MICROWAVE ASSISTED GREEN SYNTHESIS OF PARACETAMOL, ASPIRIN AND THEIR PHARMACOKINETIC STUDIES

Abstract

The research looks at a new way to make Paracetamol and Aspirin using green chemistry concepts via solvent free reaction and under microwave irradiation. The synthesis was carried out from salicylic acid and 4-aminophenol, acetic anhydride, and no catalyst. The reaction time for both the molecules was low. The yield of Paracetamol is 92.0% and Aspirin is 82.0%. The reaction progression was confirmed by TLC. The structure of the compounds was confirmed by FT-IR and Melting point. Upon literature studies, our work was focussed on the biological metabolism of these synthesized compounds. The compounds were tested for pharmacological studies. We reported the pharmacokinetics and their side effects during the metabolism in the human body. The results were interpreted.

Keywords: Paracetamol, Aspirin, Microwave method, Green Chemistry, Pharmacokinetics,

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I. INTRODUCTION

1. **Paracetamol**: Is an analgesic-antipyretic compound derived from *p*-aminophenol. Though paracetamol has good efficacy and safety on consumption, paracetamol has hepatotoxic effect as its adverse drug reaction.

Today, Paracetamol is a widely used drug in many nations and pharmaceutical formulations. Its composition drugs are used to treat and/or relieve minor aches and pains [1] and are used for cold and flu Infections due to their antipyretic activity [2]. Aspirin is known as Salicylates. It is a common drug used for minor aches, pains and fevers

It is also used to treat and relieve severe pain like post-operative pain [3] and palliative care for cancer patients. Therefore, we planned for the synthesis of this drug by green chemistry. Microwave method is a suitable method for green synthesis. 4-amino phenol treated with acetic anhydride in acidic media to form paracetamol.

Figure 1 shows the chemical structures of Paracetamol (PAR) and Aspirin (ASA).

2. **Paracetamol Aspirin:** The scope for this drug led to the manufacture of active pharmaceutical ingredients and statistics showing that over 1, 45,000 tonnes of paracetamol were synthesized every year. Green chemistry is a challenging task to follow the synthetic procedures. It is an "Engineering idea" of pollution prevention and zero waste. It also promotes the adoption of cost favor and environmental friendly methods [6-7].

The literature study shows that Aspirin is a very scope drug in the field of medical science. After literature survey, we planned to work on the synthesis of Aspirin. Aspirin is known as Salicylates. It is a common drug used for minor aches, pains and fevers. It shows anti-inflammatory activity. In this work, we synthesized the drug by salicylic acid under microwave irradiation. After the synthesis, we tested its pharmacokinetics and for side effects. The metabolism studies have been done.

One thousand one hundred and eight GPs included 8677 patients between September 1997 and March 1998: 2900 were randomised to aspirin, 2886 to ibuprofen, and 2888 to paracetamol (three patients had no code label number). 8633 patients (99.5%) were evaluable (intention-to-treat population), of whom 8233 (95%) adhered to the study protocol (per-protocol population). The main protocol deviations were allocation of treatment by the GP without using the central telephone service (177 patients), and the

use of prohibited medica- tions (215 patients). These were equally distributed among the treatment groups (fig. 1).The baseline characteristics of the treatment groups were similar, and factors probably affecting tolerability such as age, indication, concomitant medication or diseases were equally distributed (table I). The most common indications were musculoskeletal and back pain (48.3%) and symp-toms associated with sore throat, the common cold and flu (31.5%). The mean treatment duration and the mean number of tablets taken perpatient were not different between treatment groups (table I).

II. MATERIALS AND METHODS

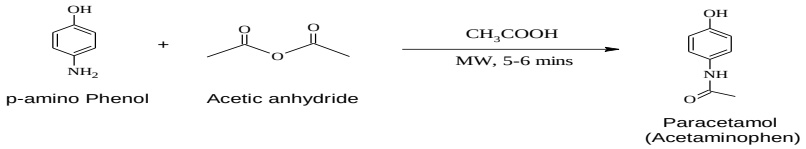
All required Chemicals are purchased from Davangere Scientifics. The reaction was carried in Microwave Oven (Convention) (20L, 23,500MHz). The TLC was checked in UV-Chamber and Iodine Chamber. The molecules were characterized by FT-IR (Bruker) in SJMIT, Chitradurga. Pharmacokinetic studies in SS research centre.

1. Experimental Section:

- **General Procedure for the synthesis of Paracetamol:** The solid 4-amino Phenol (10 Mmol) was added with acetic anhydride (10 Mmol) in an acidic medium. The sealed reaction mixture was kept in microwave oven for the reaction to proceed. The progress of the reaction was confirmed by TLC. After the reaction, the solution turns to white solid precipitate. The crude solid was recrystallized by ethanol and water. The product was purified by washing with water for 2-3 times, filtered and dried.

- **General Procedure for the synthesis of Aspirin:** The Salicylic acid solution (10 Mmol) was added with acetic anhydride (10 Mmol) in an acidic medium. Microwave oven was subjected to the reaction by inserting the reaction mixture into it. The confirmation of the reaction was done by TLC. After the reaction completion, the solution turns to white solid. The crude white was recrystallized by ethanol and water. The product was purified by water wash for 2-3 times. The solution was filtered and dried.

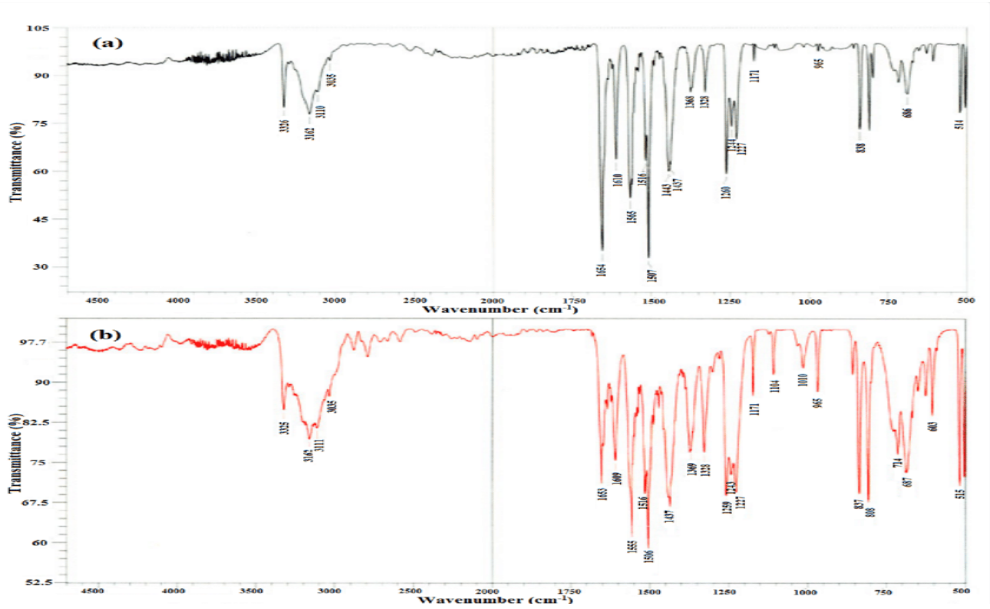
Scheme-1: Synthesis of Paracetamol and Aspirin under Microwave irradiation



2. Spectral data

- **FT-IR**

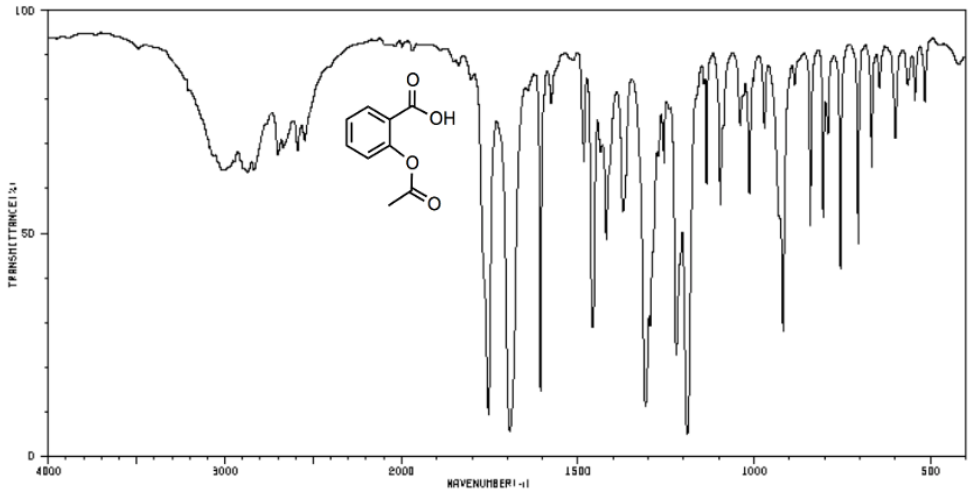
➢ Paracetamol



FT-IR (KBr) υ cm^{-1}: 3325 (-OH stretching), 3162-3035 (CH_3 stretching), 1665 (C=O, Amide), 1609 (C=C).

➢ Aspirin:

14. (6 pts.) Assign the peaks in the infrared spectrum of aspirin (below) with frequencies greater than 1500 cm^{-1} to **specific bond vibrations** AND **the functional group the bond is associated** with. Clearly indicate the specific bond vibration that is associated with the relevant peaks.



FT-IR (KBr): υ cm^{-1} 3000 (O=C-OH, carboxylic), 1757 (-O-C=O, Ester).

III. RESULTS AND DISCUSSION

Paracetamol is formed in 5-6 mins under microwave and proved that the method hastens the reaction time. The yield is increased to 15-20% compared to convention method. Similarly, it took 5-8 mins to complete the reaction for the synthesis of Aspirin. The yield increases to 10-15% compared to convention.

Pharmacokinetics and Side effects

1. **Paracetamol :** The maximum single-dose of acetaminophen for pain or fever is 1,000 mg every 4 hours as needed, up to a maximum daily intake of 4 g. The therapeutic concentrations range from 5 to 20 mg/ml. The plasma maximum concentration (Cmax) is 12.3 g/ml after oral administration of 1,000 mg acetaminophen, the area under the curve over 6 h AUC (0–6) is 29.4 g/h/ml, and the AUC extrapolated to infinity (AUC0–) is 44.4 g/h/ml (Bertolini et al., 2006) [8-9].

   The elimination half-life (t1/2) is 2.53 hours, and the time to peak concentration (Tmax) is 1.0 hour. These findings demonstrate that intravenous acetaminophen delivery results in higher peak plasma levels and occurs sooner than oral dosing [10-13].

2. **Aspirin:** Nine thousand one hundred and eight GPs included 8677 patients between September 1997and March 1998: 2900 were randomised to aspirin,2886 to ibuprofen, and 2888 to paracetamol(three patients had no code label number). 8633patients (99.5%) were evaluable (intention-to-treat population), of whom 8233 (95%) adhered to thestudy protocol (per-protocol population). The mainprotocol deviations were allocation of treatment bythe GP without using the central telephone service(177 patients), and the use of prohibited medications (215 patients). These were equally distributedamong the treatment groups (fig. 1).The baseline characteristics of the treatmentgroups were similar, and factors probably affecting tolerability such as age, indication,concomitant medication or diseases were equally distributed (table I). The most common indications were musculoskeletal and back pain (48.3%) and symptoms associated with sore throat, the common cold and flu (31.5%). The mean treatment duration and the mean number of tablets taken per patient werenot different between treatment groups (table I) One thousand one hundred and eight GPsincluded 8677 patients between September 1997 and March 1998: 2900 were randomised to aspirin,2886 to ibuprofen, and 2888 toparacetamol (three patients had no code label number). 8633 patients (99.5%) were evaluable (intention-to-treat population), of whom 8233 (95%) adhered to the study protocol (per-protocol population). The main protocol deviations were allocation of treatment by the GP without using the central telephone service (177 patients), and the use of prohibited medications (215 patients). These were equally distributedamong the treatment groups (fig. 1). The baseline characteristics of the treatmentgroups were similar, and factors probably affecting tolerability such as age, indication, concomitant medication or diseases were equally distributed(table I). The most common indications were musculoskeletal and back pain (48.3%) and symptoms associated with sore throat, the common cold and flu (31.5%). The mean treatment duration and the mean number of tablets taken per patient were not different between treatment groups (table I)

IV. CONCLUSION

Both Paracetamol and Aspirin synthesized by Green Chemistry. Pharmacokinetic studies were evaluated and reported their side effects. Overall studies concluded that drugs can be synthesized by green route under microwave method. Also, drugs are having cytotoxic effects for human.

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