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Simulation of Continuous-Flow Pharmaceutical Production of Ibuprofen using ASPEN PLUS

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Dedication

"I have always thought of doing or offering something to my parents as a token of appreciation for all they have consented to just to see me succeed, and now, the opportunity has come.

To those who gave me life, symbols of beauty, pride, wisdom, and patience.

To those who are the source of my inspiration and courage.

To my dearest mother and father.

To my brothers and sisters.

To all the members of my family.

To my teachers and friends

I dedicate this Project to all the people who have worked hard to help me complete it.

Acknowledgement

"My thanks go first to Almighty **God** for the will, health, and patience He has given me to complete my work.

I thank my supervisor, **Dr. Malika OUAGUED**, for accepting to guide this thesis, for her patience, guidance, and support during the supervision period.

I have benefited greatly from her wealth of knowledge.

My most sincere thanks are directed to my dear family."

Abstract

Ibuprofen, a widely used therapeutic molecule, has been identified as an ideal candidate for continuous pharmaceutical manufacturing (CPM) due to its high global demand and extreme societal importance. The development of a continuous production system for ibuprofen aims to improve efficiency and reduce environmental impact. Based on the data obtained through laboratory experiments and parameters calculated in this work, an industrial-scale production with a capacity of 200 tons/year of ibuprofen salt was simulated using Aspen Plus. This involves designing a steady-state process model and simulation for the continuous synthesis and purification of ibuprofen, utilizing plug flow reactors and a final separation step to achieve high API recovery.

Keywords: Ibuprofen, Continuous Manufacturing, Process modelling, Process design, Process simulation, Aspen Plus.

الملخص

يعتبر الإيبوبروفين، جزيء علاجي يستخدم على نطاق واسع، كمرشح مثالي للتصنيع الصيدلاني المستمر نظرًا لارتفاع الطلب العالمي عليه وأهميته الشديدة. يهدف تطوير نظام إنتاج مستمر للإيبوبروفين و تحسين الكفاءة وتقليل الأثر البيئي. استنادًا إلى البيانات التي تم الحصول عليها نظريا و من خلال التجارب المخبرية اضافة الى المقادير التي قمنا بحسابها، تمت محاكاة إنتاج ملح الإيبوبروفين بطاقة 200 طن/سنة باستخدام Aspen Plus. يتضمن هذا العمل تصميم نموذج لانتاج وتنقية مستمرة للإيبوبروفين، باستخدام مفاعلات أنبوبية ذات التدفق السدادي المستمر وعملية فصل نهائية لتحقيق استرداد عالي للمنتوج.

الكلمات المفتاحية: الإيبوبروفين، التصنيع المستمر، نمذجة العملية، تصميم العملية، محاكاة العملية, اسبن بلس.

Résumé

L'ibuprofène, une molécule thérapeutique largement utilisée, a été identifié comme un candidat idéal pour la fabrication pharmaceutique en continue en raison de sa forte demande et son importance sociétale extrême. Le développement d'un système de production continue d'ibuprofène vise à améliorer l'efficacité et à réduire l'impact sur l'environnement. Sur la base des données obtenues à partir des expériences en laboratoire et celles calculées dans cette étude, une production à l'échelle industrielle d'une capacité de 200 tonnes/an de sel d'ibuprofène a été simulée à l'aide d'Aspen Plus. Il s'agit de concevoir un modèle et une simulation de processus en régime permanent pour la synthèse et la purification continues de l'ibuprofène, en utilisant des réacteurs à écoulement piston et une étape de séparation finale pour obtenir une récupération élevée de l'API.

Mots-clés : Ibuprofène, fabrication continue, modélisation de processus, conception de processus, simulation de processus, Aspen Plus.

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Nomenclature

Symbols	***Description***	***Units***
A.E	Atom economy or atom efficiency	
C	Molar concentration	$mol.l^{-1}$
Cp	Heat capacity	$kJ.mol^{-1}.K^{-1}$
F	Molar flow	$mol.s^{-1}$
G	Mass flow rate	$g.h^{-1}$
k	Reaction rate constant	$L.mol^{-1}.min^{-1}$
M	Molecular weight	$g.mol^{-1}$
Q	Heating duty or power	*watt*
Q_v	Volumetric flow rate	$\mu L.min^{-1}$
r	Reaction rate equation	$mol.L^{-1}.min^{-1}$
t	Time	*s, min , h*
T	Temperature	*°C, K*
V	Volume	*µL, L*
X	Conversion	
ΔH	Molar enthalpy	$kJ.mol^{-1}$

Greek Letters

τ	Residence time	min^{-1}, h^{-1}
ζ	advancement	$\mu mol.min^{-1}$
√	stoichiometric coefficient	

Abbreviation

Abbreviation	***Full name***
API	Active pharmaceutical ingredient
BHC	Boots- Hoechst-Celanese
CF	Cystic fibrosis
CM	Continuous manufacturing
COX-1	Inhibitor of cyclooxygenase- 1
COX-2	Inhibitor of cyclooxygenase- 2
CPM	Continuous Pharmaceutical Manufacturing
DMSO	Dimethylsulfoxide
E2E	End-to-end
ETFE	Ethylene tetrafluoroethylene
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
PD	Parkinson’s disease
PDA	Patent Ductus arterosus
PDC	Pyridinium dichlorochromate
PFA	Perfluoroalkoxy
PFRs	Plug flow reactors
PGF2	Prostaglandin F2
PGs	Prostaglandins
QbD	Quality by Design
R^2	Coefficient of determination
RA and OA	Rheumatoid and osteo-arthritis

INTRODUCTION

Introduction

The pharmaceutical industry stands as one of the most dynamic sectors within the chemical industry this century. According to a report by the Centre for Responsive Politics, over 1,100 lobbyists were involved in some capacity with the pharmaceutical business in 2017. In the first quarter of that year, the health products and pharmaceutical industry spent 78 million dollars on lobbying member of the United States Congress (Lipton and Thomas, 2017).

Anti-inflammatory and analgesic drugs are produced in significant quantities annually. Key medications in this category include Aspirin, Acetaminophen (Paracetamol), and Ibuprofen. The last one, in particular, is one of the most commonly used over-the-counter medications for treating pain, fever, and inflammation due to its relatively low toxicity and infrequent association with serious adverse reactions or fatalities from ingestion (Muresan, 2018).

The Boots/Hoechst-Celanese (BHC) process exemplifies batch production for synthesizing anti-inflammatory drugs like Ibuprofen, because of its simplicity and flexibility. However, batch manufacturing has some well-known disadvantages such as scale-up difficulties, mass and heat transfer bottlenecks, long production times and possible supply chain disruptions (Yang and al., 2022).

Continuous pharmaceutical manufacturing (CPM), in turn, is process intensification strategy that enables the reduction of the number of synthesis steps and units, which can lead to significant cost savings. Furthermore, CPM enables safer operation, better scalability, enhanced process automation, smaller process footprint, enhanced mass and heat transfer, and higher throughput. As a result, CPM is considered by both academia and industry as the most viable alternative to batch manufacturing (Albert and al., 2011).

At the heart of the shift from batch to CPM technology are continuous flow reactors, which serve as the key driver of highly-intensified flow processes. They can be intensified by using temperature, pressure, light or immobilization agents. Hence, flow reactors are currently being used to synthesize APIs and whose design can affect subsequent processing steps (Jolliffe, 2018).

Inspired by this challenge, we study a continuous process for manufacturing ibuprofen for systematic reactors design. The proposed concept is evaluated to estimate the expected raw material requirements, process equipment capacities and utility requirements. Based on the data obtained through literature and laboratory-based experiments, an industrial-scale production with a capacity of 200 tons/year of ibuprofen salt was simulated using Aspen Plus.

This work is organized as follows: the first chapter contains a literature review on ibuprofen (origin, properties, galenic forms, therapeutic applications and ibuprofen synthesis). In chapter two, the studied flowsheet is described and mass balance calculations, for laboratory and industrial scale, are demonstrated. In chapter three, reactions kinetic parameters are estimated, and sizing and heat design of plug flow reactors are calculated for laboratory and industrial scale. The last one is reserved for ASPEN PLUS simulation of CPM ibuprofen process. This is then followed by general conclusion.

Chapter I.

BACKGROUND

I.1 Introduction

Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID) known for its pain-relieving, anti-inflammatory, and fever-reducing properties. It's commonly used to alleviate various conditions such as headaches, muscle aches, arthritis, menstrual cramps, and minor injuries. It's available over-the-counter and in prescription strengths, typically in the form of tablets, capsules, or oral suspension.

In this chapter, background topics relevant to Ibuprofen are discussed and a literature survey is presented. Literature is reviewed to get a holistic understanding of Ibuprofen and their pharmaceutical properties. Comparisons of the most popular technology for Ibuprofen production are done based on published information.

I.2. Presentation of Ibuprofen

Ibuprofen is one of the three commonly available over the counter non-steroidal anti-inflammatory drugs (NSAIDs), namely aspirin, ibuprofen, and acetaminophen. It is a non-selective inhibitor of cyclooxygenase- 1 (COX-1) and Cyclooxygenase-2 (COX-2). Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclooxygenases, which are involved in the synthesis of prostaglandins. Ibuprofen works by inhibiting the production of prostaglandins, substances in the body that contribute to inflammation, pain, and fever. Inflammation is a general physiological response to tissue damage characterized by swelling, pain, and heat (Bushra and Aslam, 2010).

I.3. Origin of ibuprofen

Ibuprofen was discovered in 1960 by Dr. Stewart Adams who identified the anti-inflammatory properties of aspirin-related drugs and later screened a series of acidic compounds that were synthesized by Dr. John Nicholson. Dr. Stewart Adams (Figure I.1) was a pharmacologist in the Research Department of The Boots Pure Drug Company Ltd at Nottingham, United Kingdom (Mustfa and al., 2022).

Figure I.1. A photograph of Dr Stewart Adams (Davies, 2019).

His goal was to find analgesic drugs with improved efficacy over aspirin. At the time Stewart Adams began his research, aspirin and cortisone were the standard medications used to treat rheumatoid arthritis and other painful arthritic conditions. However, the limitations of both drugs were becoming strikingly evident even at that time. Little was known about the mechanisms underlying the development of the rheumatic diseases for which these drugs were intended.

Drugs available in the 1950s and 1960s to treat pain and inflammation in rheumatic diseases included aspirin, the other salicylates, aminophenols (phenacetin), and pyrazolones, which dated back to the beginning of the century; phenylbutazone (which was originally used to solubilize aminopyrine and was accidentally discovered to be a potent anti-inflammatory drug); and the corticosteroids discovered in the 1950s. Gold salts were also found to have disease-modifying effects in rheumatoid and related arthropathies in the 1930s, although in the 1950s they were thought to be very toxic.

Since the existing remedies for rheumatic diseases were aspirin, corticosteroids, phenylbutazone, and to a lesser extent gold salts, there was a need for a more potent drug than aspirin that would not produce the potentially fatal side effect of agranulocytosis seen with phenylbutazone or the serious side effects of corticosteroids. In the 1950s, Stewart Adams and John Nicholson at Boots Company started their investigation to identify an analogue of aspirin that might be suitable for long-term use for rheumatoid arthritis. In 1961, after screening more than 600 candidates, Adams and Nicholson filed a patent for the compound 2-(4-isobutylphenyl) propionic acid, later named ibuprofen; it was granted in the following year.

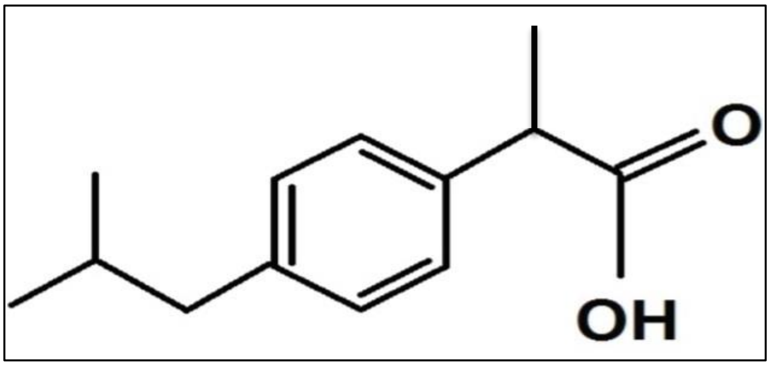
Ibuprofen compares well to the gold standard treatment for rheumatoid arthritis, aspirin, but has a better gastrointestinal side-effect profile. In 1983, ibuprofen was approved in the UK as an over-the-counter (OTC) medicine with a maximum daily dose of 1,200 mg and launched as Nurofen (Mustafa and al., 2022).

I.4. Physio-chemical properties of Ibuprofen

Ibuprofen is a white, crystalline anti-inflammatory drug used in numerous medications. It is the active ingredient marketed under various trade names including Advil, Motrin, and Nurofen. The physiochemical properties of ibuprofen are shown in Table I.1.

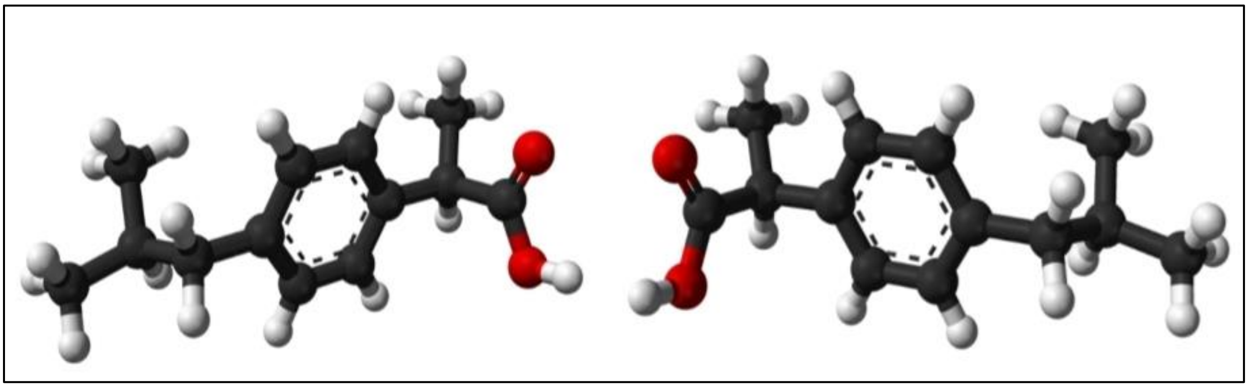
Table I.1. Physiochemical properties of ibuprofen (Mustafa and al., 2022)

Chemical properties	
Appearance	Colorless crystalline solid
Boiling Point	157°C
Brand Name	Brufen;Motrin;Nurofen;Advil;Nuprin
Density	1.029 g/cm^3
IUPAC Name	(RS)-2-(4-(2-Methylpropyl)phenyl)propanoic acid
Melting Point	77-78°C
Molar Mass	206.28 g/mole
Molecular Formula	$C_{13}H_{18}O_2$
Solubility	Insoluble in water



Scheme I.1. Structural formula of ibuprofen.

Ibuprofen has an interesting property that it can exist as a pair of enantiomers or stereoisomers that are chiral in nature. A chiral molecule and its mirror image are non-superimposable, i.e., they are like a pair of hands — left and right hands are mirror images but not identical. This chiral property occurs in molecules that have a carbon atom to which four different groups are bonded. The two enantiomers of ibuprofen are identified by the prefixes R and S (see Scheme I.2) (Mustafa and al., 2022).



Scheme I.2. 3D Appearances of R- (Left) and S+ (Right) Isomers of Ibuprofen.

Enantiomers are identical in many properties such as solubility, melting point, and boiling point. They can be distinguished by the fact that they rotate the plane of polarization of polarized light in different directions: the S enantiomer clockwise as the observer looks at the light and the R counterclockwise. The symbols R and S refer to the 3D arrangement of the atoms in space. However, the two enantiomers behave differently when interacting with other molecules such as the prostaglandins. Of the two enantiomers of ibuprofen, the S form is the pharmacologically active component that inhibits prostaglandin synthesis, while the R form has no anti-inflammatory effect (Mustafa and al., 2022).

However, it has been found that there is an enzyme in the body that converts the R form into the S. In fact, 60% of the R form is converted into S. This means that in a typical dose of ibuprofen of 400 mg, 200 mg is S+ and 200 mg R−. Of the 200 mg of R−, 60% (i.e., 120 mg) is converted into the active R form, giving a total of active form of 320 mg. Therefore, there is little point in going to the trouble of synthesizing just the S form, and ibuprofen is sold as a racemic mixture (one initially containing equal amounts of both optical isomers). However, stereospecific synthesis is also possible.

I.5. Galenic forms of Ibuprofen

Ibuprofen is available in various galenic formulations, each with different pharmacological properties. Some of the different forms of ibuprofen include:

I.5.1. Tablets and Caplets

Ibuprofen tablets are a common form of the medication and are available in various strengths, including 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg. They are usually swallowed whole with water.

I.5.2 Chewable Tablets

These tablets are designed for individuals who may have difficulty swallowing pills. They are flavored and can be chewed before swallowing.

I.5.3. Liquid Suspension

Suitable for those who have difficulty swallowing tablets or prefers a liquid form. The liquid suspension is often flavored to make it more palatable, especially for children.

I.5.4. Topical Gel or Cream

Ibuprofen is also available in topical forms for localized pain relief. Applied directly to the skin over the affected area, it can be beneficial for conditions such as muscle strains or joint pain.

I.5.5. Dissolving Tablets

These tablets are designed to dissolve in the mouth without the need for water. These tablets are convenient for those who may not have access to water or prefer immediate method of ingestion.

I.5.6. Extended-Release Tablets

Formulated to release the slowly medication over an extended period. These tablets may be taken less frequently than immediate-release forms, providing a longer duration of pain relief.

I.5.7. Intravenous (IV) formulations

In some cases, ibuprofen can be administered directly into the bloodstream through an IV. This form is used in hospital settings for rapid pain relief and anti-inflammatory effects, especially when oral administration is not possible.

I.5.8. Combination Products

Ibuprofen is sometimes combined with other medications, such as decongestants or antihistamines, to address multiple symptoms in one product.

I.5.9. Suppositories

Ibuprofen suppositories are available for individuals who cannot take oral medications or have difficulty swallowing. They are inserted into the rectum, where they dissolve and are absorbed into the bloodstream.

It's important to follow the recommended dosage and usage instructions provided by healthcare professionals or on the product's packaging. Additionally, individuals with certain medical conditions or those taking other medications should consult their healthcare provider before using ibuprofen in any form.

I.6. Clinical Pharmacology of Ibuprofen

Ibuprofen is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half-life of 1.8 to 2 hours. The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism (Ross and De Horatius, 1990). The drug is more than 99% protein bound; extensively metabolized in the liver and little is excreted unchanged.

Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti-coagulants and oral hypoglycemic needs not be altered. More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds.

Old age has no significant effects on the elimination of ibuprofen13. Renal impairment also has no effect on the kinetics of the drugs, rapid elimination still occur as a consequence of metabolism. The administration of ibuprofen tablets either under fasting conditions or immediately before meals yield quiet similar serum concentrations-time profile. When it is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption (Bushra and Aslam, 2010).

I.7. Therapeutic Applications

A low dose of ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over the counter medications. It is widely used as an analgesic, an anti-inflammatory and an antipyretic agent (Wood and al., 2006). Racemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder. A number of other actions of

NSAIDs can also be attributed to the inhibition of prostaglandins (PGs) or thromboxane synthesis (Bushra and Aslam, 2010).

The main therapeutic applications of ibuprofen are as follows:

I.7.1. Patent Ductus arterosus (PDA)

This is a frequent complication in premature infants. So far, intravenous indomethacin is the standard mode of medical therapy. However, because of adverse effects of indomethacin, other PG inhibitors such as ibuprofen have been studied for the closure of ductus arteriosus, and results indicated that ibuprofen is as effective as indomethacin (Kravs and Pharm, 2005).

I.7.2. Rheumatoid and osteoarthritis (RA and OA)

Ibuprofen is widely used in the management of numerous inflammatory, musculoskeletal and rheumatic disorders, because they are highly effective having minimal toxicities. Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours. In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms of anti-inflammatory effects. Higher doses, 1200 to 1600 mg per day have been compared with a number of NSAIDs and it has been found to be as effective and well tolerated. Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen (Tan and al., 1999).

Table I.2. Doses of Ibuprofen in adult & Children (Konstan, 2003)

Patients	Ibuprofen	Doses
Adult	Analgesia	200-400 mg, Every 4-6 hrs
	Anti-inflammatory	300 mg, Every 6-8 hrs or 400-800 mg 3-4 times daily
Children	Anti-pyretic	5-10 mg/kg. Every 6 hrs (max.40 mg/kg per day)
	Anti-inflammatory	20-40 mg/kg/day in 3-4 divided dose

I.7.3. Cystic fibrosis (CF)

High dose ibuprofen therapy has also been shown to be effective in decreasing inflammation, probably by decreasing polymorph-nuclear cell influx into the lungs (. The risk of developing GI side effects from high dose ibuprofen therapy is low in patients with CF (Konstan, 2003).

I.7.4. Orthostatic hypotension

Ibuprofen is useful in the treatment of severe orthostatic hypotension as with other NSAIDs. Toxic effects are unlikely at doses below 100 mg/kg but can be life-threatening or severe above 400 mg/kg (Volans and al., 2003).

I.7.5. Dental pain

Ibuprofen is one of the most effective and widely used NSAID in treatment of dental pain. Dental practitioners have relied on ibuprofen and other NSAIDs to manage acute and chronic orofacial pain. A dose of 400 mg of ibuprofen provides effective analgesic for the control of postoperative pain after third molar surgery. A liquid gel preparation of ibuprofen 400mg provides faster relief and superior overall efficacy in post-surgical dental pain (Konstan, 2003).

I.7.6. Dysmenorrhea, fever and headache

Non-prescription ibuprofen is useful for managing minor aches and pains, reducing fever and relieving symptoms of dysmenorrhea. Dysmenorrhea is the most common menstrual complain. Ibuprofen was superior to placebo for pain relief and menstrual fluid PGF2 alpha suppression. Cycloxygenase inhibitors reduce the amount of menstrual prostanoids release, with concomitant reduction in uterine hyper contractility (Dawood, 2006).

It has been reported that the combined use of paracetamol and ibuprofen reduce fever very rapidly. Fever almost invariably accompanies uncomplicated falciparum malaria. In a randomized double-‘blind’ study, a single dose of ibuprofen was compared with paracetamol for the treatment of fever >38·5 °C due to uncomplicated falciparum malaria. Ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4-5 hrs after dosing and thus should be considered as an antipyretic agent in the management of uncomplicated falciparum infections, providing there is no contraindication to its use (Krishna and al., 1995).

I.7.7. Prophylaxis of Alzheimers disease

The administration of NSAIDs, particularly ibuprofen markedly reduced neurodegeneration. In some studies, ibuprofen showed superior results compared to placebo in the prophylaxis of Alzheimer’s disease, when given in low doses over a long time. Further studies are needed to confirm the results before ibuprofen can be recommended for this indication (Townsend and Pratico, 2005).

I.7.8. Parkinson’s disease (PD)

Inflammation and oxidative stress have been implicated as pathogenic mechanisms in PD. Epidemiologic evidence showed that regular use of NSAIDs, particularly non aspirin COX inhibitors such as ibuprofen lower the risk of PD. It induced apoptosis significantly in early and late stages, suggesting that these anti-inflammatory agents might inhibit microbial proliferation (Elsisi and al., 2005).

I.7.9. Breast cancer

Harris et al. in 1999 conducted a study for utilization of NSAIDs in breast cancer. Breast cancer rate was decreased by approximately 50% with regular ibuprofen intake and 40% with regular aspirin intake. Results suggested that specific NSAIDs may be effective chemo preventive agents against breast cancer (Harris and al.; 1999)

I.8. Ibuprofen synthesis

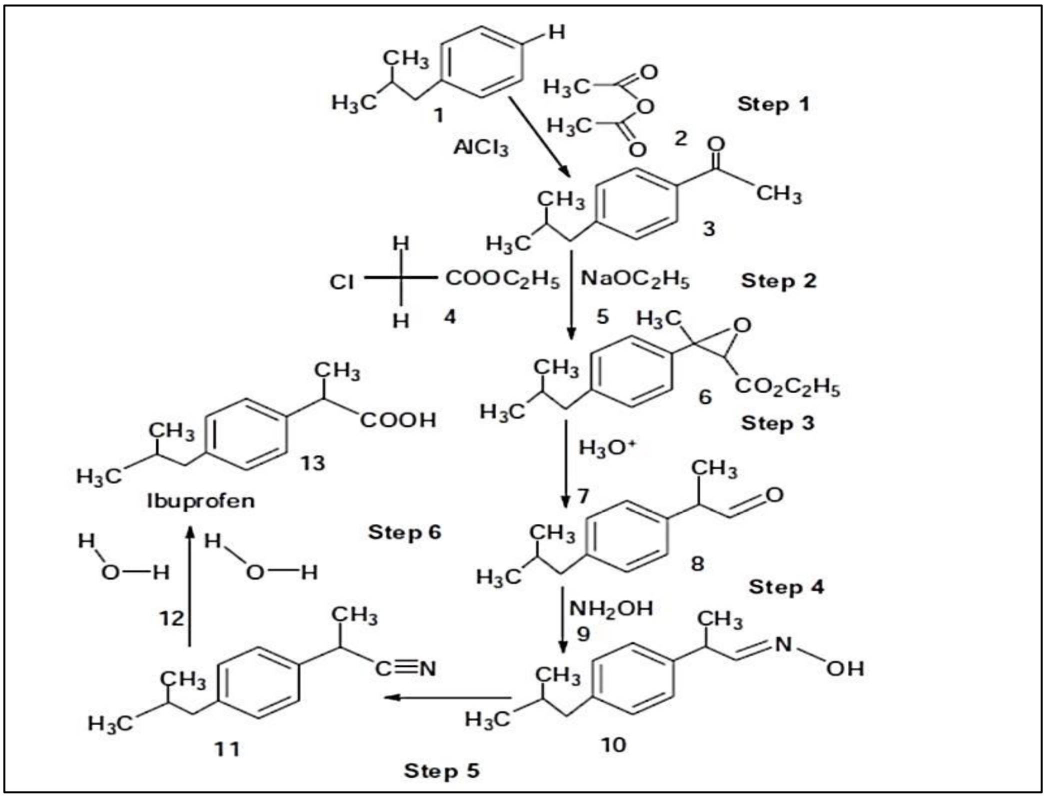
Herein, we present the recent progress in the synthesis of representative nonsteroidal anti-inflammatory drug, ibuprofen. Although this drug was discovered over 50 years ago, novel practical and asymmetric approaches are still being developed for its synthesis. In addition, this endeavor has enabled access to more potent and selective derivatives from the key frameworks of ibuprofen. The development of a synthetic route to ibuprofen is summarized, including developing methodologies, finding novel synthetic routes, and applying green chemistry.

I.8.1. Original route for obtaining Ibuprofen

The originally route, developed by the Boots Pure Drug Company-United Kingdom (the discoverers of Ibuprofen) contained six steps for Ibuprofen synthesis with stoichiometric reagents, relatively low atom efficiency and substantial inorganic salt formation (Scheme I.3) (Doble and al., 2007)

It can be observed that the classical route uses from the first step aluminium chloride in a stoichiometric amount, which is then converted into aluminium trichloride hydrate waste. Another disadvantage for this method is the number of steps for obtaining the final product. So that, the six steps used for synthesis leads to auxiliary products that are not found in the final product, since the atom efficiency is lower (Muresan, 2018).

Another negative result of this route that results from numbers of steps is energy efficiency. A lot of steps used for the final product synthesis imply a lot of energy quantities, so that the energy consumed is retrieved in the final price of the product. A lot of steps are used to obtain the final product involving a lot of catalytic reagents and intermediate products that are not reused at the final of steps.



Scheme I.3. The classical route for Ibuprofen synthesis used by Boots Company (Doble and al., 2007)

Atom economy or atom efficiency (A.E., %) is an important parameter for chemicals equations. In ideal reaction, the atom economy is 100%, it means no waste, no by-products and that all reagents were used to obtain the final product.

The atom economy was calculated with equation (Dicks and Hent, 2015):

$$\text{A.E. (\%)} = \frac{mass\ of\ atoms\ in\ desired\ product}{mass\ of\ atoms\ in\ reactants} * 100$$

In (Table I.3) were given the same parameters used to calculate the A.E. for each step of reactions for Ibuprofen synthesis under classical route (reagent chemical formula, relative molecular mass of reagents and relative molecular mass of used products).

From the data presented in (Table I.3) it could be observed that for the first step, the A.E. was 74.58%, without calculating the mass of $AlCl_3$ used as catalyst from Friedel-Crafts reaction that cannot be reused because this catalyst become waste after reaction. The second step of reaction used three reactants and the atom economy was 71.49%. It is important to mention that sodium ethoxide used as reagent was obtained in-situ from sodium hydroxide dissolves in excess of ethanol (solvent). Sodium ethoxide is extremely flammable, harmful and corrosive.

Table I.3. The atom economy (%) for classically route of Ibuprofen synthesis and parameters used to calculate him

Reactions steps	Reagents chemical formula	Relative molecular mass of used reagents	Relative molecular mass of used products	Relative molecular mass of by-products or waste	Atom economy %
Step 1	$C_{10}H_{14}$	134.0	176.0	60.0	74.58
	$C_4H_6O_3$	102.0			
Step 2	$C_{12}H_{16}O$	176.0	366.5	104.5	71.49
	$C_4H_7O_2Cl$	122.5			
	C_2H_5ONa	68.0			
Step 3	$C_{16}H_{22}O_3$	262.0	281.0	91.0	67.61
	H_3O	19.0			
Step 4	$C_{13}H_{18}O$	190.0	223.0	18.0	91.93
	NH_3O	33.0			
Step 5	$C_{13}H_{19}NO$	205.0	187.0	18.0	91.22
Step 6	$C_{13}H_{17}N$	187.0	182.0	17.0	92.38

	H_4O_2	36.0			

For the step free of the reactions for Ibuprofen synthesis using the classical route, the atom economy is lower than the first and second steps, with a value of 67.61%. It can be observed from Table 1.3 that the atom economy for the step four is higher, with a value of 91.93%.

However, it is important to mention that the hydroxylamine used as reagent may explode on heating. Another negative aspect for this reagent is: hydroxylamine is an irritant to the respiratory tract, skin, eyes and other mucous membranes. It may be absorbed through the skin, it is harmful if swallowed and it is a possible mutagen. More than that, hydroxylamine is dangerous for the environment (Riemann, 1950)

On the step five of the classical method for Ibuprofen synthesis the intermediate product is a nitrile and the atom economy is 91.22%. The last step of the route obtaining for Ibuprofen was an atom economy of 92.38%.

For the entire process it was observed that it was used only 206.0 relative molecular mass from the total relative molecular mass of reagent with a value of 514.5, 308.5 relative molecular mass was lost as waste or by-products.

If the analysis of the entire process for Ibuprofen synthesis using the classical route we can conclude some aspects: the process involved 6 steps, it was necessary 13 intermediate reagents for obtaining the final products, some reagents are very toxic, with a high negative impact on the environment, a lot of products were by-products or waste (hydrochloric acid, ammonia, acetic acid and aluminium trichloride hydrate).

Hydrochloric acid can cause skin burn, eye damage and irritation to different parts of our bodies (Dangerous Substances Directive 67/548/EEC). Ammonia is not toxic for human body, but it is toxic for fish and amphibians and if waste is thrown into water, an ecological disaster will happened.

The six steps of Boots reaction for obtaining Ibuprofen need a lot of energy consumption because most of the reactions require heating.

The last, but not the least disadvantage of the classical route for Ibuprofen synthesis is the atom economy of the entire steps with a value of 44.04%, a very low value under green chemistry principles that generate a lot of waste.

I.8.2. Green route for Ibuprofen synthesis

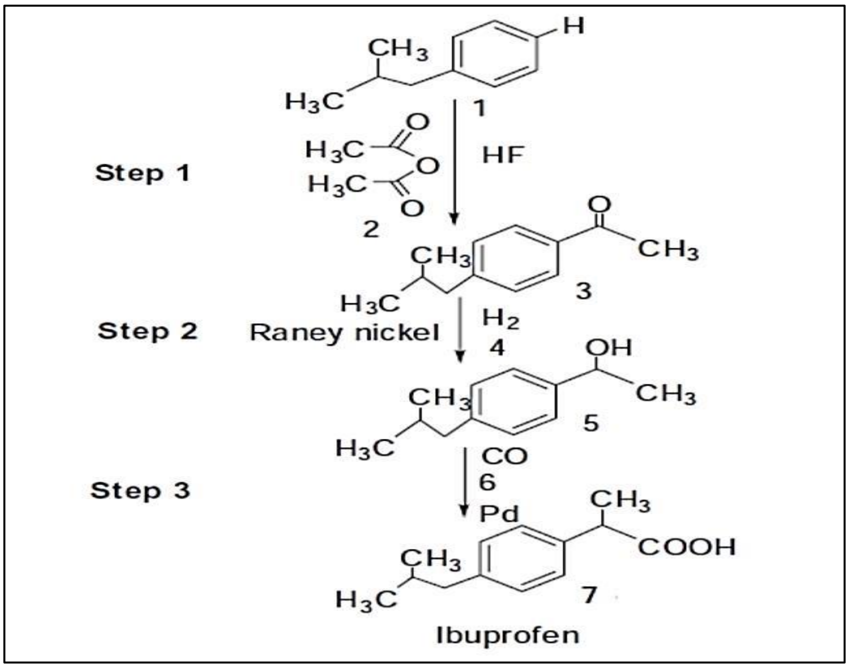
In the 1980’s was developed a new route for Ibuprofen synthesis, a green one with only three steps of reactions, involving a lower amount of waste and by-products, only seven intermediate reagents, most of them reused, and a higher atom efficiency than the classically route.

The green route was developed by the Boots- Hoechst-Celanese (BHC) Company (United States of America) (Scheme I.4) and the process won the Kirpatrick Chemical Engineering Achievement Award in 1993 and the Presidential Green Chemistry Challenge Award in 1997 (Cann and Connelly, 2000).

Table I.4 presents same parameters used to calculate the atom efficiency for each step of reactions for Ibuprofen synthesis under green route (reagent chemical formula, relative molecular mass of reagents and relative molecular mass of used products).

It can be observed from Table I.4 that from the first step of reactions with green route, the atom economy has the same value, 74.58% with the first step of reaction with classical route of Ibuprofen synthesis from isobutyl benzene and acetic anhydride.

But, the first step of reactions from green route is possible with hydrogen fluoride used as a catalyst and solvent for the reaction that can be recovered and reused repeatedly (Bond and al., 1989).



Scheme I.4. The green route for Ibuprofen synthesis used green process (Cann and Connelly, 2000).

In BHC process the bath recycles times and capital expenditure are lesser when compared to Boots process. The result is increased economic benefits of company and non-polluted reagents. More than that, the hydrogen fluoride is the single solvent used for green Ibuprofen synthesis, simplifying product recovery and minimizing fugitive emissions.

If it is considered that the acetic acid obtained as by-product from the first step of the reaction is used for other applications, the atom economy for step one with green route is 100.00%.

The second step of the green route is reduction of a ketone to an alcohol with an atom economy of 100.00%. The catalyst used was Raney nickel (spongy nickel), a fine-grained solid composed mostly of nickel derived from a nickel-aluminium alloy with stability and high catalytic activity at room temperature (Nishimura, 2001)

The last step of reactions for Ibuprofen synthesis using the green route represents carbonylation of alcohol over a Pd as catalyst that can be recycled and reused. The atom economy of the final step was 100.00%.

For the entire process it was observed that was used 206.0 relative molecular mass from the total relative molecular mass of reagent with a value of 266.0 (only 60.0 relative molecular mass was lost under acetic acid form), so that the atom economy of the entire processes for Ibuprofen synthesis using green route was 77.44%, almost double versus the value of the atom economy of the process using classical route.

Table I.4. The atom economy (%) for green route of Ibuprofen synthesis and parameters used to calculate him.

Reactions steps	Reagents chemical formula	Relative molecular mass of used reagents	Relative molecular mass of used products	Relative molecular mass of by-products or waste	Atom economy ,%
Step 1	$C_{10}H_{14}$	134.0	176.0	60.0	74.58
	$C_4H_6O_3$	102.0			
Step 2	$C_{12}H_{16}O$	176.0	178.0	0.0	100.00
	H_2	2.0			

Step 3	$C_{12}H_{18}O$	178.0	206.0	0.0	100.00
	CO	28.0			

The green route for Ibuprofen synthesis is an exquisite example of how a simple and elegant chemical/pharmaceutical manufacturing route, initially a route with a lower atom economy can be made much cleaner, much favourable and much economical through implementation of green process technology.

If we consider that about $7.2 \cdot 10^3$ tons of Ibuprofen are produced each year, we can imagine how waste is not produced, a lot of energy is not consumed, and the process does not pollute the environment.

I.9. Continuous manufacturing process CM

Continuous manufacturing process CM has been defined to be a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system, where ‘system’ is defined as an integrated process that consists of two- or more-unit operations (Lee and al., 2015).

The first regulatory approval of a drug product made by CM was in 2015. Since then, take-up by industry has been quite slow despite encouragement from the regulatory agencies. To date, there have been seven approvals. Some of these products use a combination of CM and batch manufacturing.

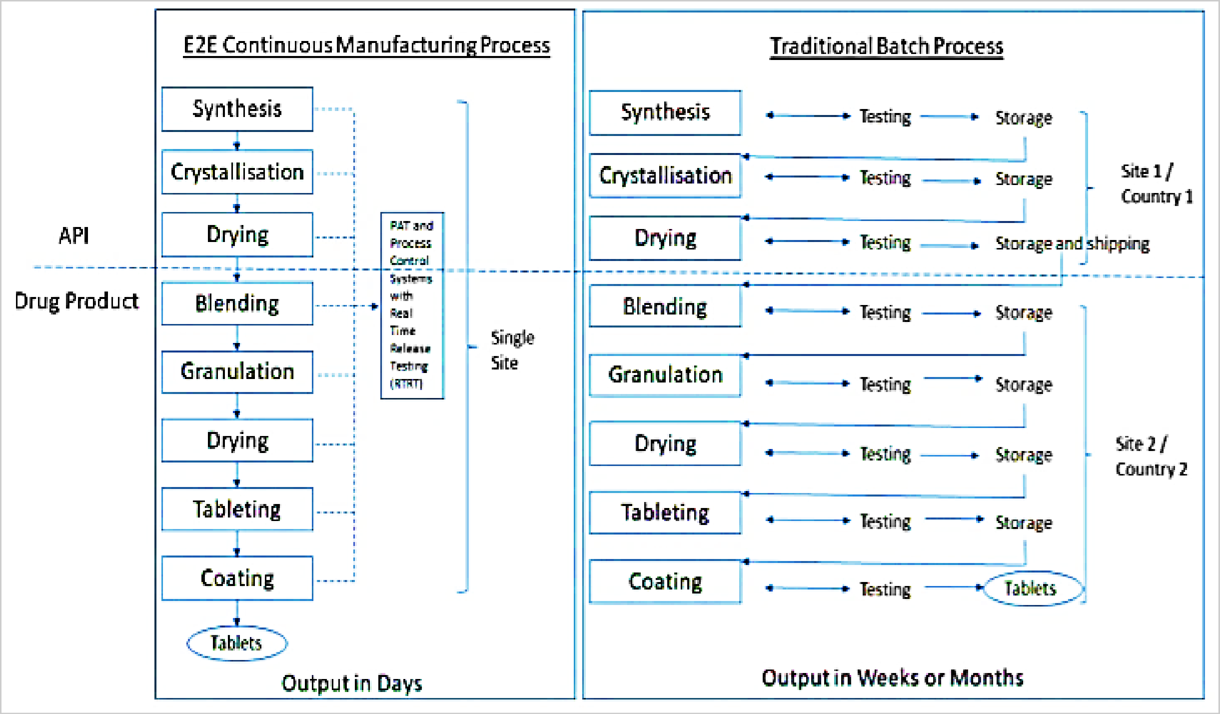


Figure I.2. Schematic of a continuous manufacturing end-to-end (E2E) process compared to a traditional batch process (Lee and al., 2015).

I.9.1. Benefits of adopting CM

In CM products are made from start to finish with no hold times or breaks in the production line. Designed for increased agility and flexibility, this production method offers greater control over manufacturing processes, resulting in numerous benefits. In table I.5, benefits of adopting CM are analysed.

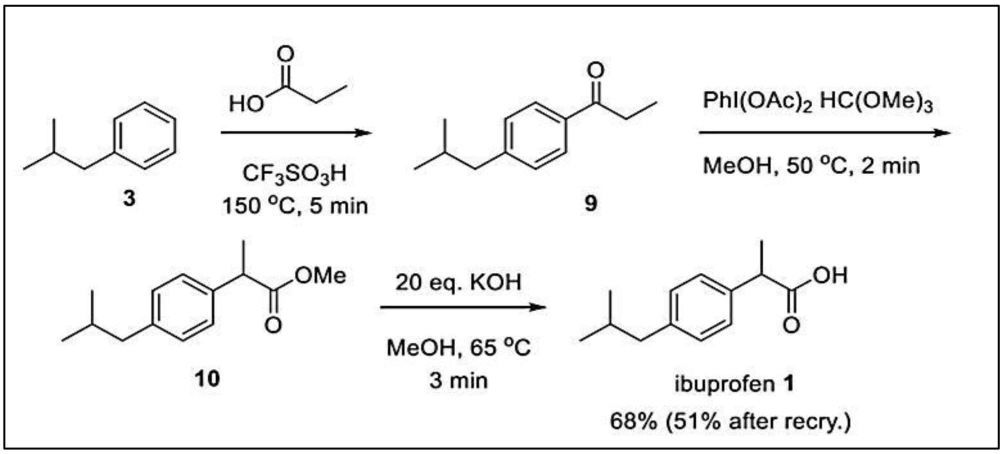
Table I.5. Benefits of adopting CM (Lee and al., 2015; Vanhoorne and Vervaet, 2020; Burcham and al., 2018)

Faster and leaner transition from development to commercial scale	- Same equipment used during development, clinical supply manufacture and commercial production with batch sizes accommodated by changing run times. - Shorter cycle times - More rapid development
Shorter supply chains	- All operations conducted on one piece of equipment in one location without hold-ups and inter-site transfers between manufacturing stages. - Improved stability as no intermediate holding periods
Supply chain security	-Enhanced domestic manufacture with reliance on high technology rather than low-cost labour. -Shorter manufacturing times meaning longer product shelf lives
Improved product quality	-Domestic manufacture. -In-process monitoring, feedback and feed-forward controls. Maintenance of a state-of-control. -Reduced dependence on end-product testing. -Decreased regulatory oversight—frees resources for other higher-risk areas. -Fully aligned with principles of Quality by Design (QbD).
Cost benefits (after initial investment)	-Lower production costs. -Improved utilization of equipment. -Lower personnel requirements. -Smaller footprint.
Supply chain responsiveness	-Batch sizes tailored to requirements by adjusting run times. -Ability to respond rapidly to demands.
Patient benefits	-More suited to niche/personalized products. -Alternative manufacturing technologies (e.g., active pharmaceutical

	ingredient (API) printed or sprayed onto a dosage form). -Lower risk of stock-outs.
Societal benefits	-Less environmental impact (less use of solvents, lower energy costs). -Less waste /improved yields. Lowered risk that a whole batch will need to be rejected if it fails end-product testing. -Higher process intensification (less use of space, energy and raw materials). -Improved safety (reduced handling and exposure to materials, easier cleaning). -Source of high-tech job.

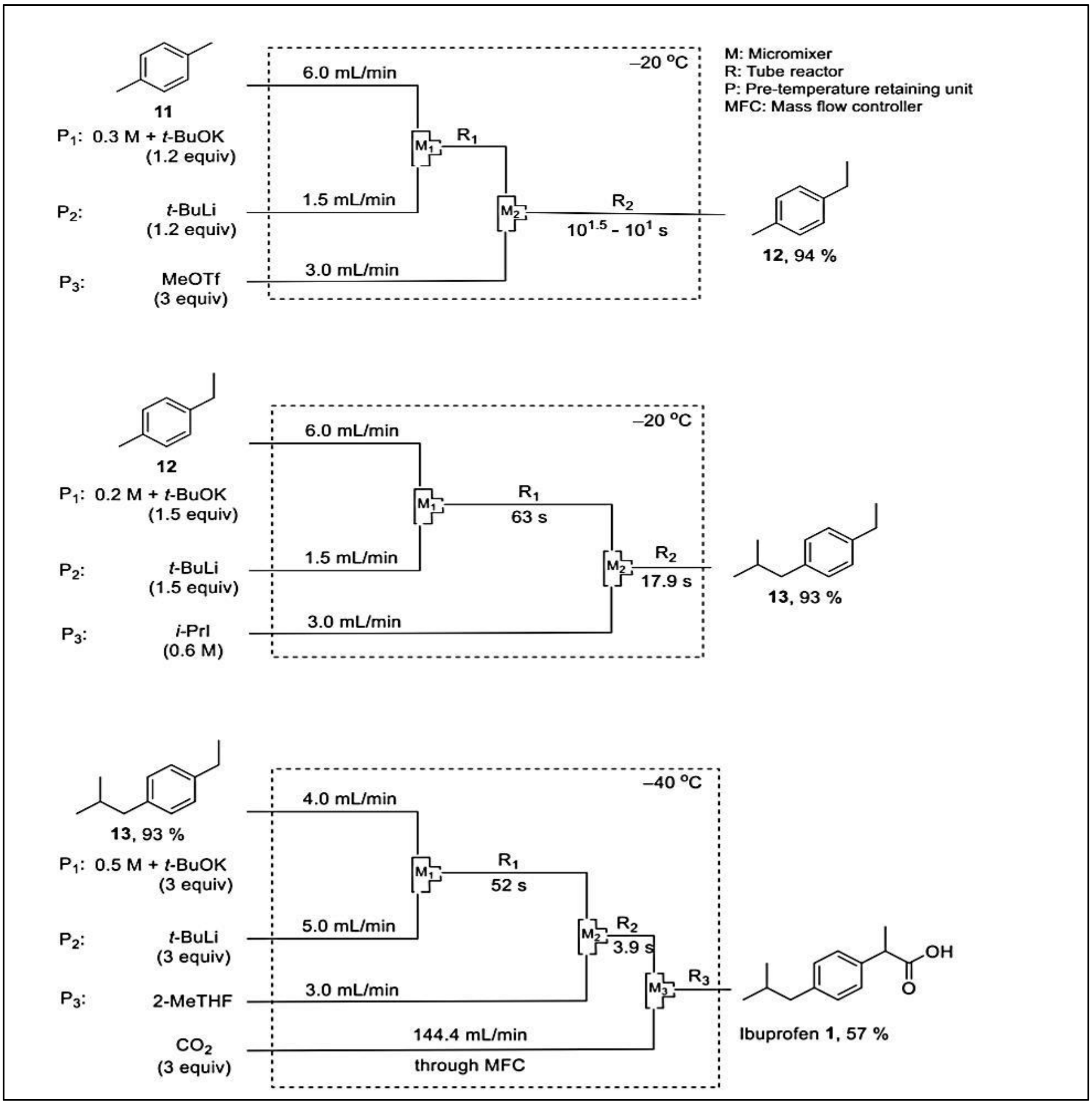
I.9.2. Application of continuous-flow synthesis for ibuprofen

The application of continuous-flow synthesis for ibuprofen is shown in Scheme I.5 (Mason and al., 2007). This synthetic route adapts the iodine-mediated 1,2-aryl migration reaction. McQuade group used trifluorosulfonic acid as a reaction catalyst instead of the conventional reagent, aluminum chloride, to achieve continuous-flow synthesis. Aluminum byproducts are incompatible in further steps. The next step was the 1,2-aryl migration reaction. Finally, saponification of the methyl ester functionality afforded ibuprofen as a light orange solid. It is noteworthy that the reaction could be completed in 10 min using a flow reactor with a 68% overall yield (51% after recrystallization). Moreover, the simplicity and efficiency of this synthetic process makes it likely to satisfy the unmet need for improved ibuprofen synthesis (Bogdan and al., 2009).



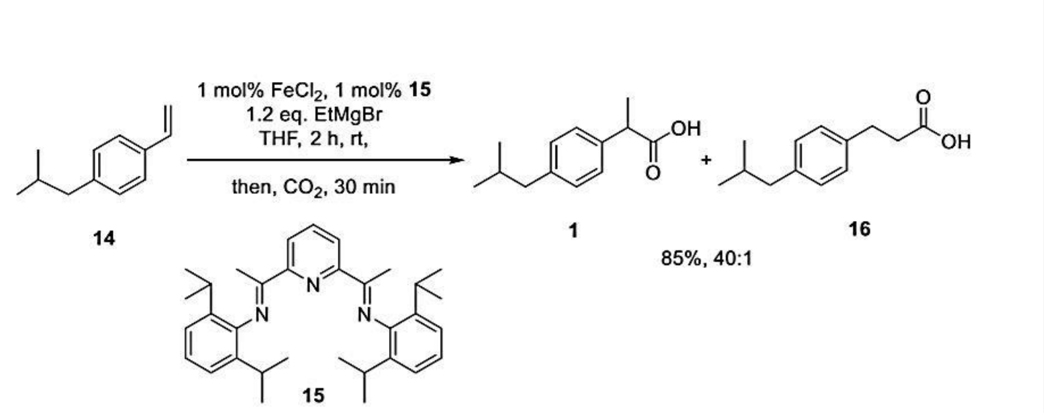
Scheme I.5. Synthetic strategy for continuous-flow synthesis of ibuprofen.

Another approach employing continuous-flow synthesis, reported in 2019, is shown in Scheme I.6. This synthesis involves direct alkylation of the benzylic anion via ‘superbase’-mediated deprotonation. Starting from p-xylene, in situ generated ‘superbase from KOtBu and tBuLi afforded the desired benzylic anion to meet with adequate electrophiles sequentially. After 10 min, the process, which employed the use of MeOTf, iPrI, and CO2, produced 2.3 g ibuprofen (50% in three steps). The readily available starting material and repeated usage of the mixed base increases the cost-effectiveness of this approach. However, the strong basicity of this procedure still requires improvement for industrial purposes (Lee and al., 2019).



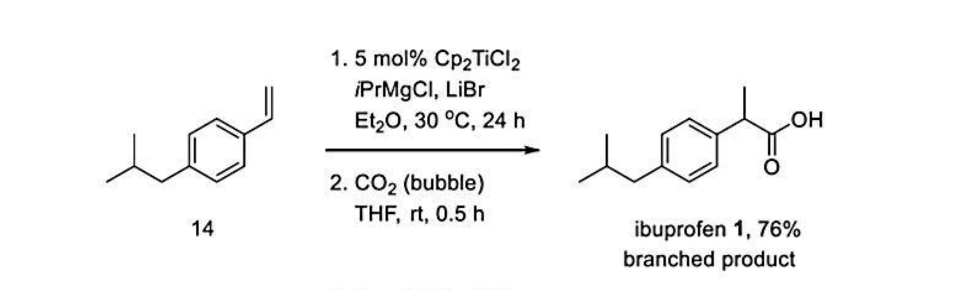
Scheme I.6. Continuous-flow synthesis of ibuprofen using C-H metalation. THF; tetrahydrofuran. Tf; trifluoromethansulfonyl.

The construction of a 2-arylpropionic acid skeleton inspired hydrocarboxylation, which is crucial for ibuprofen synthesis. Iron-catalyzed hydrocarboxylation, as reported by Thomas et al., is shown in Scheme I.7 (Greenhalgh and Thomas, 2012). Although hydrocarboxylation of styrene was expected to introduce the ibuprofen skeleton, the regioselectivity hampered it. However, the highly selective addition of CO2 was possible by employing an iron catalyst and pyridine ligand 15**.**



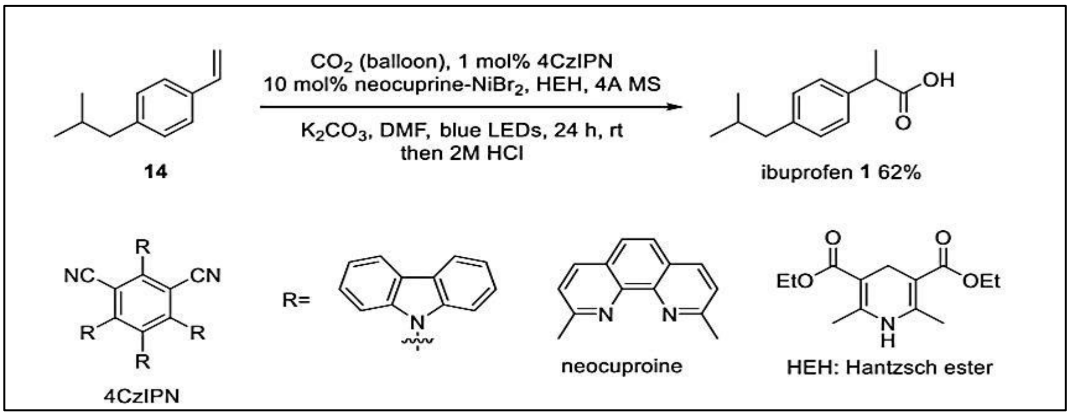
Scheme I.7. Iron-catalyzed hydrocarboxylation for ibuprofen synthesis.

Hydrocarboxylation of styrene using Cp2TiCl2 catalyst, reported by the Xi group in 2016, is shown in scheme I.8 (Shao and al., 2016). For this approach, the regioselectivity of the styrene moiety was screened using various Grignard reagents and additives.



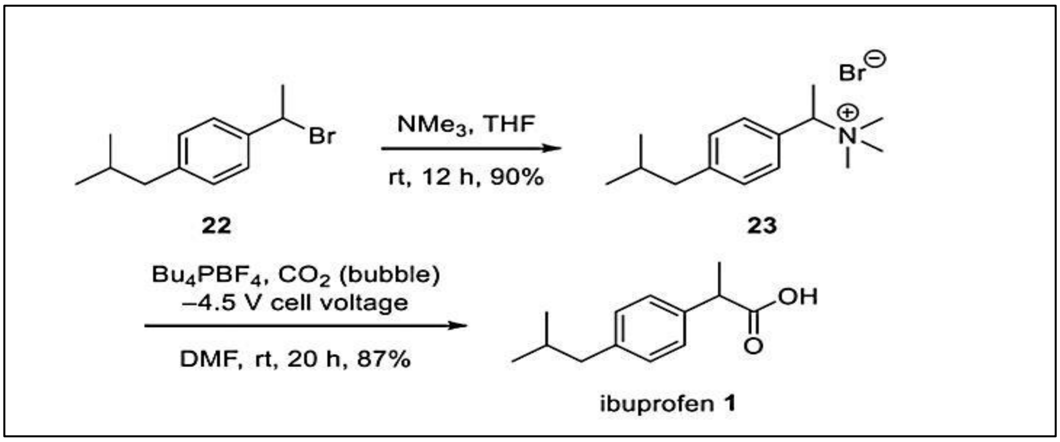
Scheme I.8. Titanium-mediated hydrocarboxylation for ibuprofen synthesis. Cp; cyclopentadienyl.

Regioselective hydrocarboxylation was also performed using a nickel catalyst in the presence of visible light, such as a blue LED, and is shown in scheme I.9. Hantzsch ester molecular sieves, and nickel catalyst were added with the aid of visible light. Conversely, König group used a neocuproine ligand to amplify the regioselectivity of this reaction. Although this reaction system uses various ligands for ibuprofen synthesis, visible-lightassisted room-temperature reactions may be valuable for environmentally friendly industrial synthesis (Meng and al., 2018).



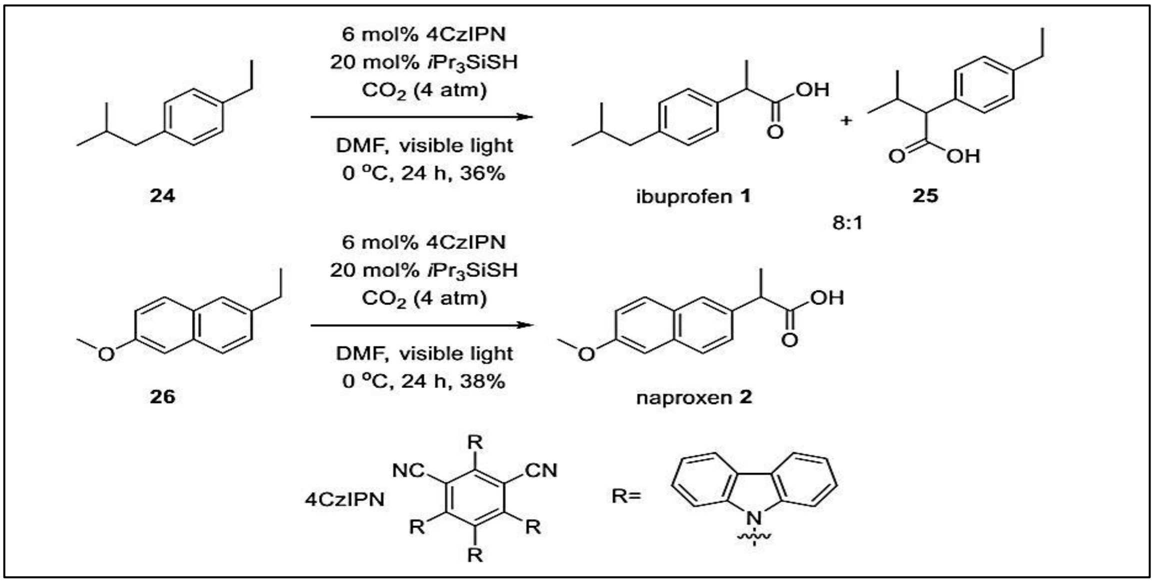
Scheme I.9. Visible light combining regioselective carboxylation for ibuprofen synthesis.

The conversion shown in scheme I.10, features electrochemical coupling of quaternary ammonium bromide **23** from benzylic bromide **22** with CO2 without further metal catalysts, complex ligands, or external reducing agents. As the voltage apparatus is renewable, this type of conversion could provide a solution the green synthesis of NSAIDs (Yang and al., 2019).



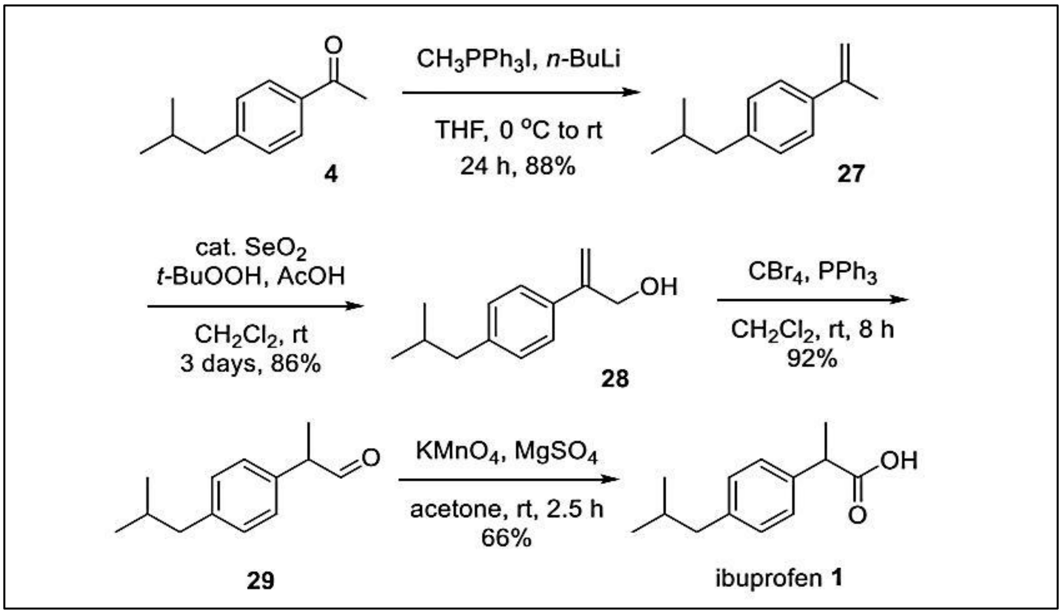
Scheme I.10. Electrochemical carboxylation for ibuprofen synthesis (Yang and al., 2019)

A more direct CO2 addition from benzylic C-H activation through photo-activation was performed in 2019. After König et al. reported blue LED-mediated photocarboxylation (as shown in Scheme I.5), they also attempted to add CO2 to the alkyl benzene substrate, which is readily available from commercial sources. Scheme I.11 shows the results of this endeavor. The resulting benzylic radical was then reduced to a carbanion intermediate via electron transfer from 4CzIPN. Finally, the resultant benzylic anion intermediate reacted with CO2 to produce the desired 2-arylpropionic acid skeleton. Visible light was necessary to complete the reaction (Michigami and al., 2017).



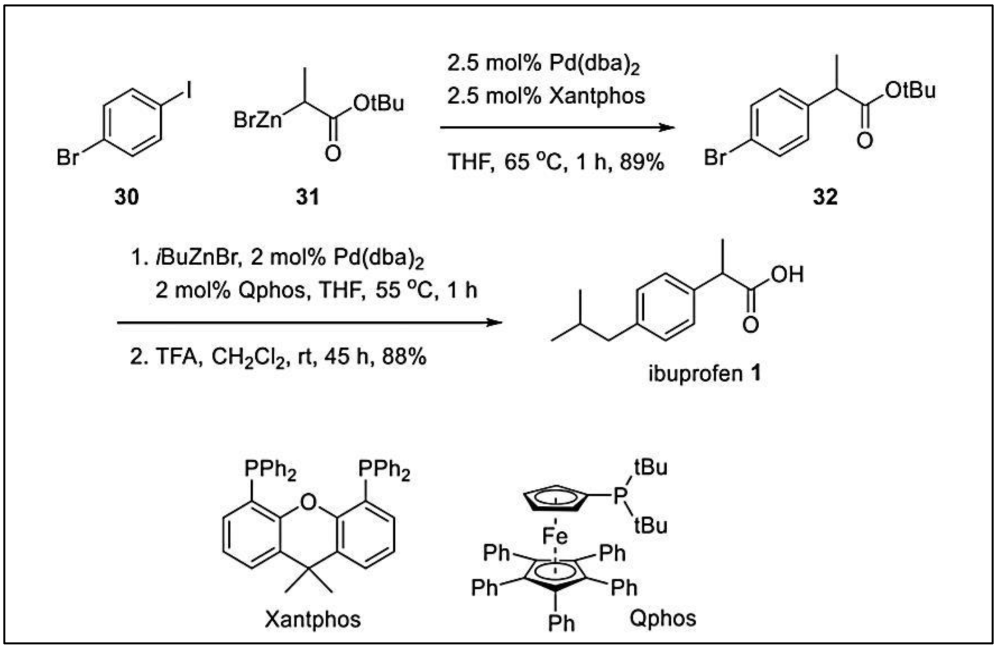
Scheme I.11. Photo-chemical carboxylation of alkyl benzene substrate for ibuprofen synthesis.

Another synthetic protocol for ibuprofen synthesis is summarized in scheme I.12. It was attempted to substitute allylic alcohol **28** by the allylic oxidation of terminal methylene **27**. However, they found that, unexpectedly, isomeric aldehyde **29** was obtained as the major product. After the mechanistic study and optimization of the reaction conditions, aldehyde **29** was produced with 92% yield, suggesting that uneventful oxidation of the aldehyde afforded ibuprofen in good yield (Gong and al., 2012).



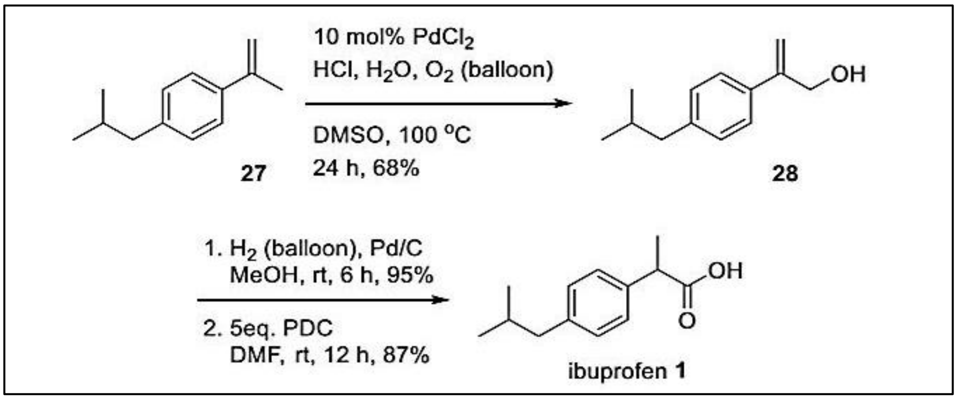
Scheme I.12. CBr4/PPh3-mediated isomeric oxidation protocol for ibuprofen synthesis (Gong and al., 2012)

A chemoselective aromatic coupling approach has also been studied and is shown in scheme I.13. In 2014, Zhang group published sequential coupling with an aromatic halide with zinc enolate, followed by an alkyl zinc reagent. Although this procedure requires complex ligands and metals, the required reaction sequence is simple.



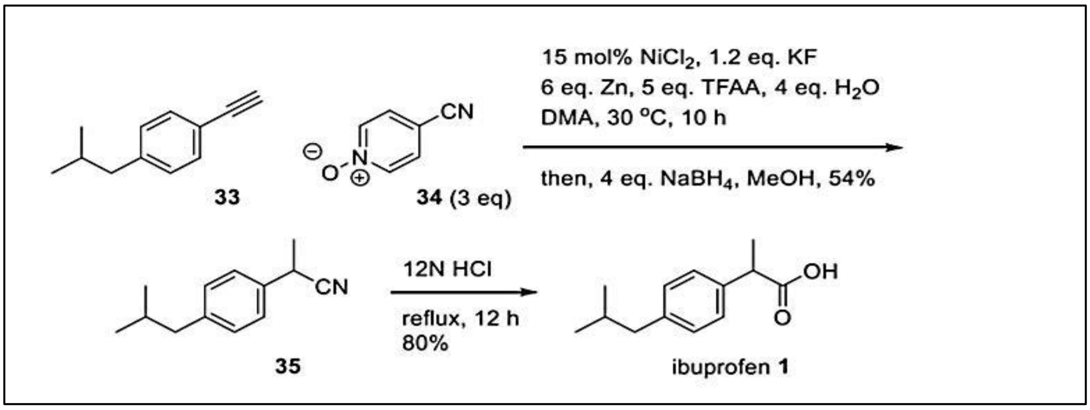
Scheme I.13. Reformatsky–Negishi approach for ibuprofen synthesis (Wong and al., 2014).

A Pd-catalyzed allylic oxidation procedure was also developed and is shown in scheme I.14. Although this conversion can be performed using SeO2/t-BuOOH as described earlier, Jiang group used oxygen gas and catalytic PdCl2. The resulting allylic alcohol 28 could be transformed into ibuprofen by employing a reduction /oxidation sequence. A novel synthetic route for ibuprofen is thus possible (Li and al.,2018).



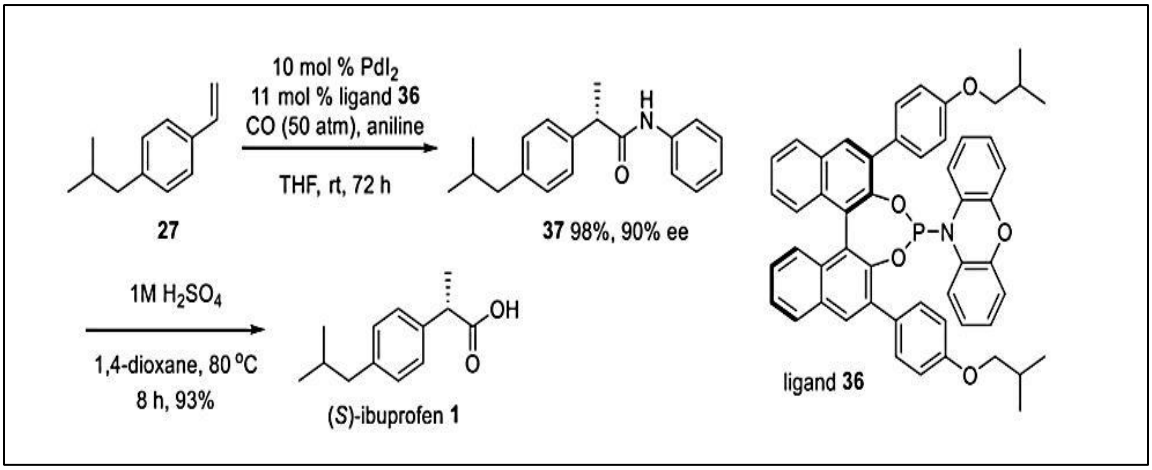
Scheme I.14. Aerobic oxidation approach for ibuprofen synthesis. DMSO; dimethylsulfoxide, PDC; pyridinium dichlorochromate (Li and al.,2018)

Another impressive strategy was developed by adding cyanide to aromatic alkynes as shown in Scheme I.15. For Markovnikov's addition of cyanide, 4-cyanopyridine N-oxide **34** was adapted for cyanide supply. After the addition of cyanide to afford terminal methylene, it underwent one-pot reduction with NaBH4. Therefore, it was possible to produce substituted benzyl cyanide **35** using this strategy, which could be transformed into ibuprofen via simple acidic hydrolysis. However, its unique synthetic approach and moderate chemical yield are highly valuable (Chen and al., 2019).



Scheme I.15. Alkyne-cyanation approach for ibuprofen synthesis. TFAA; trifluoroacetic anhydride, DMA; N,N-dimethylacetamide.

Although ibuprofen has been commercialized as a racemic mixture, enantiomerically pure (S)-ibuprofen has better efficacy and potency. Scheme I.16 is a good example of this endeavor. Incorporation of CO and aniline into the styrene **27** was accomplished enantiomerically pure manner. It features asymmetric Markovnikov-type hydroaminocarbonylation of styrene with catalysis of Pd and phosphoramidite ligand **36** (Yao and al., 2021).



Scheme I.16. Asymmetric synthesis of (S)—ibuprofen.

I.10. Conclusion

In conclusion, ibuprofen stands as a widely utilized and effective nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Its ability to inhibit the production of prostaglandins makes it valuable in managing various conditions, from minor aches and pains to chronic inflammatory diseases. Its accessibility over-the-counter and prescription forms underscores its versatility for different levels of pain and inflammation.

While ibuprofen provides relief for many, it is crucial to use it responsibly, adhering to recommended dosages and guidelines. Potential side effects, particularly those related to the gastrointestinal system, should be considered, and individuals with specific health concerns should consult healthcare professionals before use.

Chapter II.

PROCESS MODELING

II.1. Introduction

Typically, a continuous flow process is run, on laboratory scale, in the socalled “microreactor”, a small-diameter device in which the reaction takes place under rigorously controlled conditions in a confined space. Due to the small volume required, flow processes can be used to perform a fast screening of the reaction conditions, and then, the process can be performed on larger continuous reactors (scaling-up).

In this chapter, we present a flowsheet of a laboratory scale process that operates in continuous mode to produce ibuprofen. This process passes by three main reactions using a series of three plug flow reactors (PFRs). Depending on a synthesis study and mass balance equations, we calculate the flow changes of each component in all three reactors. For industrial scale, we chose a process that can manufacture 200 tons per year as an example.

II.2. Flowsheet description

The flowsheet considered here is an adaptation of a published continuous flow organic synthesis which relies on a series of three plug flow reactors (PFRs) for the production of ibuprofen. The continuous organic synthesis and purification flowsheet considered here is illustrated in (figure II.1). (Bogdan et al., 2009, Britton and Raston, 2017, Jolliffe and Gerogiorgis, 2015; 2016, Horáková and Kočí, 2022, Mureşan, 2018, Mustafa and al., 2022, Papadakis and al., 2016, Yang and al., 2022)

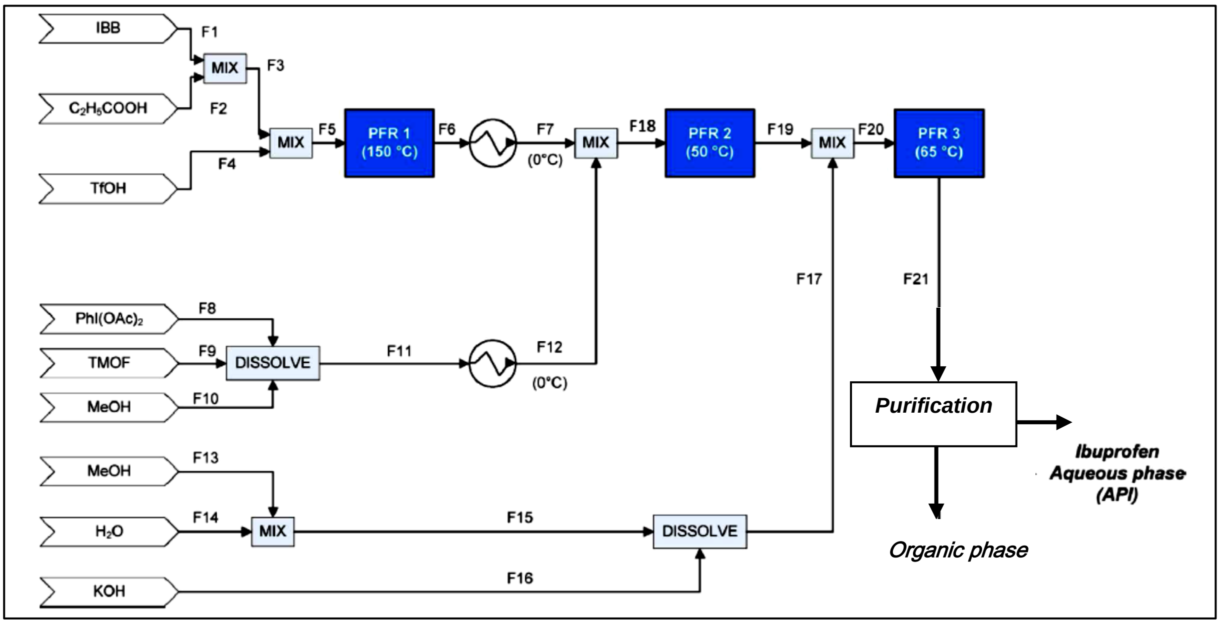
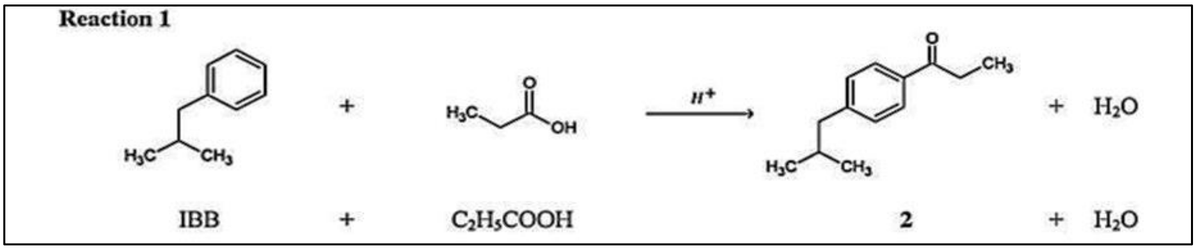


Figure II.1. Process flowsheet for continuous production of ibuprofen (Jolliffe and Gerogiorgis, 2015; 2016, Bogdan et al., 2009)

II.2.1. Reaction 1: Friedel–Crafts acylation

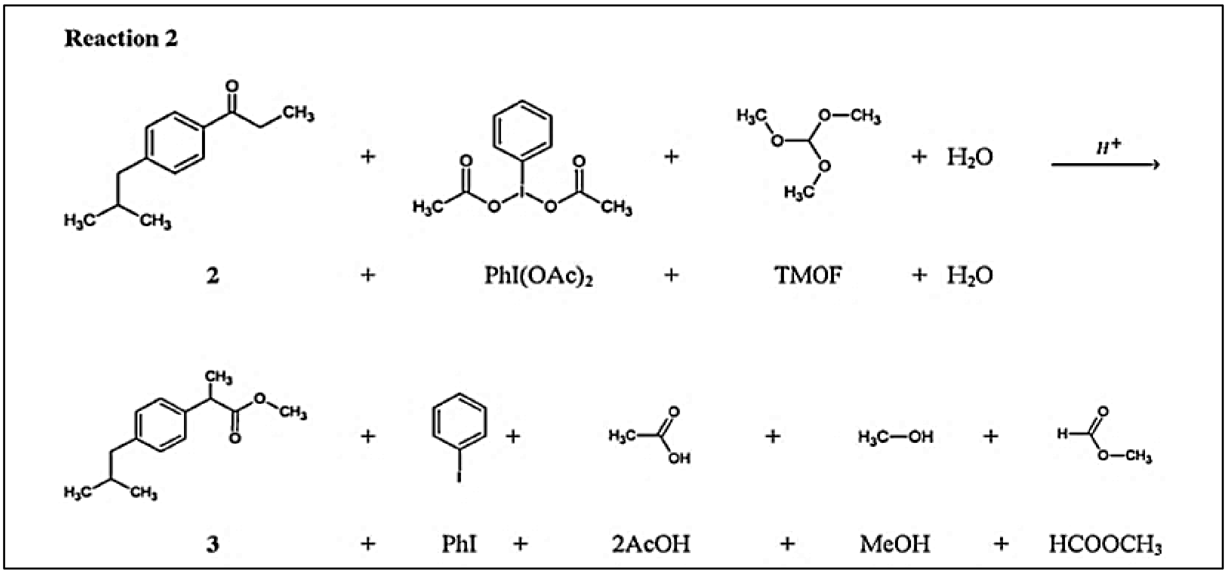
Isobutylbenzene (IBB) is mixed with propanoic acid. The resulting stream is then mixed with neat triflic acid (TfOH, an acid catalyst) and the mixture enters the first reactor, operated at 150°C: IBB undergoes Friedel–Crafts acylation to produce 1-(4-isobutylphenyl) propan-1-one (intermediate **2**) with reported conversions of 91%, and the reactor outlet stream is cooled to 0°C.+



Scheme II.1. Reaction 1: Friedel–Crafts acylation

II.2.2. Reaction 2: PhI(OAc)2-mediated 1,2-aryl migration

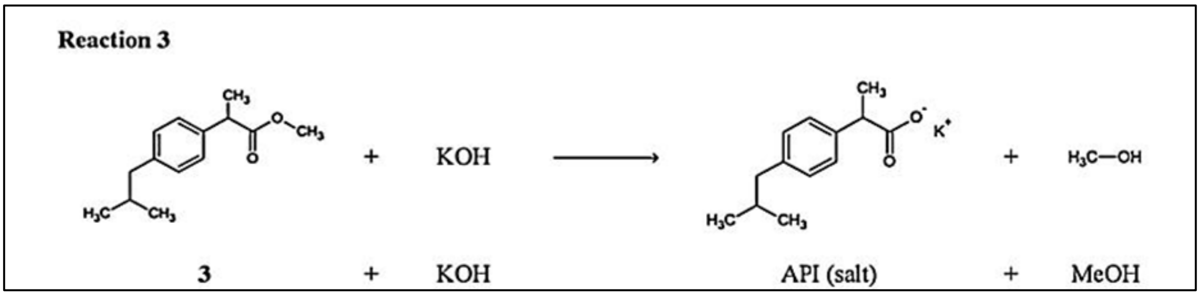
Diacetoxyiodobenzene, $PhI(OAc)_2$, is dissolved with trimethyl orthoformate (TMOF) in methanol (MeOH). The resulting stream is cooled to 0°C before mixing with the cooled first reactor product. The combined stream is fed into the second reactor, where intermediate **2** undergoes $PhI(OAc)_2$-mediated 1,2-aryl migration to produce methyl 2-(4-isobutylphenyl) propanoate (intermediate **3**) with 98% conversion and TfOH again acting as acid catalyst. The second reactor is operated at 50°C: its product is mixed with potassium hydroxide (KOH) dissolved in a methanol–water mixture and fed into the third reactor.



Scheme II.2. Reaction 2: PhI(OAc)2-mediated 1,2-aryl migration

II.2.3. Reaction 3: base hydrolysis

In the third reactor, intermediate **3** is saponified (base hydrolysed) to the salt form of ibuprofen with 99% conversion to K-ibuprofen, and a continuous final separation has been used to separate and purify ibuprofen. An important mass balance assumption is that the product of the third reactor is entirely acidified to obtain a potassium-free acid form of ibuprofen, as the salt obtained from the third reaction is unsuitable for pharmaceutical formulations (Bogdan et al., 2009).



Scheme II.3. Reaction 3: base hydrolysis

II.2.4. Ibuprofen separation

A continuous final separation step after the third reactor is essential for a CPM process, to obtain Ibuprofen (API) stream which is pure enough to be fed to secondary (downstream) processing. While the continuous synthesis of the API has lately been established at the lab-scale level focus mainly on the reactions leading to the ibuprofen salt, the purification section are still treated with batch procedures. Many variables need to be accounted for and few reference data are available, especially those needed for a reliable estimation of the separation in a continuous plant.

An exemplary flowsheet of the above process is given by Jolliffe and al., 2016: In continuous contacting tank, the incoming reactor product stream is acidified by HCl (30%). It is assumed that the product obtained through the 3rd reactor is entirely acidified to achieve a potassium-free acid form of ibuprofen and avoid the formation of the salt which is unable to use for pharmaceutical formulations. The resulting acidified stream then proceeds to a component separator operating at 65◦C.

II.3. Mass balance calculations

Performing PFR reactor design requires the calculation of the process mass balances. The starting point is a synthesis study by Bogdan et al., 2009:

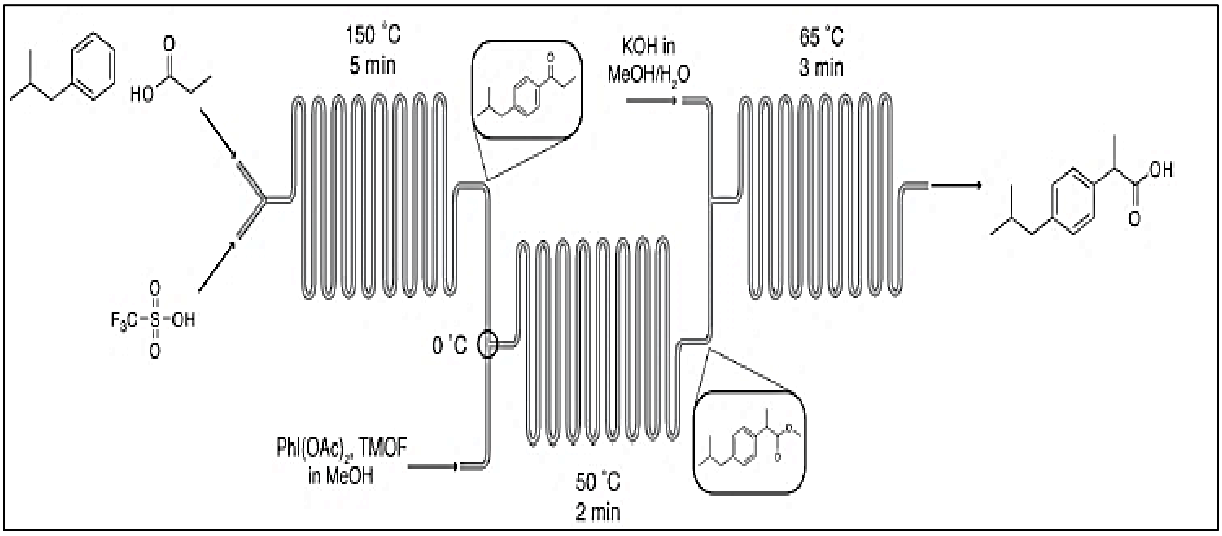


Figure II.2. Continuous Flow Ibuprofen Isolated Yield Experiment (Bogdan et al., 2009, Britton and Raston, 2017, Horáková and Kočí, 2022)

For the first reactor, a 50 cm segment of PFA tubing was wrapped into a pattern and submerged into an oil bath set to 150 °C. In one syringe was placed a solution of isobutylbenzene and propionic acid and in another syringe was placed neat triflic acid. The products were cooled to 0°C.The two syringes were placed on separate syringe pumps and flow rates were attenuated to provide the desired stoichiometry. The isobutylbenzene/propionic acid syringe was set to 15.1 µL.min^{-1} (64.9 µmol.min^{-1}) and the triflic acid syringe was set to 28.7 µL.min^{-1} (324.6 µmol.min^{-1}). The flow was initiated and the reaction stream was allowed to pass through the tubing:

To the outlet of the first reactor was attached an ETFE tee using a flangeless nut. An additional syringe was connected to the tee, a solution of $PhI(OAc)_2$ and TMOF was placed in this one. The outlet of the tee was connected to an 80 cm segment of PFA tubing wrapped into a pattern and submerged into an oil bath set to 50 °C.

In the second reactor, the additional syringe was set to 131.5 µL.min^{-1} (65.8 µmol $PhI(OAc)_2$.min^{-1}, and 259.6 µmol TMOF.min^{-1}). The tee was submerged in an ice bath to prevent off-gassing from mixing the two phases.

To the outlet of the second reactor was attached an ETFE tee using a flangeless nut. An additional syringe was connected to the tee, a solution of KOH in MeOH/H2O (4:1 v/v) was placed in this syringe. The outlet of the tee was connected to a 300 cm segment of PFA tubing, wrapped into a pattern and submerged into a water bath set to 65 °C.

In the third reactor, the syringe where was placed the KOH solution was set to 260 µL. min^{-1} (1300 µmol min^{-1}).

II.3.1. Principle of mass balance calculation:

The following assumptions have been made in the process mass balances:

- Reactions occur only inside the PFR reactors and not in any of the lines connecting them.
- Isothermal operation is ensured in all reactors via suitable heating media and thermostats.
- Temperature changes cause no phase transformation or precipitation affecting the flow.
- Side-reactions between all compounds are negligible.

Considering the following relations, we calculate the advancement of each reaction, then the molar flow rate for each component. The basis of calculation is always the limiting reactant:

$$\begin{cases} F_i = F_{A,0} + \surd_A.\zeta j & \text{(II.1)} \\ X_j = \dfrac{F_{A,0} - F_A}{F_{A,0}} = \dfrac{-(F_A - F_{A,0})}{F_{A,0}} & \text{(II.2)} \end{cases}$$

From the above equations, we obtain the advancement of each reaction “j”, which depends on the limiting reactant conversion and its initial molar flow rate:

$$X_j = \frac{-\surd_A \,.\, \zeta j}{F_{A,0}} \Rightarrow \zeta j = \frac{-Xj \,.\, F_{A,0}}{\surd_A} \tag{II.3}$$

Where:

ζj: advancement of reaction *“A”* in µmol.min^{-1};

X_j: limiting reactant conversion *“A”* in reaction *“j”;*

F_A: molar flow rate of limiting reactant *“A”* leaving the reactor in µmol.min^{-1};

$F_{A,0}$: molar flow rate of limiting reactant *“A”* fed the reactor in µmol.min^{-1};

$\surd_A$: stoichiometric coefficient of limiting reactant *“A”.*

Knowing the advancement of each reaction *“ζj”* and the initial molar flows of the component, we can make molar balances in each reactor, using equation (II.1).

Mass balances are obtained by converting the results from µmol.min^{-1} to g.h^{-1} by:

$G_i = F_i \,.\, 10^{-6} \,.\, M_i * 60$ (II.4)

Where:

G_i: Mass flow rate in g.h^{-1};

F_i: Molar flow rate in µmol.min^{-1};

M_i: molecular weight in g.mol^{-1}.

II.3.2. Mass balance calculation reactor 1

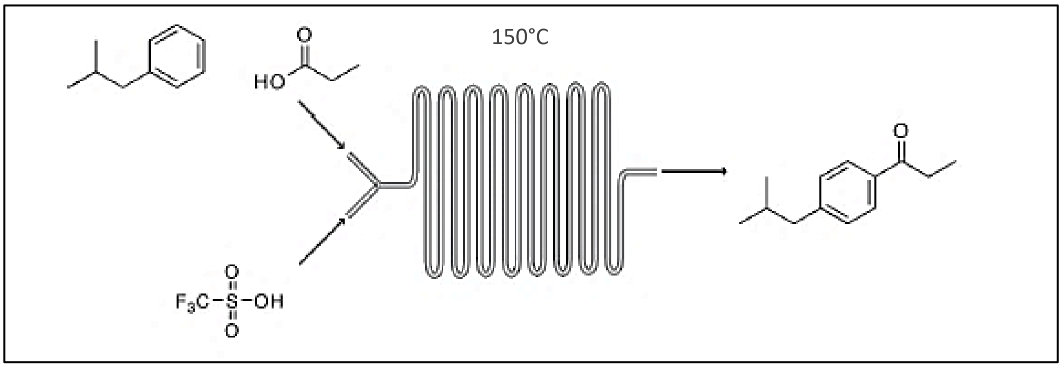


Figure II.3. Representative flow Friedel-Crafts Acylation (Bogdan et al., 2009).

a/ Calculation of the advancement:

$$\begin{cases} \text{Conversion of limiting reactant (IBB): } X_1 = 91\%; \\ \text{Molar flow rate of } IBB \text{ fed the reactor: } F_{\text{IBB},0} = 64{,}9\ \mu mol.min - 1 \end{cases}$$

The Advancement of the first reaction: $\zeta_1 = \frac{-X_1 \cdot F_{\text{IBB},0}}{-1} = 59.059\ \mu mol.min^{-1}$

b/ Calculation of reactants and products flow rates:

- *For Isobutylbenzene (IBB:)*

$F_{IBB} = F_{IBB,0} - \zeta_1 = 64.5 - 59.059 = 5.841\ \mu mol.min^{-1}$

- *For Propanoic acid:*

$F_{Prop} = F_{IBB} = 5.841\ \mu mol.min^{-1}$

- *For 1-(4-isobutylphenyl) propan-1-one (intermediate 2):*

$F_{2,1} = F_{2,0} + \zeta_1 = 0 + 59.059 = 59.059\ \mu mol.min^{-1}$

- *For Water:*

$F_{H2O,1} = F_{H2O,0} + \zeta_1 = 0 + 59.059 = 59.059\ \mu mol.min^{-1}$

The results of the molar balance in the first reactor are reported in table II.1:

Table II.1. Process molar balance in reactor 1 (µmol.min^{-1}).

Component	Stream (µmol.min^{-1})					
	F1	F2	F3	F4	F5	F6
IBB	64.9	0	64.9	0	64.9	5.841
C_2H_5COOH	0	64.9	64.9	0	64.9	5.841
TFOH (catalyst)	0	0	0	324.6	324.6	324.6
2	0	0	0	0	0	59.059
H_2O	0	0	0	0	0	59.059
Total	64.9	64.9	129.8	324.6	454.4	454.4

The flow changes of each component entering or leaving the first reaction are summarized in table II.2 and 3D histogram (figure II.4):

Table II.2. Components molar and mass flow changes in reactor 1.

Component	Stoichiometric coefficient	Flow in		Flow change		Flow out	
		µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}
IBB	-1	64.9	0.523	-59.059	-0.476	5.841	0.047
C_2H_5COOH	-1	64.9	0.288	-59.059	-0.262	5.841	0.026
TFOH	-	324.6	2.923	0	0	324.6	2.923
2	+1	0	0	+59.059	+0.674	59.059	0.674
H_2O	+1	0	0	+59.059	+0.064	59.059	0.064

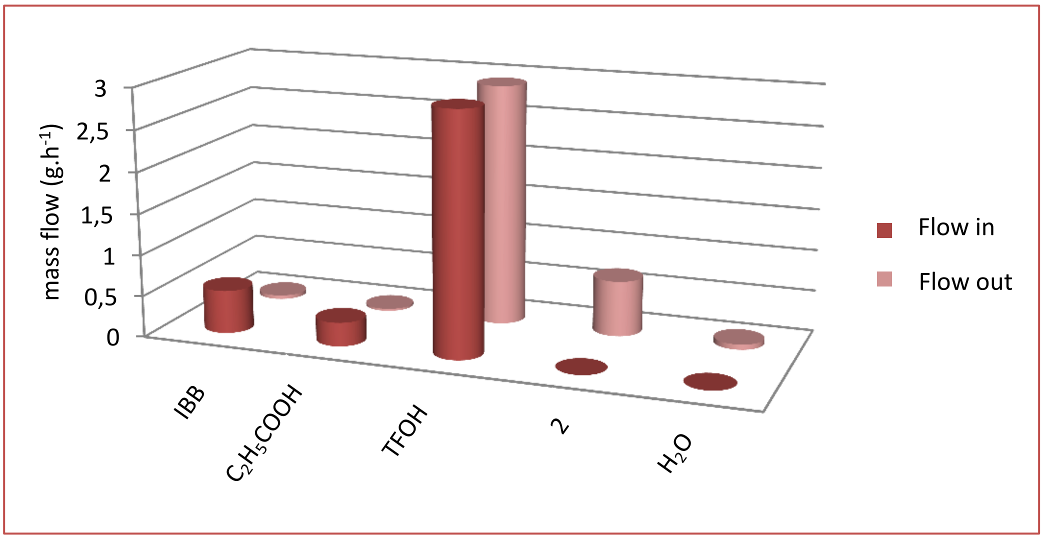


Figure II.4. Components mass flow changes in the first reactor.

As we see in figure II.4, the highest bar represents the catalyst TFOH, which justify the unchanged mass flow. The first two bars represent the reactants IBB and C_2H_5COOH

which are consumed, while the last two bars represent the products intermediate 2 and water which is produced in small quantity compared to the big quantity of intermediate 2.

II.3.3. Mass balance calculation reactor 2

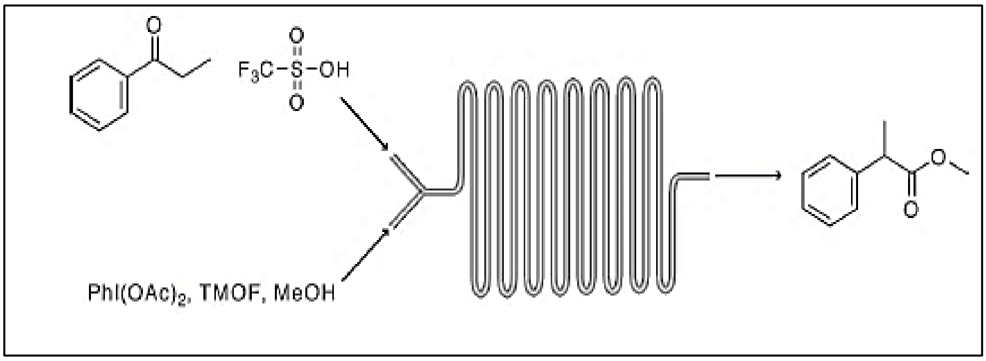


Figure II.5. Representative flow $PhI(OAc)_2$-Mediated 1,2-Aryl Migration(Bogdan et al., 2009).

a/ Calculation of the advancement:

Conversion of limiting reactant (Intermediate 2): $X_2 = 98\%$;

Molar flow rate of intermediate 2 fed the reactor: $F_{2,0} = 59.059\ \mu mol.min-1$;

The Advancement of the second reaction: $\zeta_2 = \frac{-X_2 \cdot F_{2,0}}{-1} = 57.878\ \mu mol.min^{-1}$

b/ Calculation of reactants and products flow rates:

- *For intermediate 2:*

$F_{2,2} = F_{2,1} - \zeta_2 = 59.059 - 57.878 = 1.181\ \mu mol.min^{-1}$

- *For Diacetoxyiodobenzene, $PhI(OAc)_2$:*

$F_{PhI(OAc)2} = F_{PhI(OAc)2,0} - \zeta_2 = 65.8 - 57.878 = 7.922\ \mu mol.min^{-1}$

- *For Trimethyl orthoformate (TMOF):*

$F_{TMOF} = F_{TMOF,0} - \zeta_2 = 259.6 - 57.878 = 201.722\ \mu mol.min^{-1}$

- *For Water:*

$F_{H2O,2} = F_{H2O,1} - \zeta_2 = 59.059 - 57.878 = 1.181\ \mu mol.min^{-1}$

- *For Methyl 2-(4-isobutylphenyl) propanoate (intermediate 3):*

$F_{3,2} = F_{3,0} + \zeta_2 = 0 + 57.878 = 57.878\ \mu mol.min^{-1}$

- *For PhI :*

$F_{PhI} = F_{PhI,0} + \zeta_2 = 0 + 57.878 = 57.878\ \mu mol.min^{-1}$

- *For AcOH :*

$F_{AcOH} = F_{AcOH,0} + 2\zeta_2 = 0 + 2\cdot 57.878 = 115.756\ \mu mol.min^{-1}$

- *For MeOH :*

$F_{MeOH,2} = F_{MeOH,0} + \zeta_2 = 1927{,}223 + 57.878 = 1985{,}101\ \mu mol.min^{-1}$

- *For $HCOOCH_3$:*

$F_{HCOOCH3} = F_{HCOOCH3,0} + \zeta_2 = 0 + 57.878 = 57.878\ \mu mol.min^{-1}$

The results of the molar balance in the second reactor are reported in table II.3:

Table II.3. Process molar balance in reactor 2 (µmol.min^{-1}).

Component	Stream (µmol.min^{-1})						
	F7	F8	F9	F10	F11	F18	F19
IBB	5.841	0	0	0	0	5.841	5.841
C_2H_5COOH	5.841	0	0	0	0	5.841	5.841
TFOH (catalyst)	324.6	0	0	0	0	324.6	324.6
2	59.059	0	0	0	0	59.059	1.181
H_2O	59.059	0	0	0	0	59.059	1.181
PhI(OAc2)	0	65.8	0	0	65.8	65.8	7.922
TMOF	0	0	259.6	0	259.6	259.6	201.722
MeOH	0	0	0	1927,223	1927,223	1927,223	1985,101
3	0	0	0	0	0	0	57.878
PhI	0	0	0	0	0	0	57.878
AcOH	0	0	0	0	0	0	115.756
HCOOCH3	0	0	0	0	0	0	57.878
Total	454.4	65.8	259.6	1927,223	2252.623	2707.023	2822,779

The flow changes of each component entering or leaving the second reaction are summarized in table II.4 and 3D histogram (figure II.6):

Table II.4. Components molar and mass flow changes in reactor 2.

Component	Stoichiometric coefficient	Flow in		Flow change		Flow out	
		µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}
2	-1	59.059	0.674	-57.878	-0.661	1.181	0.013
PhI(OAc)$_2$	-1	65.8	1.272	-57.878	-1.119	7.922	0.153
TMOF	-1	259.6	1.653	-57.878	-0.369	201.722	1.284
H2O	-1	59.059	0.064	-57.878	-0.063	1.181	0.001
TFOH	-	324.6	2.923	0	0	324.6	2.923
3	+1	0	0	+57.878	+0.765	57.878	0.765
PhI	+1	0	0	+57.878	+0.708	57.878	0.708
AcOH	+2	0	0	+115.756	+0.417	115.756	0.417
MeOH	+1	1927,223	3,705	+57.878	+0.111	1985,101	3,816
HCOOCH3	+1	0	0	+57.878	+0.208	57.878	0.208

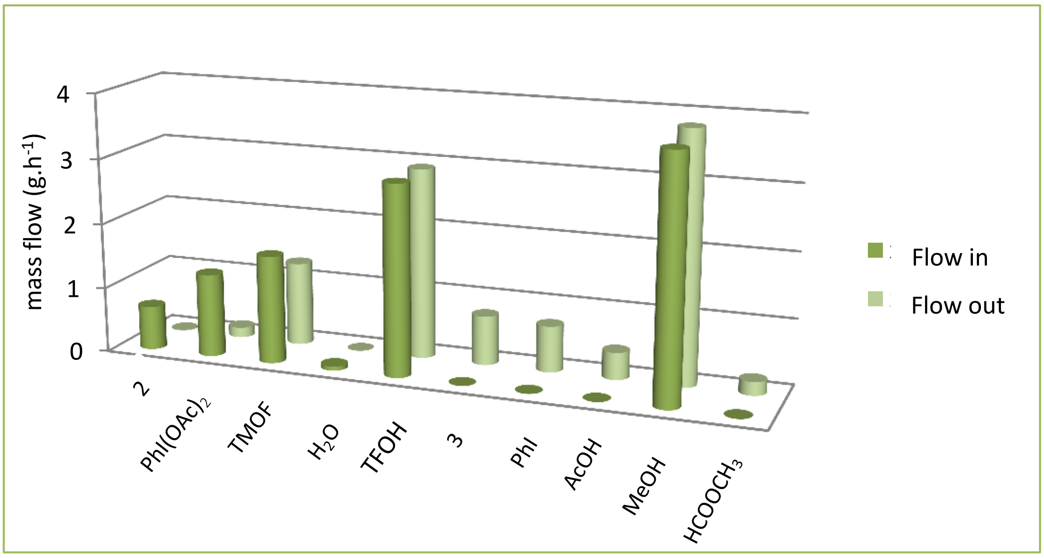


Figure II.6. Components mass flow changes in the second reactor.

As we notice from the figure II.6, the highest bar represents the solvent MeOH introduced in big quantity, also produced in the second reaction. The second highest bar represents the unchanged flow of catalyst TFOH. The reactants 2 and water are almost totally consumed, while the products are produced in different quantities.

II.3.4. Mass balance calculation reactor 3

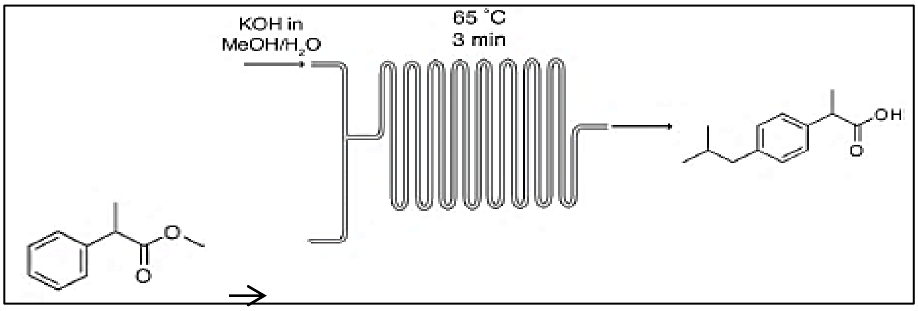


Figure II.7. Representative Flow Base hydrolysis (Bogdan et al., 2009).

d/ Calculation of the advancement:

Conversion of limiting reactant (Intermediate 3): $X_3 = 99\%$;

Molar flow rate of intermediate 3 fed the reactor: $F_{3,2} = 57.878\ \mu mol.min - 1$;

The Advancement of the second reaction: $\zeta_3 = \frac{-X_3 \cdot F_{3,2}}{-1} = 57.299\ \mu mol.min^{-1}$

e/ Calculation of reactants and products flow rates:

- *For intermediate 3:*

$F_{3,3} = F_{3,2} - \zeta_3 = 57.878 - 57.299 = 0.579\ \mu mol.min^{-1}$

- *For potassium hydroxide KOH:*

$F_{KOH,4} = F_{KOH,3} - \zeta_3 = 1300 - 57.299 = 1242{,}701\ \mu mol.min^{-1}$

- *For K-ibuprofen:*

$F_{K\text{-}ibuprofen} = F_{API,0} + \zeta_1 = 0 + 57.299 = 57.299\ \mu mol.min^{-1}$

- *For MeOH:*

$F_{MeOH,3} = F_{MeOH,2} + \zeta_1 = 5286.621 + 57.299 = 5343.92\ \mu mol.min^{-1}$

The results of the molar balances in the second reactor are reported in table II.5:

Table II.5. Process molar balance in reactor 3 (µmol.min^{-1})

Component	Stream (µmol.min^{-1})							
	F19	F13	F14	F15	F16	F17	F20	F21
IBB	5.841	0	0	0	0	0	5.841	5.841
C_2H_5COOH	5.841	0	0	0	0	0	5.841	5.841
TFOH (catalyst)	324.6	0	0	0	0	0	324.6	324.6
2	1.181	0	0	0	0	0	1.181	1.181
PhI(OAc2)	7.922	0	0	0	0	0	7.922	7.922
TMOF	201.722	0	0	0	0	0	201.722	201.722
PhI	57.878	0	0	0	0	0	57.878	57.878
AcOH	115.756	0	0	0	0	0	115.756	115.756
HCOOCH3	57.878	0	0	0	0	0	57.878	57.878
3	57.878	0	0	0	0	0	57.878	0.579
KOH	0	0	0	0	1300	1300	1300	1242,701
H2O	1.181	0	1854.42	1854.42	0	1854.42	1855.601	1855.601
MeOH	1985,101	3301.42	0	3301.42	0	3301.42	5286.621	5343.92
K-Ibuprofen	0	0	0	0	0	0	0	57.299
Total	2822,779	3301.42	1854.42	5155.84	1300	6455.84	9278.619	9278.719

The flow changes of each component entering or leaving the third reaction are summarized in table II.6 and 3D histogram (figure II.8):

Table II.6. Components molar and mass flow changes in the reactor 3.

Component	Stoichiometric coefficient	Flow in		Flow change		Flow out	
		µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}	µmol.min^{-1}	g.h^{-1}
3	-1	57.878	0.765	-57.299	-0.757	0.579	0.008
KOH	-1	1300	4,377	-57.299	-0.192	1242,701	4,184
MeOH	+1	5286.621	10.163	+57.299	+0.110	5343.92	10,273
H2O	-	1855.601	2.006	-	-	1855.601	2.006
K-Ibuprofen	+1	0	0	+57.299	+0.840	57.299	0.840

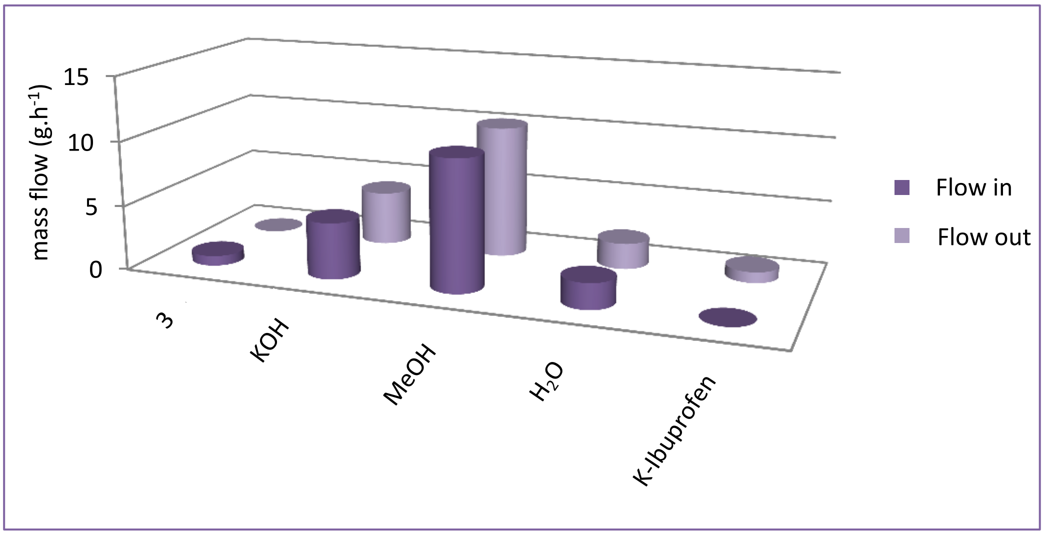


Figure II.8. Components mass flow changes in the third reactor.

As shown in figure II.8, the highest bar represents the solvent MeOH which was introduced with KOH and produced. The second highest bar represents the reactant KOH which is in excess, while the third one represents unchanged water mass flow used as a solvent. The reactant 3 is almost totally consumed and transformed to K-Ibuprofen.

The computed plantwide mass balance relies on experimental conversions reveals that the continuous system presented here can produce 0.840 $g.h^{-1}$ of potassium ibuprofen by using 0.523 $g.h^{-1}$ of isobutylbenzene (IBB), which represents 6.653 kg of potassium ibuprofen annually (using 4.142 kg of IBB) for 330 operating days per Year (about 7920 hours).

II.4. Mass balance calculations for industrial scale (scaling-up)

The production capacity of a plant for manufacturing ibuprofen typically depends on various factors such as the size of the facility, equipment efficiency, production technology, and the demand for this product. Large pharmaceutical manufacturing plants can produce hundreds to thousands of tons annually. The table below represents estimation about the expected raw materials requirements for the studied process that can manufacture 200 tons of potassium ibuprofen annually.

Table II.7: Process mass balance for industrial scale.

Component	Flow in		Flow change		Flow out	
	kmol.h^{-1}	kg.h^{-1}	kmol.h^{-1}	kg.h^{-1}	kmol.h^{-1}	kg.h^{-1}
PFR 1						
IBB	0.117	15.722	-0.107	-14.362	0.010	1.342
C_2H_5COOH	0.117	8.658	-0.107	-7.927	0.010	0.741
TFOH	0.585	87.869	-	-	0.585	87.869
2	0	0	+0.107	+20.361	0.107	20.361
H2O	0	0	+0.107	+1.928	0.107	1.928
PFR 2						
IBB	0.010	1.342	-	-	0.010	1.342
C_2H_5COOH	0.010	0.741	-	-	0.010	0.741
TFOH	0.585	87.869	-	-	0.585	87.869
2	0.107	20.361	-0.105	-19.980	0.002	0.381
H_2O	0.107	1.928	-0.105	-1.892	0.002	0.036
$PhI(OAc)_2$	0.119	38.238	-0.105	-33.820	0.014	4.509
TMOF	0.468	49.691	-0.105	-11.143	0.363	38.522
MeOH	3.476	111.38	+0.105	+3.364	3.581	114.717
3	0	0	+0.105	+23.133	0.105	23.133
PhI	0	0	+0.105	+21.421	0.105	21.421
AcOH	0	0	+0.210	+12.611	0.210	12.611
$HCOOCH_3$	0	0	+0.105	+6.305	0.105	6.305
PFR 3						
IBB	0.010	1.342	-	-	0.010	1.342
C_2H_5COOH	0.010	0.741	-	-	0.010	0.741
TFOH	0.585	87.869	-	-	0.585	87.869
2	0.002	0.381	-	-	0.002	0.381
H_2O	3. 346	60.304	-	-	3.346	60.304
$PhI(OAc)_2$	0.014	4.509	-	-	0.014	4.509
TMOF	0.363	38.522	-	-	0.363	38.522
3	0.105	23.133	-0.104	-22.912	0.001	0.220
PhI	0.105	21.421	-	-	0.105	21.421
AcOH	0.210	12.611	-	-	0.210	12.611
MeOH	9.536	305.52	+0,104	+3.307	9.64	308.827
$HCOOCH_3$	0.105	6.305	-	-	0.105	6.305
KOH	2.345	131.578	- 0.104	-5.835	2.241	125.743
K-Ibuprofen	0	0	+ 0.104	+25.414	0.104	25.414

By extrapolating results to industrial scale using scaling factor from laboratory balances, we found that the process can produce about 25.414 kg.h^{-1} of k-ibuprofen using 15.722 kg.h^{-1} of IBB, which corresponds to 200 tons of k-ibuprofen using 124.518 tons of IBB annually, for 330 operating days per Year (about 7920 hours)..

II.5. Conclusion

In this chapter, a description of continuous flow organic synthesis have been given which relies a series of three plug flow reactors (PFRs) for the production of ibuprofen. A complete reactions scheme was presented, which illustrate all reactants, products and used catalysts. Also, mass balance calculations have been developed for all reactors, with molar and mass flow changes of the components. The laboratory scale synthesis can produce about 0.840 $g.h^{-1}$ (6.653 kg/year) of potassium ibuprofen using 0.523 $g.h^{-1}$ (4.142 kg/year) of isobutylbenzene (IBB). By extrapolating results to industrial scale, we found that the process can produce about 25.414 $kg.h^{-1}$ of k-ibuprofen using 15.722 $kg.h^{-1}$ of IBB, which corresponds to 200 tons of k-ibuprofen using 124.518 tons of IBB annually.

Chapter III.

REACTORS DESIGN

III.1. Introduction

A Plug Flow Reactor (PFR) is a type of chemical reactor widely used in the chemical and process industries for continuous reactions. The PFR design assumes that fluid elements flow through the reactor as plugs, with each plug having uniform properties such as concentration and temperature. Typically, a continuous flow process is run, on laboratory scale, in the socalled “microreactor”, a small-diameter device in which the reaction takes place under rigorously controlled conditions in a confined space, then going to scaling up. The key design considerations include understanding reaction kinetics (rate laws and reaction order), thermodynamics (enthalpy changes), reactor sizing and configuration (reactor volume and length), ensuring efficient heat and mass transfer. In this chapter, we are going to determine these factors depending on experimental data.

III.2. Kinetic parameter estimation

This step is crucial in understanding and modeling chemical reaction systems. It involves determining the values of the parameters that govern the rates of reactions, such as reaction order, rate constants which is essential for the efficient design of a continuous pharmaceutical manufacturing (CPM) process. The applicability of this study is hampered by the scarcity of available experimental data. The minimum required data are: a detailed reaction mechanism network, temperature-dependent reaction kinetic data, and the operating window in which the experiments were conducted. Bogdan et al. (2009) have published kinetic data for the continuous organic synthesis reactions in their study.

The determination of reaction orders and rate constants was achieved through the assessment of various potential kinetic expressions, plotting concentration functions over time, and calculating the respective coefficients of determination (R^2) for each case (Rosen, 2014, Jolliffe and Gerogiorgis, 2015).

III.2.1. Kinetic parameters of the first Reaction

For the first reaction (Friedel-Crafts acylation), we use experimental data by varying the residence time (5, 10 min), reaction temperature (150°C), and feed concentrations:

- Isobutylbenzene feed concentration: $C_{IBB,0}$ = 1.42 M;
- Propanoic acid feed concentration: $C_{C2H5COOH,0}$ = 1.56 M.

$$\textbf{IBB} \quad + \quad \textbf{C}_2\textbf{H}_5\textbf{COOH} \quad \longrightarrow \quad \textbf{Products}$$

$$\text{at } t_0: \quad C_{IBB,0} \qquad C_{C2H5COOH,0}$$

$$\text{at } t: \quad C_{IBB,0}.(1-X_1) \qquad C_{C2H5COOH,0} - C_{IBB,0}\,.X_1$$

a. Zero Order reaction:

The differential rate equation for a zero order reaction between two substances IBB and C_2H_5COOH is written with respect to reactant IBB as follows:

$$\frac{dC_{IBB}}{dt} = -k_1 \quad \Rightarrow \quad dC_{IBB} = -k_1 \cdot dt \quad \Rightarrow \quad \int_{C_{IBB,0}}^{C_{IBB}} dC_{IBB} = \int_0^t -k_1 \cdot dt \tag{III.1}$$

The following equation is obtained by integration:

$$\boxed{C_{IBB} = -\ k_1 \cdot t\ +\ C_{IBB,0}} \tag{III.2}$$

b. First Order reaction:

The differential rate equation for a first order reaction in *IBB* is written as follows:

$$\frac{dC_{IBB}}{dt} = -\ k_1 \cdot C_{IBB} \quad \Rightarrow \quad \frac{dC_{IBB}}{C_{IBB}} = -k_1 \cdot dt \quad \Rightarrow \quad \int_{C_{IBB,0}}^{C_{IBB}} \frac{dC_{IBB}}{C_{IBB}} = \int_0^t -k_1 \cdot dt \tag{III.3}$$

The following equation is obtained by integration:

$$\boxed{LnC_{IBB} = -\ k_1 \cdot t\ +\ LnC_{IBB,0}} \tag{III.4}$$

c. Second Order reaction:

The differential rate equation for a second order reaction between two substances *IBB* and C_2H_5COOH (first order in *IBB* as well as in C_2H_5COOH) is written with respect to reactant *IBB* as follows:

$$\frac{dC_{IBB}}{dt} = -\ k_1 \cdot C_{IBB} \cdot C_{C2H5COOH} \tag{III.5}$$

With:

$$C_{IBB} = C_{IBB,0}(1 - X_1) = C_{IBB,0} - C_{IBB,0} \cdot X_1 \tag{III.6}$$

And:

$$C_{C2H5COOH} = C_{C2H5COOH,0} - C_{IBB,0} \cdot X_1 \tag{III.7}$$

By substitution of eq. *(III.6)* and *(III.7)* in eq. *(III.5)*, we obtain:

$$\frac{dC_{IBB}}{dt} = -\,k_1 \cdot \left(C_{IBB,0} - C_{IBB,0} \cdot X_1\right).\left(C_{C2H5COOH,0}\ -\ C_{IBB,0}\ \cdot X_1\right)$$

$$\Rightarrow \int_0^{X_1} \frac{-C_{IBB,0} \cdot d\,X_1}{\left(C_{IBB,0} - C_{IBB,0} \cdot X_1\right).\left(C_{C2H5COOH,0}\ -\ C_{IBB,0}\ \cdot X_1\right)} = \int_0^t k_1 \cdot dt \qquad \text{(III.8)}$$

To solve this integral, we use the method of partial fractions:

$$\frac{dx}{(a - x)(b - x)} = \frac{1}{b-a}\left(\frac{1}{a-x} - \frac{1}{b-x}\right)dx \qquad \text{(III.9)}$$

Evaluating the integral and applying the rule of logarithm gives us:

$$\frac{1}{\left(C_{C2H5COOH,0} - C_{IBB,0}\right)} \cdot \ ln\frac{c_{C_{IBB,0}} \cdot \left(C_{C2H5COOH,0} - C_{IBB,0} \cdot X_1\right)}{c_{C2H5COOH,0} \cdot\left(C_{IBB,0} - C_{IBB,0} \cdot X_1\right)} = k_1 \cdot t \qquad \text{(III.10)}$$

Which can be rearranged to:

$$\boxed{Ln\frac{C_{IBB,0} \cdot C_{C2H5COOH}}{C_{IBB} \cdot C_{C2H5COOH,0}} = k_1 \cdot \left(C_{C2H5COOH,0}\ -\ C_{IBB,0}\right) \cdot t} \qquad \text{(III.11)}$$

d. Reaction order determination:

The determination of reaction order was achieved by plotting concentration functions over time, and calculating the respective coefficients of determination (R^2) for each case. A plot of C_{IBB} (from equation (III.2)), LnC_{IBB} (from equation (III.4)), and $Ln\,\frac{C_{IBB,0} \cdot C_{C2H5COOH}}{C_{IBB} \cdot C_{C2H5COOH,0}}$ (from equation (III.11) against time results in a linear correlations:

Table III.1. Kinetic parameters of the first reaction.

Time (min)	Conversion X_1 (%)	Order 0 C_{IBB} (M)	Order 1 Ln C_{IBB}	Order 2 $Ln\frac{C_{IBB,0} \cdot C_{C2H5COOH}}{C_{IBB} \cdot C_{C2H5COOH,0}}$
0	0	1.42	0.3506	0
5.05	89	0.1562	-1.8566	0.5459
10.09	91	0.1278	-2.0572	0.6457
R^2		0.7670	0.8125	0.8358

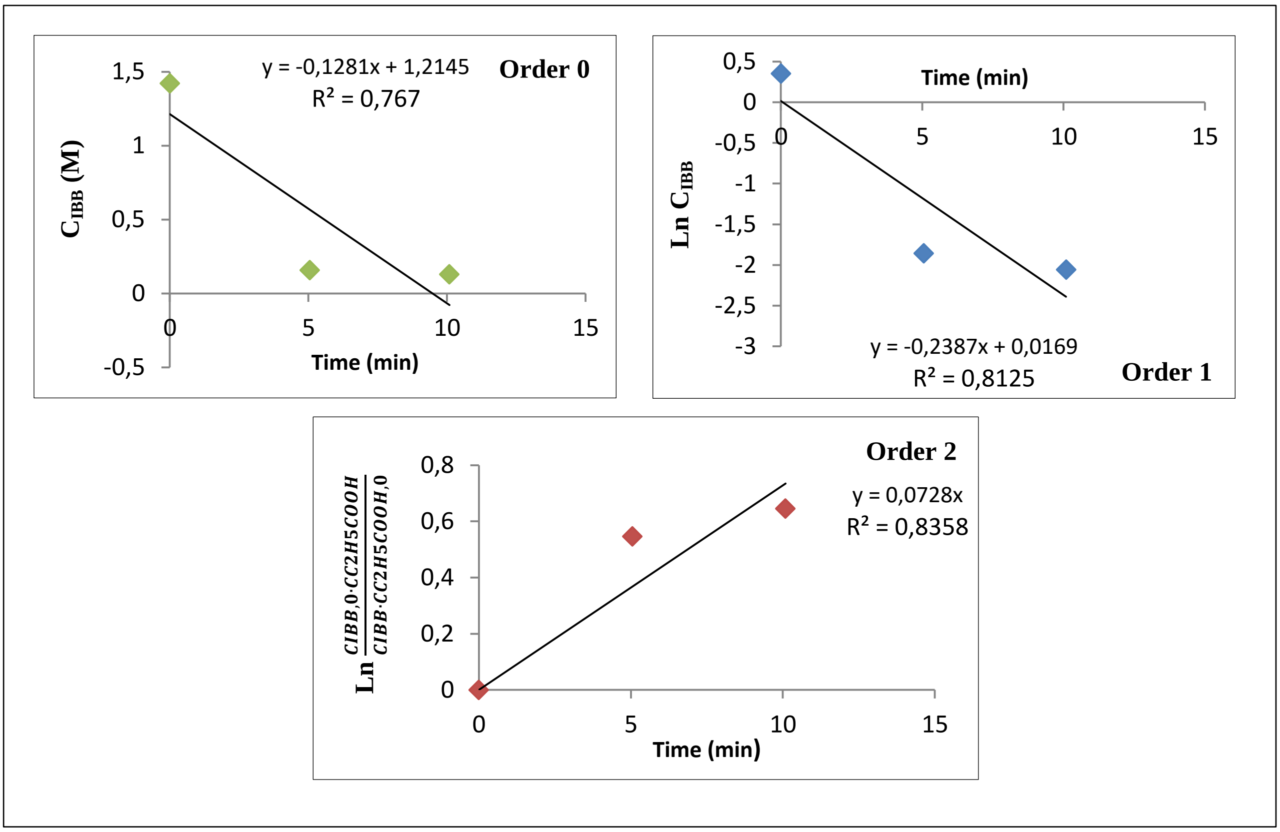


Figure III.1. Evaluation of the first reaction order.

Analysis of the results showed that a second-order reaction model best fits the experimental observations (R^2=0.8358), compared to zero-order (R^2 = 0.7670) and first-order (R^2 = 0.8125) models.

e. Reaction rate constant calculation

The reaction rate constant k can be determined from the slope of the plot of the second order model, as follow:

$$k_1 \cdot \left(C_{C2H5COOH,0} - C_{IBB,0}\right) = 0.0728 \quad \Rightarrow \quad k_1 = \frac{0.0728}{C_{C2H5COOH,0} - C_{IBB,0}} \qquad \text{(III.12)}$$

$$\boxed{k_1 = 0.52\ L.mol^{-1}.min^{-1} = 31.2\ L.mol^{-1}.h^{-1}}$$

The calculated rate constant for the first reaction is $k_1 = 31.2\ L.mol^{-1}.h^{-1}$ at 150°C.

III.2.2. Kinetics of the Second Reaction

For the second reaction (PhI(OAc)2-mediated 1,2-aryl migration), we use experimental data collected by varying the residence time (1, 2 min), reaction temperature (50°C. During their assessment of the best reaction conditions, Bogdan et al. (2009) substituted propiophenone (PEK) for intermediate 2, assuming that the results could be extrapolated to 2 due to molecular similarity. The feed concentrations are:

- Propiophenone feed concentration: $C_{PEK,0} = 0.38$ M;
- Diacetoxyiodobenzene feed concentration: $C_{PhI(OAc)2,0} = 0.39$ M.

	PEK	+	PhI(OAc)₂	→	Products
at t_0	$C_{PEK,0}$		$C_{PhI(OAc)2,0}$		
at t	$C_{PEK,0}(1-X_2)$		$C_{PhI(OAc)2,0} - C_{PEK,0} \cdot X_2$		

a. Zero Order reaction

As before, the differential rate equation for a zero order reaction between two substances PEK and $PhI(OAc)_2$ can be expressed using reactant PEK as follows:

$$\frac{dC_{PEK}}{dt} = -k_2 \Rightarrow dC_{PEK} = -k_2 \cdot dt \Rightarrow \int_{C_{PEK,0}}^{C_{PEK}} dC_{PEK} = \int_0^t -k_2 . dt \tag{III.13}$$

The following equation is obtained by integration:

$$\boxed{C_{PEK} = -k_2 \cdot t + C_{PEK,0}} \tag{III.14}$$

b. First Order reaction

The differential rate equation for a first order reaction in *PEK* is written as follows:

$$\frac{dC_{PEK}}{dt} = -k_2 \cdot C_{PEK} \Rightarrow \int_{C_{PEK,0}}^{C_{PEK}} \frac{dC_{PEK}}{C_{PEK}} = \int_0^t -k_2 . dt \tag{III.15}$$

The following equation is obtained by integration:

$$\boxed{LnC_{PEK} = -k_2 \cdot t + LnC_{PEK,0}} \tag{III.16}$$

c. Second Order reaction

The differential rate equation for a second order reaction (first order in *PEK* as well as in $PhI(OAc)_2$) is written with respect to reactant *PEK* as follows:

$$\frac{dC_{PEK}}{dt} = -k_2 \cdot C_{PEK} \cdot C_{PhI(OAc)2} \tag{III.17}$$

With:

$$C_{PEK} = C_{PEK,0}(1 - X_2) = C_{PRK,0} - C_{PEK,0} \cdot X_2 \tag{III.18}$$

And:

$$C_{PhI(OAc)2} = C_{PhI(OAc)2,0} - C_{PEK,0} \cdot X_2 \qquad \text{(III.19)}$$

By substitution of eq. (III.18) and (III.19) in eq. (III.17), we obtain:

$$\frac{dC_{PEK}}{dt} = -\, k_2 \cdot \left(C_{PRK,0} - C_{PEK,0} \cdot X_2\right) \cdot \left(C_{PhI(OAc)2,0} - C_{PEK,0} \cdot X_2\right)$$

$$\Rightarrow \int_0^{X_2} \frac{-C_{PEK,0} \cdot dX_2}{\left(C_{PRK,0} - C_{PEK,0} \cdot X_2\right).\left(C_{PhI(OAc)2,0} - C_{PEK,0} \cdot X_2\right)} = \int_0^{t} k_2 \cdot dt \qquad \text{(III.20)}$$

The following equation is obtained by integration:

$$\boxed{Ln\ \frac{C_{PEK,0} \cdot C_{PhI(OAc)2}}{C_{PEK} \cdot C_{PhI(OAc)2,0}} = k_2 \cdot (C_{PhI(OAc)2,0} - C_{PEK,0}) \cdot t} \qquad \text{(III.21)}$$

d. Reaction order determination

The determination of reaction order was achieved by plotting concentration functions over time, and calculating the respective coefficients of determination (R^2) for each case. A plot of C_{PEK} (from equation (III.14)), LnC_{PEK} (from equation (III.16)), and $Ln\,\frac{C_{PEK,0} \cdot C_{PhI(OAc)2}}{C_{PEK} \cdot C_{PhI(OAc)2,0}}$ (from equation (III.21) against time results in a linear correlations:

Table III.2. Kinetic parameters of the second reaction.

Time (min)	Conversion X_2 (%)	Order 0 C_{PEK} (M)	Order 1 Ln C_{PEK}	Order 2 Ln $\frac{C_{PEK,0} \cdot C_{PhI(OAc)2}}{C_{PEK} \cdot C_{PhI(OAc)2,0}}$
0	0	0.38	-0.9676	0
1	94	0.0228	-3.7810	0.3377
2.01	98	0.0076	-4.8796	0.8138
R^2		0.7782	0.9384	0.9892

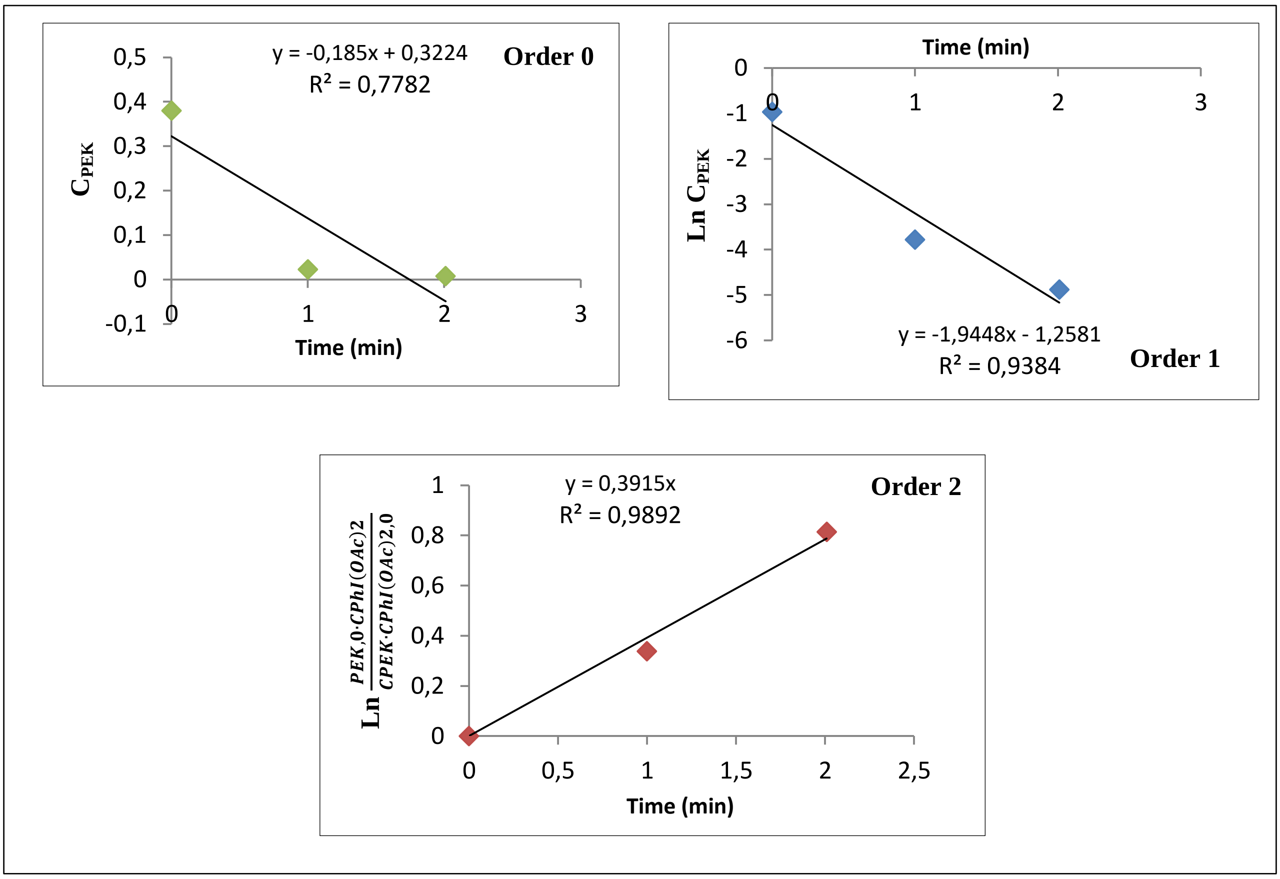


Figure III.2: Evaluation of the Second reaction order.

The data analysis from figure III.2 indicated that a second-order reaction is the most plausible case again ($R^2 = 0.9892$), compared to zero-order ($R^2 = 0.7782$) and first-order ($R^2 = 0.9384$) models.

e. Reaction rate constant calculation

The reaction rate constant *k* can be determined from the slope of the plot of second order model, which is equal to:

$$k_2 \cdot \left(C_{PhI(OAc)2,0} - C_{PEK,0}\right) = 0.3915 \Rightarrow k_2 = \frac{0.3915}{C_{PhI(OAc)2,0} - C_{PEK,0}} \tag{III.22}$$

$$\boxed{k_2 = 39.15\ L.mol^{-1}.min^{-1} = 2349\ L.mol^{-1}.h^{-1}}$$

The calculated rate constant for this reaction is $k_2 = 2349\ L.mol^{-1}.h^{-1}$ at 50°C.

III.2.3. Kinetics of the Third Reaction

For the last reaction base hydrolysis, we use data collected by varying the residence time (1, 2 min), reaction temperature (65°C), and feed concentrations:

- Intermidiate 3 feed concentration: $C_{3,0}$ = 0.3724 M;

- Potassium hydroxide feed concentration: $C_{KOH,0}$ = 5 M.

	3	+	**KOH**	⟶	**Products**
at t0	$C_{3,0}$		$C_{KOH,0}$		
at t	$C_{3,0}.(1-X_3)$		$C_{KOH,0} - C_{3,0} .X_3$		

a. Zero Order reaction

The differential rate equation for a zero order reaction between two substances Intermediate 3 and KOH is written with respect to limiting reactant intermediate 3 as follows:

$$\frac{dC_3}{dt} = - k_3 \quad \Rightarrow \quad dC_3 = - k_3 \cdot dt \quad \Rightarrow \quad \int_{C_{3,0}}^{C_3} dC_3 = \int_0^t -k_3.dt \tag{III.23}$$

The following equation is obtained by integration:

$$\boxed{\boldsymbol{C_3 = -k_3 \cdot t + C_{3,0}}} \tag{III.24}$$

b. First Order reaction

The differential rate equation for a first order reaction in *PEK* is written as follows:

$$\frac{dC_3}{dt} = -k_3 \cdot C_3 \tag{III.25}$$

Integrating and simplifying:

$$\boxed{\boldsymbol{LnC_3 = -k_3 \cdot t + LnC_{3,0}}} \tag{III.26}$$

c. Second Order reaction

The differential rate equation for a second order reaction between two substances Intermediate 3 and KOH (first order in intermediate *3* as well as in KOH) is written with respect to limiting reactant *3* as follows:

$$\frac{dC_3}{dt} = -k_3 \cdot C_3 \cdot C_{KOH} \tag{III.27}$$

Where:

$$C_3 = C_{3,0}(1 - X_3) = C_{3,0} - C_{3,0} \cdot X_3 \tag{III.28}$$

And:

$$C_{KOH} = C_{KOH,0} - C_{3,0} \cdot X_3 \tag{III.29}$$

By substitution of eq. (III.28) and (III.29) in eq. (III.25), we obtain:

$$\frac{dC_3}{dt} = -k_3 \cdot \left(C_{3,0} - C_{3,0} \cdot X_3\right) \cdot \left(C_{KOH,0} - C_{3,0} \cdot X_3\right)$$

$$\Rightarrow \int_0^{X_3} \frac{-C_{3,0} \cdot dX_3}{\left(C_{3,0} - C_{3,0} \cdot X_2\right).\left(C_{KOH,0} - C_{3,0} \cdot X_2\right)} = \int_0^t k_3 \cdot dt \qquad \text{(III.30)}$$

The following equation is obtained by integration:

$$\boxed{Ln \frac{C_{3,0} \cdot C_{KOH}}{C_3 \cdot C_{KOH,0}} = k_3 \cdot (C_{KOH,0} - C_{3,0}) \cdot t} \qquad \text{(III.31)}$$

d. Reaction order determination

The determination of reaction order was achieved by plotting concentration functions over time, and calculating the respective coefficients of determination (R^2) for each case. A plot of C_3 (from equation (III.24)), LnC_3 (from equation (III.26)), and $Ln \frac{C_{3,0} \cdot C_{KOH}}{C_3 \cdot C_{KOH,0}}$ (from equation (III.31)) against time results in a linear correlations:

Table III.3. Kinetic parameters of the third reaction.

Time (min)	Conversion (%)	Order 0 C_3 (M)	Order 1 Ln C_3	Order 2 Ln $\frac{C_{3,0} \cdot C_{KOH}}{C_3 \cdot C_{KOH,0}}$
0	0	0.3724	-0.9878	0
1	94	0.0223	-3.8010	2.7428
3	99	0.0037	-5.5930	4.5350
R^2		0.6154	0.9026	0.8693

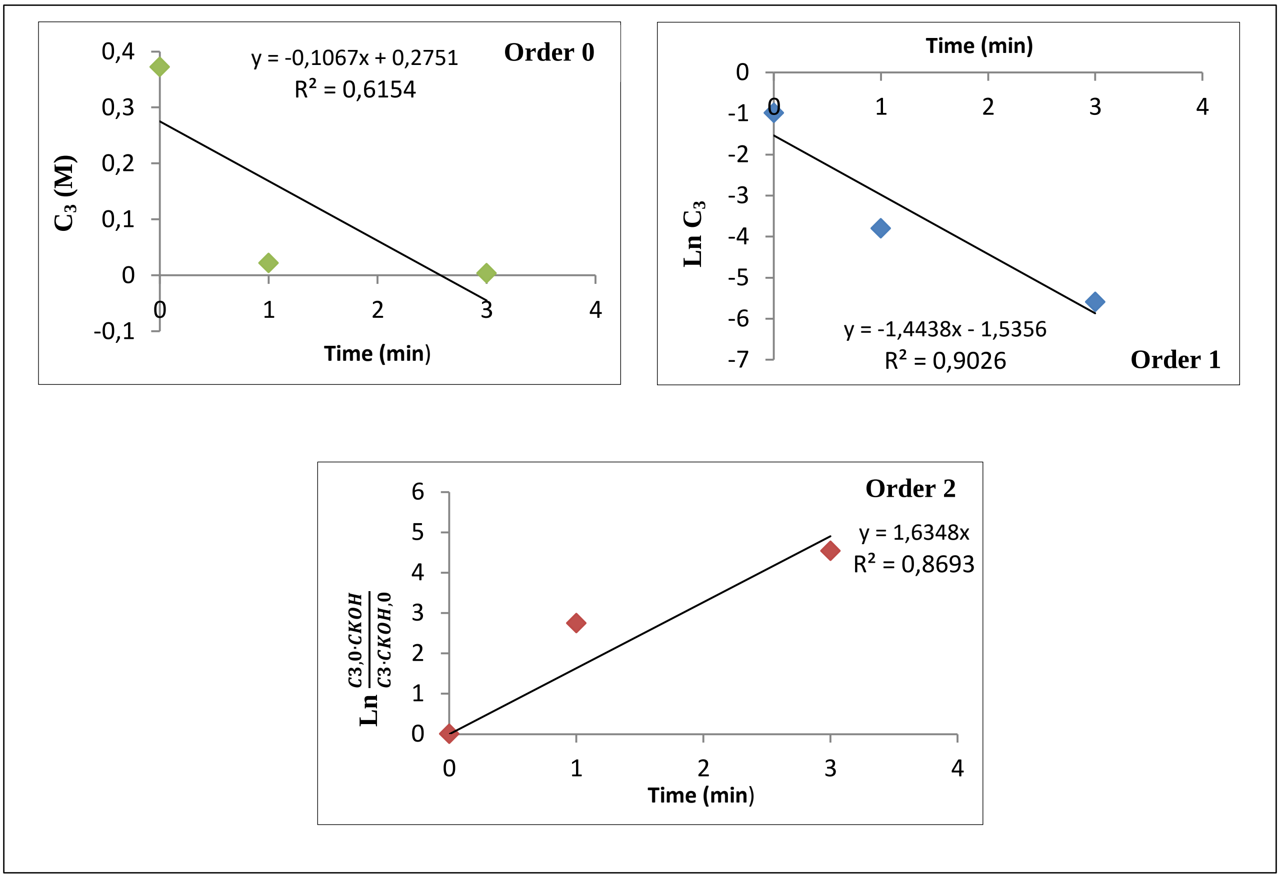


Figure III.3: Evaluation of the third reaction order.

The data analysis in figure III.3 indicated that a first-order model is the most plausible case again (R^2 = 0.9026), compared to zero-order (R^2 = 0.6154) and second-order (R^2 = 0.8693) models. However knowing that, potassium hydroxide (KOH) is in excess compared to intermediate 3 ($C_{KOH} \simeq C_{KOH,0}$), we can assume a pseudo-first-order model in this case.

e. Reaction rate constant calculation

The reaction rate constant *k* can be determined from the slope of the first order plot:

$$\frac{dC_3}{dt} = -k'_3 \cdot C_3 \cdot C_{KOH} = -k_3 \cdot C_3 \qquad \text{(III.32)}$$

With:

$$k_3 = k'_3 \cdot C_{KOH} \qquad \text{(III.33)}$$

From the slop of the first order plot, we have:

$$\boxed{k_3 = 1.4438\ min^{-1} = 86.628\ h^{-1} \quad \& \quad k'_3 = 0.289\ L.mol^{-1}.min^{-1}}$$

The reaction rate constant k_3 was estimated to be ***86.628 h^{-1}*** at an operating temperature of 65°C.

III.3. Plug flow reactor (PFR) design

Designing a plug flow reactor (PFR) is a fundamental aspect of chemical engineering, particularly in industries where continuous processing of chemical reactions is essential. The PFR is a type of chemical reactor where reactants flow through a tubular system without mixing, resulting in a highly uniform flow profile. This design allows for precise control over reaction conditions and facilitates efficient heat and mass transfer.

The key characteristic of a PFR is its axial mixing, which is minimized to maintain a plug-like flow profile. This means that each volume element of the reactor contains reactants with the same composition at any given time, leading to predictable reaction kinetics and conversion rates along the reactor length.

In PFR design, several factors must be carefully considered:

a/ Fluid Flow Modeling:

In a PFR, the fluid flowing through the reactor is modeled as a series of infinitely thin, coherent "plugs" moving in the axial direction. Each plug has a uniform composition, and the plugs do not mix in the axial direction, though they are perfectly mixed in the radial direction (Vapourtec, 2024, Elprocus, 2024).

b/ Residence Time:

The residence time of each plug is a function of its position in the reactor. In the ideal PFR, the residence time distribution is a Dirac delta function, meaning the residence time is constant for all plugs (Elprocus, 2024)

c/ Reactor Geometry:

PFRs are typically cylindrical in shape, with reactants and products flowing in and out through openings at each end. The reactor dimensions, such as length and diameter, are crucial design parameters that impact factors like residence time, heat transfer, and pressure drop (Fogler, 1992).

d/ Reaction Kinetics:

Understanding the kinetics of the chemical reaction, including rate equations and temperature/pressure dependencies, is essential for determining the required residence time to achieve the desired conversion (Fogler, 1992).

e/ Flow Rate and Residence Time:

The flow rate of reactants through the PFR and the corresponding residence time are closely related and must be carefully controlled to ensure the desired reaction performance (Fogler, 1992).

f/ Temperature and Pressure Control:

Maintaining uniform temperature and pressure throughout the PFR is critical for consistent reaction kinetics and product quality. Heat exchange mechanisms may be incorporated to control temperature, and pressure drop must be managed (Fogler, 1992).

g/ Mixing Considerations:

Unlike other reactor types, PFRs rely on minimal axial mixing to maintain the plug flow profile. Any deviation from ideal plug flow can affect reaction kinetics and product quality (Fogler, 1992).

h/ Safety and Material Selection:

Reactor design must prioritize safety, considering factors like potential exothermic reactions, pressure buildup, and hazardous reactants. The choice of construction materials is crucial for chemical compatibility and mechanical strength.

III.3.1 Residence time and volume calculations

Consider a tubular reactor in which heat is added through the cylindrical walls of the reactor (Mushtaq, 2014).

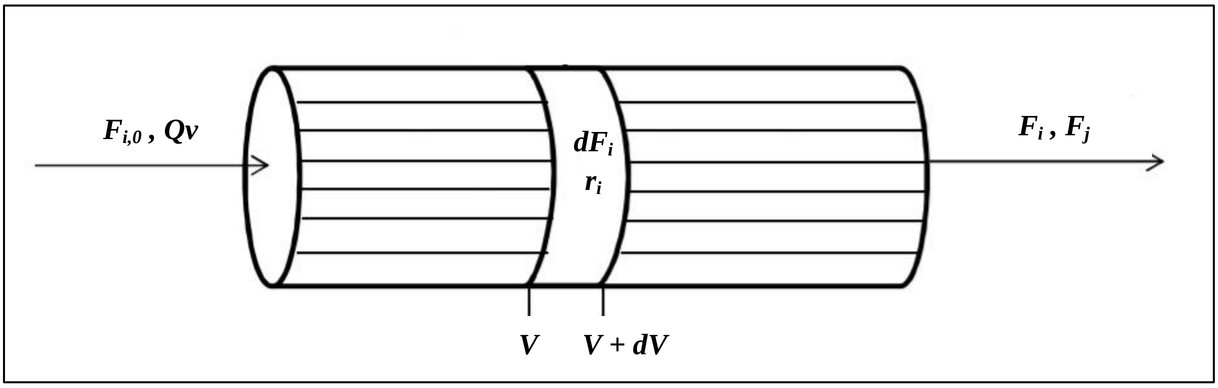


Figure III.4: a mathematical model of plug flow reactor.

Apply mole balance equation: (Fogler, 1992, Mushtaq, 2014)

(Molar flow rate of species i into the system) - (Molar flow rate of species i out of the system) + (Molar flow rate of Generation of species i in the reaction) = (Molar rate of Accumulation of species I in the reaction)

In – Out + Generation = Accumulation

The tubular reactor is operated at steady state. The concentration varies continuously down the tube, and, therefore, so does the reaction rate. Therefore, the mole balance is given as the following for species i:

$$F_{i,0} - F_i + r_i \cdot dV = 0 \quad \Rightarrow \quad F_{i,0} + r_i \cdot dV = F_I \tag{III.34}$$

Replacing $F_i = F_{i,0} + dF_i$, we get:

$$F_{i,0} + r_i \cdot dV = F_{i,0} + dF_i \quad \Rightarrow \quad r_i \cdot dV = dF_i \tag{III.35}$$

Replacing $F_i = Qv \cdot C_i$, then dividing by dV:

$$r_i \cdot dV = d(Qv \cdot C_i) = Qv \cdot dC_i \tag{III.36}$$

It can also be stated that:

$$C_i = C_{A,0}(1 - X_j) \quad \Rightarrow \quad dC_i = -C_{i,0} \cdot dX \tag{III.37}$$

The necessary volume, V, needed to reduce the entering molar flow rate, $F_{i,0}$, to some specific value of F_i is given as:

$$V = \int_{Fi,0}^{Fi} \frac{dF_i}{-ri} = -Qv \cdot C_{i,0} \cdot \int_0^X \frac{dX}{r_i} \tag{III.38}$$

Dividing by Q, we get **“τ”** which represent the residence time:

$$\boxed{\boldsymbol{\tau = \frac{V}{Qv} = -C_{i,0} \cdot \int_0^X \frac{dX}{r_i}}} \tag{III.39}$$

Where:

r_i: reaction rate equation for reactant *“i”* in mol.L^{-1}.min^{-1};

V: reactor volume in µL;

Qv: total volumetric flow rate fed the reactor in µL.min^{-1};

C_i: Concentration of limiting reactant *"i"* leaving the reactor in mol.L^{-1};

$C_{i,0}$: Concentration of limiting reactant *"i"* fed the reactor in mol.L^{-1};

τ: the residence time in min^{-1};

III.3.1.1. First reactor design

As demonstrated in the section before, Friedel–Crafts acylation is a second order reaction with a rate constant $k_1 = 31.2\ L.mol^{-1}.h^{-1}$ and the reaction rate equation is: (total volumetric flow rate $Qv_1=43.8\ \mu L.min^{-1}$)

$$r_1 = -\ k_1 \,.\, C_{IBB} \,.\, C_{C2H5COOH} = -\ k_1 \cdot (C_{IBB,0} - C_{IBB,0} \cdot X_1) \cdot (C_{C2H5COOH,0} - C_{IBB,0} \cdot X_1) \qquad \text{(III.40)}$$

The expression of residence time for the first reactor is:

$$\tau_1 = -\ C_{IBB,0} \cdot \int_0^{X_1} \frac{dX_1}{r_1} = \frac{1}{k_1} \cdot \int_0^{X_1} \frac{C_{IBB,0} \cdot dX_1}{(C_{IBB,0} - C_{IBB,0} \cdot X_1)(C_{C2H5COOH,0} - C_{IBB,0} \cdot X_1)} \qquad \text{(III.41)}$$

Evaluating the integral and applying the rule of logarithm gives us:

$$\boxed{\tau_1 = \frac{1}{k_1 \cdot (C_{IBB,0} - C_{C2H5COOH,0})} \cdot \ln \frac{C_{C2H5COOH,0} \cdot (1 - X_1)}{(C_{C2H5COOH,0} - C_{IBB,0} \cdot X_1)}} \qquad \text{(III.42)}$$

By applying equation (III.41), the residence time of the first reactor is defined:

$$\boxed{\tau_1 = 0.148\ h = 8.88\ min}$$

The residence time is used to evaluate the required reactor volume:

$$\boxed{V_1 = 388.944\ \mu L}$$

III.3.1.2. Second reactor design

1,2-Aryl migration is also a second order reaction with a rate constant $k_2 = 2349\ L.mol^{-1}.h^{-1}$ and the reaction rate equation is: (with total volumetric flow rate $Qv_2 = 175.3\ \mu L.min^{-1}$)

$$r_2 = -\ k_2 \,.\, C_2 \,.\, C_{PhI(OAc)2} = -\ k_1 \cdot (C_{2,0} - C_{2,0} \cdot X_2) \cdot (C_{PhI(OAc)2,0} - C_{2,0} \cdot X_2) \qquad \text{(III.43)}$$

The expression of residence time for the second reactor is:

$$\tau_2 = -\ C_{2,0} \cdot \int_0^{X_2} \frac{dX_2}{r_2} = \frac{1}{k_2} \cdot \int_0^{X_2} \frac{C_{2,0} \cdot dX_2}{(C_{2,0} - C_{2,0} \cdot X_2)(C_{PhI(OAc)2,0} - C_{2,0} \cdot X_2)} \qquad \text{(III.44)}$$

By analogy of the residence time integration in the first reactor, we find:

$$\boxed{\tau_2 = \frac{1}{k_2 \cdot (C_{2,0} - C_{PhI(OAc)2,0})} \cdot \ln \frac{C_{PhI(OAc)2,0} \cdot (1 - X_2)}{(C_{PhI(OAc)2,0} - C_{2,0} \cdot X_2)}} \qquad \text{(III.45)}$$

By applying equation (III.44), the residence time of the second reactor is defined:

$$\boxed{\tau_2 = 0.035\ h = 2.1\ min}$$

And the required reactor volume is:

$$\boxed{V_2 = 368.13\ \mu L}$$

III.3.1.3. Third reactor design

Base hydrolysis is a pseudo first order reaction with a rate constant $k_3 = 1.4438\ min^{-1}$ and the reaction rate equation is: (with total volumetric flow rate $Qv_3 = 435.3\ \mu L.min^{-1}$)

$$r_3 = -\, k_3 \,.\, C_3 = -\, k_3 .(C_{3,0} - C_{3,0} \cdot X_3) \qquad \text{(III.46)}$$

The expression of residence time for the second reactor is:

$$\tau_3 = -\, C_{3,0} \cdot \int_0^{X_3} \frac{dX_3}{r_3} = \frac{1}{k_3} \int_0^{X_3} \frac{dX_3}{(1-\ X_3)} \qquad \text{(III.47)}$$

By integrating, we find:

$$\boxed{\tau_3 = -\frac{1}{k_3} \cdot \ln\,(1 - X_3)} \qquad \text{(III.48)}$$

The residence time of the first reactor is then defined:

$$\boxed{\tau_3 = 3.190\ min}$$

And the required reactor volume is:

$$\boxed{V_3 = 1388.441\ \mu L}$$

Table III.4 shows a *summary* of the three plug flow micro-reactors design (under laboratory scale):

Table III.4. PFRs design results at laboratory scale.

PFRs	Flow rate in (µL.min^{-1})	Conversion (%)	Residence time (min)	Volume (µL)	Internal diameter, ID (mm)	Length (mm)
PFR 1	43.8	91	8.88	388.944	0.75	880.39
PFR 2	175.3	98	2.10	368.130	0.75	826.49
PFR 3	435.3	99	3.19	1388.441	0.75	3142.79

In this study, the global residence time and the total reactors volume are approximately 15 minutes and 2,15 ml , respectively. While the diameter was kept at the constant value of

0,75 mm, up to 14 mg/min salt ibuprofen could be synthesized through this process, using approximately 5 m tubing reactors. Through the application of flow reactors, this process has successfully reduced the reactions time from 9 hours using batch reactors to only 15 mins.

Furthermore the calculated residences times and reactors volumes are compared to the published experimental data implemented in the laboratory-scale system. The comparison shows a good agreement between the calculated and experimental results, the discrepancies are relatively small and within acceptable limits.

III.3.2 Reactors sizing for industrial scale

The dimensions of PFR using microreactors at laboratory scale are reasonably small for the target capacity, illustrating the significant benefit of space efficient equipment. In principle, the reaction scale up in microreactors is easier than in batch; three different approaches can be used to produce large amount of compounds: the first one is to run the process longer (scaling-out). Alternatively, multireactors in parallel (numbering up) can be used, or the process can be performed on larger continuous reactors (scaling-up). Therefore, using the optimized conditions in hand, we calculate reactors volumes for industrial scale that manufacture 200 tons per year. The PFRs lengths (L) and diameters (D) are estimated by applying the rules of Thumb for PFR design in liquid phase, and assuming the ratio L/D ≥100 (Donald R.Woods, 2007).

Table III.5. PFRs design results for industrial scale.

PFRs	Flow rate in (L.min^{-1})	Volume (L)	Diameter (m)	Length (m)
PFR 1	1.317	11.695	0.053	5.3
PFR 2	5.270	11.067	0.053	5.1
PFR 3	13.086	41.744	0.053	19.0

By applying the technology to a commercial scale of 200 tons of K-Ibuprofen/year, the continuous reactors volumes required would be between 11 and 42 L, with 0.053 m of diameter and a length between 5.1 m and 19 m. The sizes are very favorables compares with batch reactor volume.

III.4. Heat transfer design

Heat transfer design involves creating systems that efficiently transfer heat from one point to another. It can be achieved through various methods depending on specific requirements of the reaction.

In this continuous process, the reactions are endothermic. All three PFRs are assumed to be isothermal meaning the temperature is uniform in each reactor. To ensure this operation, we use a heat transfer medium with sufficient circulation where those reactors and process lines are submerged.

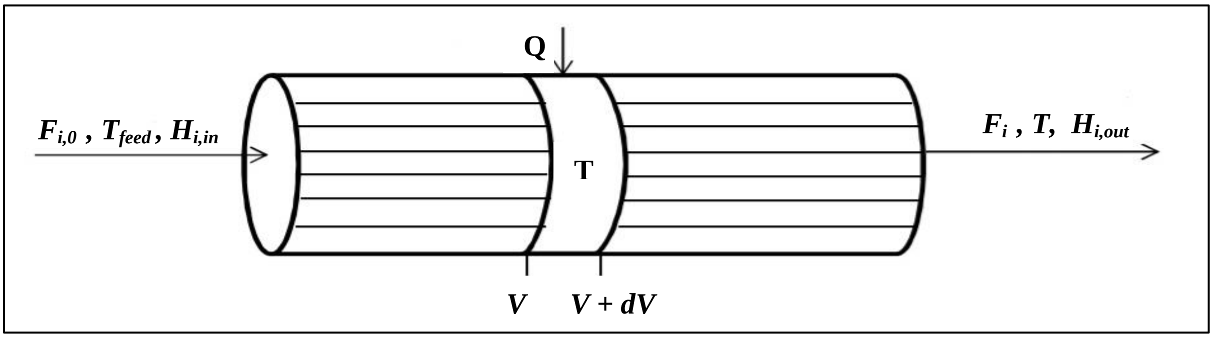


Figure III.5: a mathematical model of plug flow reactor with heat exchange.

To calculate the heating duties, we apply energy balance (Fogler, 1992, Mushtaq, 2014)

$$\left(\begin{array}{c}\text{Rate of flow}\\ \text{of heat to}\\ \text{the system}\\ \text{from the}\\ \text{surroundings}\end{array}\right) - \left(\begin{array}{c}\text{Rate of work}\\ \text{done by the}\\ \text{system on}\\ \text{the}\\ \text{surroundings}\end{array}\right) + \left(\begin{array}{c}\text{Rate of}\\ \text{energy}\\ \text{added to the}\\ \text{system by}\\ \text{mass flow}\\ \text{into the}\\ \text{system}\end{array}\right) - \left(\begin{array}{c}\text{Rate of}\\ \text{energy}\\ \text{leaving the}\\ \text{system by}\\ \text{mass flow}\\ \text{out of the}\\ \text{system}\end{array}\right) = \left(\begin{array}{c}\text{Rate of}\\ \text{Accumulation}\\ \text{of energy}\\ \text{within the}\\ \text{system}\end{array}\right)$$

For steady state isothermal plug flow reactor, with an incompressible and ideally mixed reacting liquid, the energy balance is:

$$Q + \sum_{i=1}^{n} F_{i,0} \cdot H_i\big|_{in} - \sum_{i=1}^{n} F_i \cdot H_i\big|_{out} = 0 \tag{III.49}$$

Where:

Q: heating duty or power in watt;

$F_{i,0}$: molar flow of component "i" fed the reactor in mol.s^{-1};

F_i: molar flow of component "i" leaving the reactor in mol.s^{-1};

$H_{i,in}$: molar enthalpy of component “i” fed the reactor at temperature T_{feed} in $J.mol^{-1}$;
$H_{i,out}$: molar enthalpy of component “i” leaving the reactor at temperature T in $J.mol^{-1}$.

Rearranging, equation (III.49) become:

$$Q = \sum_{i=1}^{n} F_i \cdot H_{i,out} - \sum_{i=1}^{n} F_{i,0} \cdot H_{i,in} \qquad (III.50)$$

For each component *“i”*: $F_i = F_{i,0} + \sqrt{}_i \cdot F_{A,0} \cdot X$, replacing this term and simplifying: (Debacq, 2016)

$$Q = \sum_{i=1}^{n} F_{i,0} \cdot (H_{out} - H_{in}) + F_{A,0} \cdot X . \sum_{i=1}^{n} \sqrt{}_i \cdot H_{out} \qquad (III.51)$$

Where:
$F_{A,0}$: molar flow of limiting reactant “A” fed the reactor in $mol.s^{-1}$;
X: Conversion of the limiting reactant “A”;
$\sqrt{}_i$: Stoichiometric coefficient of component “i”;
$\sum_{i=1}^{n} \sqrt{}_i \cdot H_{out}$: is the reaction enthalpy change at temperature T, $\Delta H_r(T)$ *in* $kJ.mol^{-1}$ which gives us:

$$Q = \sum_{i=1}^{n} F_{i,0} \cdot (H_{out} - H_{in}) + \Delta H_r(T) \cdot F_{A,0} \cdot X \qquad (III.52)$$

If the heat capacities can be considered constant within the temperature range, the final equation of heating duty for a PFR is:

$$\boxed{\boldsymbol{Q = \sum_{i=1}^{n} F_{i,0} \cdot Cp_i \cdot (T - T_{feed}) + \Delta H_r(T) \cdot F_{A,0} \cdot X}} \qquad (III.53)$$

With:
Cp_i: heat capacity of component “i” in $J.mol^{-1}.K^{-1}$;

III.4.1. Calculation of the enthalpy of reaction $\Delta H_r(T)$

Calculating reaction enthalpies using Hess's Law and Kirchhoff's Law is a crucial aspect of understanding the energy changes that occur during chemical reactions. It involves manipulating thermochemical equations to determine the enthalpy change of a reaction. Here's a brief overview of each law and how they're applied:

a. Hess's Law:

Hess's Law is based on the principle of conservation of energy. It states that the overall enthalpy change for a reaction is the same regardless of the number of steps in the reaction or the pathway taken, as long as the initial and final conditions are the same. In other words, the total enthalpy change for a reaction is the sum of the enthalpy changes of its individual steps. Mathematically, this is expressed as:

$$\boxed{\Delta H_r^\circ(T^\circ) = \sum \surd_i \cdot \Delta H^\circ_{f,products} - \sum \surd_i \cdot \Delta H^\circ_{f,reactants}} \tag{III.54}$$

Where:

$\Delta H_r^\circ(T^\circ)$: is the standard enthalpy change for the reaction at temperature $T°=25°C$ in kJ.mol^{-1};

$\Delta H^\circ_{f,reactants}$:is the standard enthalpy of formation of reactant in $kJ.mol^{-1}$;

$\Delta H^\circ_{f,products}$:is the standard enthalpy of formation of product in $kJ.mol^{-1}$.

b. Kirchhoff's Law:

Kirchhoff's Law extends Hess's Law to include temperature dependence. It states that the change in enthalpy for a reaction at any temperature is equal to the change in enthalpy at a reference temperature plus the integral of the heat capacity of the reactants with respect to temperature, minus the integral of the heat capacity of the products with respect to temperature. Assuming all components remain in the liquid phase throughout the flowsheet and off-gassing is negligible, Kirchhoff's Law is expressed as:

$$\Delta H_r(T) = \Delta H_r^\circ(T^\circ) + \int_{T^\circ}^{T} \Delta Cp \cdot dT \tag{III.55}$$

Where:

$$\Delta Cp = \sum \surd_i \cdot Cp_{i,products} - \sum \surd_i \cdot Cp_{i,reactants} \tag{III.56}$$

With:

$Cp_{i,products}$ & $Cp_{i,reactants}$: are the heat capacities of the products and the reactants in J.mol^{-1}.K^{-1};

After integrating by considering heat capacities constants within the temperature range studied, Kirchhoff's Law becomes:

$$\boxed{\Delta H_r(T) = \Delta H_r^\circ(T^\circ) + \Delta Cp \cdot (T - T^\circ)} \tag{III.57}$$

To use Kirchhoff's Law, we calculate the standard enthalpy change of the reaction $\Delta H_r^\circ(T^\circ)$ using Hess's Law under the standard conditions, typically at 25°C and 1 atmosphere pressure.

Both Hess's Law and Kirchhoff's Law are powerful tools in thermochemistry, allowing us to calculate enthalpy changes for reactions and understand how they vary with temperature.

They're commonly used in industries like chemical engineering and materials science to design processes and understand the energy changes involved in chemical reactions.

III.4.1.1. Enthalpy change of the first reaction at T_1=150°C

By applying equation (III.54) at standard conditions, we obtain:

$$\Delta H^\circ_{r,1}(T^\circ) = (\Delta H^\circ_{f,2} + \Delta H^\circ_{f,H2O}) - (\Delta H^\circ_{f,IBB} + \Delta H^\circ_{f,C2H5COOH}) \quad \text{(III.58)}$$

$$\Delta H^\circ_{r,1}(T^\circ) = 154.6\ kJ.mol^{-1}$$

By applying equation (III.57) at T_1 = 150 °C = 423 K, we obtain:

$$\Delta H_r(T_1) = \Delta H^\circ_{r,1}(T^\circ) + (Cp_2 + Cp_{H2O} - Cp_{IBB} - Cp_{C2H5COOH}).(T_1 - T^\circ) \quad \text{(III.59)}$$

$$\boxed{\Delta H_r\,(T_1) = 144.194\ kJ.mol^{-1}}$$

III.4.1.2. Enthalpy change of the second reaction at T_2=50°C

By applying equation (III.54) at standard conditions, we obtain:

$$\Delta H^\circ_{r,2}(T^\circ) = (\Delta H^\circ_{f,3} + \Delta H^\circ_{f,PhI} + 2\cdot \Delta H^\circ_{f,AcOH} + \Delta H^\circ_{f,MeOH} + \Delta H^\circ_{f,HCOOCH3}) - (\Delta H^\circ_{f,2} + \Delta H^\circ_{f,PhI(OAc)2} + \Delta H^\circ_{f,TMOF} + \Delta H^\circ_{f,H2O} \quad \text{(III.60)}$$

$$\Delta H^\circ_{r,2} = 69.8\ kJ.mol^{-1}$$

By applying equation (III.57) at T_2 = 50 °C = 323 K, we obtain:

$$\Delta H_r(T_2) = \Delta H^\circ_{r,2}(T^\circ) + [(Cp3 + CpPhI + 2\cdot CpAcOH + CpMeOH + CpHCOOCH3) - (Cp2 + CpPhI(OAc)2 + CpTMOF + CpH2O)].(T_2 - T^\circ) \quad \text{(III.61)}$$

$$\boxed{\Delta H_r\,(T_2) = 70.136\ kJ.mol^{-1}}$$

III.4.1.3. Enthalpy change of the third reaction at T_3=65°C

By applying equation (III.54) at standard conditions, we obtain:

$$\Delta H^\circ_{r,3}(T^\circ) = \Delta H^\circ_{f,API(salt)} + \Delta H^\circ_{f,MeOH}) - (\Delta H^\circ_{f,3} + \Delta H^\circ_{f,KOH}) \quad \text{(III.62)}$$

$$\Delta H^\circ_{r,3} = 206.7\ kJ.mol^{-1}$$

By applying equation (III.57) at T_3 = 65 °C = 338 K, we obtain:

$$\Delta H_r(T_3) = \Delta H^\circ_{r,3}(T^\circ) + (Cp_{API(salt)} + Cp_{MeOH} - Cp_3 - Cp_{KOH}).(T_3 - T^\circ) \quad \text{(III.63)}$$

$$\boxed{\Delta H_r(T_3) = 1429.1\ kJ.mol^{-1}}$$

III.4.2. Energy requirement for the first reactor:

By applying the heat balance from equation (III.53) to the first reactor, we obtain:

$$Q_1 = (F_{IBB} \cdot Cp_{IBB} + F_{C2H5COOH} \cdot Cp_{C2H5COOH} + F_{TFOH} \cdot Cp_{TFOH})\ (T_1 - T_{feed,1}) + \Delta H_r(T_1) .\ F_{IBB,0} \cdot X_1 \qquad \text{(III.64)}$$

$$\boxed{Q_1 = 0.239\ W}$$

III.4.3. Energy requirement for the second reactor:

By applying the heat balance from equation (III.53) to the second reactor, we obtain:

$$Q_2 = (F_{IBB} \cdot Cp_{IBB} + F_{C2H5COOH} \cdot Cp_{C2H5COOH} + F_{TFOH} \cdot Cp_{TFOH} + F_2 \cdot Cp_2 + F_{H2O} \cdot Cp_{H2O} + F_{PhI(OAc)2} \cdot Cp_{PhI(OAc)2}$$

$$+ F_{TMOF} \cdot Cp_{TMOF} + F_{MeOH} \cdot Cp_{MeOH}) . (T_2 - T_{feed,2}) + \Delta H_r(T_2) \cdot F_{2,0} \cdot X_2 \qquad \text{(III.65)}$$

$$\boxed{Q_2 = 0.287\ W}$$

III.4.4. Energy requirement for the third reactor

By applying the heat balance from equation (III.53) to the third reactor, we obtain:

$$Q_3 = (F_{IBB} \cdot Cp_{IBB} + F_{C2H5COOH} \cdot Cp_{C2H5COOH} + F_{TFOH} \cdot Cp_{TFOH} + F_2 \cdot Cp_2 + F_{H2O} \cdot Cp_{H2O} + F_{PhI(OAc)2} \cdot Cp_{PhI(OAc)2}$$

$$+ F_{TMOF} \cdot Cp_{TMOF} + F_3 \cdot Cp_3 + F_{PhI} \cdot Cp_{PhI} + F_{AcOH} \cdot Cp_{AcOH} + F_{MeOH} \cdot Cp_{MeOH} + F_{HCOOCH3} \cdot Cp_{HCOOCH3}$$

$$+ F_{KOH} \cdot Cp_{KOH})\ (T_3 - T_{feed,3}) + \Delta H_r(T_3) \cdot F_{3,0} \cdot X_3 \qquad \text{(III.66)}$$

$$\boxed{Q_3 = 0.388\ W}$$

We summarize the results of heat transfer design of the different reactors for laboratory scale in table III.6:

Table III.6: PFR energy requirements.

Reactor	T_{feed} (°C)	T_{PFR} (°C)	Flow rate in $g.h^{-1}$	$\Delta H_r(T)$ $kJ.mol^{-1}$	Power (W)
PFR 1	25	150	3.734	144.194	0.239
PFR 2	0	50	10.364	70.136	0.287
PFR 3	50	65	23.09	207.920	0.388

The small PFR volumes and heating duties computed illustrate the documented and realized advantages of CPM technology. Microreactors improve heat and mass transfer rates spectacularly, enabling reaction intensification under reliable control.

III.4.5. Energy requirement for industrial scale

Following the same previous steps, we calculate reactors heating duties for industrial scale.

Table III.7. Energy requirement for industrial scale.

Reactor	T_{feed} (°C)	T_{PFR} (°C)	Flow rate in kg.h^{-1}	$\Delta H_r(T)$ kJ.mol^{-1}	Power (kW)
PFR 1	25	150	112.249	144.194	8.140
PFR 2	0	50	311.55	70.136	8.618
PFR 3	50	65	694.236	207.920	11.687

Energy requirements for industrial scale ensuring high endothermic conversions under isothermal reactor operation are quite reasonable and imply high potential for energy efficiency, justifying the operating cost advantages of CPM over batch manufacturing. Actual CPM energy requirements will be slightly higher, due to auxiliary functions.

III.5. Conclusion

In the first part, the determination of reaction orders and rate constants was achieved through the assessment of various potential kinetic expressions depending on published data. The first two reactions are second order reactions and the third one is pseudo first order. After understanding reaction kinetics, and applying mass balance, we calculated the residence time and volume for all three reactors. The results are compared with experimental data, the differences are relatively small and reasonable. The heating duties are calculated using Hess's and Kirchhoff's laws to calculate reactions enthalpies then applying an energy balance. These factors are determined for each laboratory and industrial scale. The results clearly testify for the great potentialities of the flow systems; the reasons for this new interest toward continuous flow processes can be found in the intrinsic characteristics of the flow reactors.

Chapter IV.

ANALYSIS/SIMULATION AND EVALUATION OF IBUPROFEN PROCESS ON ASPEN PLUS

IV.1 Introduction

Chemical process simulation aims to represent a process of chemical or physical transformation through a mathematic model that involves the calculation of mass and energy balances coupled with phase equilibrium and with transport and chemical kinetics equations. All this is made looking for the establishment (prediction) of the behavior of a process of known structure, in which some preliminary data of the equipment that constitute the process are known.

In this chapter, we proceed our work moving to the simulation of the studied process. We explain the way to perform the simulation using Aspen Plus (V12.1), from Aspen Technology, to model and evaluate the ibuprofen production process.

IV.2 Presentation of Aspen Plus

IV.2.1 Definition of Aspen Plus

Aspen Plus is a powerful steady-state process simulation software used in process engineering field. It is widely used on both academic and industrial level. It allows engineers to model, simulate, and optimize chemical processes and systems. The software provides tools for designing and analyzing processes, predicting performance, and optimizing operations. It can simulate a wide range of processes including chemical reactions, separations, heat exchange, and other unit operations (Al-Malah, 2022).

IV.2.2. Base principles and utilities

The base principles of Aspen Plus revolve around process modeling, simulation, and optimization in the chemical and process industries. Here are the key principles:

a/ Process Modeling:

- Aspen Plus uses a wide range of unit operation models (e.g., reactors, distillation columns, heat exchangers) to represent different parts of a chemical process.
- Accurate physical property databases and estimation methods are critical for predicting the behavior of chemical species under different conditions.

b/ Thermodynamics

- Selection of appropriate thermodynamic models (e.g., equation of state, activity coefficient models) to accurately describe phase behavior and other thermodynamic properties.

c/ Chemical Kinetics:

- Incorporating reaction kinetics and mechanisms to model chemical reactions, including catalytic and non-catalytic processes.

d/ Material and Energy Balances

- Ensuring mass and energy are conserved throughout the process, which involves setting up material and energy balances for each unit operation.

e/ Simulation and Optimization:

- Performing steady-state simulations to analyze the performance of processes at equilibrium, and dynamic simulations to study transient behavior.
- Identifying optimal operating conditions, equipment sizes, and process configurations to maximize efficiency and minimize costs.

f/ Sensitivity Analysis:

- Analyzing how changes in process parameters (e.g., temperature, pressure, feed composition) affect process performance.

g/ Integration and Interfaces:

- Integrating with other software and databases for data exchange and enhanced analysis capabilities.
- Providing a user-friendly interface for model setup, simulation, and results visualization.

IV.2.3. Aspen plus applications

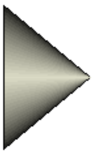
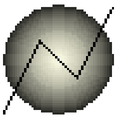
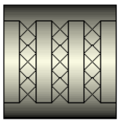
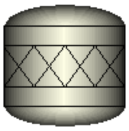
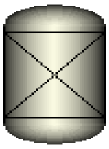
Aspen Plus® software represents the standard in the chemical process industries (CPI) for process simulation. This software serves industries such as refining, oil and gas, chemicals and petrochemicals, polymers, pharmaceuticals and specialty chemicals, power and utilities, consumer goods, food and beverage, and engineering and construction.

It is used by forty-six of the world's fifty largest chemical companies, twenty-three of the world's twenty-five largest petroleum refiners, eighteen of the world's twenty largest pharmaceutical companies, and seventeen out of the world's twenty largest engineering and construction firms that serve the CPI. This popularity is also evidenced in the academic community, where Aspen Plus continues to be the simulator of choice for studying process design and simulation. As such, providing undergraduates with a strong background in ASPEN Plus is a desirable program trait for many chemical engineering (ChE) departments, and is a recruiting consideration to many employers of ChE graduates (Rockstraw, 2005).

IV.3. Simulation of continuous Ibuprofen process with Aspen Plus

Ibuprofen production plant was simulated by using ASPEN PLUS (V12.1) with steady state mode. The equipment used from this software are shown in (Table IV.1)

Table IV.1: Equipment used in the simulation of ibuprofen process

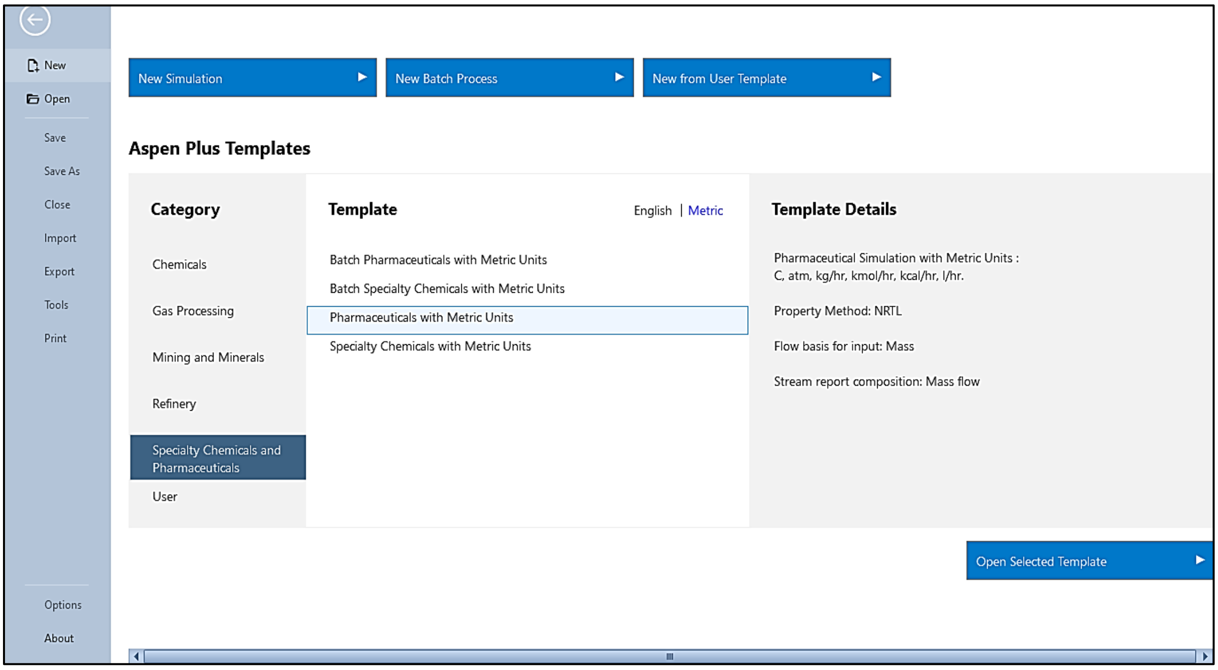
Name	Icon	Purpose
Mixers		To combine multiples streams into one stream
Heaters		To set the thermodynamic conditions of streams
RPlug		Plug flow reactor
Rstoic		Stoichiometric reactor based on known fractional conversions or extents of reaction
Spe		Component separator, separates components based on specified flows or split fractions

IV.3.1. Building the Model in Aspen Plus®

1. Starting Aspen Plus

- *Selecting a Template:*

In our case, we choose category: “Specialty Chemicals and Pharmaceuticals”, template: “Pharmaceuticals with Metric Units”.



Pharmaceutical Simulation with Metric Units : C, atm, kg/hr, kmol/hr, kcal/hr, l/hr.

Property Method: NRTL

Flow basis for input: Mass

Stream report composition: Mass flow

Figure IV.1. First steps in Aspen Plus®.

Click on “Open Selected Template”:

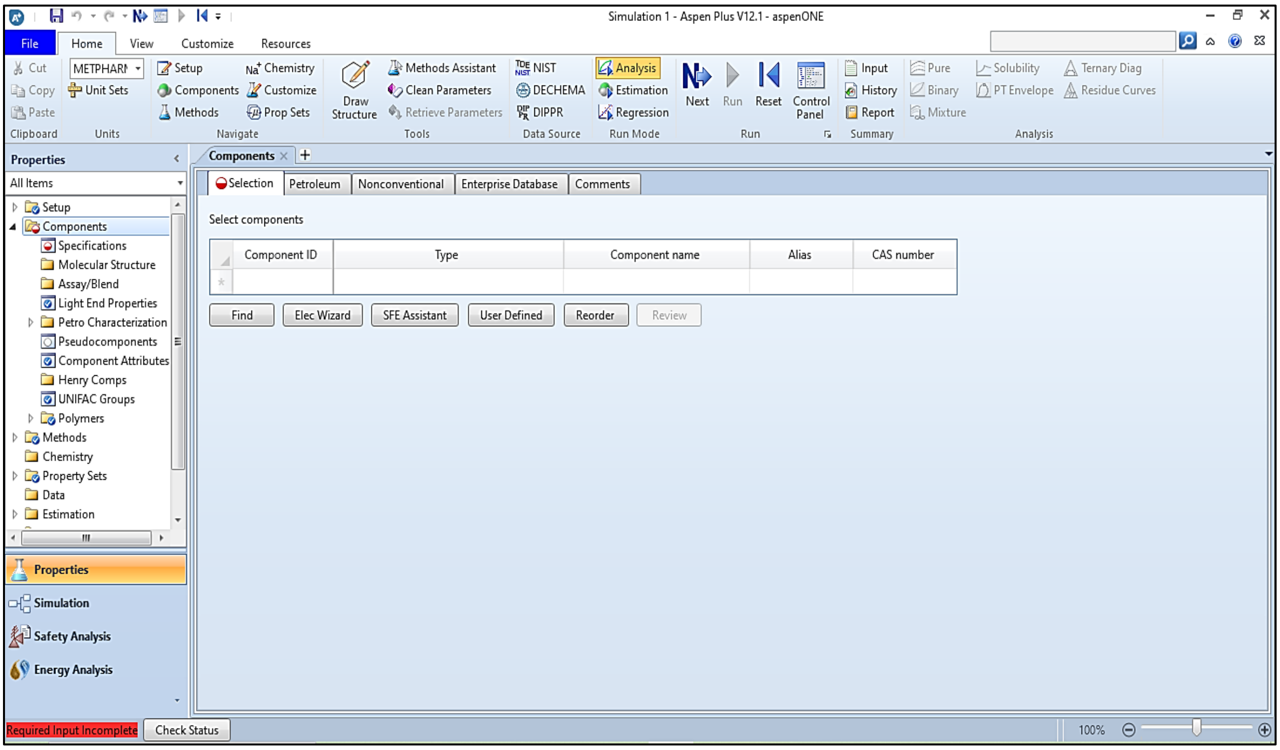


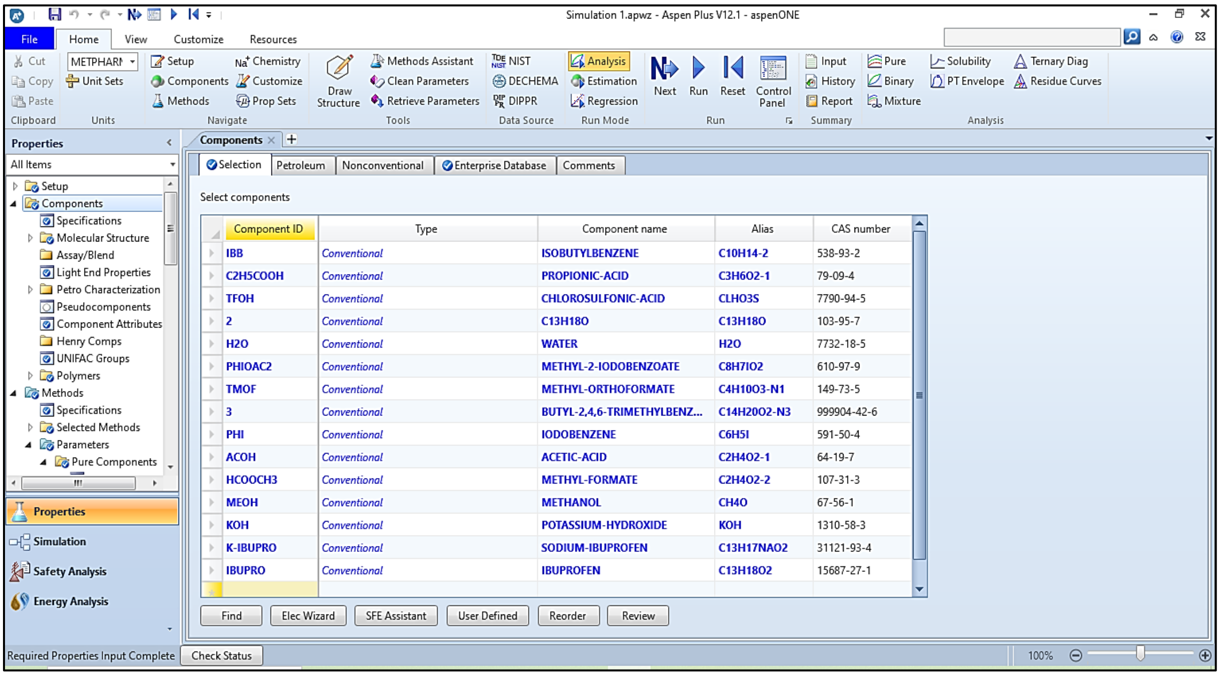
Figure IV.2. Aspen Plus® interface.

2. Properties Environment

System components and thermodynamics are typically the first inputs to be specified in building an Aspen Plus® model.

- *Selection of identified components list:*

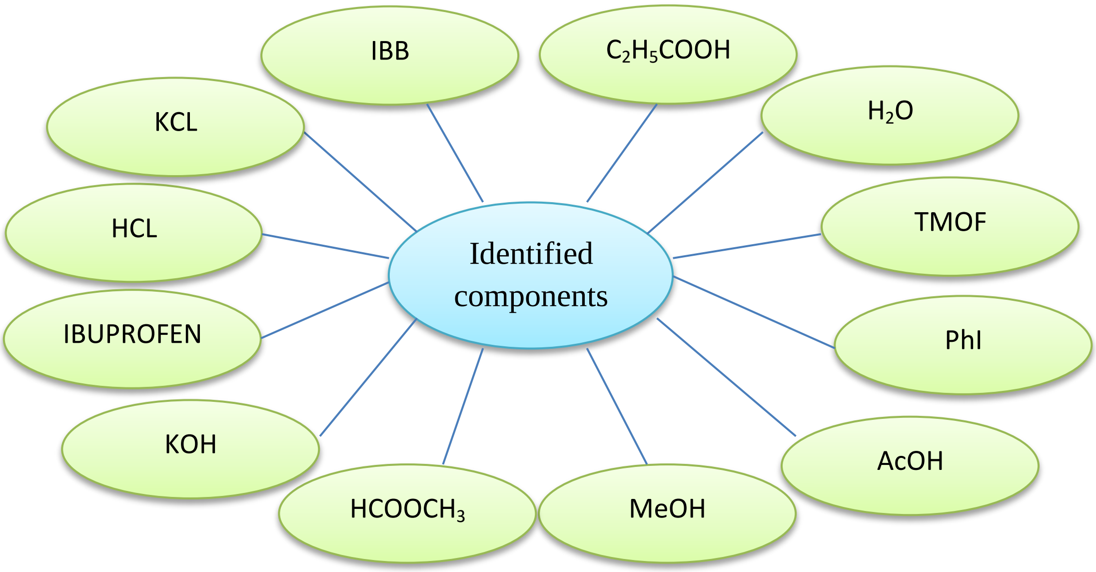
Click on “Find” button a windows to specify components is opened, and then tape component name or formula to search. Scheme IV.1 shows the identified components list used in our studied process.



Select components

Component ID	Type	Component name	Alias	CAS number
IBB	Conventional	ISOBUTYLBENZENE	C10H14-2	538-93-2
C2H5COOH	Conventional	PROPIONIC-ACID	C3H6O2-1	79-09-4
TFOH	Conventional	CHLOROSULFONIC-ACID	CLHO3S	7790-94-5
2	Conventional	C13H18O	C13H18O	103-95-7
H2O	Conventional	WATER	H2O	7732-18-5
PHIOAC2	Conventional	METHYL-2-IODOBENZOATE	C8H7IO2	610-97-9
TMOF	Conventional	METHYL-ORTHOFORMATE	C4H10O3-N1	149-73-5
3	Conventional	BUTYL-2,4,6-TRIMETHYLBENZ...	C14H20O2-N3	999904-42-6
PHI	Conventional	IODOBENZENE	C6H5I	591-50-4
ACOH	Conventional	ACETIC-ACID	C2H4O2-1	64-19-7
HCOOCH3	Conventional	METHYL-FORMATE	C2H4O2-2	107-31-3
MEOH	Conventional	METHANOL	CH4O	67-56-1
KOH	Conventional	POTASSIUM-HYDROXIDE	KOH	1310-58-3
K-IBUPRO	Conventional	SODIUM-IBUPROFEN	C13H17NAO2	31121-93-4
IBUPRO	Conventional	IBUPROFEN	C13H18O2	15687-27-1

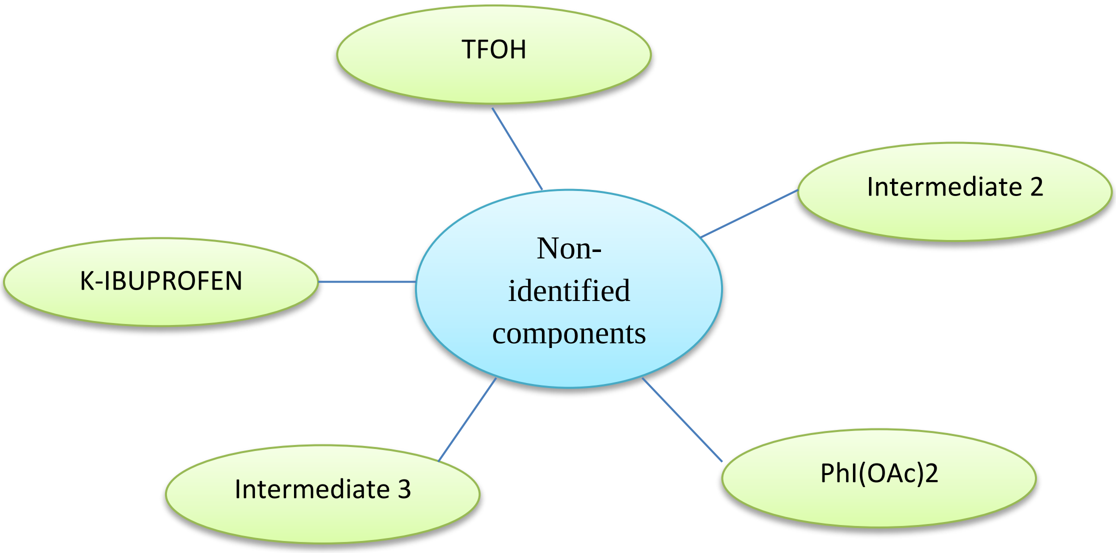
Figure IV.3. Components list in Aspen Plus software.



Scheme IV.1. Identified components

- *Selection of unidentified components list:*

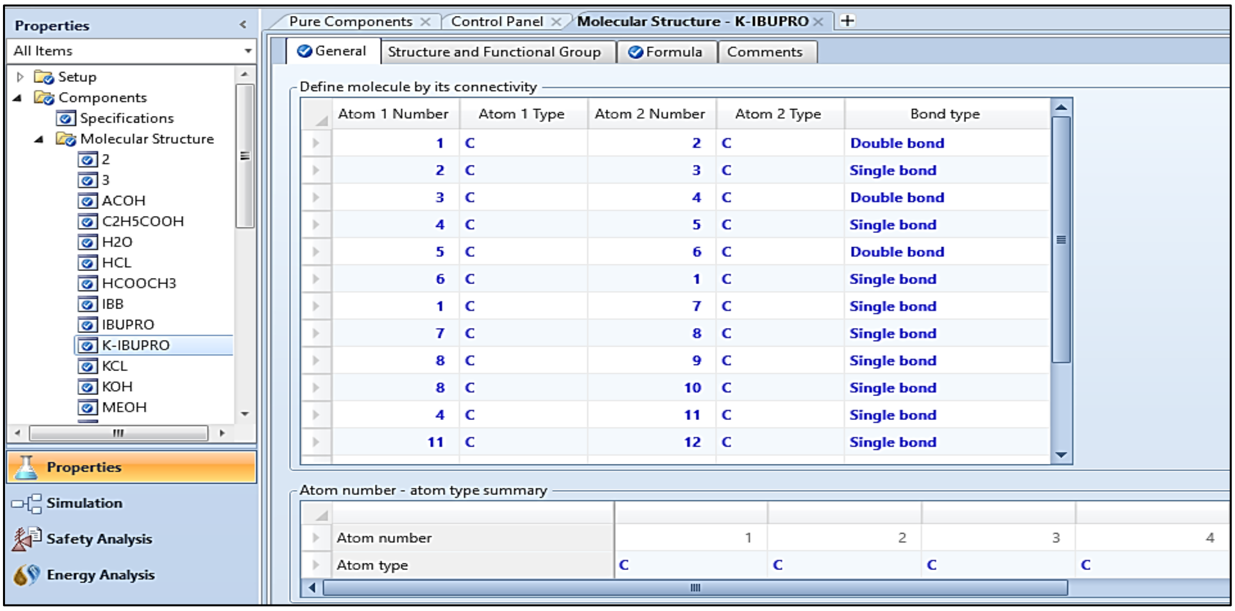
Our process contains rare components, which are not reported in Aspen Plus Data base. The simulator allows the prediction of these components properties using reduced information such as chemical structure, molecular weight, ext. (Scheme IV. 5) shows the unidentified components in the process.



Scheme IV.2. Unidentified components.

The following part illustrates the different steps to introduce the unidentified components in Aspen Plus:

Click on "Molecular Structure"



Define molecule by its connectivity

Atom 1 Number	Atom 1 Type	Atom 2 Number	Atom 2 Type	Bond type
1	C	2	C	Double bond
2	C	3	C	Single bond
3	C	4	C	Double bond
4	C	5	C	Single bond
5	C	6	C	Double bond
6	C	1	C	Single bond
1	C	7	C	Single bond
7	C	8	C	Single bond
8	C	9	C	Single bond
8	C	10	C	Single bond
4	C	11	C	Single bond
11	C	12	C	Single bond

Atom number - atom type summary

Atom number	1	2	3	4
Atom type	C	C	C	C

Figure IV.4. Window for Molecular Structure.

Click on “Structure and Functional Group”, then “Draw/Import/Edit” and draw window opened where we can edit or draw the component structure.

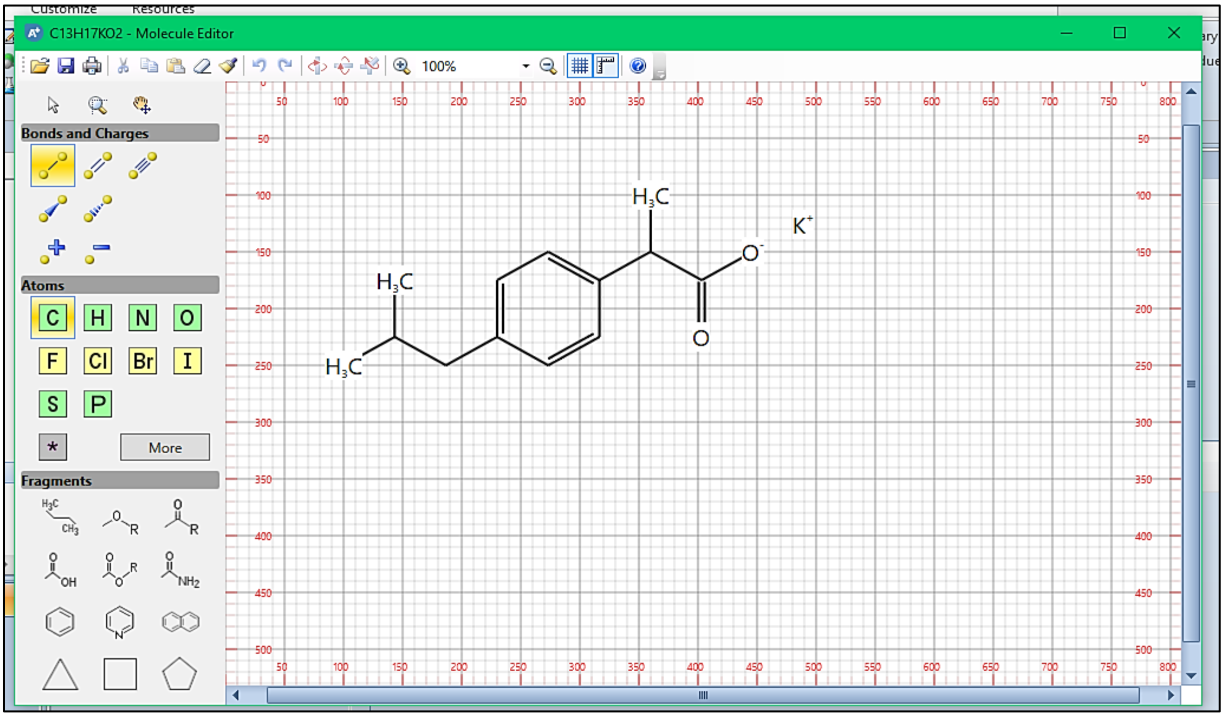


Figure IV.5. Window for Molecule Editor.

After drawing, save the structure in new file and close the window.

Click on “Calculate Bonds” so that the simulator can identify the components

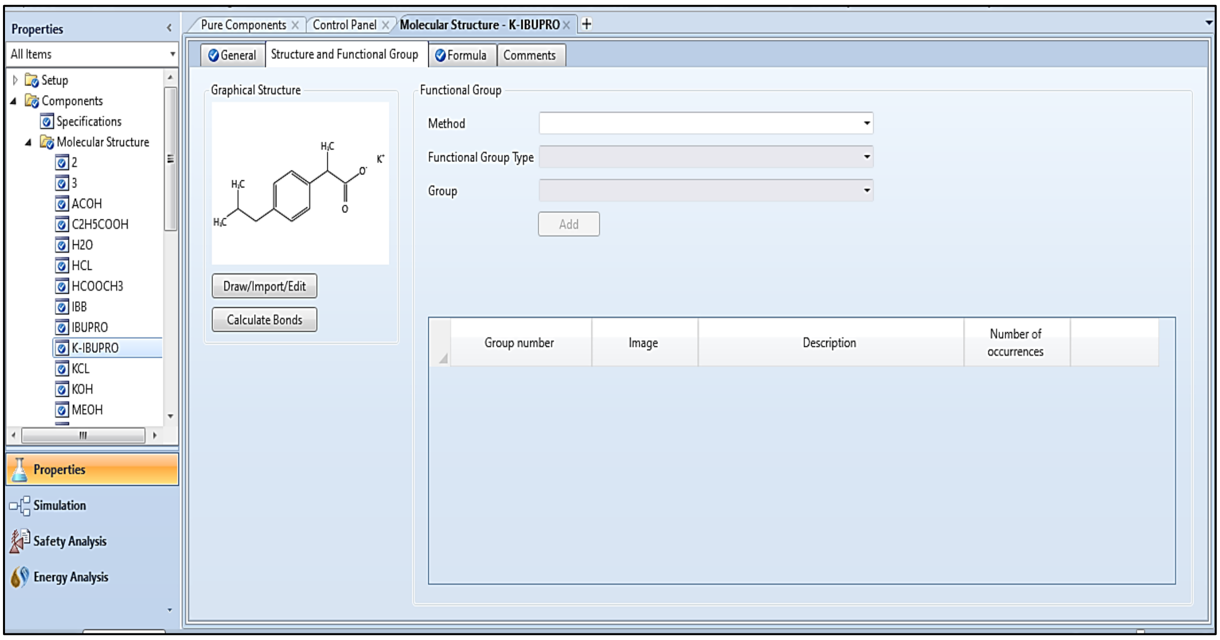
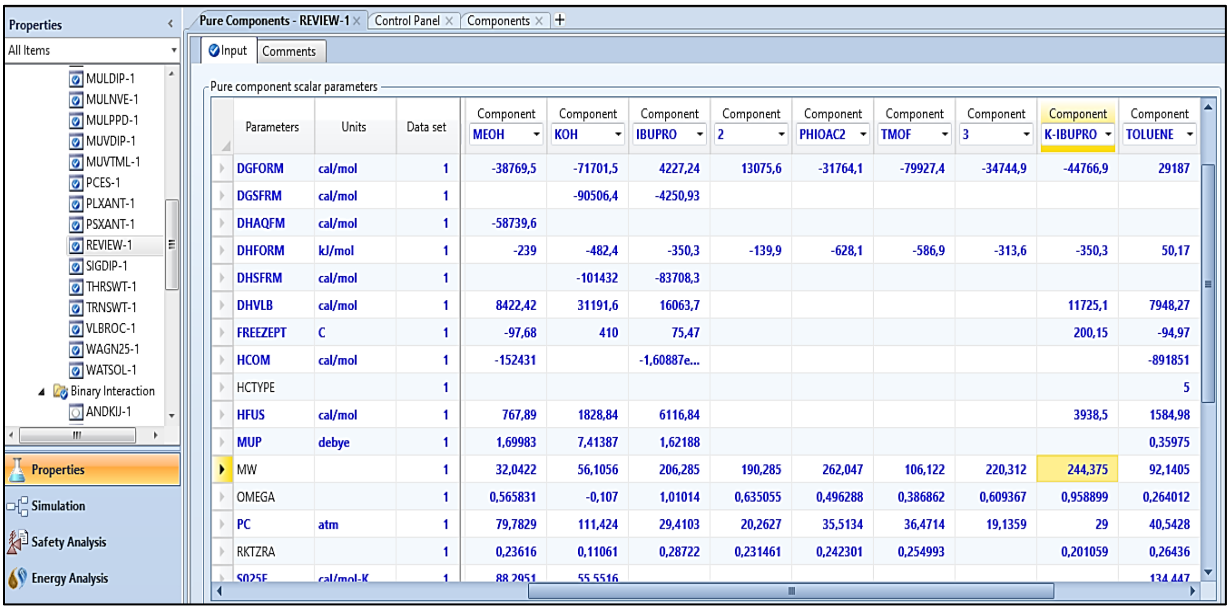


Figure IV.6. Structure and Functional Group tab

Click on “Components”, then “Review” and enter the missing parameters



Parameters	Units	Data set	Component MEOH	Component KOH	Component IBUPRO	Component 2	Component PHIOAC2	Component TMOF	Component 3	Component K-IBUPRO	Component TOLUENE
DGFORM	cal/mol	1	-38769,5	-71701,5	4227,24	13075,6	-31764,1	-79927,4	-34744,9	-44766,9	29187
DGSFRM	cal/mol	1		-90506,4	-4250,93						
DHAQFM	cal/mol	1	-58739,6								
DHFORM	kJ/mol	1	-239	-482,4	-350,3	-139,9	-628,1	-586,9	-313,6	-350,3	50,17
DHSFRM	cal/mol	1		-101432	-83708,3						
DHVLB	cal/mol	1	8422,42	31191,6	16063,7					11725,1	7948,27
FREEZEPT	C	1	-97,68	410	75,47					200,15	-94,97
HCOM	cal/mol	1	-152431		-1,60887e...						-891851
HCTYPE		1									5
HFUS	cal/mol	1	767,89	1828,84	6116,84					3938,5	1584,98
MUP	debye	1	1,69983	7,41387	1,62188						0,35975
MW		1	32,0422	56,1056	206,285	190,285	262,047	106,122	220,312	244,375	92,1405
OMEGA		1	0,565831	-0,107	1,01014	0,635055	0,496288	0,386862	0,609367	0,958899	0,264012
PC	atm	1	79,7829	111,424	29,4103	20,2627	35,5134	36,4714	19,1359	29	40,5428
RKTZRA		1	0,23616	0,11061	0,28722	0,231461	0,242301	0,254993		0,201059	0,26436
S025E	cal/mol-K	1	88,2951	55,5516							134,447

Figure IV.7. Window for Components – Review.

In the upper menu bar a section with the Run Mode is available. Three run modes can be selected (Chaves and all., 2016):

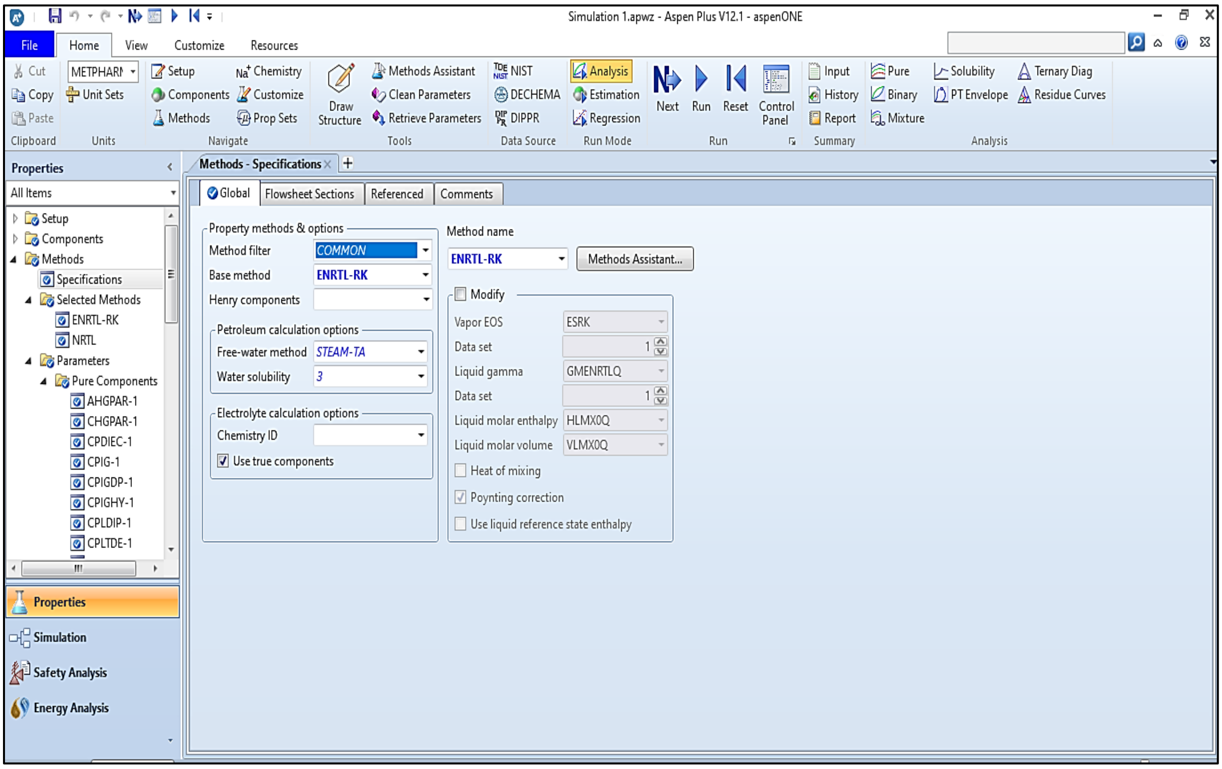
- Analysis: property analysis of pure components and mixtures. It is used also to evaluate accuracy of the models;
- Estimation: estimation of properties of components or missing which are not available in the simulator databank by means of molecular structure;
- Regression: calculation of model parameters by regression of experimental data.

Click on “Estimation”

3. Selection of property method (Thermodynamics)

Since we have liquid phase, we select the ENRTL-RK model (Elec-Non-Random Two Liquids), due to the strongly polar or even ionic character of liquid phase. It is based on the unsymmetric electrolyte NRTL property model. It uses:

- The Redlich-Kwong equation of state for vapor phase properties;
- The unsymmetric reference state (infinite dilution in aqueous solution) for ionic species;
- Henry’s Law for solubility of supercritical gases;
- Unsymmetric electrolye NRTL method of handling.



Property methods & options
Method filter: COMMON
Base method: ENRTL-RK
Henry components:

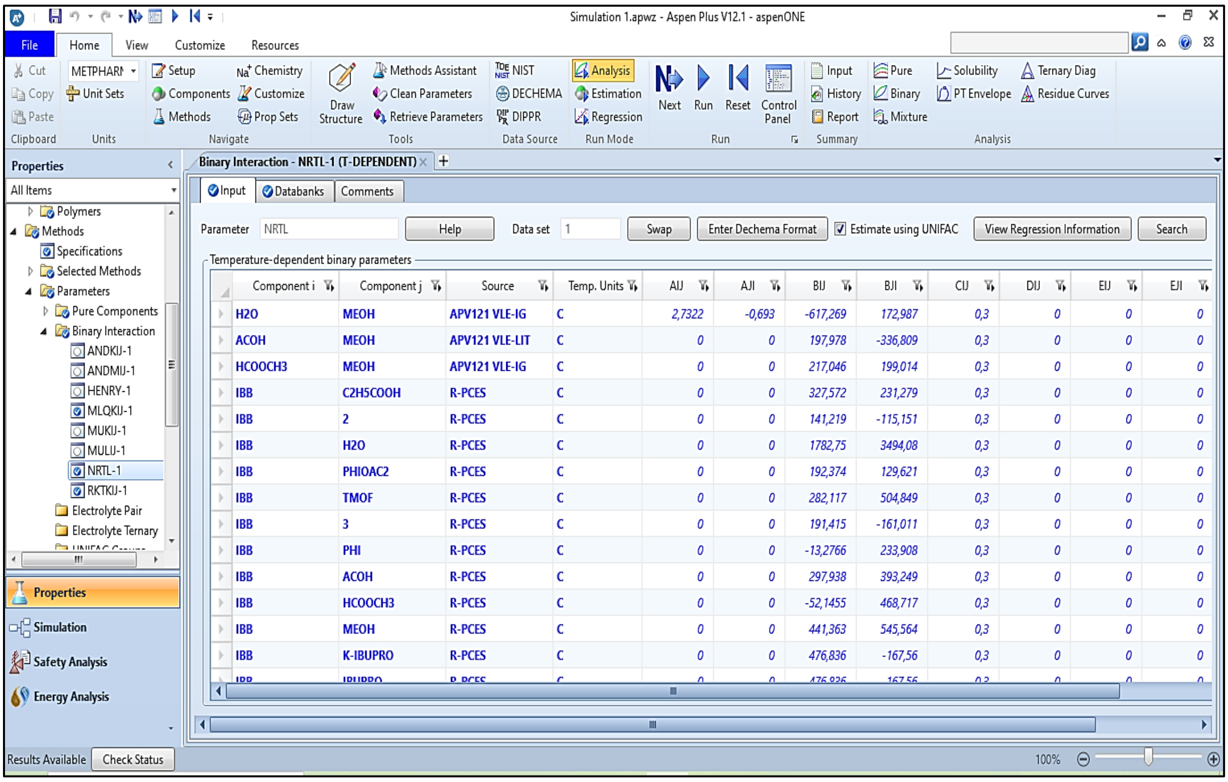
Petroleum calculation options
Free-water method: STEAM-TA
Water solubility: 3

Electrolyte calculation options
Chemistry ID:
☑ Use true components

Method name: ENRTL-RK

☐ Modify
Vapor EOS: ESRK
Data set: 1
Liquid gamma: GMENRTLQ
Data set: 1
Liquid molar enthalpy: HLMX0Q
Liquid molar volume: VLMX0Q
☐ Heat of mixing
☑ Poynting correction
☐ Use liquid reference state enthalpy

Figure IV.8. Window for the selection of the thermodynamic model.



Parameter: NRTL
Data set: 1
☑ Estimate using UNIFAC

Temperature-dependent binary parameters

Component i	Component j	Source	Temp. Units	AIJ	AJI	BIJ	BJI	CIJ	DIJ	EIJ	EJI
H2O	MEOH	APV121 VLE-IG	C	2,7322	-0,693	-617,269	172,987	0,3	0	0	0
ACOH	MEOH	APV121 VLE-LIT	C	0	0	197,978	-336,809	0,3	0	0	0
HCOOCH3	MEOH	APV121 VLE-IG	C	0	0	217,046	199,014	0,3	0	0	0
IBB	C2H5COOH	R-PCES	C	0	0	327,572	231,279	0,3	0	0	0
IBB	2	R-PCES	C	0	0	141,219	-115,151	0,3	0	0	0
IBB	H2O	R-PCES	C	0	0	1782,75	3494,08	0,3	0	0	0
IBB	PHIOAC2	R-PCES	C	0	0	192,374	129,621	0,3	0	0	0
IBB	TMOF	R-PCES	C	0	0	282,117	504,849	0,3	0	0	0
IBB	3	R-PCES	C	0	0	191,415	-161,011	0,3	0	0	0
IBB	PHI	R-PCES	C	0	0	-13,2766	233,908	0,3	0	0	0
IBB	ACOH	R-PCES	C	0	0	297,938	393,249	0,3	0	0	0
IBB	HCOOCH3	R-PCES	C	0	0	-52,1455	468,717	0,3	0	0	0
IBB	MEOH	R-PCES	C	0	0	441,363	545,564	0,3	0	0	0
IBB	K-IBUPRO	R-PCES	C	0	0	476,836	-167,56	0,3	0	0	0

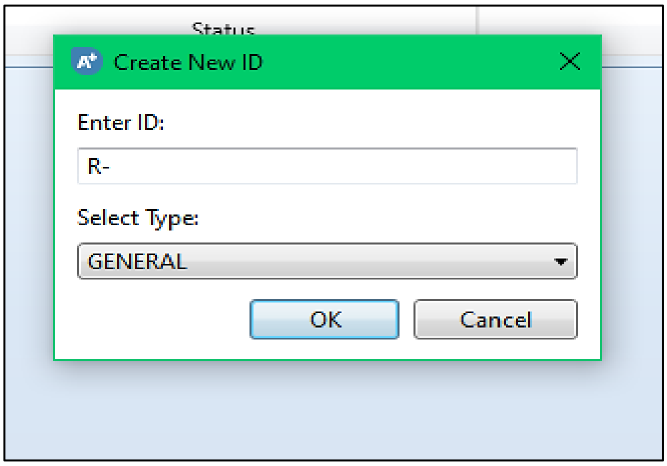
Figure IV.9. Binary parameters of the model used in the system.

4. Simulation environment

The Simulation environment is the part of the software where the equipment, streams and reactions involved in the process are specified.

- *Defining reactions and formation of reaction sets:*

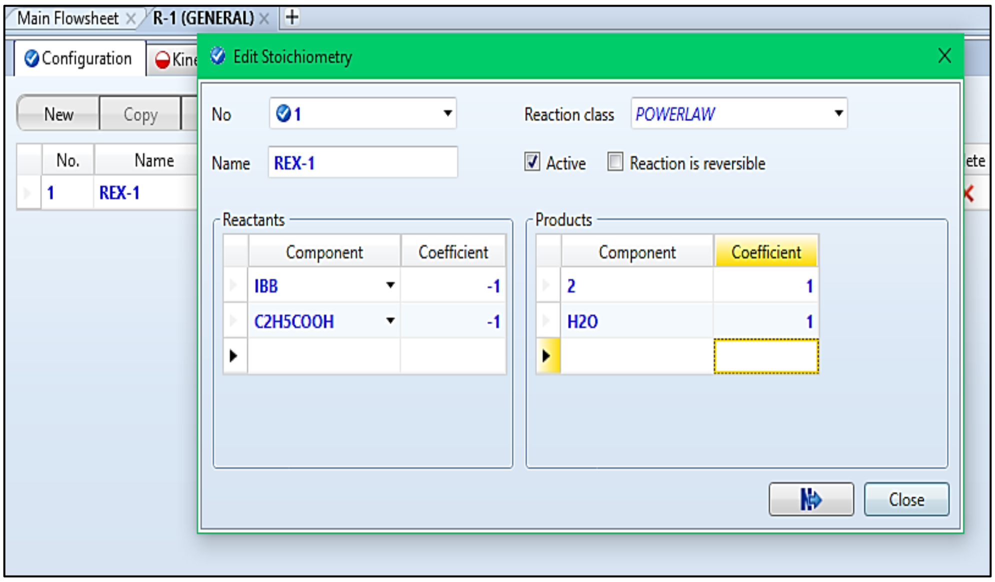
In this simulation, the procedure of ibuprofen production involves sets of reactions: Friedel-Crafts Acylation, PhI(OAc)$_2$-Mediated 1,2-Aryl Migration and Base hydrolysis. All three reactions are "POWERLAW" type but first we choose "GENERAL" type. Figures IV.10, IV.11 and IV.12 give input information to set reactions in Aspen Plus.



Enter ID: R-

Select Type: GENERAL

Figure IV.10. Specification of reactions type to be included in Aspen Plus®.



No: 1

Name: REX-1

Reaction class: POWERLAW

☑ Active ☐ Reaction is reversible

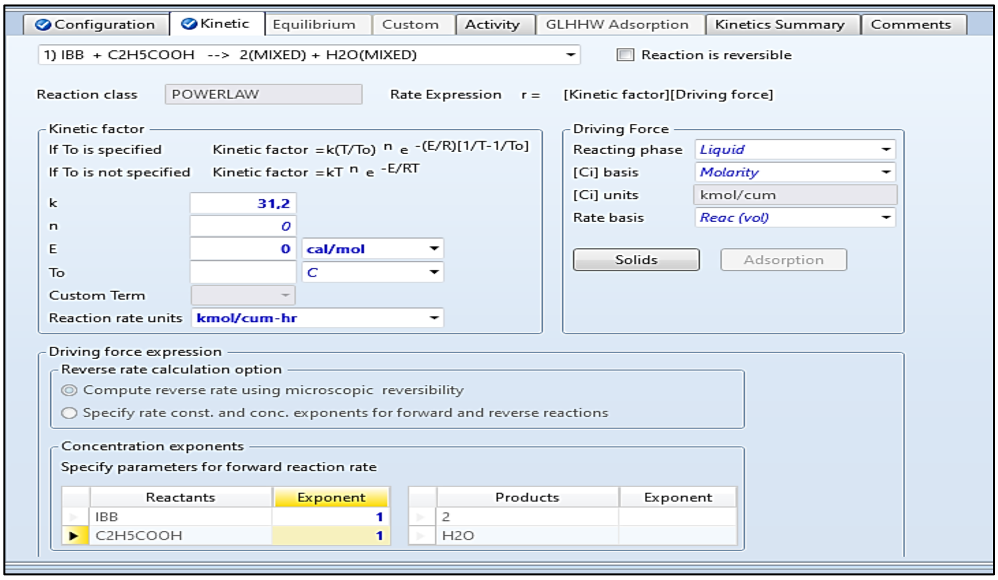
Reactants

Component	Coefficient
IBB	-1
C2H5COOH	-1

Products

Component	Coefficient
2	1
H2O	1

Figure IV.11. Example of configuration tab for the Friedel-Crafts Acylation reaction



1) IBB + C2H5COOH --> 2(MIXED) + H2O(MIXED)

☐ Reaction is reversible

Reaction class: POWERLAW

Rate Expression r = [Kinetic factor][Driving force]

Kinetic factor

If To is specified: Kinetic factor $=k(T/To)^{n}\,e^{-(E/R)[1/T-1/To]}$

If To is not specified: Kinetic factor $=kT^{n}\,e^{-E/RT}$

k	31,2	
n	0	
E	0	cal/mol
To		C
Custom Term		
Reaction rate units	kmol/cum-hr	

Driving Force

Reacting phase	Liquid
[Ci] basis	Molarity
[Ci] units	kmol/cum
Rate basis	Reac (vol)

Driving force expression

Reverse rate calculation option

○ Compute reverse rate using microscopic reversibility

○ Specify rate const. and conc. exponents for forward and reverse reactions

Concentration exponents

Specify parameters for forward reaction rate

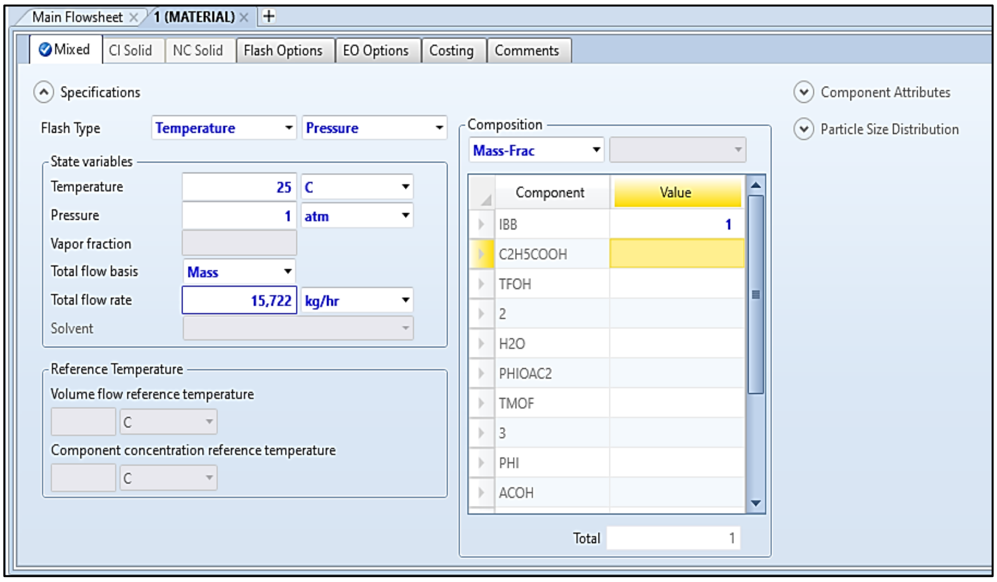
Reactants	Exponent
IBB	1
C2H5COOH	1

Products	Exponent
2	
H2O	

Figure IV.12. Example of kinetic tab for the Friedel-Crafts Acylation reaction.

- *Installing the feed streams and different units:*

a. Streams: The streams are characterized by different parameters: temperature, pressure, total flow rate and phase. For the component compositions, these can be given in different forms: flow rate, molar or mass fraction, concentration etc. in this process 25 streams are used to connect different equipment.



Flash Type: Temperature | Pressure

State variables

Temperature	25	C
Pressure	1	atm
Vapor fraction		
Total flow basis	Mass	
Total flow rate	15,722	kg/hr
Solvent		

Reference Temperature

Volume flow reference temperature: C

Component concentration reference temperature: C

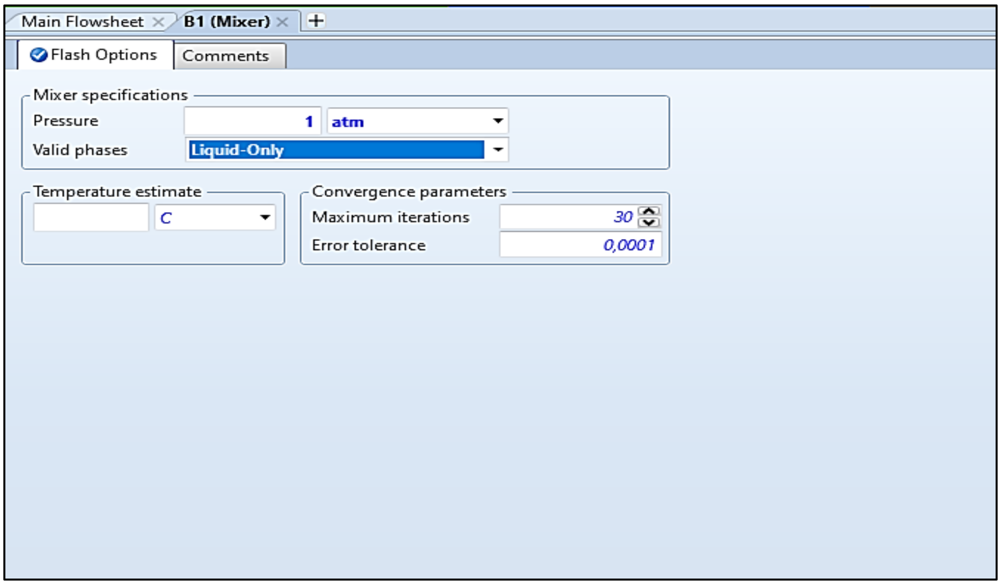
Composition: Mass-Frac

Component	Value
IBB	1
C2H5COOH	
TFOH	
2	
H2O	
PHIOAC2	
TMOF	
3	
PHI	
ACOH	

Total 1

Figure IV.13. Window of specifications for stream Feed.

b. Mixers: the process contains five mixers. For each mixer, pressure value and mixture phase must be specified



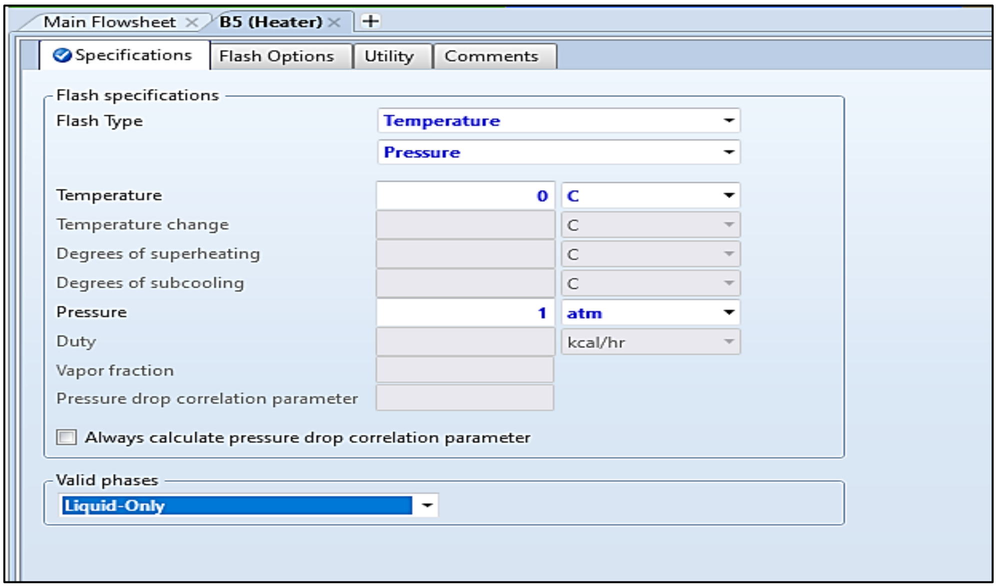
Mixer specifications
Pressure: 1 atm
Valid phases: Liquid-Only

Temperature estimate: C

Convergence parameters
Maximum iterations: 30
Error tolerance: 0,0001

Figure IV.14: Specification for the Mixer in Aspen Plus®.

c. **Coolers:** in Aspen Plus, heaters can be used as coolers. They are characterized by different parameters: temperature, pressure and mixture phase. We need two coolers.



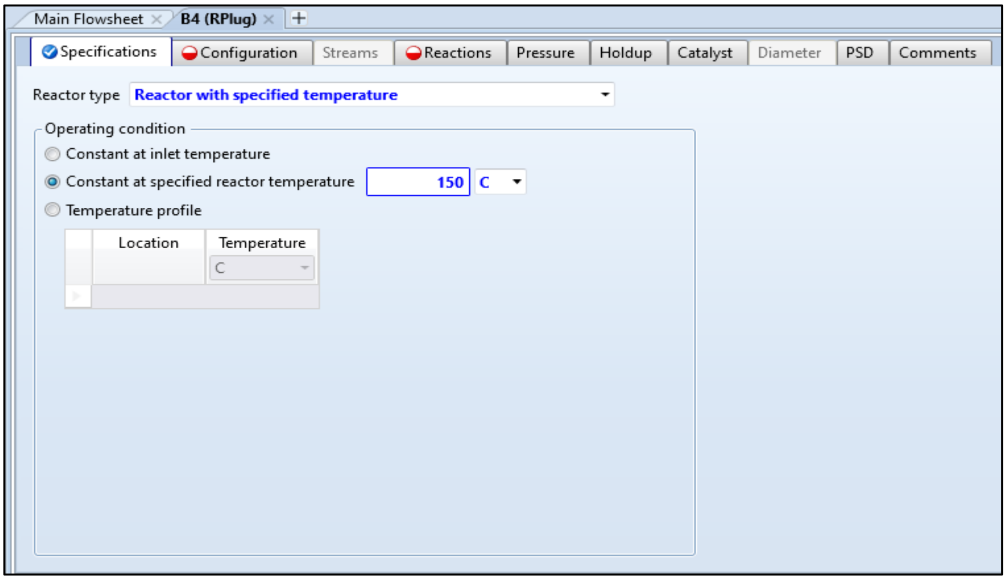
Flash specifications
Flash Type: Temperature
Pressure
Temperature: 0 C
Temperature change: C
Degrees of superheating: C
Degrees of subcooling: C
Pressure: 1 atm
Duty: kcal/hr
Vapor fraction
Pressure drop correlation parameter
☐ Always calculate pressure drop correlation parameter

Valid phases: Liquid-Only

Figure IV.15: Specification for the Cooler in Aspen Plus®.

d. **Plug flow reactors:** the process contains three PFRs:

First, the thermal condition of the reactor must be specified, different options are given, we select "Reactor with specified temperature" for isothermal reactors and enter its value.



Reactor type: Reactor with specified temperature

Operating condition

○ Constant at inlet temperature

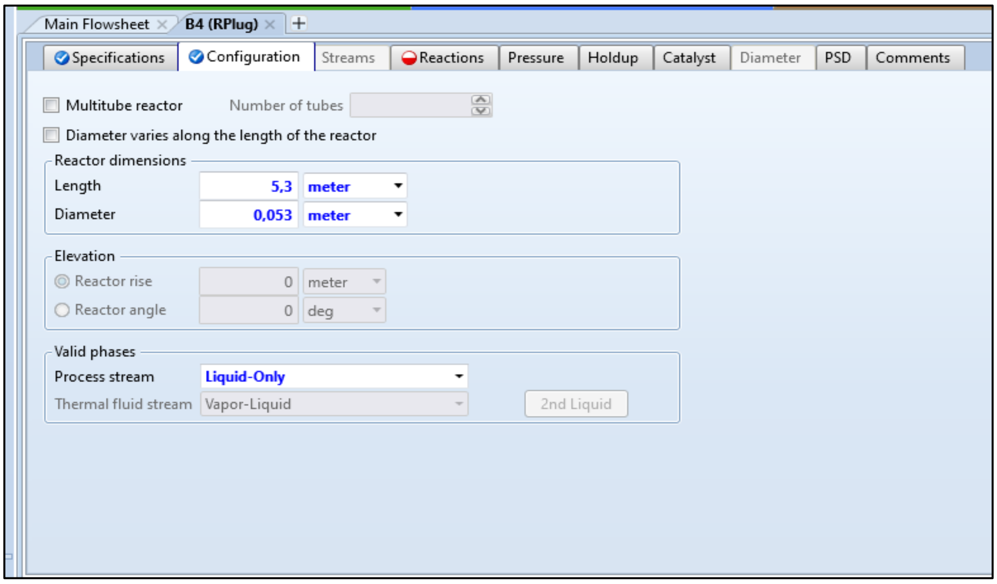
● Constant at specified reactor temperature: 150 C

○ Temperature profile

Location	Temperature
	C

Figure IV.16: RPlug Module configuration in Aspen Plus®

Then, select tab Configuration where reactor dimensions (length and diameter) must be specified with the stream phase.



☐ Multitube reactor — Number of tubes

☐ Diameter varies along the length of the reactor

Reactor dimensions

Length: 5,3 meter

Diameter: 0,053 meter

Elevation

○ Reactor rise: 0 meter

○ Reactor angle: 0 deg

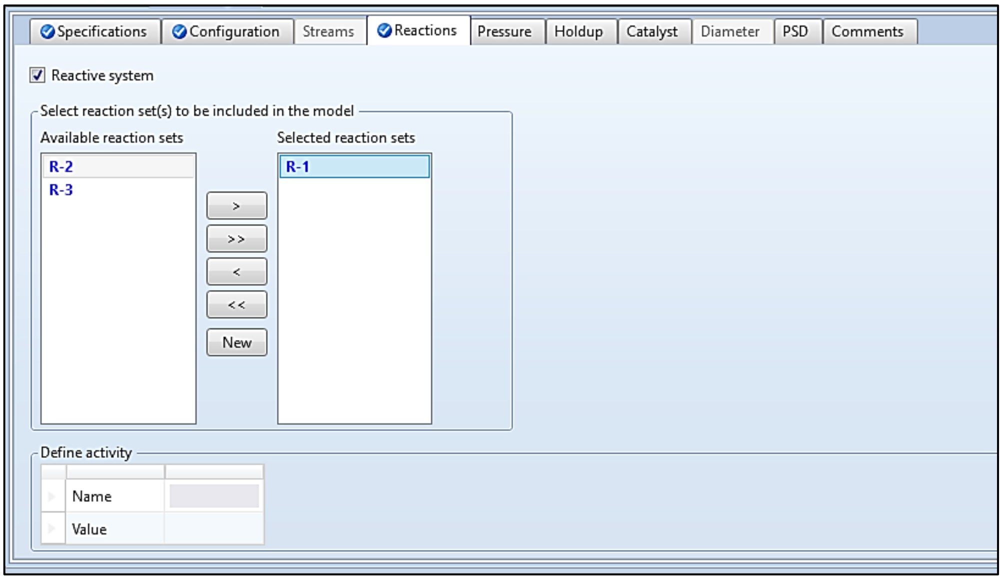
Valid phases

Process stream: Liquid-Only

Thermal fluid stream: Vapor-Liquid

Figure IV.17. Geometric configuration of the reactor module PFR in Aspen Plus®

The next step is to select the Reactions tab, where the reaction set created earlier is entered.



☑ Reactive system

Select reaction set(s) to be included in the model

Available reaction sets: R-2, R-3

Selected reaction sets: R-1

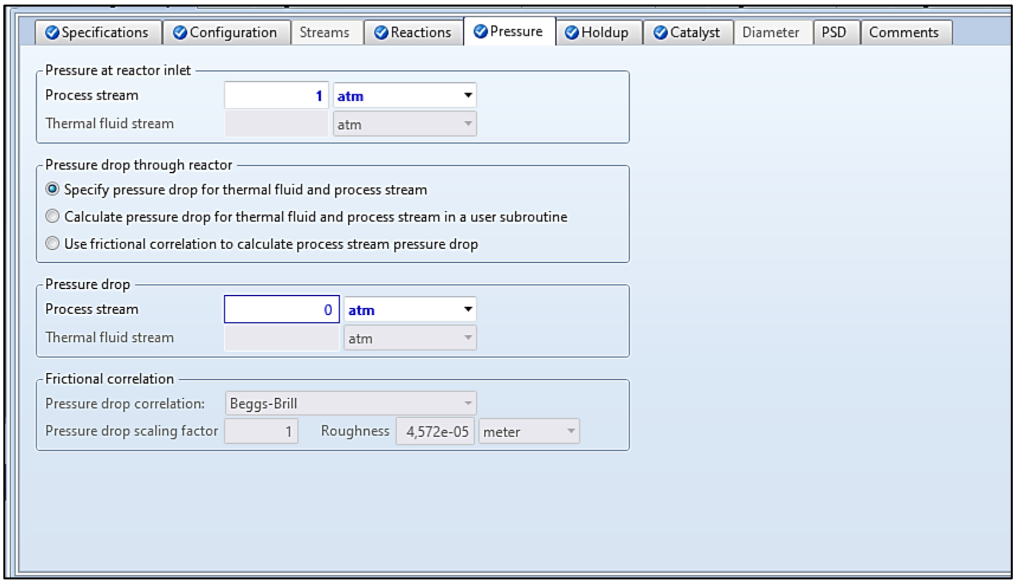
Define activity

Name

Value

Figure IV.18. Reactions tab of RPlug reactor module in Aspen Plus®

Finally, we specify pressure values in the reactor. In this way the configuration of tubular reactor is completed.



Pressure at reactor inlet

Process stream 1 atm

Thermal fluid stream atm

Pressure drop through reactor

● Specify pressure drop for thermal fluid and process stream

○ Calculate pressure drop for thermal fluid and process stream in a user subroutine

○ Use frictional correlation to calculate process stream pressure drop

Pressure drop

Process stream 0 atm

Thermal fluid stream atm

Frictional correlation

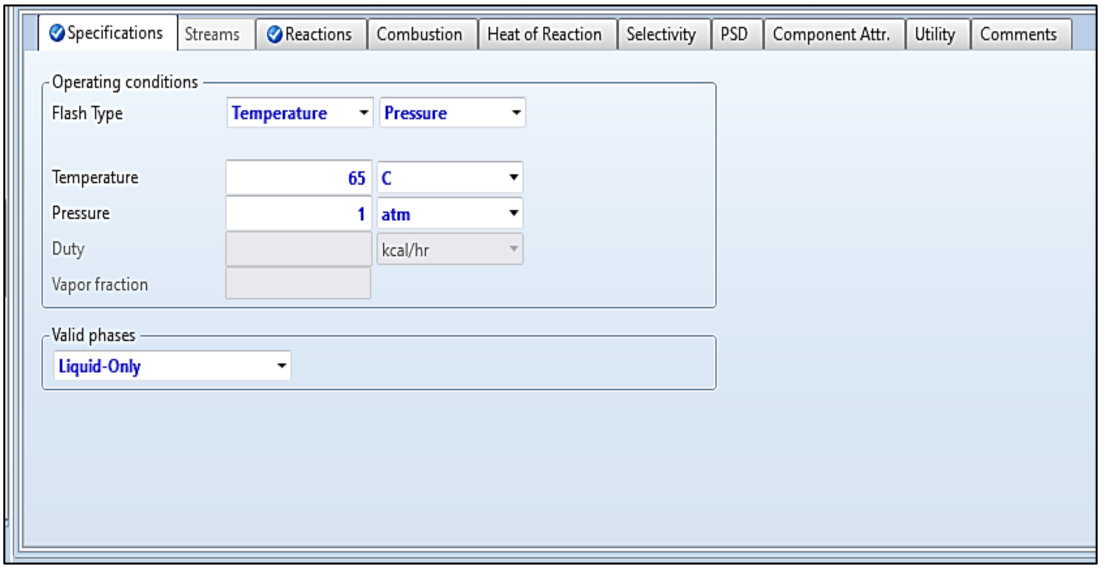
Pressure drop correlation: Beggs-Brill

Pressure drop scaling factor 1 Roughness 4,572e-05 meter

Figure IV.19. Pressure tab of RPlug reactor module in Aspen Plus®

e. Acidification tank: RStoic is used as an acidification tank.

First, introduce reactor thermodynamic conditions (temperature, pressure and stream phase)



Operating conditions

Flash Type: Temperature, Pressure

Temperature: 65 C

Pressure: 1 atm

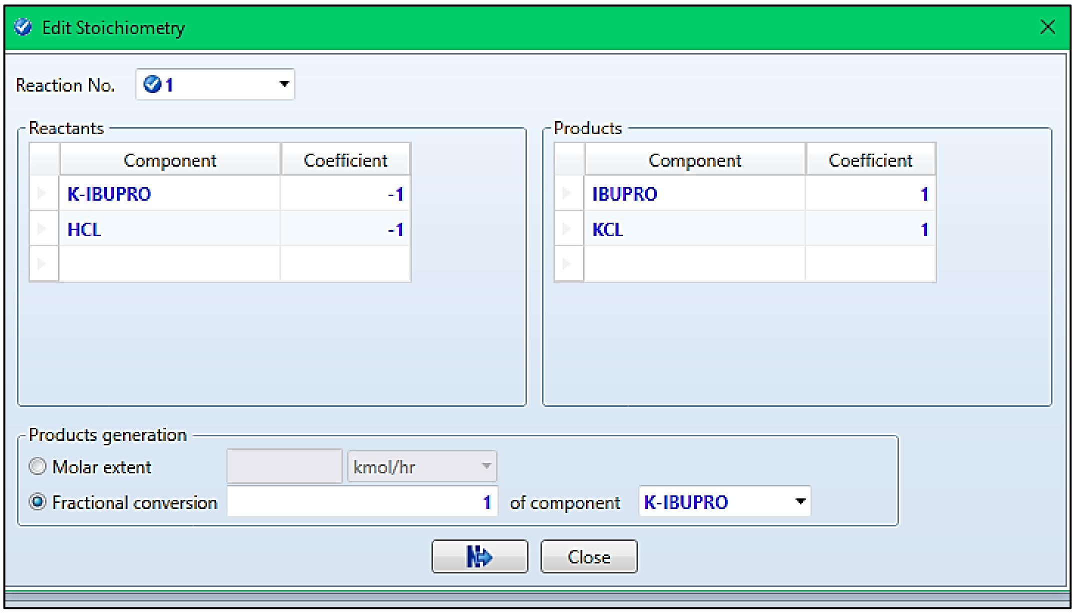
Duty: kcal/hr

Vapor fraction

Valid phases: Liquid-Only

Figure IV.20. RStoic configuration in Aspen Plus®

Next, click on the Reaction tab to create a new reaction. After carrying out this action, the following window appears where the specifications of the reaction are entered (reactants, products, stoichiometric coefficients and information about reaction conversion). In our case, 1 fractional conversion of K-Ibuprofen is specified.



Reaction No. 1

Reactants

Component	Coefficient
K-IBUPRO	-1
HCL	-1

Products

Component	Coefficient
IBUPRO	1
KCL	1

Products generation

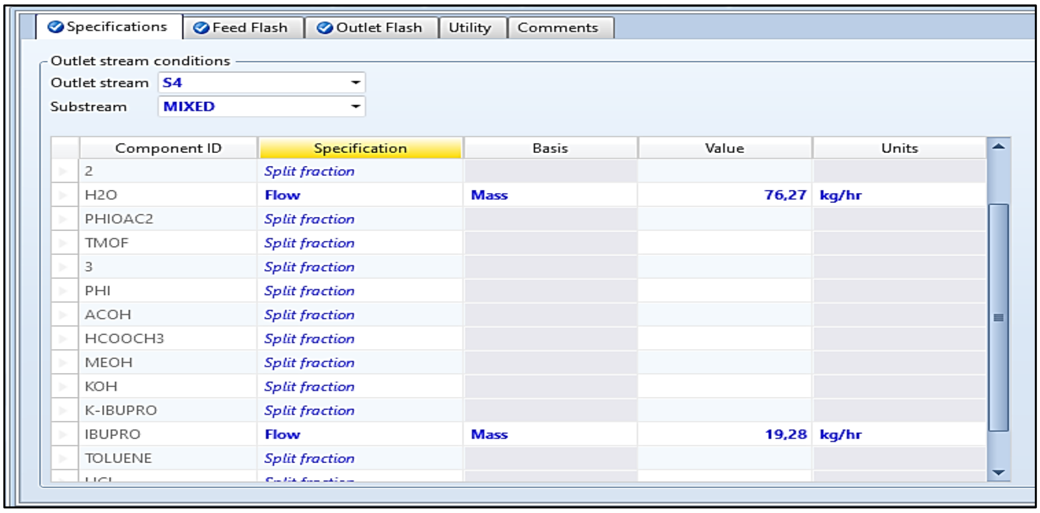
○ Molar extent kmol/hr

● Fractional conversion 1 of component K-IBUPRO

Figure IV.21. Specification window of the reaction for RStoic in Aspen Plus®.

f. Separator: a components separator is selected.

First, specify outlet steam and choose the components with specified fractions or flows.



Outlet stream conditions

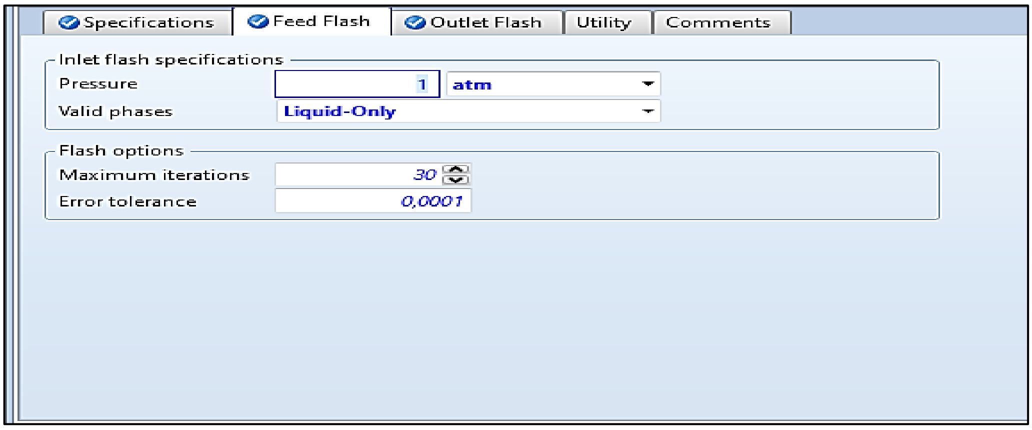
Outlet stream: S4

Substream: MIXED

Component ID	Specification	Basis	Value	Units
2	Split fraction			
H2O	Flow	Mass	76,27	kg/hr
PHIOAC2	Split fraction			
TMOF	Split fraction			
3	Split fraction			
PHI	Split fraction			
ACOH	Split fraction			
HCOOCH3	Split fraction			
MEOH	Split fraction			
KOH	Split fraction			
K-IBUPRO	Split fraction			
IBUPRO	Flow	Mass	19,28	kg/hr
TOLUENE	Split fraction			

Figure IV.22. Separator specification in Aspen Plus®.

Introduce Feed and Outlet Flash conditions.



Inlet flash specifications

Pressure: 1 atm

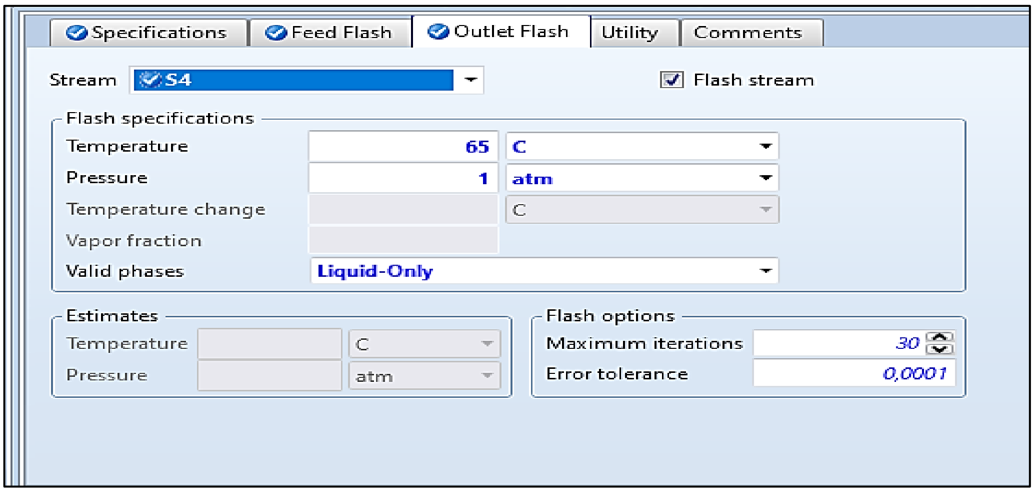
Valid phases: Liquid-Only

Flash options

Maximum iterations: 30

Error tolerance: 0,0001

Figure IV.23. Feed Flash conditions.



Stream: S4

☑ Flash stream

Flash specifications

Temperature: 65 C

Pressure: 1 atm

Temperature change: C

Vapor fraction

Valid phases: Liquid-Only

Estimates

Temperature: C

Pressure: atm

Flash options

Maximum iterations: 30

Error tolerance: 0,0001

Figure IV.24. Outlet Flash conditions.

Finally, connect all units with the appropriate steams and the flowsheet of the process of Ibuprofen production is ready.

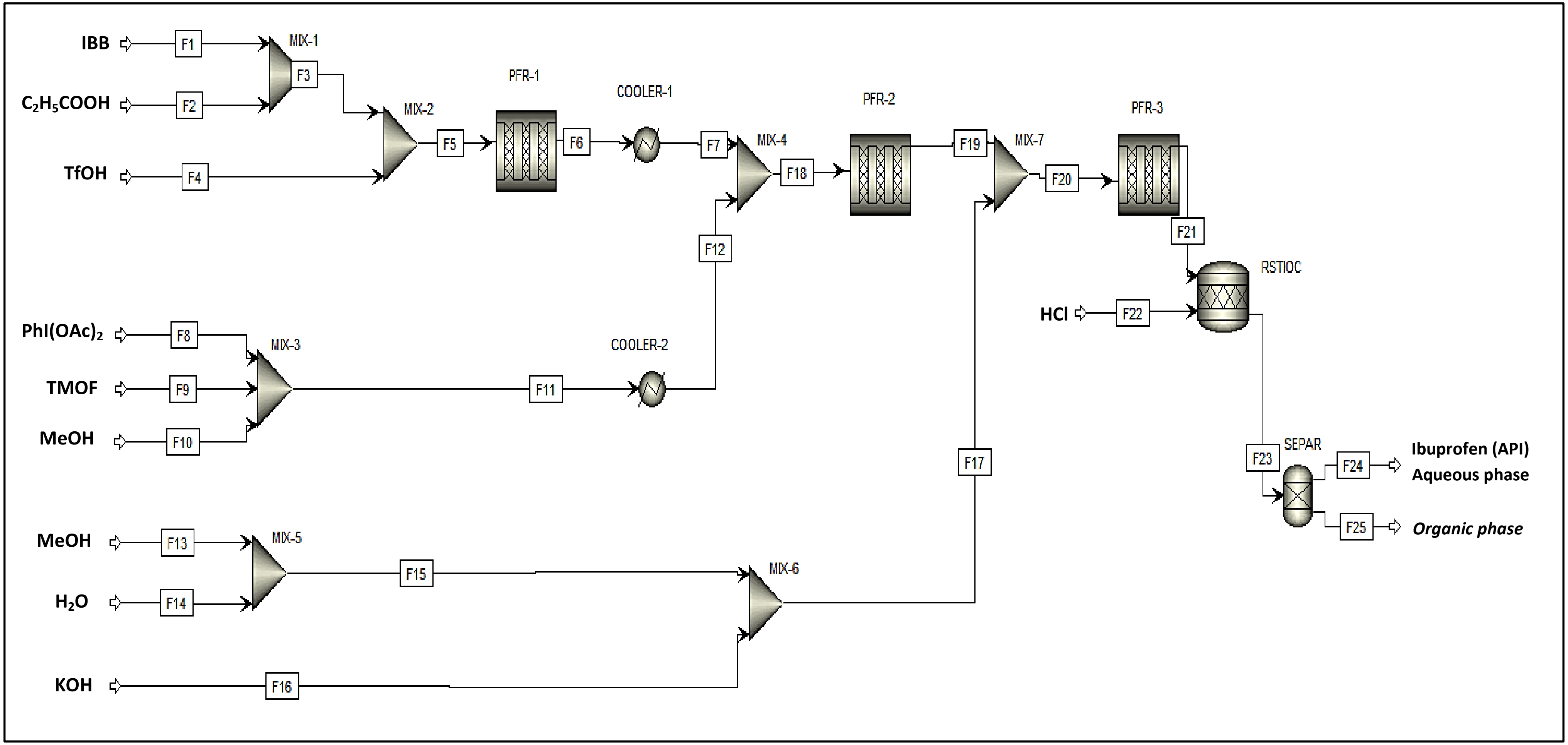


Figure IV.25. Process flow diagram of continuous Ibuprofen production process in Aspen plus.

IV.4. Simulation results of continuous Ibuprofen production

After performing the simulation, we get the results of the industrial scale process which are organized in tables and graphs.

IV.4.1. Process input and output obtained through simulation

We report in table IV.2 and table IV.3, the streams properties (temperature, density, enthalpy, different flows and mass fraction) and plug flow reactors performance, respectively

Table IV.2. a. Process input and output of ibuprofen process (first reactor).

Stream Name Units	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
From	**-**	**-**	***MIX-1***	**-**	***MIX-2***	***PFR-1***
To	***MIX-1***	***MIX-1***	***MIX-2***	***MIX-2***	***PFR-1***	***COOLER-1***
Temperature C	25	25	19,96802783	25	24,73105434	150
Molar Density mol/cc	0,006635969	0,013139433	0,008994071	0,025198808	0,018329439	0,016573899
Mass Density gm/cc	0,890687443	0,973361863	0,937036309	2,936287084	2,082262749	1,882829723
Enthalpy Flow kW	-3237,16969	-15607,19543	-18844,36512	-116995,6198	-135839,9849	-127453,0295
Average MW	134,22116	74,07944	104,1837749	116,52484	113,6021003	113,6021003
Mass Flows kg/hr	15,722	8,658	24,38	87,86900002	112,249	112,249
IBB kg/hr	15,722	0	15,722	0	15,722	1,24482614
C2H5COOH kg/hr	0	8,658	8,658	0	8,658	0,6677477
TFOH kg/hr	0	0	0	87,86900002	87,86900002	87,86900002
2 kg/hr	0	0	0	0	0	20,52428738
H2O kg/hr	0	0	0	0	0	1,943138777
Mass Fractions						
IBB	1	0	0,644872847	0	0,140063609	0,011089864
C2H5COOH	0	1	0,355127153	0	0,07713209	0,005948808
TFOH	0	0	0	1	0,782804301	0,782804301
2	0	0	0	0	0	0,18284606
H2O	0	0	0	0	0	0,017310967
Volume Flow l/hr	17,65153436	8,894944761	26,01820202	29,92520742	53,90722188	59,61718082

Table IV.2. b. Process input and output of ibuprofen process (second reactor).

Stream Name Units	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F18**	**F19**
From	***COOLER-1***	-	-	-	***MIX-3***	***COOLER-2***	***MIX-4***	***PFR-2***
To	***MIX-4***	***MIX-3***	***MIX-3***	***MIX-3***	***COOLER-2***	***MIX-4***	***PFR-2***	***MIX-7***
Temperature C	0	25	25	25	25,43162105	0	0,396704975	50
Molar Density mol/cc	0,019662894	0,006008212	0,009402081	0,019401328	0,016397603	0,016904941	0,017400256	0,01642163
Mass Density gm/cc	2,233746098	1,574432991	0,997763896	0,621660468	0,799027062	0,823748811	1,06752025	0,986527987
Enthalpy Flow kW	-132850,9141	-24848,73293	-70010,44953	-230352,983	-325212,1654	-327798,3702	-460649,2843	-451658,5121
Average MW	113,6021003	262,04685	106,1216	32,04216	48,72828532	48,72828532	61,35083646	60,07491304
Mass Flows	112,249	38,238	49,691	111,38	199,309	199,309	311,558	311,558
IBB kg/hr	1,24482614	0	0	0	0	0	1,24482614	1,24482614
C2H5COOH kg/hr	0,6677477	0	0	0	0	0	0,6677477	0,6677477
TFOH kg/hr	87,86900002	0	0	0	0	0	87,86900002	87,86900002
2 kg/hr	20,52428738	0	0	0	0	0	20,52428738	0,000610689
H2O kg/hr	1,943138777	0	0	0	0	0	1,943138777	5,78171E-05
PHIOAC2 kg/hr	0	38,238	0	0	38,238	38,238	38,238	9,97431246
TMOF kg/hr	0	0	49,691	0	49,691	49,691	49,691	38,24500191
3 kg/hr	0	0	0	0	0	0	0	23,76223268
PHI kg/hr	0	0	0	0	0	0	0	22,0040031
ACOH kg/hr	0	0	0	0	0	0	0	6,477111981
HCOOCH3 kg/hr	0	0	0	0	0	0	0	6,477111981
MEOH kg/hr	0	0	0	111,38	111,38	111,38	111,38	114,8359835
Mass Fractions								
IBB	0,011089864	0	0	0	0	0	0,003995488	0,003995488
C2H5COOH	0,005948808	0	0	0	0	0	0,002143253	0,002143253
TFOH	0,782804301	0	0	0	0	0	0,282030954	0,282030954
2	0,18284606	0	0	0	0	0	0,065876297	1,96011E-06
H2O	0,017310967	0	0	0	0	0	0,006236844	1,85574E-07
PHIOAC2	0	1	0	0	0,191852852	0,191852852	0,122731562	0,032014304
TMOF	0	0	1	0	0,249316388	0,249316388	0,159491973	0,122754036
3	0	0	0	0	0	0	0	0,07626905
PHI	0	0	0	0	0	0	0	0,070625704

ACOH	0	0	0	0	0	0	0	0,020789426
HCOOCH3	0	0	0	0	0	0	0	0,020789426
MEOH	0	0	0	1	0,55883076	0,55883076	0,357493629	0,368586214
Volume Flow l/hr	50,25145881	24,28683864	49,80236327	179,1653252	249,4396117	241,9536118	291,852075	315,8126319

Table IV.2. c. Process input and output of ibuprofen process (third reactor).

Stream Name Units	**F13**	**F14**	**F15**	**F16**	**F17**	**F20**	**F21**
From	**-**	**-**	***MIX-5***	**-**	***MIX-6***	***MIX-7***	***PFR-3***
To	***MIX-5***	***MIX-5***	***MIX-6***	***MIX-6***	***MIX-7***	***PFR-3***	***RSTIOC***
Temperature C	25	25	31,03360343	25	29,16478642	38,43191755	65
Molar Density mol/cc	0,019401328	0,055351231	0,02511923	0,033235779	0,023624466	0,021139475	0,021109389
Mass Density gm/cc	0,621660468	0,997167932	0,678131344	1,864714662	0,776267483	0,871888793	0,870647892
Enthalpy Flow kW	-394613,3974	-263528,6665	-658142,064	-353686,684	-1011828,748	-1463487,26	-1444571,633
Average MW	32,04216	18,01528	26,99650222	56,10564	32,85862491	41,24458037	41,24458037
Mass Flows	190,803	60,26800001	251,071	131,578	382,649	694,207	694,207
IBB kg/hr	0	0	0	0	0	1,24482614	1,24482614
C2H5COOH kg/hr	0	0	0	0	0	0,6677477	0,6677477
TFOH kg/hr	0	0	0	0	0	87,86900002	87,86900002
2 kg/hr	0	0	0	0	0	0,000610689	0,000610689
H2O kg/hr	0	60,26800001	60,26800001	0	60,26800001	60,26805783	60,26805783
PHIOAC2 kg/hr	0	0	0	0	0	9,97431246	9,97431246
TMOF kg/hr	0	0	0	0	0	38,24500191	38,24500191
3 kg/hr	0	0	0	0	0	23,76223268	0,252653105
PHI kg/hr	0	0	0	0	0	22,0040031	22,0040031
ACOH kg/hr	0	0	0	0	0	6,477111981	6,477111981
HCOOCH3 kg/hr	0	0	0	0	0	6,477111981	6,477111981
MEOH kg/hr	190,803	0	190,803	0	190,803	305,6389835	309,0582212
KOH kg/hr	0	0	0	131,578	131,578	131,578	125,5909344
K-IBUPROFEN kg/hr	0	0	0	0	0	0	26,07740759
Mass Fractions							

IBB	0	0	0	0	0	0,001793163	0,001793163
C2H5COOH	0	0	0	0	0	0,000961886	0,000961886
TFOH	0	0	0	0	0	0,126574638	0,126574638
2	0	0	0	0	0	8,79694E-07	8,79694E-07
H2O	0	1	0,240043653	0	0,157502045	0,086815687	0,086815687
PHIOAC2	0	0	0	0	0	0,014367923	0,014367923
TMOF	0	0	0	0	0	0,05509164	0,05509164
3	0	0	0	0	0	0,034229319	0,000363945
PHI	0	0	0	0	0	0,031696602	0,031696602
ACOH	0	0	0	0	0	0,009330231	0,009330231
HCOOCH3	0	0	0	0	0	0,009330231	0,009330231
MEOH	1	0	0,759956347	0	0,498637132	0,440270674	0,44519606
KOH	0	0	0	1	0,343860823	0,189537127	0,180912803
K-IBUPROFEN	0	0	0	0	0	0	0,037564311
Volume Flow l/hr	306,924776	60,43916785	370,2394858	70,56200217	492,9344698	796,210486	797,345295

Table IV.2. d. Process input and output of ibuprofen process (purification).

Stream Name Units	**F22**	**F23**	**F24**	**F25**
From	**-**	**RSTIOC**	**SEPAR**	**SEPAR**
To	**RSTIOC**	**SEPAR**	**-**	**-**
Temperature C	65	65	65	65
Mass Density gm/cc	0,717304675	0,873571668	1,076095878	0,222952626
Enthalpy Flow kW	-73741,68695	-1526598,207	-340316,1707	-1184562,635
Average MW	21,23865745	40,04213529	22,64387308	45,60796717
Mass Flows	22,86	717,067	98,282	618,785
IBB kg/hr	0	1,24482614	0	1,24482614
C2H5COOH kg/hr	0	0,6677477	0	0,6677477
TFOH kg/hr	0	87,86900002	0	87,86900002
2 kg/hr	0	0,000610689	0	0,000610689

H2O kg/hr	16,002	76,27005783	76,27	5,78271E-05
PHIOAC2 kg/hr	0	9,97431246	0	9,97431246
TMOF kg/hr	0	38,24500191	0	38,24500191
3 kg/hr	0	0,252653105	0	0,252653105
PHI kg/hr	0	22,0040031	0	22,0040031
ACOH kg/hr	0	6,477111981	0	6,477111981
HCOOCH3 kg/hr	0	6,477111981	0	6,477111981
MEOH kg/hr	0	309,0582212	0	309,0582212
KOH kg/hr	0	125,5909344	0	125,5909344
K-IBUPROFEN kg/hr	0	0	0	0
IBUPROFEN kg/hr	0	22,01276302	22,012	0,000763017
HCL kg/hr	6,858	2,967263799	0	2,967263799
KCL kg/hr	0	7,955380775	0	7,955380775
Mass Fractions				
IBB	0	0,001735997	0	0,002011726
C2H5COOH	0	0,000931221	0	0,001079127
TFOH	0	0,122539456	0	0,142002473
2	0	8,51649E-07	0	9,86917E-07
H2O	0,7	0,106363921	0,776032234	9,34526E-08
PHIOAC2	0	0,013909875	0	0,016119189
TMOF	0	0,053335326	0	0,061806608
3	0	0,000352342	0	0,000408305
PHI	0	0,030686119	0	0,035560014
ACOH	0	0,009032785	0	0,010467468
HCOOCH3	0	0,009032785	0	0,010467468
MEOH	0	0,431003269	0	0,499459782
KOH	0	0,175145327	0	0,202963767
K-IBUPROFEN	0	0	0	0

IBUPROFEN	0	0,030698335	0,223967766	1,23309E-06
HCL	0,3	0,004138057	0	0,004795307
KCL	0	0,011094334	0	0,012856454
Volume Flow l/hr	31,86930297	820,8450733	91,33201051	2775,410233

Table IV.3. Plug flow reactors properties.

Parameters	**RPlug**		
	PFR-1	***PFR-2***	***PFR-3***
Reactor dimensions length [meter]	5,3	5,1	19
Reactor dimensions diameter [meter]	0,053	0,053	0,053
Pressure at reactor inlet: process stream [atm]	1	1	1
Reactor temperature [C]	150	50	65
Residence time [min]	11.6685	2.13972	3.14577
Conversion rate	0.9208	0.9999	0.9893

As shown in table IV.2, temperatures and pressures are constant and stable in all three PFRs, coolers, acidification tank and separator. These explain that process simulation is done in the desired conditions.

Furthermore the mass conservation is verified in all process units means each unit input equals its output. Compared these results to the calculated results in chapter II (Table II.7), we notice similarity in products quantities. The obtained value through simulation for K-Ibuprofen is **26,077 kg/hr**, corresponding to **206 tons/year**, while the calculated value using experimental data is **25.41 kg/hr,** corresponding to **200 tons/year**. These differences can be justified by little difference in PFRs conversion rates obtained from simulation and experimental data.

Table IV.3 shown closeness of the simulated conversion rates to the measured values in laboratory scale. We had **91%** conversion rate while the simulated one is **92%** for the first reactor, for the second PFR, we had **98%** while simulation is almost **100%.** For PFR-3, the simulated conversion gave **99%** while the experimental data is **98%.**

In the separation part, from steam “F23”, K-Ibuprofen is totally acidified and converted to Ibuprofen but stills mixed with other components. After separation, from steam “F24”, we get **22,012 kg/hr** of ibuprofen (API) about **174.335 tons** produced annually.

IV.4.2. Energy consumption

We report in table IV.4 and figure IV.26, energy consumption of different equipment.

Table IV.4. Energy consumption of different equipment obtained through simulation.

Equipment	**Code**	**Heat duty (kW)**
Cooler 1	COOLER-1	-6.27774
Cooler 2	COOLER-2	-3.00776
Plug flow reactor 1	PFR-1	9.75403
Plug flow reactor 2	PFR-2	10.4563
Plug flow reactor 3	PFR-3	21.9989
Acidification tank	RSTOIC	-9.63532
Separator	SEPAR	1.99966

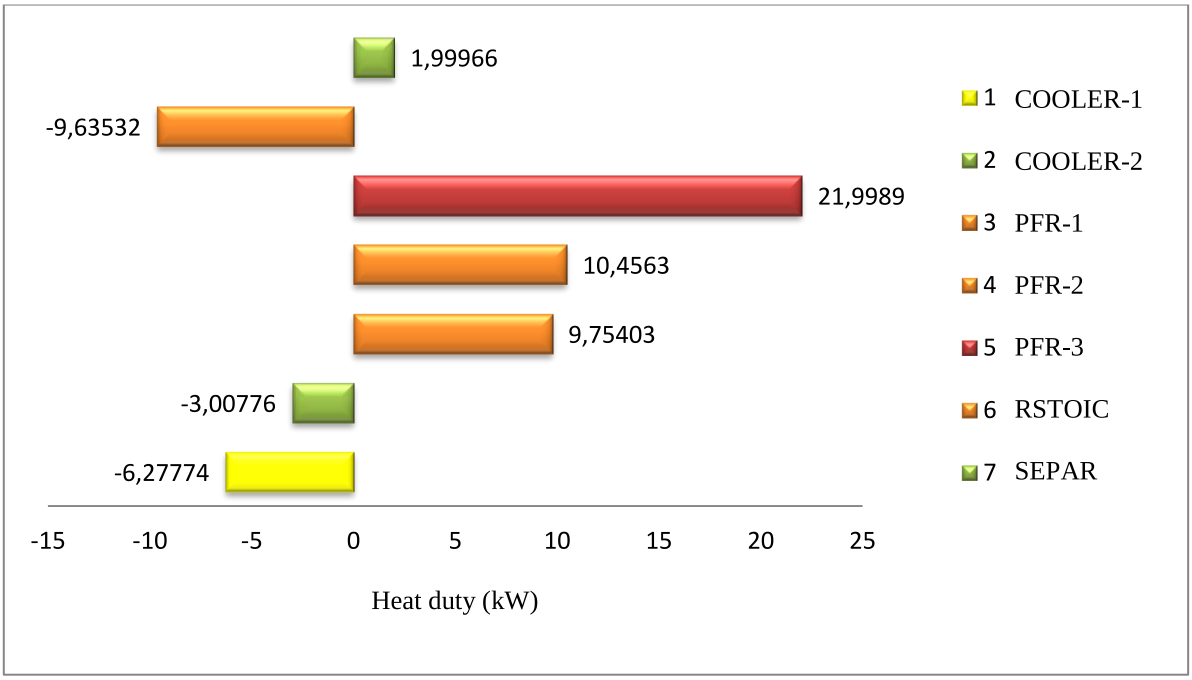


Figure IV.26. Bars graph for energy consumption

Typically, using coolers means transferring energy from inside a system to the outside environment that both coolers heat duties are negative. For the first cooler, the heat dissipation is twice heat dissipation of the second cooler, which is explained by temperature differential, larger temperature differential requires more work.

For the PFRs, the heat duties are positive due to the nature of the reaction involved. Endothermic reactions absorb heat from the surroundings to proceed. The third reactor consumes more energy than other reactors affected by its volume or length (19 m). The simulated results are compared to the calculated results in chapter III (Table III.7), we notice some differences between them. These differences can be justified by the simplifications in manual calculations done by ignoring the mixtures enthalpies and supposing temperature independency of the thermodynamic properties, unlike Aspen Plus simulation.

For the acidification tank, its reaction involves a strong acid HCl which is considered as exothermic reaction (releases heat) that explain the negative heat duty.

IV.4.3. Profile of composition and heat duty over plug flow reactors

We report in figures IV.27, IV.28, and IV.29 the profile of components mass fractions along the length of PFR-1, PFR-2, and PFR-3 respectively.

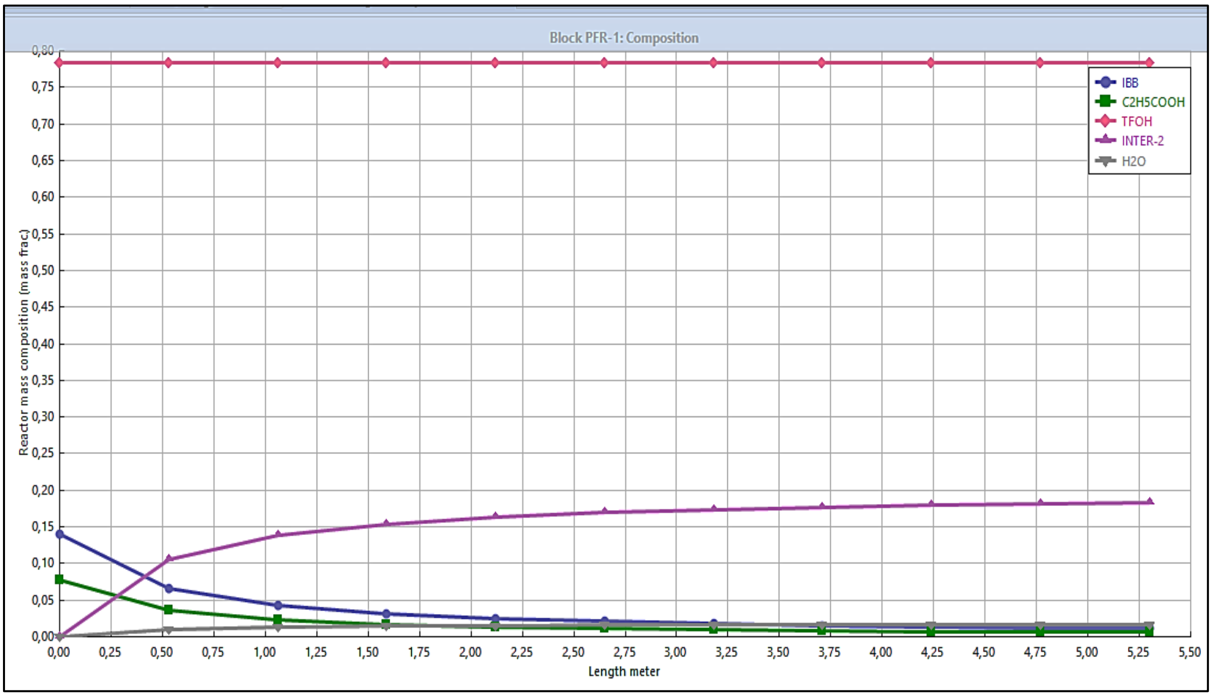


Figure IV.27. Components composition dependence in PFR-1 length.

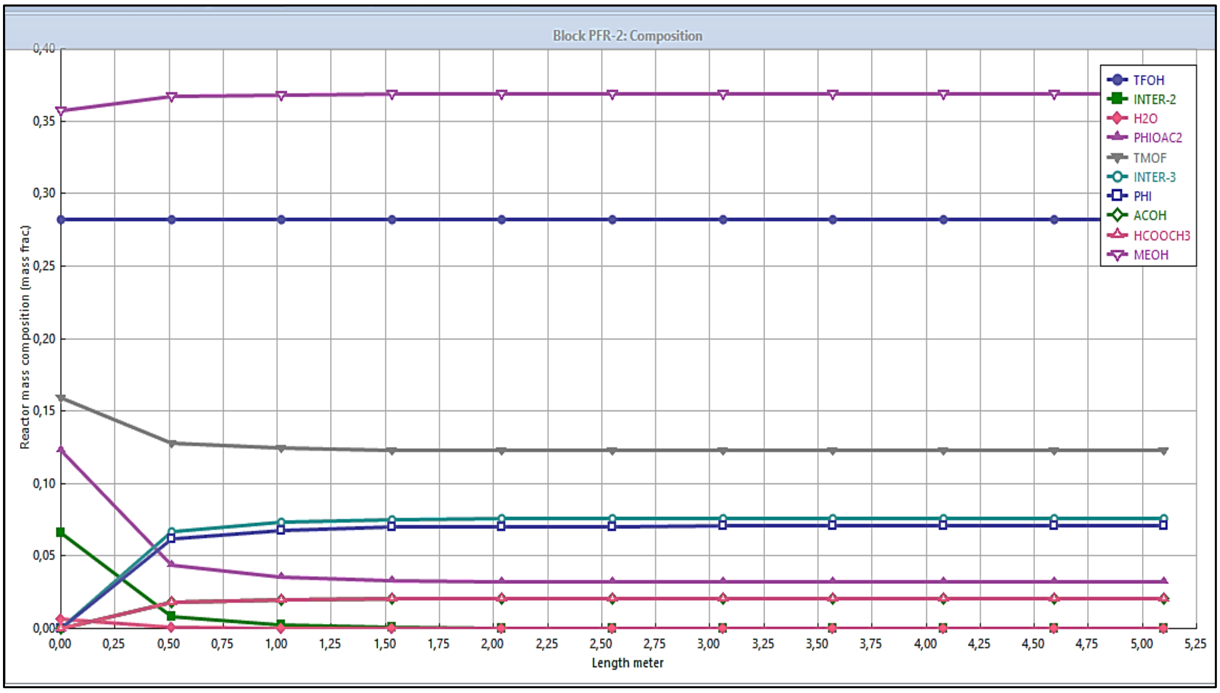


Figure IV.28. Components composition dependence in PFR-2 length.

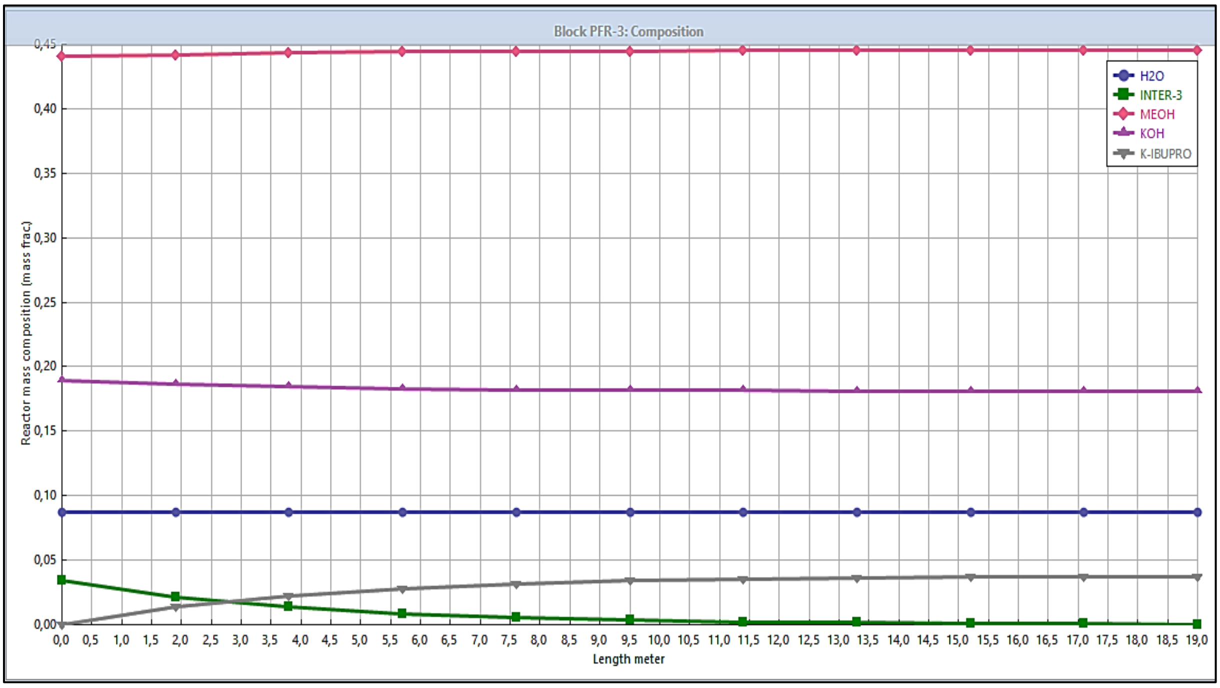


Figure IV.29. Components composition dependence in PFR-3 length.

Figures above show how the components mass fractions change along PFR length. It can be shown that for low value of PFR length, the mass fraction of product is quite small and increasing with increasing PFR length. Contrary to the reactants, where mass fractions decrease with increasing PFR length due to their consumption. These results verified the theory of PFR that, for PFR conversion changes with the position of reacting components in the reactor. We observe from the figures unchanged mass fraction of catalyst and solvent over the reactors.

It can be noted that many factors can affect the simulation results, like assuming a perfect and instantaneous mixing of reactant, ignoring any side reactions, and estimating properties of unidentified components. Furthermore, scaling-up factor by moving from experimental results obtained in laboratory scale (microreactor) to simulation of reactors in industrial scale. Since these values come from a plant of significant size, such value can therefore be considered as representative of continuous ibuprofen process performance in industrial scale.

IV.5 Conclusion

The aim of this chapter was to develop a model that is able to simulate the steady-state output of the industrial scale continuous manufacturing of ibuprofen that was studied in the earlier chapters of this thesis. We have presented Aspen Plus which is considering as powerful software used widely in chemical process simulation. Therefore, we used Aspen Plus to analyze, simulate and evaluate ibuprofen production process. The knowledge about the chemistry and kinetics of the process accrued from the results of these studies has been incorporated into the model to improve the performance and predictability.

After building the simulation, Aspen Plus calculates all different parameters and profiles (mass, composition, temperature, pressure, heat duty and etc.) through the process. The obtained results are very satisfying.

CONCLUSION

Conclusion

Continuous manufacturing represents a significant shift in industrial production process, especially in the pharmaceutical sector, due to its numerous advantages over traditional batch manufacturing like maximizing yield and reducing time, cost, raw materials and energy consumption. We focus on ibuprofen continuous manufacturing, this drug is widely used for its analgesic, anti-inflammatory and antipyretic properties.

This work presents a steady-state process model and simulation for the continuous production of ibuprofen.

The process passes by three main reactions using a series of three plug flow reactors (PFRs). Based on published data of a synthesis study, the mass balance calculations have been developed for all reactors, with molar and mass flow changes of the components. Reactions order and kinetic parameter estimation have been determined. After that, we could design the plug flow reactors. Energy requirements for ensuring high endothermic conversions under isothermal reactor operation are also quite reasonable. All the results were scaled up from laboratory scale to industrial scale.

According to the simulation conducted on this process, we can draw some interesting conclusions: The process is simulated using Aspen Plus, this powerful tool allowed us to model the process, have a preview of how it works in the real-world and see the performances of the installed equipment under specific conditions. The simulation results was compared to the calculated results and measured data, we have noticed a similarity in mass balances and reactions conversion, and some little differences in heat duties. The obtained value through simulation for K-Ibuprofen was 26,077 kg/hr, corresponding to 206 tons/year, while the calculated value using experimental data was 25.41 kg/hr, corresponding to 200 tons/year. The productivity of the process was estimated to be 22,012 kg/hr of ibuprofen (API) corresponding to 174.335 tons annually. This process has successfully reduced the reactions time from 9 hours using batch reactors to only 15 mins. The obtained results are very satisfying, the comparisons show good agreements and the differences are relatively small and within acceptable limits.

As pictured in this work, the continuous flow technologies offer important and attractive features exploited in the industrial process. It is not surprising that recently also the pharmaceutical companies have turned their attention to the use of flow chemistry in the preparation of APIs. It is a trend that cannot be stopped and will gain further strength in the future, enforced by the possibility to combine the synthesis of chemicals in flow with new analytical technologies for inline monitoring of the process and with enabling technologies for speeding up the isolation and purification steps.

It can be also noted that productivity is not the only criteria for selecting a suitable process, there are some other factors also which should be taken into account while selecting, includes; safe operation within the feasible space of temperature, pressure, concentration and residence time, environmental acceptability, good controllability properties: stable operation and easy rejection of disturbances, Constant product quality, low capital and operating costs.

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https://www.vapourtec.com/flow-chemistry/plug-flow-reactor-pfr/

https://www.elprocus.com/plug-flow-reactor/

Appendices

Appendix 1. Chemical components nomenclature.

Symbol	***Name***
AcOH	Acetic acid
$AlCl_3$	Trichloride aluminium
CO	Carbon monoxide
CO2	Carbon dioxide
C_2H_5COOH	Propanoic acid
C_2H_5ONa	Sodium ethoxide
$C_4H_6O_3$	Acetic anhydride
$C_4H_7O_2Cl$	Ethyl chloroacetate
$C_{12}H_{16}O$	Hexanophenone
$C_{12}H_{18}O$	Ibuprofen
$C_{13}H_{17}KO_2$	Potassium ibuprofen
$C_{13}H_{17}N$	Selegiline
$C_{13}H_{19}NO$	Ibuprofenamide
$C_{16}H_{22}O_3$	Homosalate
HCL	Hydrochloric acid
HCOOCH3	Methyl formate
H_2	Hydrogen
H2O	Water
H_3O	Hydronium
H_4O_2	Oxoniumhydroxyd
IBB	Isobutylbenzene
KCL	Potassium chloride
KOH	Potassium hydroxide
MeOH	Methanol
PEK	Propiophenone
PhI	Iodobenzene
$PhI(OAc)_2$	Diacetoxyiodobenzene
TFOH	Triflic acid
TMOF	Trimethyl orthoformate

Appendix 2. Physical properties of CPM flowsheet stream components

component	***Molecular weight ($g.mol^{-1}$)***	***Density ($g.cm^{-1}$)***	***Melting point (°C)***	***Boiling point (°C)***	***Cp (T = 25°C) ($J.mol^{-1}.K^{-1}$)***	***$\Delta°H_f$ ($kJ.mol^{-1}$)***
IBB	134.22	0.844	-51.7	170.9	242.79	-69.9
2	190.29	0.960	18.4	248.8	242.76	-139.9
3	220.31	1.100	38.3	287.0	264.95	-313.6
Ibuprofen	206.29	1.030	74.5	157.0	278.98	-350.3
C_2H_5COOH	74.08	0.990	-21.2	140.9	158.59	-510.4
H_2O	18.02	1.000	0.0	100.0	75.37	-285.8
TFOH	150.08	1.708	-40.0	161.9	110.53	-
$PhI(OAc)_2$	322.10	1.814	162.5	456.8	200.16	-628.1
TMOF	106.12	0.970	-53.0	102.8	136.50	-586.9
MeOH	32.04	0.792	-97.2	64.9	81.42	-239.0
$HCOOCH_3$	60.05	0.980	-100.0	32.0	93.65	-367.9
AcOH	60.05	1.049	16.5	118.0	66.58	-442.2
PhI	204.01	1.850	-31.4	188.0	95.05	-234.0
KOH	56.11	1.050	406.0	1327.0	64.89	-482.4