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PYROLYSIS OF WASTE PHARMACEUTICALS AS A NOVEL TREATMENT FOR A CIRCULAR ECONOMY: ANALYSIS OF KINETICS, THERMODYNAMICS, AND PRODUCTS CHARACTERISTICS

by
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ABSTRACT

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Title: Pyrolysis of Waste Pharmaceuticals as a Novel Treatment for a Circular Economy: Analysis of Kinetics, Thermodynamics, and Products Characteristics

In this expanding pharmaceutical market, the issue of drug pollution constitutes a significant concern that needs to be widely addressed because of its global relevance. Sustainable waste management requires that industries transition from the existing linear model to a circular economy; that incorporates wastes as raw materials for producing new products. In this study, pyrolysis was suggested as an economically and environmentally sustainable treatment for pharmaceutical waste within the context of circular economy. Fast pyrolysis was conducted at 500℃ on each of immediate release tablets of 500 mg paracetamol and 600 mg ibuprofen drug products, with the liquid and gas products analyzed using GC-MS (gas chromatography-mass spectroscopy) and micro GC-TCD (gas chromatography-thermal conductivity detector), respectively. The pyrolytic behavior of each pharmaceutical product was studied through kinetic and thermodynamic analysis. The data obtained by thermogravimetric analysis (TGA) were used to estimate the activation energy (E) through model-free isoconversional models of Kissenger-Akahira-Sunose (KAS) and Flynn-Wall-Ozawa (FWO). The pre-exponential factor (A) was evaluated using Kissinger model and followed by thermodynamic parameters determination.

The average E values for the pyrolysis of the paracetamol drug product using KAS and FWO methods were found to be 125.9 and 128.8 $kJ.mol^{-1}$, respectively. For ibuprofen drug product pyrolysis, the average E values were 77.9 and 82.0 $kJ.mol^{-1}$ for the first decomposition stage, and were found to be 136.0 and 138.9 $kJ.mol^{-1}$ for the second decomposition stage, using KAS and FWO models, respectively. The small difference between E and ΔH values ($\sim 5\ kJ.mol^{-1}$) indicated the small energy barrier to overcome. The results showed that the pyrolysis liquids consisted of the active pharmaceutical ingredient, along with other compounds of commercial importance, while pyrolysis gas from both drugs consisted of carbon monoxide, methane, and ethylene. Methane was the most abundant in the pyrolysis gas of paracetamol drug product (39.16 mol%), while ethylene was the most prominent in that of ibuprofen drug product (49.99 mol%). Both pyrolysis liquid and gas products were high-value products that may be repurposed, as the active pharmaceutical ingredient (API) may be recycled to produce new tablets, and the other compounds may be utilized as fuels or chemical feedstocks.

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CHAPTER 1

INTRODUCTION

1.1. Pharmaceutical Waste Generation

The global consumption of pharmaceuticals was accentuated with the increased prevalence of medical conditions. The COVID-19 pandemic caused an increase in global demand for pharmaceutical drugs to an unprecedented level [1]. Moreover, the world human population exceeded 7 billion in the year 2017, and it is predicted to reach 9.7 billion by 2050. Therefore, more pharmaceuticals will be needed to deal with the growing population and the surge of human diseases. It was reported that the expenses on pharmaceuticals increased from 887 billion USD in 2010 to nearly 1.42 trillion USD in 2021, and are expected to reach about 1.8 trillion USD in 2026 [2].

Inevitably, pharmaceutical waste generation will increase with this high consumption rate. On the consumer level, pharmaceutical wastes are produced when medicines are not completely consumed by their expiration date, changes occur in the treatment regimen or dosage, and surplus medicines remain after completing treatment [3]. It was estimated that the share of household medicines becoming waste varies from 3% to as high as 50% [4]. In pharmacies, pharmaceutical waste can be generated due to improper inventory management or poor storage [5].

1.2. Pharmaceutical Waste Disposal Practices

Pharmaceuticals enter the environment through improper disposal practices. They are either flushed in toilets or disposed of into municipal waste bins. Pharmaceuticals flushed via toilets enter the sewage system, whereas waste water treatment plants

(WWTPs) are not designed to remove pharmaceuticals, leading to accumulation in water bodies. Also, pharmaceuticals disposed of with municipal solid waste can contaminate soil and groundwater if the leachate from landfills is not collected properly. The collected leachate is usually directed into WWTPs, resulting in the discharge of pharmaceutical residues into surface water [4]. Moreover, open burning of pharmaceutical waste is still practiced mainly in developing countries causing air contamination through carbons, dioxins, and furans emissions. The exposure to pharmaceuticals in the environment, even at low concentrations, results in negative effects on biota [6].

Pharmaceutical waste is still not disposed of properly in developing countries with the absence of waste management programs [5]. Otherwise, in many countries, take-back programs are established where people are encouraged to drop off their unwanted or expired pharmaceuticals to take-back sites such as the local pharmacy, that passes them on for disposal by approved methods [7]. These countries rely on high temperature incineration (>1200 °C) which is considered effective in disintegrating pharmaceutical wastes. This method is recommended by The U.S. Environment Protection Agency (EPA) and used within the European Union, where adequate exhaust gas cleaning is used to reduce air pollution [8]. In a life cycle assessment study by Cook et al. (2012) of several disposal options, it was shown that although incineration of unused pharmaceuticals can reduce API emissions to the environment, it is associated with significant non-API emissions [9]. Similar programs are established in other countries including United Kingdom, Australia, and New Zealand [8]. However, this method is considered highly expensive and requires specialized waste combustors [10]. Thus, cost-effective and eco-friendly techniques must be investigated to replace high temperature incineration [6].

1.3. Circular Economy

The circular economy model has received considerable attention in research recently where the waste becomes the raw material for the generation of valuable products. In this approach, waste production and resources consumption are being minimized. This circular model has the potential to protect the environment and improve economic growth. The concept of circular economy can be applied to waste pharmaceuticals due to the possibility of producing valuable materials [8, 11].

In the United States, the worth of pharmaceutical waste generated from households was estimated to be more than USD 1 billion every year. In the United Kingdom, this value is about EUR 300 million every year [8]. The currently adopted waste handling methods result in a significant loss of high value materials [12]. Active pharmaceutical ingredients in most medications remain stable for many years after their expiration dates [12]. Nevertheless, almost all of the expired pharmaceuticals is discarded and no attempt is made to recover the API [13]. The API can be recovered to be further introduced into new drug products. It is the most valuable component in the medicine and its environmental impact is considered more significant than that of the excipients [13]. Most pharmaceutical ingredients are highly pure, costly to make, and considered high value chemicals [8]. Moreover, it was reported that APIs recovery is more economically attractive than synthesizing APIs from scratch [13].

Recycling the API from expired drugs can be considered, as it has been shown that some are extremely well preserved long after their labeled expiring dates [8]. The chemical composition of pharmaceutical drugs changes over time which reduces their effectiveness and safety. So, stability tests are performed by drug manufacturers on pharmaceutical drugs to determine their expiry dates [14]. The expiration date does not

indicate that the medication is no longer effective or unsafe to use after this date. However, it is the last day that the manufacturer guarantees the full potency and safety of a pharmaceutical. Research studies indicate that many medications still retain 90% of their original potency for at least five years after the expiration date, and sometimes longer. Also, many pharmaceuticals retain a significant amount of their potency even 10 years after the labeled expiration date [15].

1.4. Effects of Pharmaceuticals in the Environment

In the last few decades, studies have been carried out significantly for pharmaceutical residue detection in the environment. Globally, over 600 pharmaceutically active compounds have been reported to be found in water bodies [16]. Drug pollution has the potential to cause serious ecological imbalances [6]. For instance, some pharmaceuticals are endocrine-disrupting chemicals (EDCs) so that they interfere with the endocrine system by mimicking natural hormones. The serious effects of their ingestion range from amphibians and fish feminization to cancer and obesity in humans [17]. Furthermore, antibiotic pollution can develop antibiotic resistance, which contributes to the dissemination of infections that are becoming more difficult to be treated. Antibiotic resistance results in an alarming number of deaths reaching 700,000 deaths annually worldwide [18].

Analgesic and antipyretic drugs are ranked the most consumed drugs globally. They are extensively used because they can remedy the most prevalent symptoms and diseases among people and can be purchased without a medical prescription. Paracetamol and ibuprofen are the most popular analgesics [19]. Paracetamol was found to have the highest concentration in aquatic environment among all the analgesia family [20]. The

value of the global paracetamol market was estimated to be around USD 801.3 million in 2014 exceeding 149.3 thousand tons [12], and was incorporated in the composition of more than 300 pharmaceutical preparations [21]. Unlike other analgesic drugs, paracetamol is not considered a non-steroidal anti-inflammatory drug (NSAID) since it has mere anti-inflammatory effect [20]. While ibuprofen is ranked the third most popular NSAID globally, and is also one of the main drugs in the Essential Drug List developed in 2010 by World Health Organization (WHO) [19].

The wide prevalence of paracetamol and ibuprofen in the environment poses significant threat to the ecosystem. The discharge of paracetamol into the aquatic environment can expose the aquatic animals to hepatotoxicity and nephrotoxicity, which either leads to their death or affects the next level of consumers. Furthermore, feeding paracetamol contaminated water to plants can inhibit their growth, and can result in paracetamol accumulation in the roots and grains. Thus, the consumers will indirectly consume all the accumulated paracetamol after the contamination of the edible part of the crops [20]. Moreover, many studies were conducted on the effect of ibuprofen on aquatic species; it was demonstrated that moderate genetic and cellular damage were generated after exposure to the environmentally relevant concentrations of ibuprofen (0.2, 2, and 8 µg/L). It was also reported that a delay in hatching of eggs was induced at a concentration of 0.1 µg/L [19].

1.5. Thesis Objectives

The aim of this study was to examine the potential of applying pyrolysis, which is defined as the thermal degradation of organic compounds in the absence of oxygen at very high temperatures, as an approach to promote the circular economy through the

generation of valuable feedstock and the recovery of API from paracetamol and ibuprofen drug products. This was achieved through the following objectives:

- The study of pyrolysis kinetics through the estimation of the activation energy (E) with thermogravimetric analysis (TGA) using model-free isoconversional methods of Kissinger Akahira Sunose (KAS) and Flynn Wall Ozawa (FWO), and the pre-exponential factor (A) by means of the Kissinger method.
- The study of pyrolysis thermodynamics through the determination of enthalpy change (ΔH), Gibb's free energy change (ΔG), and entropy change (ΔS) of the process using Eyring equations.
- The identification of liquid pyrolysis products using gas chromatography-mass spectroscopy (GC-MS), and gaseous products using micro gas chromatography-thermal conductivity detector (micro GC-TCD).

CHAPTER 2

LITERATURE REVIEW

2.1. Pyrolysis

Pyrolysis is considered a potential waste disposal method, which is the thermal decomposition of organic material by cracking the chemical bonds in an anaerobic environment generating solid, liquid, and gas products. The literature on pyrolysis of plastics, microalgae, tire, paper, wood, and food wastes has been published extensively, where high-value fuels and chemicals can be produced [22]. Waste valorisation is gaining interest from the scientific community because it can alleviate the environmental impact of waste and achieve economic sustainability [23].

Pyrolysis processes can be classified based on the heating rate into slow and fast pyrolysis [22]. The pyrolysis product yields and their chemical compositions are highly dependent on the operating conditions such as temperature or heating rate [24]. Generally, slow pyrolysis is used to produce solid products (char), whereas fast pyrolysis results in the production of liquid products [25]. It is a flexible process by which desired products can be obtained by changing operating conditions accordingly. Moreover, pyrolysis can be economical in terms of operation as reported in a review about the pyrolysis of plastic waste into high value liquid fuel, gas and char [26].

There has been some research work addressing the pyrolysis of pharmaceutical sludge, which is generated from the treatment of pharmaceutical wastewater. Its pyrolysis garnered a lot of interest recently, where many studies highlighted the environmental and economic benefit of such treatment. A study conducted by Yu et al. (2020) investigated the co-pyrolysis of wastewater pharmaceutical sludge and Ginkgo biloba leaf residue as

a potential to produce clean energy. The interactions between sludge and biomass were considerably discussed in many research studies because the pyrolysis of sludge only will not produce high-quality fuel. The production of Ginkgo biloba extract in large quantities generates consequently a significant amount of biomass residue. The provided results showed that co-pyrolysis of pharmaceutical sludge and Ginkgo biloba residue is a promising technology that can improve the quality of the produced fuel. In this way, these two types of waste are converted into sustainable energy products instead of discarding them and contaminating the environment [27].

Liu et al. (2020) studied the char produced from the pyrolysis of pharmaceutical sludge and examined its use as an adsorbent agent to remove tetracycline (TC), a widely used antibiotic, from wastewater. The study demonstrated that pyrolysis managed to produce a valuable adsorbent which can therefore compensate for the cost of the pyrolysis treatment. This economic benefit was provided while also mitigating the environmental impact of the generated pharmaceutical sludge. Furthermore, this work investigated the possibility to obtain a low-cost treatment and high-value adsorbent by studying the properties of the produced bio-char under different conditions. Pyrolysis temperature was one of these factors having a significant effect on the produced bio-char characteristics [28]. Liu et al. (2021) were also the first to carry out a kinetic analysis for pharmaceutical sludge pyrolysis, while the previous research works focused on municipal sludge kinetics. Moreover, the study of the pyrolysis products of pharmaceutical sludge showed that bio-oil and bio-gas can be used as a renewable energy source [29].

Sludge chars produced by pyrolysis were banned as soil improver due to the lack of research about the ability of this treatment to remove contaminants from the resulting char. Mosko et al. (2021) addressed this knowledge gap and assessed the effectiveness of

pyrolysis to remove from anaerobically stabilized sludge many groups of organic pollutants where pharmaceuticals group was one of them. The results confirmed the safety of the resulting char as soil improver, so that pyrolysis at 400 ℃ managed to eliminate pharmaceuticals to below detection limits. Finally, sludge pyrolysis at temperature greater than 600 ℃ was suggested to ensure an effective technique that can remove additional organic pollutants groups from the resulting sludge char [30].

These aforementioned studies have applied pyrolysis to treat pharmaceutical sludge, but there were only few research works that investigated the pyrolysis of waste medications. Filippis et al. (2012) studied the pyrolysis of unused and expired pharmaceuticals with their packaging materials, as a safe disposal method while producing alternative energy sources, and found that the pyrolysis oil derived from the process has similar energy properties to that derived from lignocellulosic biomass, and may potentially be used as a combustible product to be used as a fuel. It was shown that pyrolysis can be a viable alternative to the conventional applied thermal methods [31].

Bean et al. (2016) evaluated the effectiveness of a microscale combined pyrolysis and gasification in situ treatment system launched by Pyropure Ltd (Hampshire, UK) to treat pharmaceutical waste. The trials involved the treatment of a mixture of 17 pharmaceuticals from various therapeutic classes in three waste types. The results revealed a 99 % destruction of each of the 17 selected pharmaceuticals without the production of known active transformation products, and the waste type had no effect on pharmaceuticals destruction. Moreover, emissions of the other gaseous pollutants (NO_x, particulates, dioxins, furans, and metals) were within acceptable levels. This treatment technology which can be used on-site in pharmacies, hospitals, clinics, and manufacturing plants, will help to reduce the environmental impact of pharmaceuticals while providing

compelling cost-benefits to the user. In addition to saving the cost of waste transport to high temperature incineration facility, it was shown that a valuable amount of energy can be generated in the form of heat for a high plastic content load enabling better on-site energy recovery than that in incinerators [32].

These two studies have considered the pyrolysis of waste pharmaceuticals mixed with other types of waste, through which high-value energy products are generated or energy is recovered. However, the potential of pyrolysis to produce valuable products from pharmaceuticals only has not been investigated before, which reflects the novelty of this work.

2.2. Recovery of API from Pharmaceuticals

Waste pharmaceuticals have been considered an important source of valuable chemical compounds. Recently, several studies worked on the recovery of API from pharmaceutical matrices, where most of the techniques involve solvent extraction. However, the use of volatile and toxic organic solvents represents the main drawback of this technique.

These methods are further investigated to be greener and more efficient. For instance, a new extraction technology based on aqueous biphasic system (ABS) with eco-friendly components was investigated by Marić et al. (2021) to extract acetaminophen and caffeine from one medication, and theophylline from the other. The results showed that the ABS comprising of water-soluble polaxamer (Pluronic PE 6200) and salting-out agent (sodium citrate) managed to extract all APIs to the Pluronic-rich phase with high recovery efficiencies between 79.4 and 97.90%; insoluble excipients were removed as residues while hydrophilic excipients remained in the citrate-rich aqueous phase.

Acetaminophen and caffeine were further separated by an Ionic liquid/PL6200-based ABS. This system was considered as a green, efficient, and sustainable method for API recovery [12].

Since excipients are not always mentioned with API and its dose on the pharmaceutical product label, Pratama et al. (2020) aimed in their study to develop a protocol to retrieve the APIs from unused pharmaceuticals irrespective of the excipient contents and compositions. The study investigated the recovery of acetaminophen, tetracycline HCl, and ibuprofen from a mixture of two or more brands of their drug products by solid−liquid extraction. To choose the suitable solvent that can be a "good solvent" for the API and a "bad solvent" for as many excipients as possible, the solubility of the APIs and excipients was evaluated in 23 common solvents. The huge number of excipients was represented by only some common excipients. The results showed that highly pure APIs were retained with recovery yields of 58.7 wt %, 73.1 wt %, and 67.6 wt % for acetaminophen, tetracycline HCl, and ibuprofen, respectively [13].

This thesis work investigated the potential of pyrolysis as an application to the concept of circular economy for the production of valuable materials and API recovery from waste pharmaceuticals, particularly paracetamol and ibuprofen drug products. The study provided insights into pyrolysis products characteristics to examine the possibility of re-introducing them into the manufacturing process. Also, kinetic and thermodynamic analysis was conducted, which provides a basis for pyrolysis system design, optimization, and scaling up for commercialization.

CHAPTER 3

EXPERIMENTAL WORK

3.1. Materials

Immediate release tablets of paracetamol and ibuprofen were purchased from a local pharmacy. Paracetamol tablets contains 500 mg of paracetamol ($C_8H_9NO_2$) each as well as the following excipients: maize pregelatinized starch, maize starch, purified talc, stearic acid, hypromellose, povidone, glycerol triacetate, potassium sorbate, and carnauba wax [33]. Ibuprofen tablets consists of 600 mg of ibuprofen ($C_{13}H_{18}O_2$) each and the following excipients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, purified talc, sodium laurilsulfate, and titanium dioxide [34].

Chromatography-grade ethyl acetate from Fisher Scientific (New Hampshire, USA) was used to dilute the collected pyrolysis liquid product for GC-MS analysis. A mixture of 25 gas components of known mole percentage from INFICON (Bad Ragaz, Switzerland) was used for GC-TCD calibration to calculate the mole percentages of the gaseous pyrolysis product.

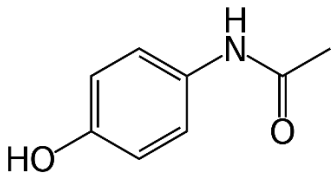

Figure 1: Chemical Structure of Paracetamol.

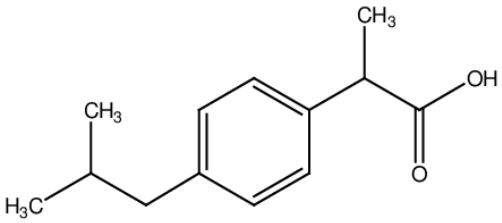

Figure 2: Chemical Structure of Ibuprofen.

3.2. Thermogravimetric Analysis (TGA)

TGA is a widely used technique in thermal analysis that tracks the mass loss of a sample as a function of temperature at a constant heating rate in a controlled atmosphere [35]. During TGA, a sample pan resides in a heating furnace, and the temperature within the oven is measured by a thermocouple, while the mass of the sample is measured by a precision balance. The environment of the sample is controlled by a purge gas flow.

TGA was performed using a TG209 F1 Libra analyzer from Netzsch (Selb, Germany). A sample of the powdered drug product weighing ~15 mg was added to an alumina ceramic crucible and heated from ambient temperature to 550℃, and the analysis was repeated at four different heating rates of 10, 20, 30, and 40℃/min under an inert nitrogen flow for each drug product. The data from the four runs were analyzed using kinetic models to understand the pyrolysis kinetics of the paracetamol and ibuprofen drug products. Moreover, the derivative thermogravimetric (DTG) curve was determined, which is the first derivative of the TGA curve.

Figure 3: TGA Analyzer.

3.3. Differential Scanning Calorimetry (DSC)

DSC is another thermal analysis technique that monitors the heat effects resulting from physical and chemical changes of a substance as a function of temperature at a constant heating rate in a controlled environment [36]. As the temperature changes, DSC measures the heat released or absorbed by the sample based on the temperature difference between the sample and the reference material [37].

A sample of the powdered drug product was placed in a lidded alumina pan in a TA Q2000 DSC analyzer from TA Instruments (Delaware, USA). The sample was heated from room temperature to 500℃ at a heating rate of 10℃/min under purge gas flows of 20 mL/min of nitrogen and 20 mL/min of helium. The physicochemical changes taking place during the pyrolysis of each drug product were identified from the complementary information provided from TGA and DSC curves [35]. These thermal analysis methods are characterized by the fast sample measurement, the easy detection of physical properties, and the requirement of a small amount of sample [21].

Figure 4: DSC Analyzer.

3.4. Pyrolysis

Fast pyrolysis experiment was conducted for each drug product in a fixed bed reactor that is heated by an electric furnace. This reactor is considered the simplest type in laboratory-scale studies because it is easy to design [24]. Dual heating zone electric furnace (OTF1200XIIR4-AF) from Zhengzhou CY Scientific Instrument (Henan, China) was used (Figure 5). A quartz reactor tube (75 cm length and 3/8" outer diameter) was filled with a powdered sample of approximately half a tablet of the drug product, which was held in place with two pieces of quartz wool on either side. The filled tube was then placed in the furnace when the set point temperature of 500℃ was reached.

The inlet of the quartz tube was connected to the nitrogen gas tank, while the outlet was connected via Tygon® tubing to a cooled condenser to collect the pyrolysis liquid products. The outlet of the condenser was connected via Tygon® tubing to a Tedlar® bag in which the gaseous pyrolysis products were collected. The experimental setup is presented in Figure 6.

Before starting the run, the reactor was flushed with helium gas and the gas flow of 80 mL/min was maintained during the whole process in order to prevent the presence of oxygen in the system and to discharge the gas and liquid once they were produced to

avoid secondary reactions. Ten minutes were provided for the products to be collected, and the char was removed at the end of the run.

Figure 5: Electric Furnace.

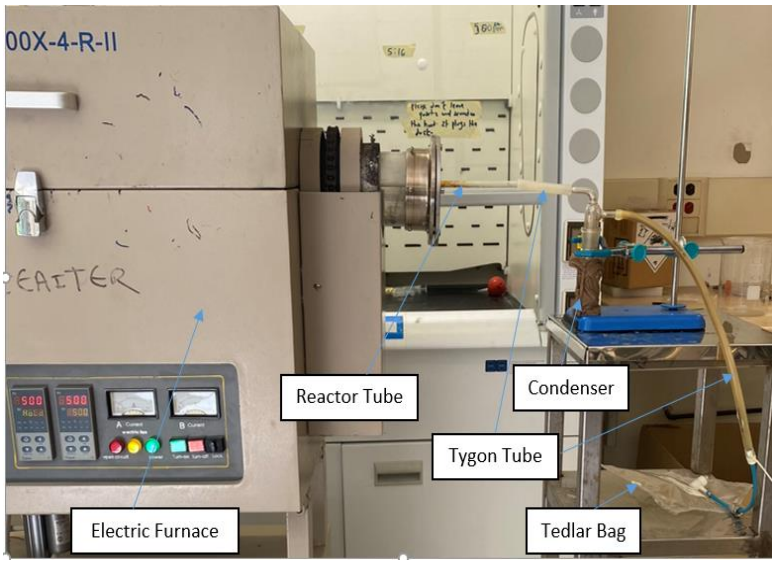

Figure 6: Pyrolysis Experiment Set Up.

3.5. Pyrolysis Products Yields

To determine the yield of the liquid, non-condensable gas, and char, the empty and filled reactor tube, condenser, and Tygon® connection tube between the reactor and condenser were weighed before and after the pyrolysis run.

The mass of liquid produced was determined by summing the differences in mass of the condenser and connection tube before and after the experiment.

$$m_{liquid} = \left(m_{condenser,after} - m_{condenser,before}\right) + \left(m_{connector,after} - m_{connector,before}\right) \quad (1)$$

The mass of char produced was obtained by subtracting the difference in mass of the empty and filled reactor tube before and after the experiment from the mass of the crushed tablet.

$$m_{char} = m_{tablet} - \left(m_{empty\ reactor,after} - m_{empty\ reactor,before}\right) - \left(m_{filled\ reactor,before} - m_{filled\ reactor,after}\right) \quad (2)$$

The mass of gas produced was calculated by subtracting the mass of liquid and char produced from the mass of the crushed tablet.

$$m_{gas} = m_{tablet} - m_{char} - m_{liquid} \quad (3)$$

The yield of each pyrolytic product was calculated by dividing the mass of each product by the mass of the crushed tablet.

$$Y_{liquid} = \frac{m_{liquid}}{m_{tablet}} * 100 \quad (4)$$

$$Y_{char} = \frac{m_{char}}{m_{tablet}} * 100 \quad (5)$$

$$Y_{gas} = \frac{m_{gas}}{m_{tablet}} * 100 \quad (6)$$

3.6. Gas Chromatography-Mass Spectroscopy (GC-MS)

GC-MS experiment was performed to identify the compounds in the liquid pyrolysis product. GC-MS are two techniques coupled to provide an effective qualitative and quantitative evaluation of chemical compounds in a mixture. GC allows the separation of the components, while MS works on the identification of each chemical compound individually [38].

During GC, the components of the mixture are carried by a gas stream (mobile phase) through the column. Each component will spend a different time in the column depending on its interaction with the stationary phase [38]. If the sample was a liquid, it is vaporized in the GC inlet before entering to the column [39]. Within MS, the compounds are first ionized. Some of the molecules are fragmented into an ion and a neutral of lower mass. The molecules that are not fragmented forms an ion of the same mass known as the "molecular ion" which is the heaviest [40]. Then, the mass analyzer separates these ions of different masses based on their m/z (mass-to-charge ratio) before reaching the ion detector [39].

A chromatogram showing the retention time and the signal intensity of each compound is generated, along with a mass spectrum for each data point representing the distribution of ionized molecules based on their m/z. By MS, unknown compounds are identified by matching the obtained mass spectra of each compound to the libraries of mass spectral data [40].

In this experiment, the liquid pyrolysis products were collected from the condenser and diluted with 5 mL of GC-grade ethyl acetate solvent to avoid overloading of the detector and causing its damage. The resultant solution was filtered with a 0.2 μm syringe filter prior to analysis to remove solid particles or impurities which may damage

the GC-MS instrument. The pyrolytic oil sample was analyzed using Trace GC Ultra from Thermo Scientific equipped with SLB-5ms capillary column (30 m × 0.25 mm × 0.25 µm) from Supelco™ and coupled with the DSQ II MS from Thermo Scientific. A splitless sample injection with a volume of 1 µL was applied and Helium was used as a carrier gas at a rate of 1 mL/min. The injector temperature was set at 250℃, and the GC oven was initially set at 40℃ and held for 3 minutes, then ramped up to 320℃ at a rate of 5℃/min and held for 8 minutes. A solvent delay of 5 minutes was applied in order to prevent detector damage, and the interface with MS was set at 300℃.

The compounds in the sample were identified by matching the generated mass spectra to those of the pre-identified compounds stored in the NIST and Wiley® libraries present in the MS software. A mass-match percentage was produced which reflects how well the mass spectrum of an unknown compound matches the library's spectrum, and only spectra with a match percentage above 90% were considered.

The GC software also calculates the area of each peak as a percentage of the total area underneath the chromatogram, where a higher peak area percentage denotes higher relative abundance of the compound in the mixture. However, it should be noted that the area percentage does not directly indicate the concentration of the compound in the sample. A calibration curve for each component should be obtained by analyzing a series of known concentrations of a compound and plotting the area percentage of the compound against the concentration. The calibration curve can then be used to determine the concentration of the compound in unknown samples based on the area percentage. In this study, only a qualitative analysis was performed due to the large number of compounds in the liquid product.

Figure 7: GC-MS Analyzer.

3.7. Micro Gas Chromatography (Micro GC)

The gaseous pyrolysis products collected in Tedlar® bags were analyzed using a 4-module Micro GC Fusion® gas analyzer from INFICON equipped with micro Thermal Conductivity Detector (μTCD), which is at least 10 times more sensitive than a traditional TCD. This system allows the analysis of trace amounts of gases in the sample. The Micro GC is equipped with four independent columns. CP-Molsieve column (20 m x 0.25 mm), RT-U-Bond column (12 m x 0.25 mm), RT-Q-Bond column (12 m x 0.25 mm), and RT-Alumina-Na_2SO_4 column (10 m x 0.25 mm) are the columns installed in micro GC. The incorporation of multiple columns allows for more comprehensive analysis of the sample, as each column is designed for the separation of a specific range of compounds.

In this experiment, the sample injection time was set at 450 milliseconds, and the injector was heated to 100°C. Helium was used as a carrier gas at a rate of 1 mL/min. The detector temperature was set at 70°C, and the TCD data rate was set at 50 Hz. The column temperature was held at 100°C for 120 seconds, and ramped up to 220°C, and held for a further 100 seconds.

TCD is based on the thermal conductivity of the analyte. The measurement principle relies on the resistance change of an electrically-heated filament as the analytes from the GC column flow over it along with the carrier gas. The temperature and the resistance of a filament remains constant as long as only the carrier gas flows over it. But when eluting compounds flow over it, having lower thermal conductivity than the carrier gas, the temperature of the filament rises. This alters the resistance of the filament, and consequently causes a change in the current flowing through the Wheatstone bridge circuit. This change in current is proportional to the concentration of the compound in the sample and is recorded as a chromatogram [41].

Micro GC was calibrated with a gas mixture of 25 components (hydrogen, oxygen, nitrogen, carbon monoxide, carbon dioxide, methane, ethane, ethylene, acetylene, propane, propylene, isobutane, n-butane, 1-butene, isobutylene, trans-2-butene, cis-2-butene, 1,3-butadiene, isopentane, n-pentane, cis-2-pentene, trans-2-pentene, methyl-2-butene, n-hexane, n-heptane). The analysis of the pyrolysis gas sample generated a chromatogram where each peak was assigned to its corresponding component based on the retention time. Moreover, a quantitative analysis was performed based on the calibration mixture of known composition to determine the composition (%mol) of each component in the gas sample.

Figure 8: Micro GC-TCD Gas Analyzer.

CHAPTER 4

KINETIC MODELS

4.1. Kinetic Parameters

Kinetics deals with measurement and parameterization of the process rates. The kinetic parameters were determined based on model-free methods which are the most commonly used methods for studying pyrolysis kinetics. These approaches are considered inherently simple because they allow the estimation of activation energy without the need to understand the reaction mechanism [42], unlike model-fitting methods that consume more time [43]. Isoconversional models were applied which are the most deployed in kinetic studies. The generated data from TGA at different heating rates were fitted to these models in order to determine the activation energy of each of the paracetamol and ibuprofen drug products pyrolysis.

The general form of a solid state reaction rate is represented by Eq. (7) [42]:

$$\frac{d\alpha}{dt} = k(T)\, f(\alpha) \tag{7}$$

where α is the conversion fraction of the material, $k(T)$ is the rate constant, $f(\alpha)$ is the reaction model for a solid-state reaction that depends on the reaction mechanism.

The extent of conversion (α) is determined experimentally as a fraction of the total mass loss during the process. It is expressed by:

$$\alpha = (m_0 - m_t)/(m_0 - m_f) \tag{8}$$

where m_0 is the initial mass, m_t is the mass at time t , and m_f is the final mass of the sample.

Using Arrhenius equation, Eq. (7) is written as:

$$\frac{d\alpha}{dt} = A\, exp\left(-\frac{E}{RT}\right) f(\alpha) \tag{9}$$

where A is the pre-exponential factor (min^{-1}), R is the ideal gas constant (J.$mol^{-1}.K^{-1}$), E is the activation energy ($J.mol^{-1}$) , T is the absolute temperature (K).

Introducing the constant heating rate, β (℃.min^{-1}), Eq. (10) is obtained:

$$\frac{d\alpha}{dT} = \frac{A}{\beta}\, exp\left(-\frac{E}{RT}\right) f(\alpha) \tag{10}$$

where $\beta = dT/dt$

The integration of Eq. (10) yields Eq. (11) represented as:

$$g(\alpha) = \int_0^{\alpha} \frac{d\alpha}{f(\alpha)} = \frac{A}{\beta}\int_0^{T} exp\left(-\frac{E}{RT}\right) dT \tag{11}$$

where $g(\alpha)$ is the integral reaction model.

The isoconversional principle states that the reaction rate at a constant conversion fraction (α) depends only on temperature. In this case, an activation energy value can be determined for each value of α without any assumption of the reaction model. This can be easily demonstrated by taking the logarithmic derivative of the reaction rate (Eq. (7)) at a constant value of α.

$$\left[\frac{\partial ln(d\alpha/dt)}{\partial T^{-1}}\right]_{\alpha} = \left[\frac{\partial ln\, k(T)}{\partial T^{-1}}\right]_{\alpha} + \left[\frac{\partial ln\, f(\alpha)}{\partial T^{-1}}\right]_{\alpha} \tag{12}$$

$f(\alpha)$ is constant at a constant α, then the second term in the right hand side of Eq.(12) is zero. Thus,

$$\left[\frac{\partial ln(d\alpha/dt)}{\partial T^{-1}}\right]_{\alpha} = -\frac{E_{\alpha}}{R} \tag{13}$$

Eq. (13) shows that the temperature dependence of the isoconversional rate can be used to estimate isoconversional values of the activation energy without any knowledge about the reaction model.

The isoconversional principle can be applied to the differential (Eq. 10) or integral (Eq. 11) equation. Because the temperature integral in Eq. (11) does not have an analytical solution, there are different approximations for the integral giving rise to a number of integral isoconversional methods [42].

Flynn Wall Ozawa (FWO) and Kissinger Akahira Sunose (KAS) are integral isoconversional models which are frequently used due to their good validity and adaptability [44]. KAS and FWO models are described in Eq. (13) and (14) respectively:

KAS method

Considering the approximation given by Murray and White, Eq. (13) is obtained:

$$\ln\left(\frac{\beta}{T^2}\right) = \ln\left(\frac{AR}{EG(\alpha)}\right) - \frac{E}{RT} \tag{13}$$

$\ln\left(\frac{\beta}{T^2}\right)$ is plotted against $\left(\frac{1}{T}\right)$ to determine the activation energy from the slope of the straight line.

FWO method

Introducing Doyle's approximation, the FWO model can be expressed by Eq. (14):

$$\ln(\beta) = \ln\left(\frac{AE}{RG(\alpha)}\right) - 5.331 - 1.052\frac{E}{RT} \tag{14}$$

The activation energy is calculated from the slopes of the straight lines obtained by plotting $\ln(\beta)$ against $\left(\frac{1}{T}\right)$.

TGA data of the drug product under inert environment for multiple heating rates is modeled using Equation (13) and (14), and the activation energy (E) is evaluated from their slopes for a specific conversion α.

As recommended in the literature, E values should be determined in a wide range of α with a small step (0.1) since these methods assumes E to be constant only for small

intervals of conversion. If E is found to be constant over the entire conversion range, it is likely that the process is dominated by a single reaction step [42].

Kissinger method

Isoconversional methods can estimate E along a range of α. For predicting A, Kissinger method, which is also model-free, can be used that is expressed by the following equation [44]:

$$ln\left(\frac{\beta}{{T_m}^2}\right) = ln\left(\frac{AR}{EG(\alpha)}\right) - \frac{E}{RT_m} \quad (14)$$

where T_m is the peak temperature in the derivative thermogravimetric (DTG) curve identified as the decomposition temperature.

Kissinger method is usually avoided for the prediction of the activation energy since it provides a single value of activation energy for overall conversion regardless of the kinetic complexity of the process. It cannot be applied to study multistep kinetics that requires more than a single value of the activation energy. However, it is often considered for pre-exponential factor estimation at each conversion degree using the values of E obtained from isoconversional methods. The pre-exponential factor (A) is found using the following equation [44]:

$$A = \beta\left(E/{RT_m}^2\right)\exp(E/RT_m) \quad (15)$$

4.2. Thermodynamic Parameters

After the determination of the kinetic parameters, thermodynamic parameters: change of enthalpy (ΔH), Gibb's free energy (ΔG), and entropy (ΔS) were obtained using the following equations [43]:

$$\Delta H = E - RT \quad (16)$$

$$\Delta G = E + RT_m \ln\left(\frac{K_B\, T_m}{hA}\right) \tag{17}$$

$$\Delta S = \frac{\Delta H - \Delta G}{T_m} \tag{18}$$

where K_B is the Boltzmann constant ($1.381 \times 10^{-26}\, kJ.K^{-1}$), and h is the Plank constant ($6.626 \times 10^{-37}\, kJ.s$).

CHAPTER 5

KINETIC MODELING AND PRODUCTS CHARACTERIZATION

5.1. TGA-DTG-DSC Curves Analysis

5.1.1. Paracetamol

The TGA and DSC curves depict complementary the physicochemical changes happening during the pyrolysis of the drug product [35]. TGA is a well-known thermal analysis method. It is applied in the research and development of various materials in order to analyze their composition, their thermal stability, and the kinetics of decomposition [37].

TGA and DTG curves of paracetamol drug product at four different heating rates are shown in Figures 9 and 10, respectively. These curves provide an understanding of the thermal behavior of the drug product. TGA tracks the mass loss of the sample as a function of temperature, and DTG shows the rate of change of mass as a function of temperature [35]. It was noticed that TGA curves followed the same trend at different heating rates. The consistency in the decomposition profile reflected that the thermal decomposition is not affected by the heating rate. Moreover, TGA and DTG curves shifted to higher temperatures at higher heating rates. This curve shift can be explained by the fact that the heat efficiency decreases with the increase of the heating rate [29].

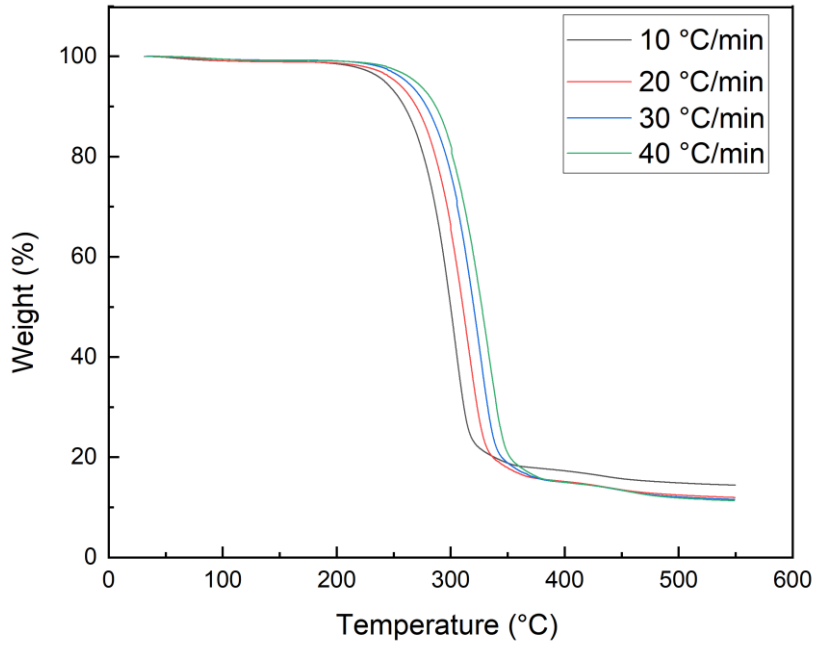

Figure 9: TGA Curves of Paracetamol Drug Product at Different Heating Rates.

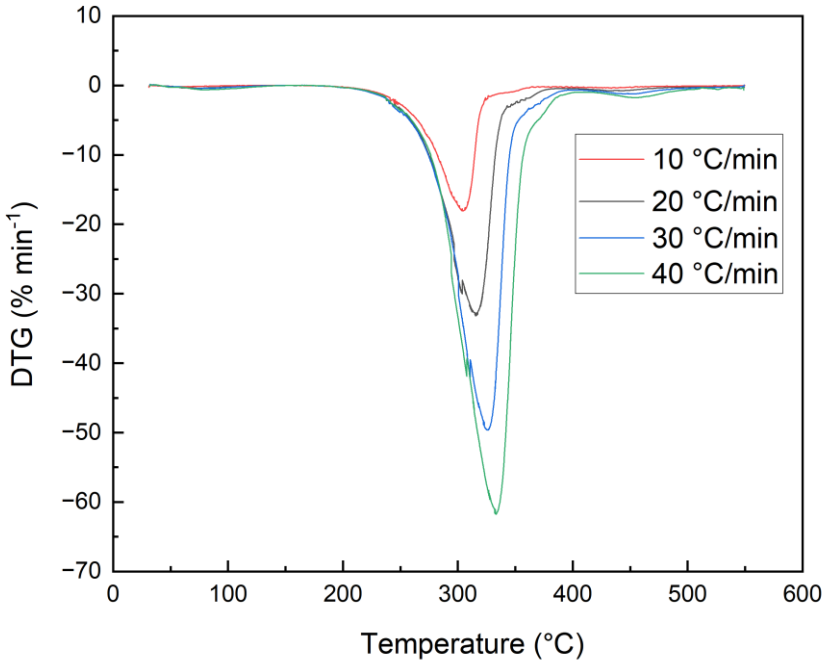

Figure 10: DTG Curves of Paracetamol Drug Product at Different Heating Rates.

TGA curve showed a single decomposition stage for the paracetamol drug product, which can be verified by the corresponding single peak in the DTG curve. Considering the heating rate of 10 ℃/min, the decomposition step started at 200.3 to 364.1°C with a mass loss of 80.40%. This stage was followed by a typical tail where very little mass loss (~3%) was observed up to 500°C and a residual mass of 14.86% was obtained. The decomposition temperature denoted by the DTG curve (T_m) was 304.7℃, which corresponds to the maximum rate of mass loss during the thermal event. The decomposition data of the paracetamol drug product at different heating rates were presented in Table 1, where T_i is the initial temperature, T_e is the final temperature, MS is the mass loss, and T_m is the decomposition temperature.

Table 1: Decomposition Data of Paracetamol Drug Product at Different Heating Rates.

Heating rate (℃/min)	T_i (℃)	T_e (℃)	MS (%)	T_m (℃)
10	200.3	364.1	80.40	304.7
20	204.2	378.1	82.89	316.6
30	209.9	388.5	83.72	325.7
40	212.5	395.4	83.83	334.2

DSC is a versatile technique that can be used to obtain the thermal parameters of a substance such as melting and decomposition temperature. Figure 11 represents the DSC curve of the paracetamol drug product obtained at a heating rate of 10°C/min. DSC analysis monitors the amount of energy absorbed or released by a sample as its temperature changes [37]. Two endothermic events were noted-one peak at 178.1°C, and another broad one at 354.2°C, which can be attributed to the melting and decomposition temperature of the sample respectively.

These values are in accordance with those corresponding to pure paracetamol in the literature. A study by Jendrzejewska et al. (2020) showed that the DSC analysis of pure paracetamol displayed the first endothermal peak at 172°C caused by the fusion event. Meanwhile, the second endothermal peak appeared at 364°C associated with the thermal decomposition of the drug [21]. The slight shift of the peaks relative to those of pure paracetamol was expected due to the presence of excipients [45]. The interactions between the API and excipients can have complex and varied effects on the thermal properties of the substance. Moreover, a thermal analysis of several brands of paracetamol-containing drugs was performed in their study and found that the DSC curves between 25-500℃ presented two endothermic peaks-a very sharp peak ranging from 174-176℃ indicating their melting temperature, and another broader, shorter one ranging from 339-359℃, associated with the thermal decomposition of the drug [21]. These findings are consistent with the two endothermic peaks shown in Figure 9.

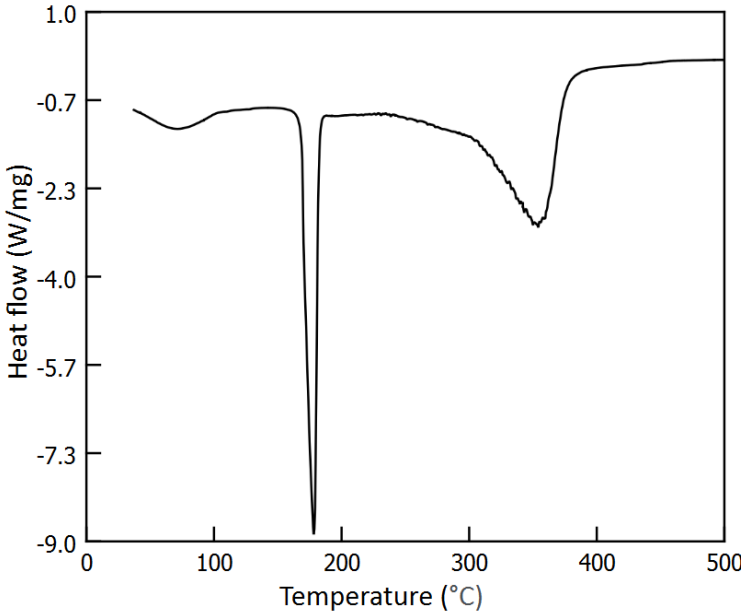

Figure 11: DSC Curve of Paracetamol Drug Product at a Heating Rate of 10 ℃ min^{-1}.

5.1.2. Ibuprofen

TGA and DTG curves of the ibuprofen drug product at four heating rates are shown in Figures 12 and 13, respectively. These curves shifted to higher temperatures at higher heating rates, and showed a similar decomposition behaviour.

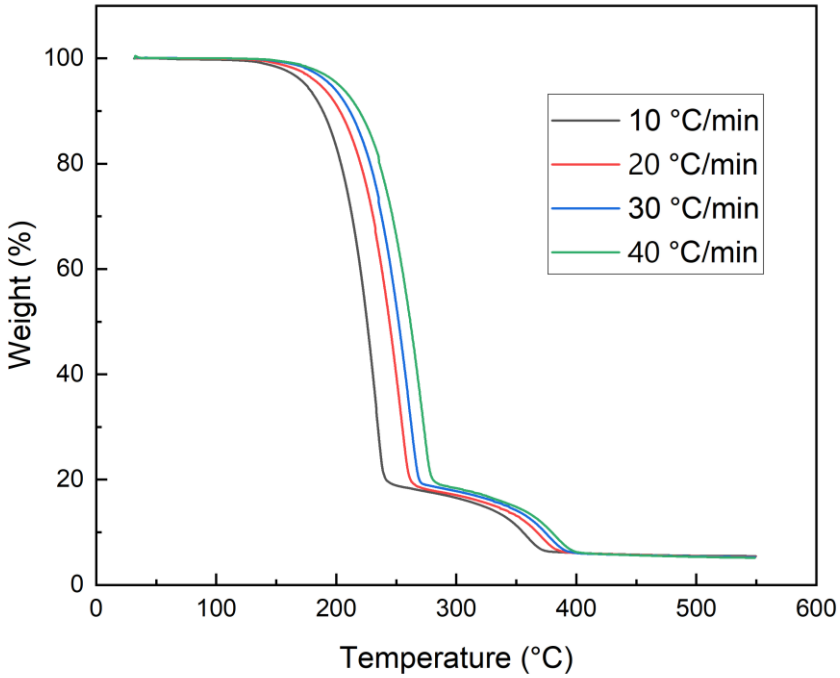

Figure 12: TGA Curves of Ibuprofen Drug Product at Different Heating Rates.

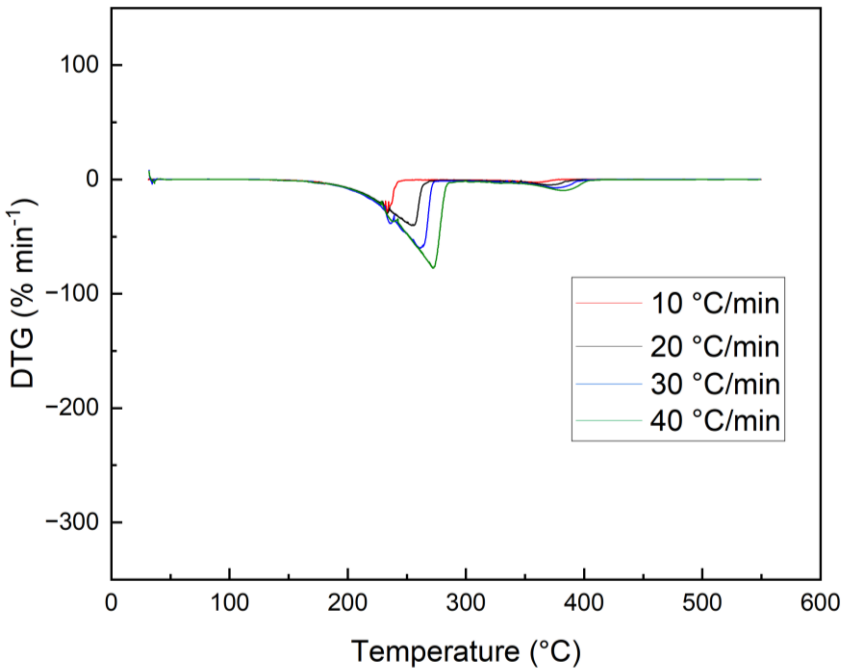

Figure 13: DTG Curves of Ibuprofen Drug Product at Different Heating Rates.

TGA curve showed two decomposition stages for the ibuprofen drug product, which can be verified by the corresponding two peaks in the DTG curve. Considering the heating rate of 10 ℃/min, a major decomposition step started at 135.4 to 240.7 ℃ with a mass loss of 78.92%. This stage was followed by a minor decomposition step until 372.8 ℃ with a mass loss of 13.75%, and a residual mass of 6.57% was obtained. The DTG curve showed two peaks at 234.9 and 359.0 ℃ respectively corresponding to the decomposition temperatures (T_m). The ibuprofen drug product showed additional decomposition stages compared to the pure ibuprofen in literature that presented a single decomposition step with a decomposition temperature (T_m) of 207 ℃ at 10 ℃/min [46]. This can be attributed to the presence of excipients and their possible interactions with the active pharmaceutical ingredient. The decomposition data of the ibuprofen drug product at different heating rates were presented in Table 2.

Table 2: Decomposition Data of Ibuprofen Drug Product at Different Heating Rates.

Heating rate (℃/min)	Stage 1				Stage 2			
	T_i (℃)	T_e (℃)	MS (%)	T_m (℃)	T_i (℃)	T_e (℃)	MS (%)	T_m (℃)
10	135.4	240.7	78.92	234.9	240.7	372.8	13.75	359.0
20	145.0	264.8	80.17	256.7	264.8	381.9	12.25	370.5
30	160.3	270.6	79.66	263.5	270.6	391.5	12.95	375.6
40	170.1	283.7	79.43	271.2	283.7	397.0	12.86	382.8

5.2. Kinetic and Thermodynamic Analysis

5.2.1. Paracetamol

Knowledge of pyrolysis process kinetics and thermodynamics is required in order to obtain a successful industrial application. This analysis is essential to design reactors where thermal conversions occur. The study of pyrolysis kinetics and thermodynamics provides significant data for mathematical modelling, which is important for process parameters optimization, and the improvement of the design of new reactors [29].

The estimation of kinetic and thermodynamic parameters is important to understand the pyrolytic behavior of the pharmaceutical drug. Based on TGA curves obtained at different heating rates, the temperature corresponding to a fixed value of conversion fraction (α) was found for each heating rate. Fitting these experimental data to KAS and FWO models, the slopes of the straight lines shown in Figures 14 and 15, respectively, were used to calculate E for a range of α. A and the thermodynamic parameters ($\Delta H, \Delta G, \Delta S$) were then determined at 10 ℃.min^{-1} using Eqs. 15-18. The findings from KAS and FWO methods were listed in Tables 3 and 4, respectively.

The activation energy represents the minimum amount of energy required to undergo the reaction, which reflects on the difficulty of thermal degradation [29]. The lower the activation energy, the easier for the reaction to occur [47]. The average E values for paracetamol drug product pyrolysis from KAS and FWO were 125.9 and 128.8

$kJ.mol^{-1}$, respectively. E values estimated by these two methods were different due to the different approximations applied to calculate the temperature integral. The correlation coefficient (R^2) value of the plots for the two methods was 0.99, which reflected a satisfactory linearity at each conversion degree. E was considered constant over the whole conversion range, which indicated that the thermal decomposition process is dominated by a single-step reaction as demonstrated previously from the DTG curve (Figure 10). The pre-exponential factor (A) represents the frequency of successful collisions between reactant molecules [48]. The average A values for paracetamol drug product pyrolysis from KAS and FWO were found to be 1.8×10^9 and 3.4×10^9, respectively. The results were in agreement with a study by Calvino et al. that applied KAS method to estimate the kinetic parameters of the thermal degradation of different brands of paracetamol tablets under nitrogen environment [49].

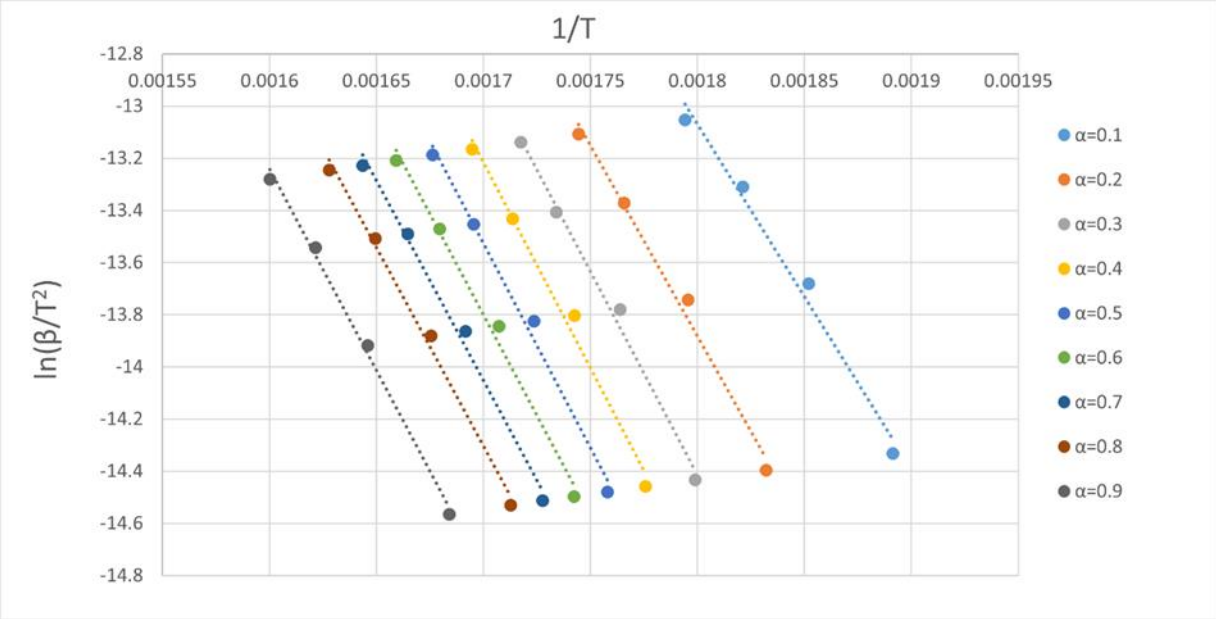

Figure 14: Linear Fit Plots using KAS Method for Paracetamol Drug Product.

Table 3: Kinetic and Thermodynamic Parameters for Each Conversion Degree using KAS Method for Paracetamol Drug Product.

α	$E\ (kJ.mol^{-1})$	R^2	$A\ (s^{-1})$	$\Delta H(kJ.mol^{-1})$	$\Delta G(kJ.mol^{-1})$	$\Delta S(J.mol^{-1}.K^{-1})$
0.1	109.7	0.985	5.4×10^{7}	105.3	168.8	-109.9
0.2	121.3	0.990	6.8×10^{8}	116.8	168.4	-89.2
0.3	129.7	0.993	4.1×10^{9}	125.0	168.0	-74.4
0.4	130.9	0.989	5.3×10^{9}	126.2	167.9	-72.3
0.5	130.3	0.991	4.7×10^{9}	125.6	168.0	-73.4
0.6	128.6	0.991	3.3×10^{9}	123.8	168.1	-76.6
0.7	127.3	0.993	2.4×10^{9}	122.4	168.1	-79.1
0.8	126.7	0.994	2.2×10^{9}	121.8	168.1	-80.2
0.9	128.8	0.996	3.4×10^{9}	123.8	168.1	-76.5
Average	125.9	-	-	121.2	168.2	-81.3

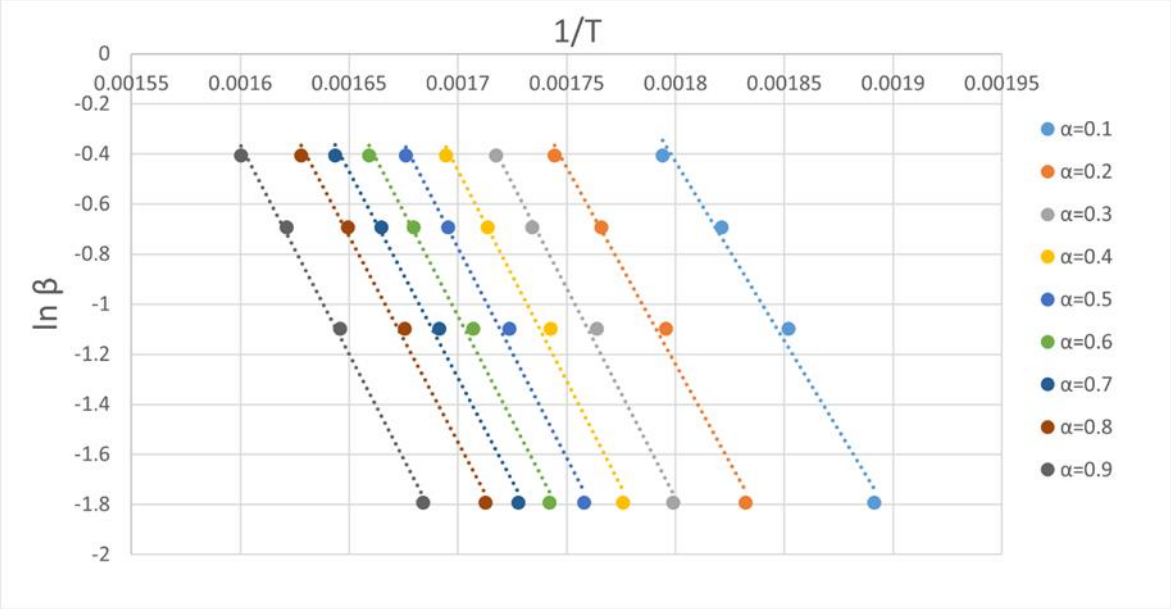

Figure 15: Linear Fit Plots using FWO Method for Paracetamol Drug Product.

Table 4: Kinetic and Thermodynamic Parameters for Each Conversion Degree using FWO Method for Paracetamol Drug Product.

α	$E\ (kJ.mol^{-1})$	R^2	$A\ (s^{-1})$	$\Delta H(kJ.mol^{-1})$	$\Delta G(kJ.mol^{-1})$	$\Delta S(J.mol^{-1}.K^{-1})$
0.1	112.9	0.987	1.1×10^{8}	108.5	168.7	-104.2
0.2	124.2	0.992	1.3×10^{9}	119.6	168.2	-84.1
0.3	132.2	0.994	7.1×10^{9}	127.6	167.9	-69.8
0.4	133.5	0.991	9.4×10^{9}	128.8	167.9	-67.6
0.5	133.1	0.992	8.5×10^{9}	128.3	167.9	-68.5
0.6	131.5	0.993	6.1×10^{9}	126.8	167.9	-71.3
0.7	130.3	0.994	4.7×10^{9}	125.5	168.0	-73.5
0.8	129.9	0.995	4.3×10^{9}	125.0	168.0	-74.4
0.9	132.0	0.997	6.8×10^{9}	127.1	167.9	-70.7
Average	128.8	-	-	124.1	168.1	-76.0

The enthalpy change (ΔH) represents the amount of energy exchanged during a chemical reaction [50]. The average values of ΔH estimated from KAS and FWO for pyrolysis of the paracetamol drug product were 121.2 and 124.1 $kJ.mol^{-1}$, respectively. The positive values of ΔH indicated that the pyrolysis of the pharmaceutical is an endothermic process, representing the total energy needed for its decomposition. The small difference between ΔH and E values (~5 $kJ.mol^{-1}$) showed that minimal additional energy is required for the reaction to occur. The small potential energy barrier reflects the ease of reaction [44].

The change in Gibb's free energy (ΔG) reflects the reaction feasibility and direction [47]. The average values of ΔG from KAS and FWO were 168.2 and 168.1 $kJ.mol^{-1}$, respectively. Positive values of ΔG indicated a non-spontaneous reaction that requires energy to occur. The entropy change (ΔS) represents the degree of disorder (randomness) in the reaction system [51]. The average values of ΔS from KAS and FWO

were -81.3 and -76.0 $J.mol^{-1}.K^{-1}$, respectively. The negative values of ΔS marked the lower disorder degree of the pyrolysis products than that of the reactants [44].

5.2.2. Ibuprofen

Similarly as described in section 5.2.1 for the paracetamol drug product kinetics, E, A, and the thermodynamic parameters (ΔH, ΔG, ΔS) were determined for a range of α for ibuprofen drug product pyrolysis. The plots of the fitted TGA experimental data to KAS and FWO models were presented in Figures 16 and 17, respectively, and the findings from KAS and FWO methods were shown in Tables 5 and 6, respectively.

The E values for the first decomposition stage of the ibuprofen drug product (α = 0.1-0.8) from KAS and FWO were 75.4-79.7 and 80.0-83.7 $kJ.mol^{-1}$, respectively. The E value for the second decomposition stage ($\alpha = 0.9$) was 136.0 and 138.9 $kJ.mol^{-1}$ from KAS and FWO, respectively. The E value of the pure ibuprofen undergoing a single decomposition step in inert environment was found to be around 91 $kJ.mol^{-1}$ at α = 0.5 by Ferreira et al. through FWO model [46]. This difference in E values between the pure API and the drug product is related to the presence of excipients that have an effect on the decomposition behavior of the drug product. The correlation coefficient value (R^2) of the plots for the two methods was 0.99, which showed that both models were suitable for the study of the pyrolysis kinetics of the ibuprofen drug product.

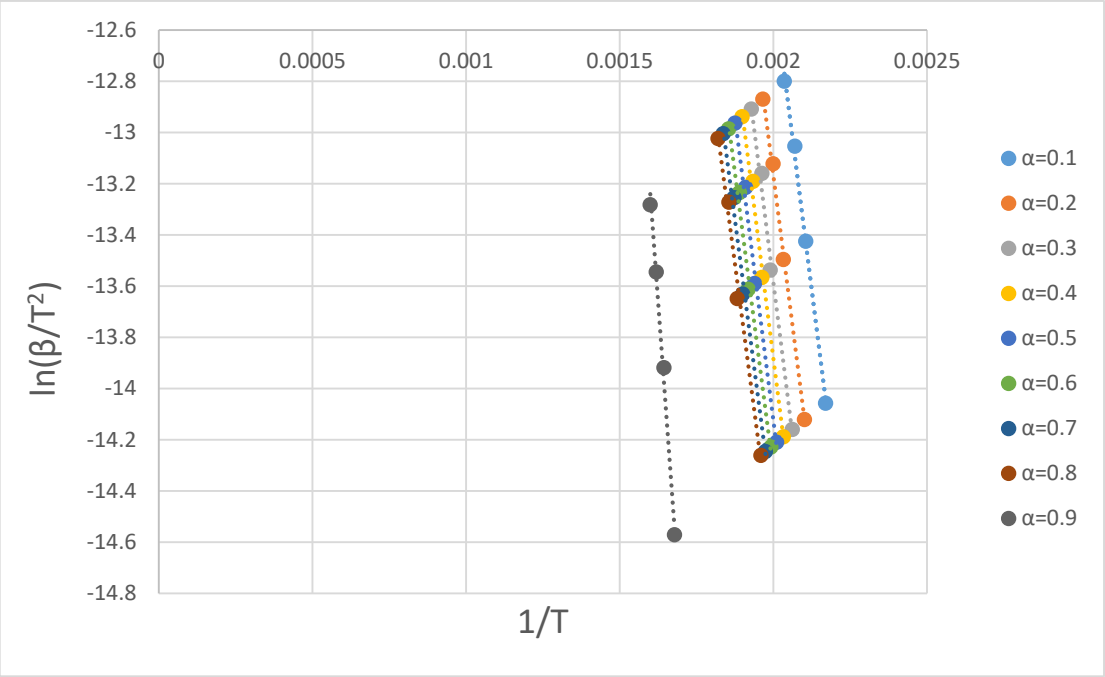

Figure 16: Linear Fit Plots using KAS Method for Ibuprofen Drug Product.

Table 5: Kinetic and Thermodynamic Parameters for Each Conversion Degree using KAS Method for Ibuprofen Drug Product.

α	$E\ (kJ.mol^{-1})$	R^2	$A\ (s^{-1})$	$\Delta H(kJ.mol^{-1})$	$\Delta G(kJ.mol^{-1})$	$\Delta S(J.mol^{-1}.K^{-1})$
0.1	79.0	0.998	8.17×10^5	75.2	148.2	-143.7
0.2	77.9	0.997	6.18×10^5	73.9	148.3	-146.3
0.3	79.7	0.992	9.71×10^5	75.7	148.2	-142.7
0.4	78.9	0.994	7.89×10^5	74.8	148.2	-144.5
0.5	78.2	0.993	6.69×10^5	74.1	148.2	-145.9
0.6	77.1	0.991	5.09×10^5	72.9	148.3	-148.3
0.7	76.6	0.991	4.45×10^5	72.4	148.3	-149.5
0.8	75.4	0.990	3.33×10^5	71.2	148.4	-151.9
0.9	136.0	0.992	1.19×10^9	131.1	184.9	-85.3

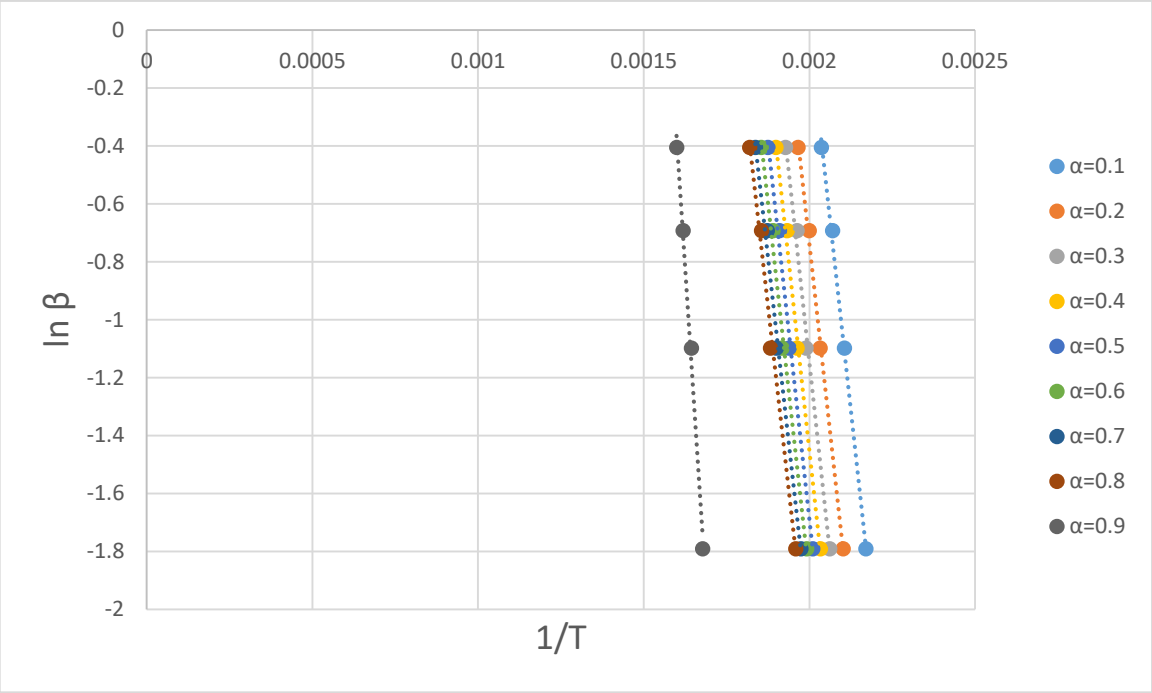

Figure 17: Linear Fit Plots using FWO Method for Ibuprofen Drug Product.

Table 6: Kinetic and Thermodynamic Parameters for Each Conversion Degree using FWO Method for Ibuprofen Drug Product.

α	$E\ (kJ.mol^{-1})$	R^2	$A\ (s^{-1})$	$\Delta H(kJ.mol^{-1})$	$\Delta G(kJ.mol^{-1})$	$\Delta S(J.mol^{-1}.K^{-1})$
0.1	82.6	0.998	2.0×10^{6}	78.8	148.0	-136.2
0.2	81.8	0.997	1.6×10^{6}	77.9	148.1	-138.2
0.3	83.7	0.994	2.6×10^{6}	79.7	147.9	-134.4
0.4	83.0	0.995	2.2×10^{6}	78.9	148.0	-135.9
0.5	82.5	0.994	1.9×10^{6}	78.3	148.0	-137.1
0.6	81.5	0.993	1.5×10^{6}	77.3	148.1	-139.2
0.7	81.1	0.993	1.4×10^{6}	76.9	148.1	-140.2
0.8	80.0	0.992	1.0×10^{6}	75.8	148.1	-142.4
0.9	138.9	0.994	2.11×10^{9}	133.9	184.9	-80.5

The values of ΔH estimated for the first decomposition stage (α = 0.1-0.8) of the ibuprofen drug product from KAS and FWO were 71.2-75.7 and 75.8-79.7 $kJ.mol^{-1}$, respectively. The ΔH value for the second decomposition stage ($\alpha = 0.9$) from KAS and

FWO increased to 131.1 and 133.9 $kJ.mol^{-1}$, respectively. The small difference between ΔH and E values (4-5 $kJ.mol^{-1}$) reflected that the reaction can be initiated by providing a little amount of additional energy. The positive values of ΔG along the conversion degrees indicated that the pyrolysis reaction of the drug product is non-spontaneous that requires energy to occur, and the negative values of ΔS indicated a decrease in disorder during the pyrolysis of the ibuprofen drug product.

5.3. Pyrolysis Products Yields

The pyrolysis experiment yielded three different types of products: liquid, non-condensable gas, and a solid char. The mass of each product, as well as its corresponding yield which is the fraction of the initial mass of crushed drug product, are presented below in Table 7 and 8 for paracetamol and ibuprofen drug products, respectively. Eq. (1) through (6) were used to calculate the products masses and yields. Approximately half a tablet of the paracetamol drug product was used for the pyrolysis experiment.

Table 7: Products Yields of Paracetamol and Ibuprofen Drug Products Pyrolysis.

	Paracetamol		**Ibuprofen**	
Product	Mass (g)	Yield (%)	Mass (g)	Yield (%)
Liquid	0.26	61.66	0.28	57.89
Gas	0.14	31.82	0.18	38.03
Char	0.03	6.52	0.02	4.08

5.4. Liquid Products Characterization by GC-MS

5.4.1. Paracetamol

To identify the formed compounds, the liquid sample from paracetamol drug product pyrolysis was characterized by gas chromatography-mass spectroscopy, and the resulting chromatogram was shown in Figure 18. 19 peaks were obtained; 15 whose mass-match percentage was over 90%. The molecular formula of each compound as well as its retention time, the peak area percentage, the compound family, and the mass-match percentage were listed in Table 9.

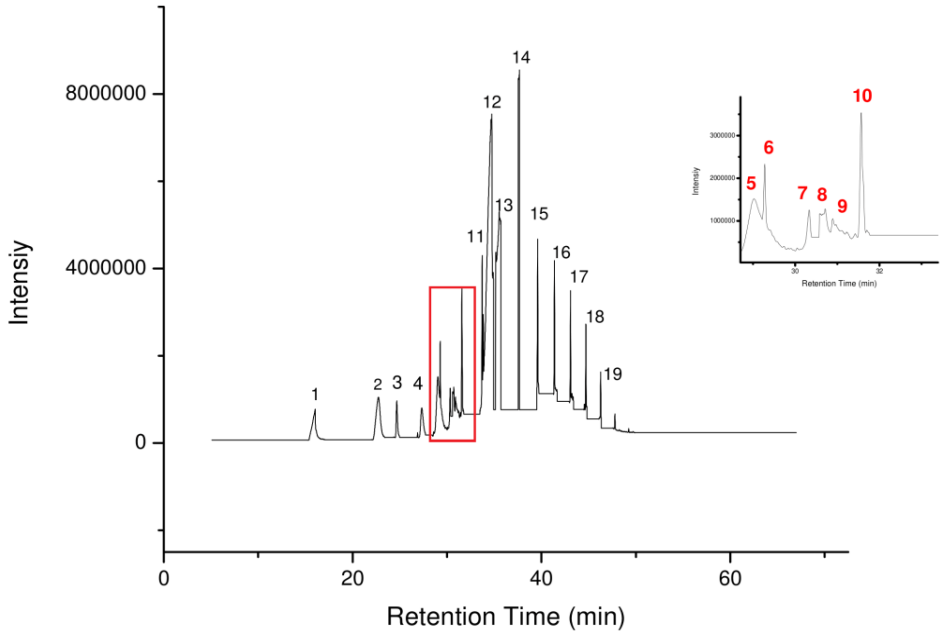

Figure 18: Chromatogram of Liquid Sample from Paracetamol Drug Product Pyrolysis. *The area surrounded by the red rectangle is enlarged for clarity (top right).

Table 8: List of Compounds Identified in the Pyrolysis Liquid of Paracetamol Drug Product.

Peak No	Retention Time (min)	Compound Name	Formula	Area % of Peak	Family	Mass-Match Percentage
1	16.03	2-Pyrrolidinone	C_4H_7NO	4.23	Lactam	91
2	22.74	p-Aminophenol	C_6H_7NO	7.40	Aromatic Amine/Phenol	94
3	24.67	Paracetamol	$C_8H_9NO_2$	2.10	Aromatic Amide/Phenol	91
4	27.33	Methylparaben	$C_8H_8O_3$	3.18	Parabens	97
5	29.02	Acetic acid	$C_2H_4O_2$	6.05	Carboxylic Acid	10
6	29.28	Hexadecane	$C_{16}H_{34}$	3.57	Alkane	98
7	30.33	2,6,10-Trimethylpentadecane	$C_{18}H_{38}$	1.81	Alkane	81
8	30.71	2-Methyl-8-quinolinol	$C_{10}H_9NO$	2.98	Quinoline	62
9	30.88	Pentadecane	$C_{15}H_{32}$	1.99	Alkane	35
10	31.57	Heptadecane	$C_{17}H_{36}$	3.76	Alkane	98
11	33.72	Octadecane	$C_{18}H_{38}$	4.63	Alkane	99
12	34.73	Paracetamol	$C_8H_9NO_2$	44.74	Aromatic Amide/Phenol	94
13	35.52	Paracetamol	$C_8H_9NO_2$	3.40	Aromatic Amide/Phenol	93
14	37.73	Paracetamol	$C_8H_9NO_2$	1.13	Aromatic Amide/Phenol	94
15	39.60	Heneicosane	$C_{21}H_{44}$	2.70	Alkane	98
16	41.38	Docosane	$C_{22}H_{46}$	2.58	Alkane	99
17	43.08	Tricosane	$C_{23}H_{48}$	1.98	Alkane	99
18	44.70	Tetracosane	$C_{24}H_{50}$	1.78	Alkane	99
19	46.27	Pentacosane	$C_{25}H_{52}$	0.83	Alkane	98

The formation of 2-pyrrolidinone can be attributed to the decomposition of polyvinylpyrrolidone, also known as povidone, listed as an excipient in the paracetamol drug product. It is used in tablets as a binder. Povidone could have been decomposed into its monomer N-vinylpyrrolidone, which in turn produced 2-pyrrolidinone. It has been reported in a study that the pyrolysis of povidone forms the monomer N-vinylpyrrolidone

[52]. 2-pyrrolidone is largely adopted in the pharmaceutical industry for the formulation of drugs [53]. It is also used for the production of pyrrolidone nootropics, especially piracetam [54], which are known as “smart drugs”. They work on improving human thinking and memory, especially in cases of impairment of these functions [55]. Moreover, 2-pyrrolidone is used as a solvent in the cosmetics industry which is the largest consumer. The global 2-pyrrolidone market is expanding as a result of the rapid growth of the pharmaceutical and cosmetics industry [53].

The production of long chain straight alkanes with carbon number ranging from C15-C25 may stem from the pyrolysis of Carnauba wax, which is listed as an excipient of the analyzed pharmaceutical. A study by Asperger et al. found that the pyrolysis of Carnauba wax yielded a series of straight chain alkanes, caused by the thermal fragmentation of ester linked long alkyl chains present in the Carnauba wax [56]. Additionally, the presence of heptadecane in the pyrolysis products may be resulting from the thermal degradation of stearic acid (n-octadecanoic acid), also listed as another excipient in the treated drug. A study by Maher et al. presented that the pyrolysis of stearic acid forms heptadecane by decarboxylation. It also showed that decarboxylation is followed by thermal cracking forming shorter chain series of *n*-alkane and α-olefin, then subsequent reactions including isomerization and addition occurs forming C18+ alkanes. Thus, the production of long chain alkanes from the pyrolyzed pharmaceutical may also correspond to stearic acid [57]. These long chain alkanes fall within the diesel and motor oil range of hydrocarbons [58], and after separation and purification from the rest of the matrix, may potentially be used as a fuel source or a mechanical lubricant, or may undergo further catalytic cracking to obtain valuable short chain alkanes which may be used as gasoline [59].

p-Aminophenol is another product resulting from the pyrolysis of the drug under study. It is known to be the primary decomposition product of paracetamol [60], which shows that part of the API degraded during pyrolysis. p-Aminophenol is of great commercial importance as an intermediate for the production of analgesic and antipyretic drugs such as paracetamol, acetanilide, and phenacetins. It is also used as a dyeing agent in chemical industries [61]. Additionally, paracetamol was also identified in the pyrolysis liquid, whose peak area comprises 44.74% of the total chromatogram area. Hence, the pyrolysis of expired medications could potentially be used as a process, which may lead to the recycling of the API for further pharmaceutical products after purification from the rest of the components in the matrix. In this case, it would be imperative to purify the API that is to be recycled from any traces of p-Aminophenol, as ingesting it has been shown to potentially cause nephrotoxicity and teratogenicity. p-Aminophenol is usually formed during the synthesis of paracetamol or during its storage as a main impurity in the paracetamol formulation. Due to its adverse effects, the amount of p-aminophenol in paracetamol substance should be strictly controlled. The United States Pharmacopeias (USP) and British Pharmacopeias (BP) limit this amount to 50 ppm (0.005% w/w) [62].

Methyl paraben is also a pyrolytic product of the studied drug belonging to the Parabens family also known as p-Hydroxybenzoates. They act as preservatives and antimicrobial compounds, which expand their use among industries. They are used in pharmaceuticals, cosmetics, and especially in food industries. Since 2013, almost all canned or packaged food contained parabens in their compositions [63].

This section entailed an attempt to attribute each product to the pyrolysis of a specific ingredient in the tablet based on literature. A complex reaction network might have been generated from the pyrolysis of the main ingredient (paracetamol) and led to

the formation of most of the identified compounds in gas and liquid products. This requires the study of the reaction mechanism which was not the aim of this study.

5.4.2. Ibuprofen

GC-MS analysis of the liquid sample obtained from the pyrolysis of ibuprofen drug product generated a chromatogram with five peaks (Figure 19). Four whose mass-match percentage was over 90%. Table 10 presented the molecular formula of each compound and the corresponding peak characteristics.

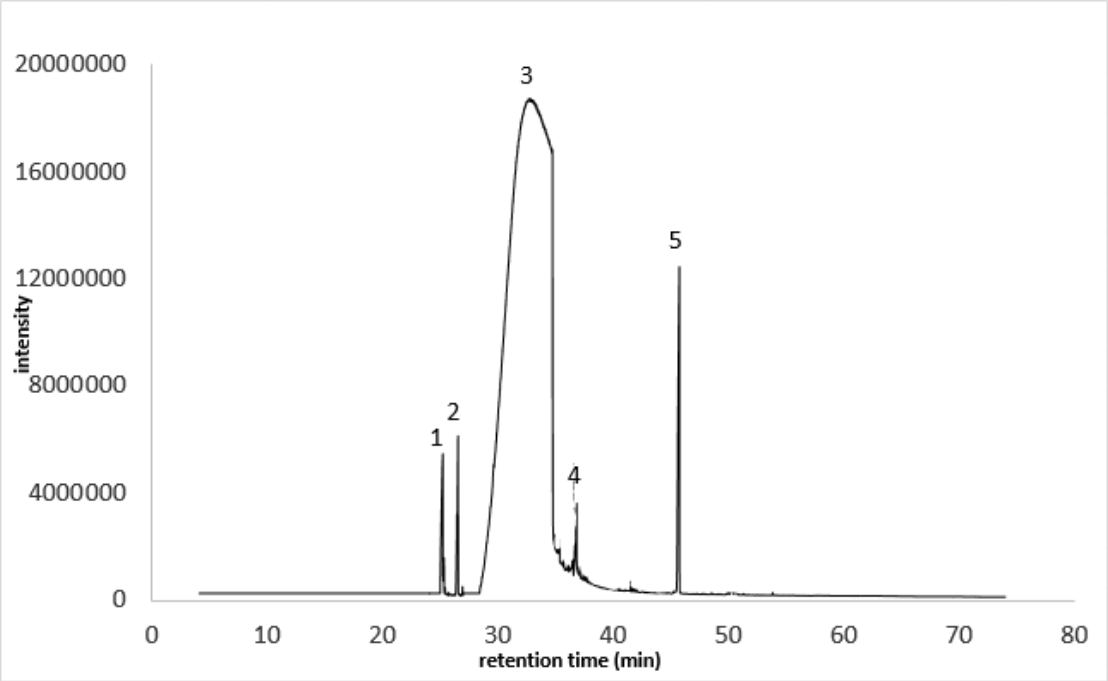

Figure 19: Chromatogram of Liquid Sample from Ibuprofen Drug Product Pyrolysis.

Table 9: List of Compounds Identified in the Pyrolysis Liquid of Ibuprofen Drug Product.

Peak No	Retention Time (min)	Compound Name	Formula	Area % of Peak	Mass-Match Percentage
1	25.19	1-Decene	$C_{10}H_{20}$	1.09	94
2	26.52	Ibuprofen methyl ester	$C_{14}H_{20}O_2$	0.75	99
3	32.69	Ibuprofen	$C_{13}H_{18}O_2$	95.59	99
4	36.80	Hexadecanoic acid	$C_{16}H_{32}O_2$	0.55	99
5	45.70	1-Phenyl-3-amino-2-pyrazoline	$C_9H_{11}N_3$	2.00	50

Ibuprofen has been identified with a peak area accounting for 95.59% of the total chromatogram area. The API can be recycled for further incorporation into the manufacturing of new tablets. Ibuprofen methyl ester was originated from ibuprofen decomposition during pyrolysis. A study by Wang et al. reported the identification of ibuprofen methyl ester as a result of the UV-LED catalytic degradation of ibuprofen solution [64]. 1-decene and hexadecanoic acid were also identified among liquid products. 1-decene is a valuable chemical that has a large global market valued at USD 1.2 billion in 2022 and is expected to reach USD 1.7 billion by 2028. The increased use of 1-decene in the production of polyalphaolefin (PAO) is contributing to this growth, as PAO is a synthetic lubricant widely employed in the automotive and manufacturing industries. Additionally, the growing demand for packaged food products is another factor driving growth, as 1-decene is used in the production of polymers like polyethylene, which are utilized for packaging purposes [65]. Hexadecanoic acid, known as palmitic acid, is also an important product that is widely used in soap and cosmetics industries, driving its market value to USD 399.7 million in 2022. It is introduced in the formulation of several esters, fatty alcohols, and fatty amines [66].

5.5. Gas Products Characterization by Micro GC

5.5.1. Paracetamol

The gaseous products from paracetamol drug product pyrolysis were analyzed by micro GC-TCD, where the compounds in the gas sample were detected by the columns of modules ‘A’ and ‘C’ of the gas analyzer. Both the chromatograms from modules ‘A’ and ‘C’ were shown in Figures 20 and 21, respectively, with the peaks labeled with the names of the corresponding compounds. The gases present in the sample were found to be CH_4, CO, CO_2, and C_2H_4, and their mole percentages were presented in Table 11.

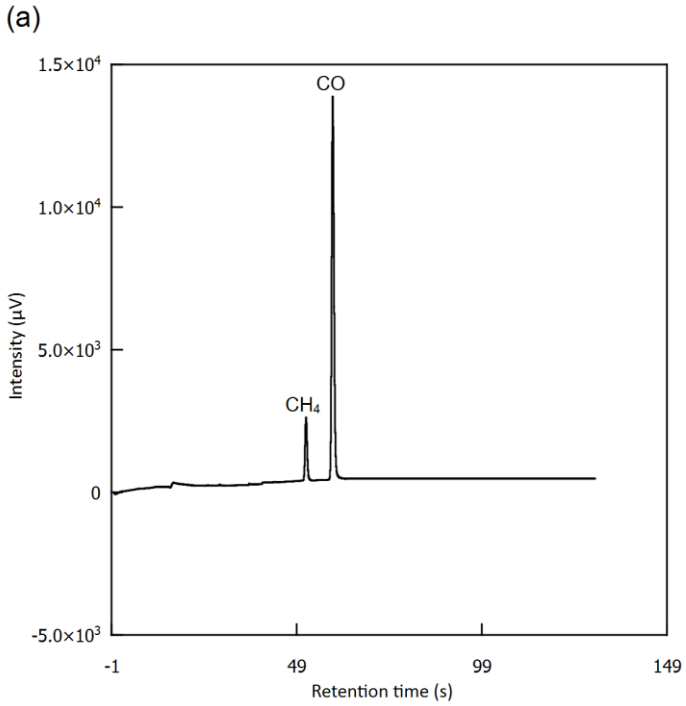

Figure 20: Chromatogram of Gas Sample from Paracetamol Drug Product Pyrolysis (Module A).

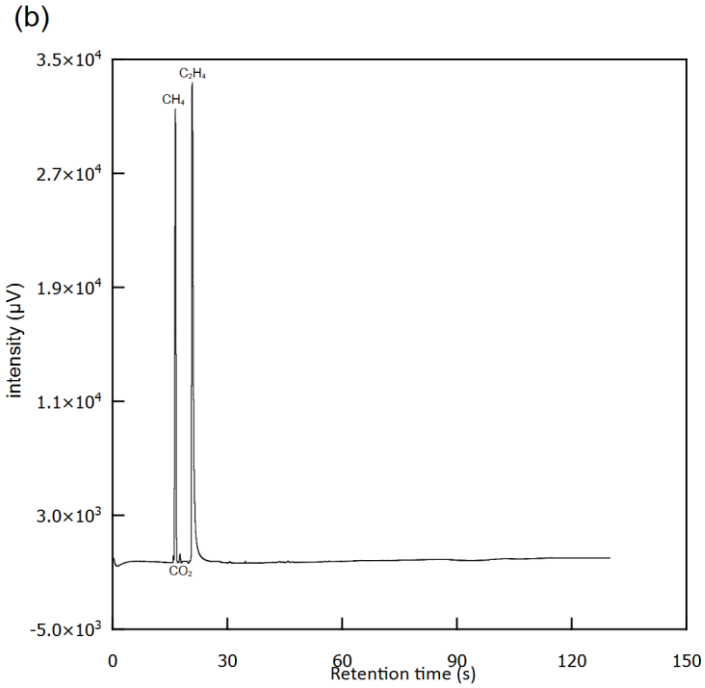

Figure 21: Chromatogram of Gas Sample from Paracetamol Drug Product Pyrolysis (Module C).

Table 10: List of Compounds Identified in the Pyrolysis Gas of Paracetamol Drug Product.

Module	Retention Time (s)	Compound Name	Formula	Mole Percent
A/C	103.68/32.68	Methane	CH_4	39.16
A	118.10	Carbon Monoxide	CO	26.97
C	35.12	Carbon Dioxide	CO_2	0.54
C	41.52	Ethylene	C_2H_4	33.05

Methane was the most abundant product in the pyrolysis gas, accounting for 39.16 mol% of the gas sample. Methane may be originated from the pyrolysis of stearic acid, as it has been shown in a study that methane is produced due to the thermal cracking of heptadecane, the primary pyrolytic product of stearic acid [57]. The next most abundant gas product was ethylene, accounting for 33.05 mol% of the gas sample. This may be also

associated with the pyrolysis of stearic acid, where the thermal cracking of heptadecane produces a range of alkenes [57].

Carbon monoxide and carbon dioxide were found in the gas sample in 26.97 and 0.54 mol% respectively. This may indicate decarbonylation and decarboxylation reactions, which are the primary reactions in the pyrolysis of stearic acid. The carbon dioxide was present in much lower quantities than the carbon monoxide, which denotes that decarbonylation is the more prominent step of the pyrolysis of stearic acid rather than decarboxylation, which is concurrent with the findings of Asomaning et al. [67]. Additionally, the thermal degradation of hypromellose, which is also an excipient of the studied drug product, has been shown to produce carbon monoxide and carbon dioxide in a study by Lim et al. [68].

The gases produced from the pyrolysis of the paracetamol drug product are suitable for recycling and subsequent usage in several industries. The capture and conversion of CO, a major air pollutant in the atmosphere, into chemicals or fuels, can mitigate the release of CO into the environment while producing compounds of value. For instance, carbon monoxide has a role in the synthesis of several compounds such as acetic acid, acetic anhydride, polycarbonates, and polyketones. When combined with hydrogen, the resulting mixture known as syngas is used in the production of valuable hydrocarbons by Fischer-Tropsch process, also in the production of aldehydes from alkenes by hydroformylation known as the oxo process. Carbon monoxide is also used as a reducing agent in metallurgical processes such as the Mond process for the refinery of Nickel, which is a process applied for the extraction and purification of nickel [69].

Ethylene is considered a valuable compound with a multitude of purposes. The large global demand for ethylene is due its versatile uses. It is mainly used in the synthesis

of polyethylene, ethylene dichloride, ethylene oxide, and ethylbenzene [70]. Polyethylene, which is a type of plastic, is utilized to create a variety of products such as food packaging, bags, and bottles. Ethylene oxide is introduced in the manufacturing of textiles and antifreeze. Ethylene dichloride is a feedstock for PVC pipes manufacturing. Additionally, ethyl benzene is used in the production of styrene, a synthetic rubber used in tires and foam insulation [71]. The global ethylene market size was USD 166,520 million in 2019 and is projected to reach USD 245,005 million by 2027 [72].

Methane gas has also diverse range of applications. It is extensively used as a fuel source for industrial and residential uses. It also serves as a feedstock to produce syngas via steam reforming or dry reforming reaction, from which many valuable chemicals are synthesized such as methanol or Fischer-Tropsch hydrocarbons [73]. Moreover, the produced methane can be further recycled to provide the heat needed to sustain the pyrolysis reaction, which reduces the need for external energy sources.

5.5.2. Ibuprofen

The compounds in the gas sample from ibuprofen drug product pyrolysis were detected by the columns of modules ‘A’ and ‘C’ of the micro GC-TCD gas analyzer. The chromatograms from modules ‘A’ and ‘C’ were shown in Figures 22 and 23, respectively. The identified gases were the same as those produced from paracetamol drug product pyrolysis (CH_4, CO, CO_2, and C_2H_4), and their mole percentages were presented in Table 12.

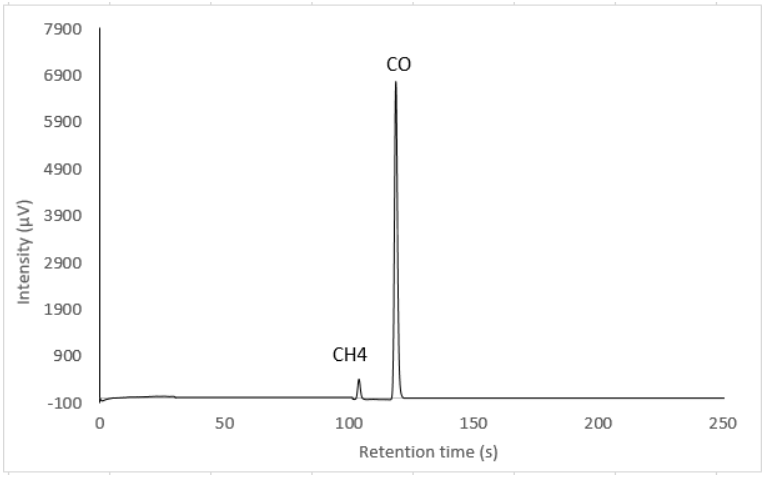

Figure 22: Chromatogram of Gas Sample from Ibuprofen Drug Product Pyrolysis (Module A).

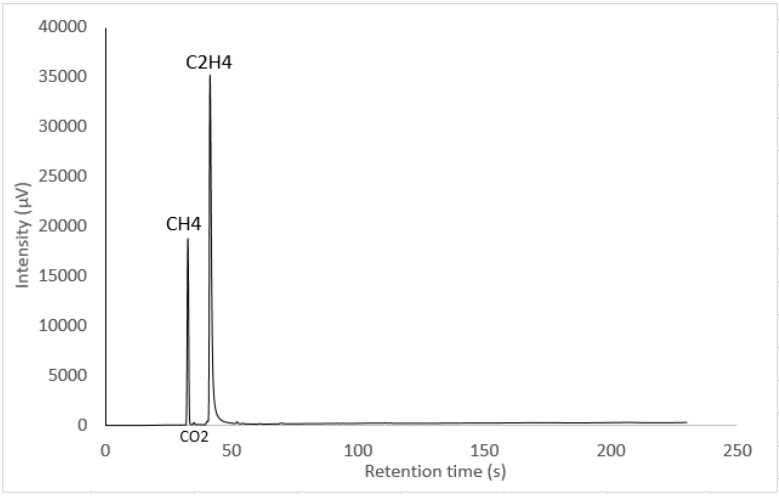

Figure 23: Chromatogram of Gas Sample from Ibuprofen Drug Product Pyrolysis (Module C).

Table 11: List of Compounds Identified in the Pyrolysis Gas of Ibuprofen Drug Product.

Module	Retention Time (s)	Compound Name	Formula	Mole Percent
A/C	102.34/32.66	Methane	CH_4	28.64
A	118.74	Carbon Monoxide	CO	21.05
C	35.08	Carbon Dioxide	CO_2	0.28
C	41.42	Ethylene	C_2H_4	49.99

The analysis of liquid products by GC-MS and gas products by micro GC-TCD demonstrated that the pyrolysis of each of paracetamol and ibuprofen drug products can yield compounds with high commercial value, in addition to recovering the API. The wide variety of pyrolysis products requires their separation and purification before they can be introduced into industrial processes.

5.6. Economic Aspect

The application of pyrolysis to paracetamol and ibuprofen drug products showed its potential to generate products that have direct commercial applications, in addition to recovering the API (paracetamol and ibuprofen). Compared to the traditional treatment methods of waste pharmaceuticals, pyrolysis can present significant economic superiorities owing to the production of valuable chemicals, while offering remarkable environmental benefits. One of the studies that carried out a life-cycle economic assessment of waste pyrolysis is that by Hong et al. (2018), which mentioned the generation of a net profit of $189.96/t from medical waste pyrolysis considering the costs related to investment, electricity, labor, and human health protection [74].

Minimizing the costs associated with pyrolysis system is important in order to develop an efficient process. Generally, capital costs are the main contributor to the overall cost with 30-40%. Additionally, energy costs are significant as this treatment is energy-intensive. Recycling the generated methane gas back to the pyrolysis process can serve the heating requirements, which improves its economic feasibility. Labor cost should be also considered which generally comprises 12-15% of the overall cost, in addition to transportation cost. Moreover, efforts must be made to enhance the yield of valuable products and maximize the revenues.

As pyrolysis of paracetamol drug product showed along the recovery of API, the production of a valuable series of long chain alkanes that can be associated with important revenues, the optimization of the system by improving pyrolysis conditions and process design, and developing catalysts is substantial and worth further exploration [22]. Also, future work can involve economic assessment of the feasibility of scaling up the pyrolysis process for commercial applications. On the other hand, pyrolysis of ibuprofen drug product needs to be further explored at different conditions for better decomposition and production of compounds of higher resale value along with API recovery.

CHAPTER 6

CONCLUSION

The global crisis of pharmaceutical pollution has made it imperative to adopt treatment methods of pharmaceutical waste with minimal impact on the environment. Circular economy has gained considerable attention recently as a model that can promote environmental protection and economic growth. This study aimed to investigate pyrolysis as a treatment method of pharmaceutical waste in the context of circular economy. Fast pyrolysis experiment was conducted on each of paracetamol and ibuprofen drug products, the most popular among analgesic drugs, at 500℃. The analysis of the resultant pyrolysis liquid by GC-MS identified substances which potentially have resale value, including the API. Long chain alkanes were identified in the pyrolysis liquid of paracetamol drug product, while 1-decene and hexadecanoic acid were found in that of ibuprofen drug product. The gases evolved from the pyrolysis of each drug were analyzed by micro GC-TCD, where carbon monoxide, carbon dioxide, methane, and ethylene were found in both samples, each of which has multiple industrial uses on their own or as an intermediary for other valuable products. Methane was the most abundant in the pyrolysis gas of paracetamol drug product (39.16 mol%), while ethylene was the most prominent in that of ibuprofen drug product (49.99 mol%). Carbon dioxide was merely present in both samples. Moreover, kinetic and thermodynamic analysis was performed, which are vital for effective design as well as for scaling of the reactors. Model-free isoconversional KAS and FWO methods were applied to determine the kinetic and thermodynamic parameters through the generated experimental TGA data. The average E values for the pyrolysis of the paracetamol drug product using KAS and FWO methods were found to be 125.9 and

128.8 $kJ.mol^{-1}$, respectively. For ibuprofen drug product pyrolysis, the average E values were 77.9 and 82.0 $kJ.mol^{-1}$, for the first decomposition stage, and were found to be 136.0 and 138.9 $kJ.mol^{-1}$ for the second decomposition stage, using KAS and FWO models, respectively. The small difference between E and ΔH values ($\sim$5 $kJ.mol^{-1}$) reflected that the reaction can be initiated by providing a little amount of additional energy.

This research work opens perspectives for the application of pyrolysis to waste pharmaceuticals as a promising alternative treatment method, that can provide a remarkable economic and environmental benefit compared to traditional treatment methods. In view of the potential of pyrolysis to generate useful products from paracetamol and ibuprofen drug products, more studies are needed to set the optimal reaction parameters and reactor design in order to make pyrolysis technology a commercially viable route for waste treatment and materials recovery. Furthermore, it would be worth exploring the pyrolysis of other pharmaceutical products and their potential for recovering high market value products along with the API from waste through a circular model.

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