the tablets. The tablet press used is the SVIAC PR 12, basic machine, high capacity rotary tablet press. This machine is constructed in conformity with the Good Manufacturing Practices (GMP) and according to the European Security Norms.

The free flowing powder mixture is fed into the tablet press by gravity. The dosing method used on the tablet press is by excess. The die is fed at a maximum, and then the excess of powder is erased. That method ensures an excellent regularity in weight at any machine speed.

The tablet press used for the production of the R-fluoxetine based tablet will be equipped with a “smiley face” stamp. This results in the production of tablets with a “smiley face” impression on the top of the tablet.

The produced tablets are stored in a hopper, which is also used as the feed for the packaging equipment.

Packaging

The tablets are packed into blisters. The blisters used for the S-norfluoxetine based tablet will have a day indication to help achieve daily intake. Three blisters containing 28 tablets each will be packed into a box. The R-fluoxetine based tablets will be packed into blisters containing 12 tablets. These blisters will have a cardboard casing. Three cardboard-cased blisters will be packed into a box.

The packing-line used, comprises the following units.

- Servac 130 ST Blisterpacker
- PUG ST 2 K Conveyor
- Contina 160 Cartoning Machine
- GUK FA 21/4 CARTONAC 68 Leaflet Folder and Inserter

The Servac 130 ST Blisterpacker is a fully automatic intermittently operating blisterpacker. The machine comprises a fabricated framework, which houses the drives and gear trains. The framework supports the various stations, which are mounted at the front of the machine.

PVC film is drawn from a reel and is fed to the deep-draw station. The foil is then deep-drawn into tooling; this process is aided by compressed air. The forward draw of the foil is affected intermittently. The deep-drawn foil passes through a filling station where product is placed into the formed blisters. The machine is fitted with an automatic feeding equipment for tablets or capsules where product is placed into a Stainless Steel hopper and is automatically placed into the blister pockets. The machine is equipped with a product detection station, which checks for the presence of product. If product is missing from one of the pockets the blister is later rejected.

The filled blisters are sealed with aluminum foil, which is drawn from a reel. The reel is driven from a separate drive unit. The deep-draw and sealing tools are water-cooled. A supply of cooling water and compressed air is required. After sealing there is a short cooling station. Coding of the blisters takes place with a row of steel embossing types. Finally, the foil enters the cutting station where the blisters are cut out and are left on a conveyor. There is a device, which marshals the blisters into two lanes onto a Type PUG conveyor. The remaining foil is rolled-up automatically.

The Contina 160 Cartoning Machine is a fully automatic and continuously operating Cartoning machine suitable for cartoning blisters and adding leaflets. The machine comprises of a steel frame, which houses the drive and gear train which supports the product chain, the carton chain, the leaflet folder and the carton magazine.
Hinged guards cover the moving parts of the carton chain.

The blisters to be cartoned are fed from the PUG conveyor, which places the blisters into the blister pockets. The pockets move according to the product chain. The blisters are then placed into the product chain, which transports them to the cartoning station.

The machine is fitted with a GUK FA 21/4 CARTONAC 68 Leaflet Folder and Inserter. The leaflets are extracted by vacuum suckers and are placed into a magazine. Then they pass through a folding mechanism after which they are clipped to the product feed chain.

Blisters are pushed into the carton together with a leaflet. At the same time one of the carton flaps is coded and the filled carton is then progressively closed, and subjected to a final compression by two parallel running belts.

6. Cost calculations

In this chapter the total costs made for the production of the designed product are calculated. The different costs factors are evaluated and estimated.

As a design group for a major pharmaceutical producer only the marginal costs made for the production of the designed product will be calculated. So only the costs directly related to the product will be taken into account. Cost factors as overhead and rent for the factory will therefore not be used for the cost calculation.

The marginal costs that will be included in the cost calculations are:

- Raw materials
- Personnel
- Equipment
- Waste
- Utilities
- Maintenance
- Distribution
- Marketing
- Research & Development (FDA approval)
- Opportunity costs

Each cost factor will be discussed in the following paragraphs.

6.1 Raw materials

The used chemicals can be divided in two segments. First the chemicals used for the production of the drug substances S-norfluoxetine and R-fluoxetine. The other part is the chemicals used for the production of the product, such as tablet coloring agent.

The amounts and prices for the used raw materials can be found in appendix XV. The total costs for raw materials are € 16.5 million.

6.2 Research and development

As in all pharmaceutical industries the content of the product must be specified exactly. To ensure a uniform distribution of every tablet of the drug substance it is not possible to check the drug substance afterwards. Statistically it is not justified to check a number of tablets to ensure a drug substance uniformity of all tablets. So to make sure that every tablet contains exactly that wanted amount the production process must be completely fine-tuned. After designing a product on paper an intensive amount of research is needed. All side products, no matter what amount, must be identified and analyzed for toxicology and pharmacology. Furthermore the pressing of the tablet must be investigated to make sure the tablet has a uniform drug substance distribution and sufficient strength. All of

these properties are hard to predict and can only be observed by doing intensive experiments.

This results in the fact that the research and development for the introduction of a new process and product is a very expensive process. All production steps must be carefully simulated and investigated.

The designed product must first be tested on a laboratory scale to evaluate if the designed formulation can be pressed into a tablet.

The costs made for this research are estimated at € 150 million. This includes personnel, equipment and raw materials for research. This estimation is done on basis of FDA experience.

These costs will be written of in 10 years.

6.3 Personnel

The production process can be divided into 10 units. Per unit one worker is needed for transportation of the chemicals, supervision etc. The plant will run 24 hours a day; so 3 shifts per day are needed. Per shift one overall supervisor is needed. This concludes in a staff of the production of the drug substance of 33 workers.

The tableting and packaging process are fully automated. Only one supervisor per shift is needed.

A total of 3 overall process managers are hired.

In total about 39 workers are needed for the entire production process. The average cost per workers is estimated at € 150.000 per year. This results in a personnel cost of € 5.9 million per year.

6.4 Equipment

The total cost for the equipment are calculated with the Lang-method. The fixed capital cost of the project is given of a function of the total purchase equipment cost by the equation: $Cf = f_L Ce$ [11]

Where Cf = fixed capital cost,
Ce = the total delivered cost of all the major equipment
f_L = Lang factor, is 3.6 for a mixed fluids-solids processing plant [11].

The calculation of the total delivered cost of all the major equipment is shown in Appendix XV. This results in a fixed capital cost for the equipment of € 4.5 million. This

investment will be written of in 5 years resulting in a yearly equipment cost of about € 1 million.

6.5 Utilities

The costs made for utilities are € 1 million per year. The calculations are given in appendix XV.

6.6 Maintenance

For the maintenance of the process € 2.5 million is reserved. This includes the replacement of broken parts and cleaning of the machines.

6.7 Distribution

The distribution of the product to the hospitals, pharmacies etc. is contracted out. The distribution is done by 9 distributors (see Figure 4.7). The total costs made for distribution are € 10 million per year. These costs are based on price-offers made by the distributors.

6.8 Marketing

A total of € 10 million per year is reserved for marketing. These costs include advertising, sales representatives, etc. The advertising costs will be higher is the first two years of production when a market share is conquered. When this market share is established costs for marketing will decrease.

6.9 Opportunity costs

For the purchase of the equipment and the research for the FDA approval investment money is required. While this design is done for a major pharmaceutical company this company can do the investment for this project. But the money invested in this project could also be used for other projects, so these costs can be seen as opportunity costs.
The typical rate for opportunity costs is 8%. The total investment for this project is about € 155 million. This result in opportunity costs of € 12.4 million per year.

6.10 Waste

The waste generated by the process will be contracted out to a waste-processing company. 250 million tablets are produced at a weight of 200 mg, which cumulates to 50 tons of product. A total 176 tons of material is used to produce the tablets. This results in a waste of 126 tons per year. According to chemical health and safety [25] the average cost of one kg of waste is € 10 per kg. This results in a waste cost of € 1.26 million based on

1996 prices. Therefore costs made for waste processing in 2002 will be estimated at € 2 million per year.

6.11 Total cost

The total cost per year are shown in the table below.

Table 6.1 Yearly costs

Cost Object	**Amount (Million €)**
Chemicals	1.6
Personnel	5.9
Equipment	1.0
Maintenance	2.5
Distribution	10.0
Marketing	10.0
Research & Development	15.0
Opportunity costs	15.0
Waste	3.0
Utilities	1.0
Total Cost	**65.0**

7. Economic Feasibility

This chapter will evaluate the market for designed product. The market will be analyzed and market share estimation is made. Finally the product is economically evaluated.

7.1 Market Situation

According to a soon-to-be-released study from Business Communications Co., Inc. *RB-130 The Expanding Market for Psychotherapeutic Drugs***,** the market for psychotherapeutic drugs represents the third largest therapeutic category in terms of worldwide sales and is estimated at just under €21 billion in 2000. This market is expected to grow at an AAGR (average annual growth rate) of 13% during the 5-year forecast period to reach nearly €38 billion by 2005.[2]

The leading company in the psychotherapeutic drug sector is Eli Lilly, which holds about 30% of the market with two products - the antidepressant Prozac® and the antipsychotic Zyprexa. Other leading competitors in the market are Pfizer, SmithKline Beecham, Novartis, Johnson & Johnson and Pharmacia & Upjohn.

Antidepressants comprise bulk of the market for psychotherapeutic drugs, with an estimated market of nearly €12 billion in 2000. Growing at an AAGR of 9.8%, this market is expected to exceed €19 billion in 2005, accounting for more than 45% of the total for that year.

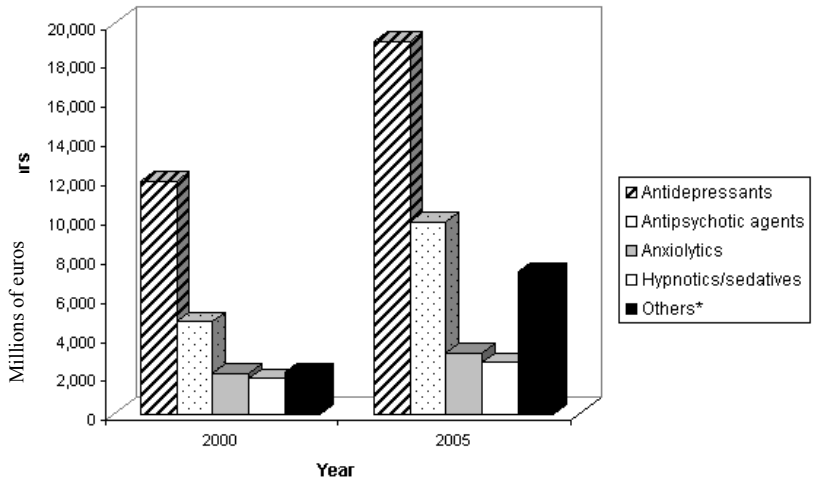


Figure 7.1 Market for Psychotherapeutic Drugs, 2000-2005 (€ Millions)

Antidepressants experienced 18 percent sales growth in 2000, to €13.4 billion or 4.2 percent of all audited global pharmaceutical sales. North America was the dominant market, accounting for 74.6 percent of sales and a 19 percent growth rate. In Europe,

sales fell by 1 percent, while the Africa/Asia/Australia region and Latin America, minor players in this market, accounted for 4.5 percent and 2.4 percent sales growth, respectively. Lilly's Prozac® was the leading product in the class with a market share of 21.5 percent.

7.2 SWOT analysis

A common used method for analyzing the market position of a product or company is the SWOT analysis. SWOT stands for Strength, Weaknesses, Opportunities and Threats. Making a SWOT analysis provides the producer with a clear perspective to the product and its market positions and possibilities. The following give a SWOT-analysis for the designed product [18].

7.2.1 Strengths

The most important strength of the designed product is the fact that it has less and less severe side effects. One of the major disadvantages of Prozac® is the amount and severity of the side effects. The lower amount of metabolites and drug substance in the designed product will result in not only less side effects but also less severe side effects.

Furthermore the designed product will better serve the different market segments within the anti-depressant market. Chronical and occasional users will both have a different product better suited for their wishes and demands.

The designed product will also be competitive because of the price advantage over the existing anti-depressant Prozac®. The price of the designed product will be 40 % lower than Prozac®.

7.2.2 Weaknesses

The weakness of the product is the problem of entering the pharmaceuticals market.
The pharmaceutical market is a relative brand bonded market; patients do not easily change to another pharmaceutical brand. Therefore it is expected that 50% of the current Prozac® users will keep using Prozac® initially. A lot of effort has to be made to achieve the wanted market share.

7.2.3 Opportunities

The opportunities of the designed product lay in its medical superiority. Once the patients and the medical world are convinced of the medical superiority of the product a large market share can be achieved. Both market volume and market share are expected to grow in the future. Market volume is expected to grow because of the global antidepressant trend and because of economical growth in developing countries. Market share is expected to grow because of the medical superiority of the designed product; the lower amount and lower severity of the side effects will convince more and more patients

to use the designed product. Eventually the complete market share of the current anti-depressant Prozac® can be conquered.

7.2.4 Threats

The most important threat for the designed product is its competitors. While the patent for the drug substance fluoxetine has expired, other companies can copy the idea. It is thus important to achieve a steady market share in the first years after introduction.

7.3 Market share

The pharmaceutical market is a relative brand bonded market; patients do not easily change to another pharmaceutical brand. Therefore it is expected that 50% of the current Prozac® users will keep using Prozac® initially. The other 50% will choose for a cheaper generic product. As the generic pharmaceutical is a profitable market, competition from other generic pharmaceutical companies is expected. A total of ten competitive companies are taken into account. Initially these companies will have an equal market share from the remaining 50%. Therefore the designed product will initially have a market share of around 5%. Which results in a yearly production of 250 million tablets.

7.4 Product Price

Fluoxetine is currently marketed under the name Prozac® by Eli Lilly. The current market price is € 2,50 per tablet containing 20 mg of racemic fluoxetine. Generally a price reduction of about 30% is observed for generic products. This is sufficient because the innovative producer does not drop its product price, as this would indicate an unjustified high profit in the past. Therefore it is expected that the generic competition will price their product at € 1,75 per tablet. To also have an additional price competitive advantage over the competition the designed product will be sold at € 1,50 per tablet.

7.5 Economic evaluation

To evaluate the profitability of the project the costs, investments, income and profit are evaluated.

As can be seen in paragraph 6.11 the total costs per year are € 65 million. A total investment of € 155 million is needed.
A total of 245 million tablets are produced per year. If the aimed market share is achieved and a price of € 1,50 is maintained, the total income is € 367,5 million per year.

At a total cost of € 65 million per year a total of € 302,5 million per year is earned. After a tax reduction of 35%, the overall profit is € 196,5 million per year.

However the first 2 years of the project have to be dedicated to research and FDA approval. This means no income is earned in these 2 years. The investment done for this research is € 150 million, written of in 10 years. So the first 2 years the project will have

a yearly loss of € 15 million. After this period another investment of € 5 million is required for the production-equipment.

As can be seen above this project will be very profitable. The investment made for this project will be recovered within 3 years, and has a rate of return of 427%. As the market share is expected to grow in the future, higher profits can be achieved.

These calculations are shown in appendix XV.

8. Conclusions and recommendations

The patent for the use of fluoxetine as drug substance will expire in 2003. The object of this project was to design a product that can compete with the current anti-depressant Prozac® marketed by Eli Lilly. This was done by analyzing the weaknesses of Prozac®. Two major disadvantages of Prozac® were found. The different types of depression are all treated with only one product. Furthermore Prozac® has a rather large amount of side effects.

The drug substance of the current anti-depressant Prozac® is the racemic fluoxetine. The designed product is spilt into two different tablets. A tablet for the chronical user of anti-depressants containing the (S)-norfluoxetine enantiomer, and one tablet for occasional anti-depressant users containing the (R)-fluoxetine enantiomer is designed.

The (S)-norfluoxetine and (R)-fluoxetine are produced according to a selected chemical synthesis found in literature. Several changes and adaptations are made to create an optimal synthesis route for the production of the enantiomerically pure (nor)fluoxetine. This synthesis route starts with enantiomer pure styrene oxide, which makes it easier to produce (S)-norfluoxetine and (R)-fluoxetine. This route results in a practical and inexpensive method for preparing the drug substance.

Using the (S)-norfluoxetine and (R)-fluoxetine instead of the racemic fluoxetine results in a number of advantages of the designed product over the current Prozac®. First the different market segment are better served use the different enantiomers. Although the amount and severity of side effect are hard to predict, the side effects for the designed product will most probably be less and less severe than the side effects of Prozac®.

Overall a practical and inexpensive route for the production of the drug substance is designed. The drug substance will be used in a drug product with excellent competitive aspects. Resulting in a highly profitable investment with excellent future prospects.

Recommendations and comments

The bottleneck in the designing process of a pharmaceutical is fact that the exact composition of the product streams has to be known. In the design phase of the project some assumptions concerning yields, reaction products etc are made. This is unacceptable in the design of pharmaceuticals. A complete design for pharmaceuticals will therefore have to be grounded with experimental data. Processes as tablet pressing and the compound interaction are very hard to predict. A first conceptual design will therefore inevitably contain unforeseen practical impracticability's.
The result of the expiring patent on the market situation is hard to expect. The number of new competitors and patient's pharmaceuticals use will have a significant role on the market share. A complete market analysis will bring more inside into these factors, which is therefore highly recommended before starting the production. Selling the pure distillate solvents can generate extra profits.