Pain Relief Trio: A Comparative Analysis of Paracetamol, Aspirin, and Ibuprofen

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ABSTRACT

Paracetamol, aspirin and ibuprofen are among the most commonly used analgesics. These three drugs not only have a function as pain relievers, but also have functions as anti-pyretics and anti-inflammatories. This article aims to provide a comprehensive review and compare the three drugs in terms of pharmacology, chemistry, and industry using a narrative literature review (NLR) approach. Paracetamol has effectiveness in relieving mild to moderate pain, while aspirin has advantages as an anti-inflammatory suitable for conditions such as arthritis and also as an antiplatelet in cardiovascular disease. Meanwhile, ibuprofen shows strong effects in reducing inflammation for various types of pain and reducing fever. In the perspective of their production on an industrial scale, these three drugs have been produced in large quantities through more environmentally friendly industrial processes. Aspirin production uses ionic liquids instead of acid solvents; paracetamol production uses direct amidation of hydroquinone; and ibuprofen production is done through Aryl-1,2-translocation rearrangement with isobutyl benzene as raw material. This review emphasizes the importance of a sustainable industry approach, informed decision-making by healthcare professionals, and careful monitoring to optimize pain relief outcomes and reduce potential risks.

Keyword: Aspirin; Painkillers; Ibuprofen; Medicine; Paracetamol

INTRODUCTION

Pain is one of the most common symptoms experienced by people suffering from all ages, and has a significant impact on daily life. Over-the-counter pain relievers are often the initial choice of pain relief for some people (Trajanovska et al., 2010; Younes et al., 2011). Among the most widely used painkillers are paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), namely aspirin and ibuprofen (Corrêa et al., 2017). These three drugs are not only effective in treating pain, but have the function of reducing fever (anti-pyretic) and reducing inflammation (anti-inflammatory). The analgesic and antipyretic effects are achieved through mechanisms that require inhibition of the activity of the cyclooxygenase (COX) enzyme, which has an important role in the production of prostaglandins (Gerriets, et al., 2021). COX-1 and COX-2 enzymes have different functions, and inhibition of each enzyme can lead to different therapeutic outcomes and side effects (Atchison, et al., 2013).

Paracetamol is used for joint pain, middle earache, headache, toothache, neuralgia, and pain due to flu and lumbago (Cranswick and Coghlan, 2000; Hazlewood et al., 2012). The mechanism of action of paracetamol is by inhibiting the production of prostaglandins in the

brain and spinal cord so that it can reduce pain and reduce fever. Meanwhile, aspirin and ibuprofen work by inhibiting COX-1 and COX-2 enzymes that are responsible for prostaglandin production. Aspirin is used as a painkiller and fever reducer, and can be used in low doses as a blood thinner (anti-platelet) to prevent blood clots (Pawar et al., 2013). Meanwhile, ibuprofen is often used in the treatment of chronic pain, acute osteoarthritis, and rheumatoid arthritis (van Uum et al., 2020). In terms of mechanism of action, efficacy, and side effects the three drugs differ. Over-administration or inappropriate use can result in a range of undesirable effects, the severity of which is influenced by factors such as the individual's medical history, dosage, and frequency of use (Riley et al., 2017).

Although there are many studies that discuss each drug extensively and separately, comparative studies involving all three drugs together are rare. Therefore, this article aims to provide a comprehensive review of the comparison of the three drugs (paracetamol, aspirin and ibuprofen) referring to various recent studies and research. The article compares and explores the mechanism of action of the three drugs, including their effects on prostaglandin production, therapeutic benefits and side effects. In addition to comparing the clinical aspects of the drugs, another important aspect is also comparing the drug synthesis process and mechanism. Furthermore, the industrial production process and capacity were also compared as this is one of the important factors in drug production (van Rensburg and Reuter, 2019). The high global demand for the analgesic's paracetamol, aspirin, and ibuprofen requires adequate production capacity to meet the needs of patients worldwide.

This article discusses paracetamol, aspirin and ibuprofen from various aspects, namely pharmacology, chemistry, and production on an industrial scale. Through this study, it is expected to identify the advantages and disadvantages of using the three analgesics, as well as the drug production process on an industrial scale.

METHOD

The study was conducted using NLR, which involved a literature search and analysis of various relevant sources, comparing the data obtained, and drawing conclusions based on the findings by summarizing the similarities and differences between the three drugs in terms of effectiveness, safety, tolerability, drug synthesis, and industry conditions. A comprehensive review was achieved through a detailed literature review process. Overall, the method for conducting a narrative review of paracetamol, aspirin, and ibuprofen is shown in Fig 1.

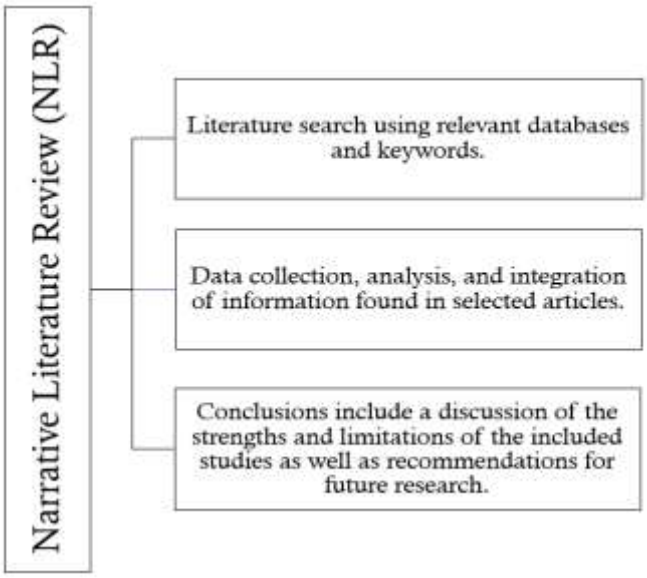

Fig 1. Flowchart of the NLR process.

DISCUSSION

Drug History of Paracetamol, Aspirin, and Ibuprofen

One of the earliest common threads in the history of these three drugs is the use of salicylic acid as a pain reliever. Salicylic acid is the active ingredient in aspirin and has been used for centuries to treat pain and inflammation. However, the compound was not widely used due to its considerable adverse side effects, including stomach irritation and bleeding. In the late 1800s, chemists began modifying salicylic acid to make a more effective and tolerable painkiller. This led to the development of aspirin by Felix Hoffmann at the Bayer pharmaceutical company in 1897.

In the following decades, scientists continued to develop new painkillers, including paracetamol and ibuprofen. Paracetamol was first synthesized in 1877 by Harmon Northrop Morse, but it wasn't until the 1950s that it began to be widely used as a pain reliever. Ibuprofen was developed in the 1960s by British chemist Stewart Adams, who was looking for a safer and more effective alternative to aspirin. These three drugs play an important role in managing pain and improving the quality of life for millions of people. Each drug has its own distinct properties and uses and has a history rooted in the search for safer and more effective pain relief.

Table 1. Comparison of COX Selectivity and Drug Pharmacokinetics of Aspirin, Ibuprofen and Paracetamol (Rang *et al*., 2012)

Drug molecules	COX selectivity	Pharmacokinetics			Benefits	Risk
		Half-life ($t_{1/2}$)	Protein binding (%)	Oral bioavailability (%)		
Aspirin (*acetylsalicylic acid*)	Weakly COX-1 selective	~20 minutes	80-90	20-70	Analgesic, antipyretic, anti-inflammatory Reduction in cardiovascular events and mortality	Bleeding
Ibuprofen	Nonselective	2-4 hours	99	80-100	Analgesic, antipyretic, anti-inflammatory	Cardiovascular side effects
Paracetamol (*acetaminophen*)	Weak and similar affinity for COX-1 and COX-2	2 hours	20-50	70-100	Analgesic, antipyretic. Fewer gastrointestinal effects	Cardiovascular side effects

Pharmacological Aspects of Paracetamol, Aspirin, and Ibuprofen

Aspirin

Aspirin, a non-steroidal anti-inflammatory drug (NSAID), has been widely used by the public as an effective pain reliever at doses >325 mg per day. At low doses, aspirin can inhibit the conversion of arachidonic acid into prostaglandins and thromboxanes by inhibiting cyclooxygenase (COX) enzymes, especially cyclooxygenase-1 (COX-1). This is beneficial in patients at high risk of arterial thrombotic complications due to arterial occlusive disease (Collins et al., 2009). The general mechanism of action of aspirin involves inhibition of platelet activation and aggregation. Thromboxane A2 is a potent promoter of platelet aggregation resulting from the COX-1 enzyme. Thus, aspirin, by irreversibly inactivating COX-1, thereby blocking the formation of thromboxane A2, produces a potent antiplatelet effect (Weissmann, 1991). On the other hand, higher doses of aspirin (hypoalbuminemia) at 250-300 mg have anti-inflammatory effects by inhibiting COX-1 and COX-2 (Ornelas et al., 2017). At higher doses of aspirin as well, typically used for analgesia (e.g., 650 mg 3x daily), sufficient concentrations are achieved to inhibit COX-1 in the gastrointestinal mucosa. The anti-inflammatory and anti-platelet mechanisms of aspirin have been found to have positive effects on cardiovascular disease risk (Dai and Ge, 2012) stroke, and potentially several types of cancer including colorectal cancer (Garcia-Albeniz and Chan, 2011).

Clinical trials of aspirin treatment suggest that aspirin has a protective role against colorectal cancer. Regular use of aspirin can reduce the recurrence of colorectal adenoma,

colorectal cancer, and mortality from colorectal cancer (Thun et al., 2012). Research conducted by Shami et al. (2022) showed that low-dose aspirin (75-300 mg/day) in adults (≥40 years) without a history of atherosclerotic cardiovascular disease reduced the risk of colorectal cancer and gastric cancer. Whereas eicosanoids, the metabolic products of arachidonic acid via the cyclooxygenase pathway are the cause of gastrointestinal cancer development. Therefore, aspirin works by blocking the COX enzyme (Table 1), with gastrointestinal cancer mortality rates shown to be reduced with regular aspirin use (Cathcart et al., 2012).

In addition to its anti-inflammatory and anti-platelet effects, aspirin is commonly used to reduce fever (antipyretic effect) and relieve minor pain (analgesic effect). High-dose tablets of 500-1000 mg are used for severe pain and inflammation (Ugurlucan et al., 2012). In preventing vascular disorders in pregnancy, such as preeclampsia and intrauterine growth restriction, and maternal disorders such as antiphospholipid syndrome, at low doses, aspirin is more commonly used (Rolnik et al., 2022).

Paracetamol

Paracetamol is known as one of the most common non-prescription drugs for primary care therapy, secondary care (postoperative) and other emergency treatments. The advantage of using this paracetamol drug is that it can be given by oral, rectal or intravenous routes, so paracetamol is provided in various dosage forms such as tablets, injections, drops, powders and others (Bannwarth and Phourcq, 2003). The analgesic effect of this drug is used for a variety of pain relief applications, both as a single drug and as a complementary therapy to other drugs such as opiates (Wahyuni et al., 2019).

The maximum dose of paracetamol for adults and children older than 12 years is a maximum of 4 grams/day. The mechanism of action of paracetamol is still not fully understood, but the effect is probably achieved through inhibition of the prostaglandin synthesis center (Graham and Scott, 2003). In contrast to NSAIDs, paracetamol does not directly inhibit COX function outside the central nervous system, and its central action is not through direct blockage of the active site but rather through reduction of COX activity (Lipton et al., 2000) as seen in Table 1.

Administration of 1000 mg paracetamol resulted in greater pain reduction, from moderate or severe pain to no pain (19% and 10% respectively) compared to placebo (Diener et al., 2005). Paracetamol belongs to category B, where the risk is small or even non-existent in some cases. It is safe to use at any stage of pregnancy to relieve pain and lower body temperature. Paracetamol is also safe for short-term use within the recommended therapeutic

dose. However, if pregnant women take excessively high daily doses continuously, it can cause severe anemia, fatal kidney disease in their babies, as well as increased occurrence of cryptorchidism (Schenkel et al., 2022).

Ibuprofen

Ibuprofen has been widely used in various countries to relieve symptoms of pain, inflammation, and fever. At low doses (800-1,200 mg per day), ibuprofen has a good safety profile comparable to paracetamol (Rainsford, 2009). Ibuprofen has the same low gastro-intestinal (GI) effects as paracetamol (acetaminophen) and fewer Gl effects than aspirin (Rainsford, 2013). Ibuprofen works in a similar way to aspirin. It can be used for backaches, strains and sprains, as well as pain from arthritis. Like aspirin, it is also good for toothache and menstrual pain.

Dysmenorrhea is a medical condition involving pain during menstruation, which can vary in quality and timing Dysmenorrhea can be primary, which is usually mediated by prostaglandin production during ovulation, or secondary to other diseases such as endometriosis or pelvic inflammatory disease. NSAIDs, especially ibuprofen, are often the treatment of choice and are FDA-approved to treat primary dysmenorrhea due to their efficacy and safety (Nie et al., 2020). The paracetamol, aspirin, and ibuprofen tolerability study (PAIN) evaluated the use of OTC analgesics by 8677 patients with acute pain and counted significant adverse events (defined as moderate, serious, or severe, requiring a second physician consultation or discontinuation of therapy). The PAIN trial reported that OTC ibuprofen (1200 mg/day) was similar to paracetamol 3000 mg/day in the rate of side effects (13.7% vs 14.5%) but ibuprofen had significantly fewer effects than aspirin 3000 mg/day (13.7% $p<0.001$). Although ibuprofen is widely accepted as an effective treatment for pain, further research is needed to improve the effectiveness of its clinical use in the treatment of pain.

Side Effects of Paracetamol, Aspirin, and Ibuprofen Drugs

Gastrointestinal (GI) side effects are largely attributed to COX-1 inhibition, while simultaneously anti-inflammatory, analgesic, and anti-pyretic effects are mediated by COX-2 inhibition. Aspirin works with weak COX-1 selectivity, causing severe GI side effects including diarrhea, vomiting, nausea and abdominal pain. Paracetamol works by inhibiting COX-1 and COX-2 and provides analgesic and antipyretic effects, but has low anti-inflammatory activity (Tomić et al., 2017). Walsh et al. reported that Gl and AEs (adverse renal events) were not higher in infants <6 months of age prescribed ibuprofen compared to those

aged 6-12 months. In pregnant women, paracetamol and NSAIDs are suitable for mild to moderate pain, but NSAIDs should be avoided in the third trimester because of the risk to the fetus (Black et al., 2019).

Jensen et al. analyzed the differential risk of cryptorchidism with the use of acetaminophen, aspirin and ibuprofen during pregnancy. The results showed that exposure to ibuprofen and aspirin was not associated with cryptorchidism whereas prolonged consumption of acetaminophen by pregnant women for more than 4 weeks, especially during the early and middle stages of pregnancy, may lead to increased occurrence of cryptorchidism. Similarly, a side effect associated with aspirin use is mild to moderate dyspepsia where one will feel pain, bloating, and abdominal discomfort which is often reported in a minority of cases (McCarthy, 2012). Ibuprofen has a lower risk for adverse effects related to the gastrointestinal tract, liver, kidneys, and other adverse drug reactions which rarely occur compared to other NSAIDs (Rainsford, 2009).

Drug Effectiveness of Paracetamol, Aspirin, and Ibuprofen

Aspirin is more commonly consumed as an analgesic (anti-pain) and antiplatelet (anti-plaque formation in blood vessels). Paracetamol and ibuprofen, on the other hand, are more commonly used as temperature reducers (antipyretics). In children with fever, ibuprofen is recommended as it is safer than paracetamol which is more geared towards adults as shown in Table 2.

Table 2. Drug Effectiveness of Aspirin, Ibuprofen and Paracetamol

Medicine	Age of participant	Dosage and route	Findings	Reference
Aspirin	18-50 years old	1000 mg/kg Oral	Aspirin provides analgesic effectiveness comparable to acetaminophen (300 mg) and codeine (30 mg) therapy in individuals with postoperative headache and dental pain	(Gatoulis *et al.*, 2012)
	Post-operative patients	900 mg/kg Oral	Pain management with aspirin is faster than paracetamol 1000 mg in the early postoperative period after dental surgery	(Wray, 2003)
	18-88 years old	Dose variation (60-250 mg/day) Intravenous	Patients treated with aspirin (268 patients) or acetaminophen (13 patients) showed a significant reduction in platelet aggregation.	(Kao *et al.*, 2022)
Ibuprofen	≤ 2 years	≤ 5 mg/kg and >5 mg/kg Oral	Ibuprofen is significantly more effective than paracetamol in reducing pediatric fever	(Tan *et al.*, 2020)

Paracetamol	≤ 16 years	10 mg/kg Intravenous	Ibuprofen provides significantly earlier temperature reduction in the first 2 hours for pediatric fever compared to patients receiving 10 mg/kg paracetamol	(Khalil *et al*., 2017)
	18-65 years	400 mg/kg Oral	Ibuprofen and paracetamol at a dose of 1000 mg/kg were both effective in reducing fever and pain.	(Can *et al*., 2021)
	Adults (26-45 years old) and Elderly (≥60 years old)	4 g/day Oral	Paracetamol is effective for mild to moderate acute pain in many adults with liver, kidney or cardiovascular disease, gastrointestinal disorders and asthma.	(Alchin *et al*., 2022)
	Female 25-35 years old	110-150 mg/kg Oral	Paracetamol as the safest analgesic to treat pain during pregnancy compared to aspirin	(Black *et al*., 2019)

Chemical Aspects of Paracetamol, Aspirin, and Ibuprofen Drug synthesis route

Aspirin

The synthesis of aspirin involves the reaction between salicylic acid and acetic anhydride in the presence of a catalyst, such as sulfuric acid or phosphoric acid, to form aspirin and acetic acid as a by-product. The next step, recrystallization for purification of the aspirin product.

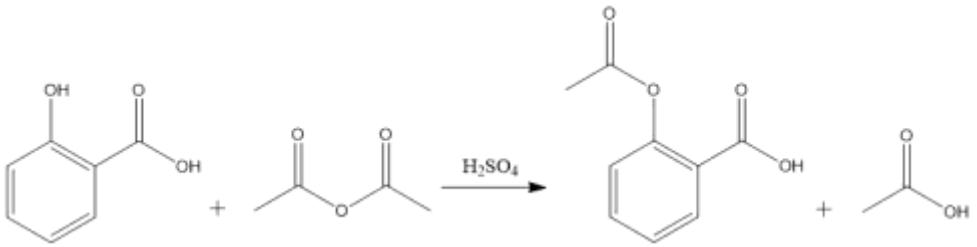

Fig 2. Aspirin synthesis scheme

Several new methods and modifications have been developed to improve reaction efficiency and yield. For example, Nazari (2012) found that the use of Preyssler nanocatalyst for aspirin synthesis significantly increased the reaction rate and improved aspirin yield. Basically, the synthesis of aspirin from salicylic acid occurs through an acetylation process in an acidic medium. Although sulfuric acid is used in relatively small amounts in the synthesis of aspirin, there are several factors to consider regarding the environmental impact. The use of acid can be replaced with more environmentally friendly solvents, one of which is ionic liquid. In a study conducted by Amado Alviz and Alvarez (2017), the environmental impact of using ionic liquids ([Bmim]Br) over volatile organic solvents in the production of

acetylsalicylate. The study found that the use of ionic liquids has a lower impact on global warming potential, ozone layer depletion potential, and human toxicity potential. However, it has a higher impact on eutrophication potential and photochemical oxidation potential. Overall, the use of ionic liquids can be a more environmentally friendly alternative to traditional solvents in the aspirin production process.

Paracetamol

At the industrial level, there are 3 synthesis routes to produce paracetamol. The three routes are para-nitro chlorobenzene (PNCB) route 1, phenol route 2, and nitrobenzene route 3. (Gayflor- Kpanaku et al., 2013). In the PNCB route, para-aminophenol (PAP) is hydrolyzed with sodium hydroxide (and subsequently acidified) and then hydrogenated to para-nitrophenol. Generally, this route approach yields about 38% yield and requires 4 reaction steps from benzene (Fig 3). The second route where para-nitrophenol is prepared by direct nitration of phenol also produces para-aminophenol in 5 steps from benzene, but gives a resulting yield of about 54%. Another alternative route is the nitrobenzene route with PAP obtained via 4 steps from benzene including the hydrogenation reaction of nitrobenzene to phenylhydroxylamine which is transformed under acidic conditions to the desired para-aminophenol via a Bamberger rearrangement (Joncour et al., 2015).

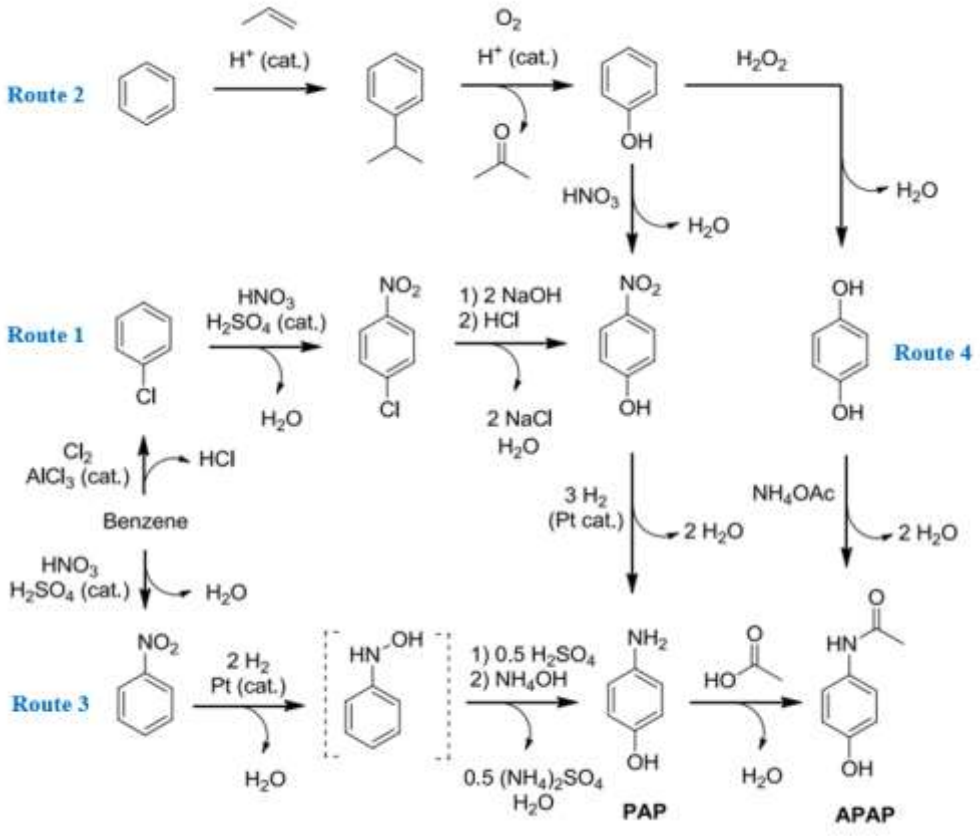

Fig 3. Several routes of paracetamol synthesis (Gayflor-Kpanaku *et al*., 2013)

From the atomic economy (percentage of total reactant mass successfully converted into the desired product), it appears that route 1 is the smallest. The determination of the best method is not only considered through atomic economy, but from several other parameters including the availability and cost of starting materials, the efficiency of the chemical reactions involved, and the process conditions required to execute each step. In addition, the cost will also depend on the scale of the production process, as processes with larger scales often benefit from economies of scale. Nevertheless, each route has its advantages and disadvantages that can be taken into consideration when choosing the most optimal and suitable route to be developed in Indonesia.

Development of greener processes for paracetamol production has been undertaken with various attempts at replacing sulfuric acid which is corrosive but generally gives low selectivity. One of the most promising routes is the direct amidation of hydroquinone (route 4) with acetamide as it produces only water as a by-product. Hydroquinone is produced industrially by direct oxidation of phenol which is also used as starting material for the production of para-nitrophenol (Joncour *et al*., 2014).

Ibuprofen

Two methods of synthesizing ibuprofen on an industrial scale are the Boots route and the Hoechst route. The Boots route is a traditional route patented by the Boots Company consisting of 6 steps and starting with the compound (2-methylpropyl) benzene with an atomic economy of only 40.04% (Crina *et al*., 2018).

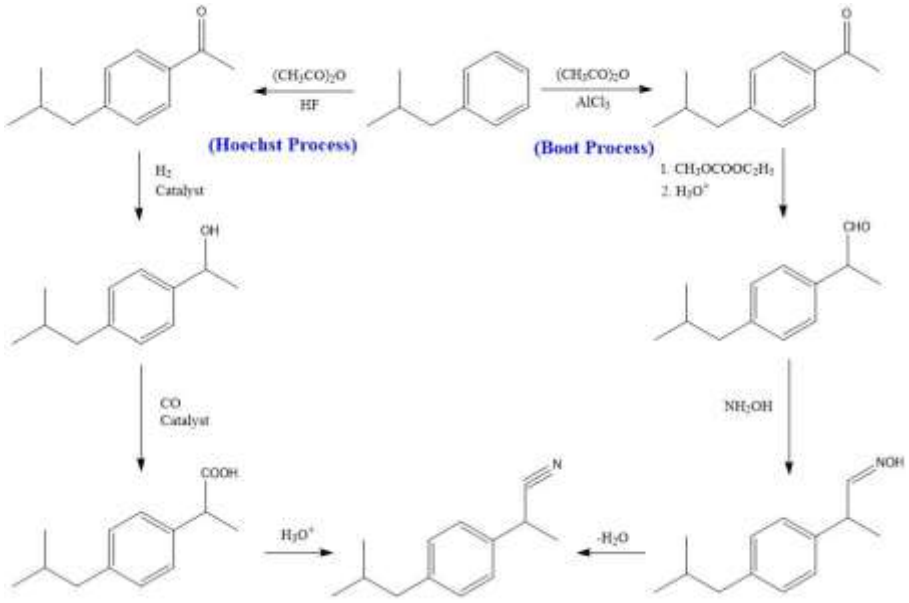

Fig 4. Hoechst route and Boots route of ibuprofen synthesis

Although the Boots synthesis method is the method of choice for the ibuprofen manufacturing industry and has produced hundreds of tons of ibuprofen, it has also produced a large amount of by-products and waste (de Gama et al., 2022). In 1992, the Boots Hoechst-Celanese Company (BHC) developed a greener synthesis procedure consisting of only three steps using recyclable HF as an alternative to $AlCl_3$ (Speight, 2019), with an overall atomic economy of 77.44%.

Ma (2018) investigated the synthesis of ibuprofen using Aryl-1,2-translocation rearrangement with isobutyl benzene as raw material. This method is commonly used in the country of China by Shandong Xinhua Pharmaceutical Company. The synthesis process includes Friedel-crafts acylation where isobutyl benzene reacts with 2-chloropropionyl chloride; hydrolysis reaction; ketal reaction; product rearrangement reaction with catalyst; and hydrolysis to obtain ibuprofen. The reaction equations are listed below:

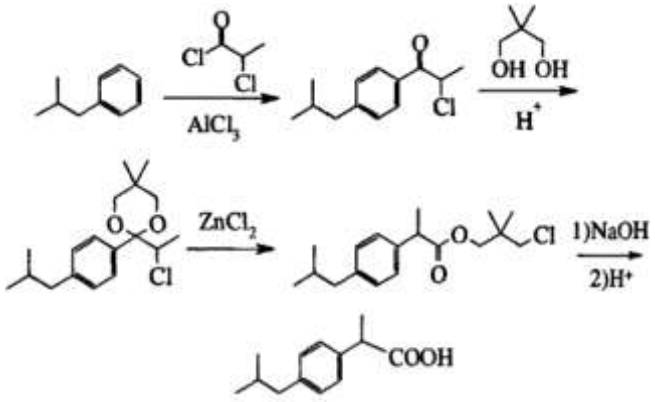

Fig 5. Synthesis of ibuprofen using Aryl-1,2-translocation rearrangement (Qu, 2019)

The advantages of this synthesis are: (1) avoiding by-products due to acylation with aromatic impurities if petroleum ether is used as solvent, (2) avoiding toxicity and solvent residue in the reactor if dichloroethane is used as solvent, (3) lower requirements of cold brine, (4) lowering energy cost and equipment corrosion and so on (Qu, 2019). Compared with the BHC method, the yield of each step of the aryl-1,2-translocation rearrangement method is high, and the catalyst is cheap and easy to obtain. However, the production process of ibuprofen by this synthesis on an industrial scale, provides temperature control problems that may cause side reactions.

Industrial Aspects

State of the Drug Industry

About 40,000 tons of aspirin, one of the most commonly used drugs, are produced globally each year (Aspirin Foundation, 2023). The demand for aspirin drugs is increasing as the aspirin active ingredient pharmaceutical industry develops with a compound annual growth

rate (CAGR) of 2.4%. The global aspirin market size is expected to grow to US$2,558 billion by 2027. Currently, industries producing aspirin drugs include Bayer AG, Hebei Jingye Chemical, JQC (Huayin) Pharmaceutical, Perrigo Company, L.N.K. International, Thermo Fisher Scientific, Taj Pharmaceuticals Limited, Advance Pharmaceutical, and Allegiant Health with China and the United States holding significant market share in aspirin consumption (Globenewswire, 2022a). Bayer's Germany plant produces the most aspirin compared to other plants.

The growth of ibuprofen market size is estimated to be around $645 million by 2023 with a compound annual growth rate (CAGR) of 2-3%. (Inc, 2021). Another study by Beroe shows that the total annual global demand for ibuprofen is expected to reach 45,233 MT by 2022. Some of the major manufacturers of ibuprofen such as Xinhua Pharmaceutical, IOLCP, Biocause Granules, Shasun, BASF and SI Group are leaders in the industry, with about 81% market share. China, India, North America and Europe respectively 48%; 30%; 29% and 26% are the largest suppliers of ibuprofen (Globenewswire, 2022b). From the data, developed countries have higher demand for ibuprofen than developing countries.

Paracetamol, a supportive drug during the COVID-19 pandemic, has a global market estimated to be worth US$ 126.2 million in 2022 and is estimated to be US$ 121.7 million by 2028 at a CAGR of -0.6%. The top four global manufacturers hold a share of more than 55% including Mallinckrodt, Anqiu Lu'an, Granules India, Zhejiang Kangle. Europe is the largest supply center, with a share of more than 50%, followed by China, and the United States, both of which have sales of more than 30% (Globenewswire, 2022c). All three drugs, as OTC medicines, are popular painkillers that are also used to treat fever. China and India are the most dynamic hubs of the pharmaceutical market, being the fifth and ninth largest economies in the world, respectively, which has attracted many pharmaceutical companies around the world. (Shkvarya et al., 2016). Their mass sourcing and manufacturing capabilities; production skills; regulatory knowledge of local companies; and low product costs make them the first choice of global drug companies for sourcing raw materials and drug products.

Limited costs, knowledge, technology and lack of support from the government in producing raw materials and drug products have hampered the growth of the pharmaceutical industry in Indonesia. However, the independence of the domestic pharmaceutical industry has recently developed with contributions from the government although its competitiveness tends to be weak compared to foreign countries. This is because the quantity share is still small. Unlike China, India and Europe, which have many consumers so that in one production, the production costs are able to provide considerable profits.

Based on data from the Food and Drug Monitoring Agency (BPOM, 2016), the current number of pharmaceutical industries is 208 companies, consisting of 4 state-owned enterprises, 35 multinationals and 169 Indonesian national private companies. The majority of the pharmaceutical industry in Indonesia is still engaged in the formulation industry or the finished drug manufacturing industry. This has caused the need for imports of raw materials for drug manufacturing to increase. On the other hand, Indonesia, which is relatively new in the world of active ingredient manufacturing, does not have much process and material efficiency. Therefore, it is necessary to contribute from scientists and researchers as well as the government in developing various methods to be able to make cost savings. (Ruskar et al., 2021).

CONCLUSION

This analysis compares paracetamol, aspirin and ibuprofen regarding pharmacology, chemistry and industrial aspects. Therapeutically, paracetamol is effective in managing mild to moderate pain, while aspirin has additional anti-inflammatory properties suitable for conditions such as arthritis as well as antiplatelets in cardiovascular disease. Ibuprofen, as an NSAID, shows strong anti-inflammatory effects for various types of pain and reduces fever. Regarding side effects, all three drugs have the potential to cause adverse reactions. Paracetamol, if taken in excessive doses, may pose a risk of liver toxicity. Aspirin has a higher risk of gastrointestinal complications, and ibuprofen has the potential to cause stomach ulcers and cardiovascular events if used over a long period of time or in susceptible individuals. These three drugs are produced on a large scale using industrial processes and several studies have been conducted for environmentally friendly synthesis methods. The development of a more environmentally friendly synthesis process of the three drugs was carried out by using ionic liquids instead of acid solvents; direct amidation of hydroquinone; and Aryl-1,2-translocation rearrangement with isobutyl benzene as raw materials for aspirin, paracetamol and ibuprofen, respectively.

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