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International Journal of Pharmacy and Herbal Technology (Online)

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Microwave assisted synthesis of paracetamol by using its derivative (Acetic anhydride) Acetyl chloride

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ABSTRACT

Synthetic processes are made more efficient, less harmful solvents are used, greenhouse gases are reduced and waste is eliminated through the use of green chemistry. Sustainability will involve chemical synthesis. Chemical synthesis has been transformed by the use of microwaves. To put it simply, conventional methods only produce small molecules. Many chemists have adopted the use of microwaves for synthesis due to their economic advantages, higher yield rates, and other benefits. Microwaves are being used for both drug discovery and chemical synthesis. The use of paracetamol and its derivatives in microwaves has been initiated by pharmaceutical research to enhance efficiency and reaction kinetics. Recent modifications to the reaction conditions, solvent selection, and optimization of parameters for synthesis of paracetamol derivatives using microwaves are detailed in this abstract

The foundation of microwave-assisted organic synthesis (MAOS) is the effective heat transfer made possible by dielectric heating, which in turn depends primarily on the solvent's or reagent's capacity to absorb microwave radiation. In the last 20 years, there has been a sharp increase in the utilisation of microwave radiation due to its novel and inventive uses in the fields of material sciences, biological processes, organic and peptide synthesis, polymer chemistry, and nanotechnology. The synthesis of several heterocycles by multi-component reactions (MCRs), cross-coupling reactions, C-H activation reactions, insertion reactions, peptide synthesis, and a variety of other reactions is made possible by the recent MW-assisted catalytic processes that are summarised in this chapter.

Keywords: *microwave radiation, Paracetamol, microwave synthesis, dipole polarization, conduction mechanism*

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Received on 06 July, 2024, Accepted 15 July, 2024

Please cite this article as: Dhandore Rutuja et.al Microwave assisted synthesis of paracetamol by using its derivative (Acetic anhydride) Acetyl chloride.
International Journal of Pharmacy And Herbal Technology 2024.

INTRODUCTION

The use of microwave radiation in microwave synthesis speeds up reaction times. Within the range of 0, there is also a wavelength of microwave radiation. A 1-inch gauge is the measurement. The use of p-aminophenol, which is readily available and quick to prepare, can result in high yields for paracetamol, also known as Acetaminophen (Tylenol). Acetaminophen is produced by combining P-aminophenol and acetyl chloride in a home microwave. The primary objectives of Green Chemistry are to increase the effectiveness of synthetic methods, reduce exposure to toxic solvents, simplify synthetic pathways, and minimize waste. The use of microwave irradiation to directly attach the reaction molecule and pass thermal conductivity has been common in numerous organic syntheses, leading to an increase in temperature. Microwaves provide chemists with an opportunity to experiment with new theories and processes, which enhances their creativity. It is now possible for chemical chemists to work on the same compound in minutes, rather than spending several hours or days working on it. Microwave conditions can be used to irradiate certain reactions without solvents. The combination of mineral-supported catalysed reactions with microwave (radiation) can result in clean chemical processes, often without the need for solvents, which increases reaction rates and yields while reducing complexity. The use of microwaves in synthesis is an example of green chemistry. Many chemists have adopted the use of microwaves for synthesis due to their economic advantages, higher yield rates, and other benefits. Microwaves are being used for both drug discovery and chemical synthesis.[1]

Organic synthesis in the traditional sense requires more time for heating, use of complex apparatus and additional solvents/reagents. The use and disposal of waste in these processes can result in health and safety issues for workers and environmental concerns. The primary objectives of Green Chemistry are to increase the effectiveness of synthetic methods, reduce exposure to toxic solvents, simplify synthetic pathways, and minimize waste. Green chemistry places significant emphasis on microwave synthesis, which is advantageous due to its environmental benefits.[2]

The process of organic synthesis on a large scale involves the use of catalysts and basic chemical ingredients from the petrochemical industry, followed by separation, purification, and storage. Organic synthesis in the traditional sense requires more time for heating, use of complex apparatus and additional solvents/reagents. The use and disposal of waste in these processes can result in health and safety issues for workers and environmental concerns. The primary objectives of Green Chemistry are to increase the effectiveness of synthetic methods, reduce exposure to toxic solvents, simplify synthetic pathways, and Minimize waste. Green chemistry places significant emphasis on microwave synthesis,Which is advantageous due to its environmental benefits.[3,4]

Chemical fusion is now produced using microwaves, thanks to the advancements in synthetic chemistry.The combination of mineral-supported catalysed reactions with microwave (radiation) can result in clean chemical processes, often without the need for solvents, which increases reaction rates and yields while reducing complexity. The electromagnetic radiations that are present in the environment are referred to as EM waves.The wavelength of microwaves is between 0 and 1 mm. Does 1 have a value of 1? Three 300 GHz processors in total. Many telecommunications and microwave radar equipment use band frequencies in this area. [5,6]

The global focus of Green Chemistry is on the creation of chemical products and processes that prevent or terminate the use of potentially harmful substances for human health.

It is a term created by the US Environmental Protection Agency to describe the implementation of 'principles' that reduce or eliminate hazardous substances in the design, production and use of chemical products. This can be accomplished by applying twelve Green Chemistry Principles.

Preventing waste is preferable to treating or cleaning it after it has been produced.

The incorporation of all materials into the final product is a key aspect of synthetic Methods.

Synthetic methods should be formulated to incorporate less hazardous/toxic chemicals.

Chemical products must be designed to achieve the intended function without compromising their safety.

Avoid using solvents and auxiliary substances and ensure their unnecessary use when possible.

Energy consumption in chemical processes should be reduced, and synthetic methods

Should use ambient temperature and pressure if possible.

It is more effective for a raw material to be replenished than depleted whenever possible.

Avoid excessive derivatization and minimize its frequency.

Catalytic reagents are more effective than stoichiometric receptacles.

Chemical products must be designed to decompose into harmless degradation products that do not remain in the environment after their function is over.

The development of analytical techniques should facilitate real-time, in-process monitoring and control before hazardous substances are produced.

Chemical processes may result in accidents, and the substances and their forms should be chosen to minimize these risks.

Conventional heating, despite being inefficient and time-consuming. Has been found to be creatively limiting. Microwaves provide chemists with an opportunity. To experiment with new theories and processes, which enhances their creativity. [7,8,9]

MECHANISM OF MICROWAVE HEATING

The different reactions of materials to microwave radiation mean that they are not susceptible to heating.

Materials can be made transparent or non-transparent based on their reaction with microwaves.

Resonant microwaves can be created from materials that contain sulphur,) including other substances. Stainless Steel

Materials that can be utilized in the microwave setting e.g., Microwave chemistry is dependent on three mechanisms that affect the absorption of water in microwaves:

Dipolar polarization

Conduction mechanism (the opposite end of the wave), and Interfacial Polarization.

Figure No .1: Raga's Microwave System

The production of heat by microwave irradiation requires a dipole moment in the substance. Heat is lost when a dipole moves in relation to an alternating electric field due to molecular friction. Polar solvent molecules like water, methanol have the ability to generate heat.[10]

The oscillating field's frequency range is crucial for maintaining adequate inter-particle interaction during dipolar polarization. Within frequencies ranging from 3 to 30 GHz, inter-particle interaction is necessary to achieve motion. The ideal solution can be employed to heat polar solutions. In the absence of an electric current, the conduction system generates heat. The presence of an electromagnetic field in a conductor causes electrons or ions to oscillate and produce electric current. The conductor's heat is produced when the current opposes it internally. The presence of multiple isolated ions or hydrogen bonds in the sample can cause the electric field to drive the individual ion molecules through the solution, but otherwise, energy may be wasted due to the material's high polarity. When an electrical conductor is irradiated, its charge carriers (electrons, ions, etc.) are affected by the exposure. They encounter this situation. They are the ones who have a part to play. [11,12]

A method that involves both conduction and dipolarity is known as interfacial polarization. Heating systems do not require any non-conducting material for their conductor. A similar process is used in depolarisation to absorb radiation and heat it up. In solvents that are polated, the forces responsible for restricting the mobility of ions are equivalent to inter-particle interactions and act as a solvent for polar molecules in the metal powder's surroundings. [13]

MICROWAVE VERSUS CONVENTIONAL SYNTHESIS

The conventional synthesis involves the use of a furnace or oil bath to heat reactor walls. Convection or conduction (Figure 1). The core of the sample takes a considerable amount of time to reach its target temperature. Energy transfer in the Reacting is characterized by its slow and inefficient performance. Heat is generated through the interaction between the interior of the material and the process of microwave assisted synthesis.[14]

The use of microwaves has several advantages over conventional synthesis, including faster reaction optimization, better stability and speed, and improved efficiency in analogue chemistry. This reduces both the energy and solvent consumption, while also allowing for the production of complex compounds. In the field of medicinal chemistry, microwave synthesis can be utilized to impact efforts in three main ways: lead generation, hit-to-lead efforts, and lead optimization. The use of dedicated rotors or microtiter plate systems can be used in conjunction with microwave chemistry. The use of multimode microwave devices can result in several hundred reactions during a single microwave experiment. [15,16]

BENEFITS OF MICROWAVE ASSISTED SYNTHESIS

By using microwaves, the reaction can be accelerated, yielding better yields and purity, produced more evenly over longer periods of time with less energy consumption, processed through heating to increase reactions' reproducibility, and synthetic routes are made cleaner. Organic synthesis can be made easier by using microwaves, as it accelerates chemical reactions up to 1,000 times faster than traditional heating methods. Due to the higher temperatures in the microwave than in a conventional heating system, reactions are typically faster and can occur in less than ten minutes. By using microwave irradiation, the yield is increased while the formation of side product is reduced, leading to improved purity. The result is that the process is accelerated and made more effortless to purify. During microwave synthesis, aspirin is produced at a higher rate of 85% and 97%.[17]

The utilization of microwave radiation for heating results in a considerable reduction in energy consumption.

Energy is conserved when using microwaves to heat up the sample, as the entire apparatus does not require heating. The usual method involves heating the solvent and then filling the oil bath's walls with it. A temperature difference between the solvent and the walls of an oil bath is caused by distributed heating. Microwaves are used to heat the solvent and solute mixture until a uniform temperature is reached. The use of microwaves to heat compounds can result in reduced or eliminated solvent usage, which is a key factor in the chemical reaction. The syncing process is considered to be environmentally and economically sustainable, as it is accomplished through a solvent-free method that incorporates reagents on mineral support.The uniformity of the heating in microwaves allows for more precise reactions, allowing for better control of process parameters. Temperature monitoring is a straightforward method for monitoring chemical reactions. [18,19]

LIMITATIONS OF MICROWAVE ASSISTED SYNTHESIS

A few grams is the equivalent of using the microwave equipment available in the market. The scalability of microwave equipment can still be improved, despite recent advancements in the field. Materials that absorb heat are not suitable for microwaves as they do not provide sufficient heating. The incompressible nature of sulphur means that microwaves cannot warm it up, as it is exposed to radiation. The uncontrolled occurrence of radioactive decay can be caused by the reaction of too many radioisotopes in microwaves, which cannot be controlled due to their reaction speed. The damaging effects of polar acid-based reactions can be observed, such as the destruction of polymer vessels used for heating by microwave irradiating concentrated sulphuric acid. The uncontrolled occurrence of explosive reactions in high-pressure conditions can be caused by microwave reactions. Health risks are associated with microwaves as they penetrate through. The range of high frequency microwaves extends beyond the human skin to reach bodily organs, while low frequency ones are restricted to human flesh. Microwaves have been found to cause complete deterioration of body tissues and cells over extended periods. [20,21,22]

METHODOLOGY

The synthesis of paracetamol by using its derivative Acetyl chloride a classic organic chemistry experiment. Below is a detailed experimental procedure:

Materials and Reagents:

P-aminophenol
Acetyl chloride
Conc. HCL
Ethanol (C2H5OH)
Equipment
Reflux apparatus
Erlenmeyer flask
Suction filtration apparatus
Analytical balance
Beaker
Watch glass.

Figure No .2: Chemical reagents

APPLICATIONS OF MICROWAVE ASSISTED SYNTHESIS

To speed up the chemical synthesis process, it is necessary to use microwave irradiation. By utilizing microwaves, synthetic products can be made more pure and easily available, while also increasing yield through faster reactions. Additionally, the availability of high-capacity microwave equipment has enabled experiments to be conducted that yielded results ranging from milligrams to kilograms without altering reaction parameters. Drug discovery can be made through synthesis that is produced using microwaves. The use of microwaves in organic synthesis is the most researched method, with many experiments already being conducted to prove their effectiveness. During this stage, lead compounds are utilized by chemists to create multiple candidate drugs. Organic synthesis can be achieved through the use of these methods in diverse circumstances. Oxidation of hexane nitrile leads to a 200 % increase in yield and hydrolysis of the polychloric acid (cycloheXene) is increased to 150 percent by using microwave batch reactor.

The use of sealed, transparent containers for solvent heating through microwaves allows for organic synthesis at pressures that are higher than traditional methods. By keeping the container tightly closed, the reactor pressure can be raised, enabling the reaction to occur at significantly higher temperatures. Organic synthesis initiated by microwaves is greatly expedited due to the high reaction rate. The use of microwaves for amplification of reactions has resulted in the creation of organic synthesis that is both eco-friendly and solvent-free. The solvent-free organic syntheses can be classified into three groups:

feed-down reaction with reactants;

solid phase transfer catalysis (PTC)

solid mineral supports.

Were made using microwaves. Without the use of solvents, superior yields were achieved by synthesizing A3B and A4 type mesoporphyrinic complexes through microwave irradiation. [23,24, 25]

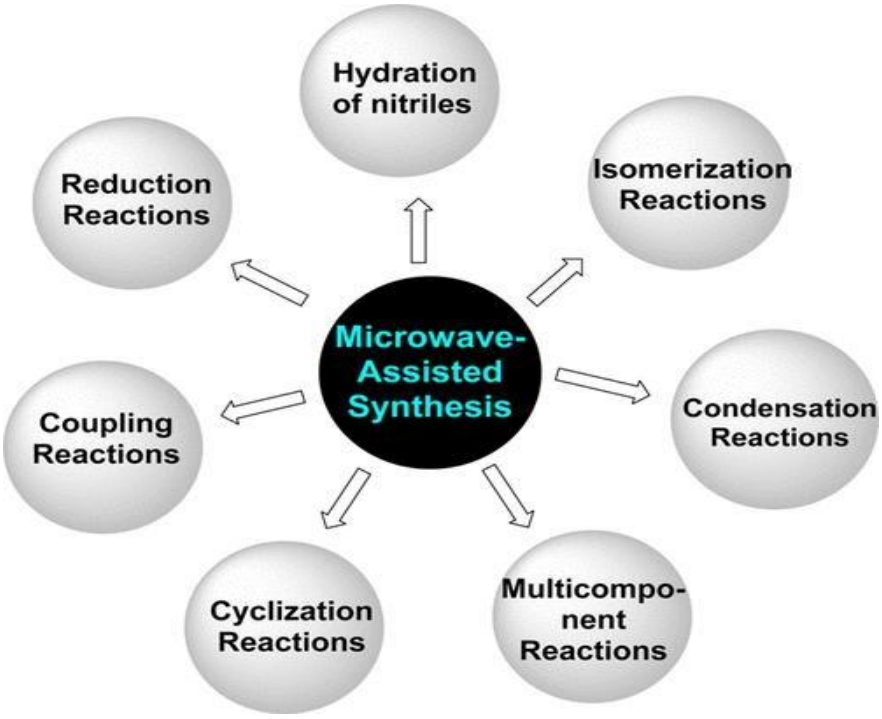
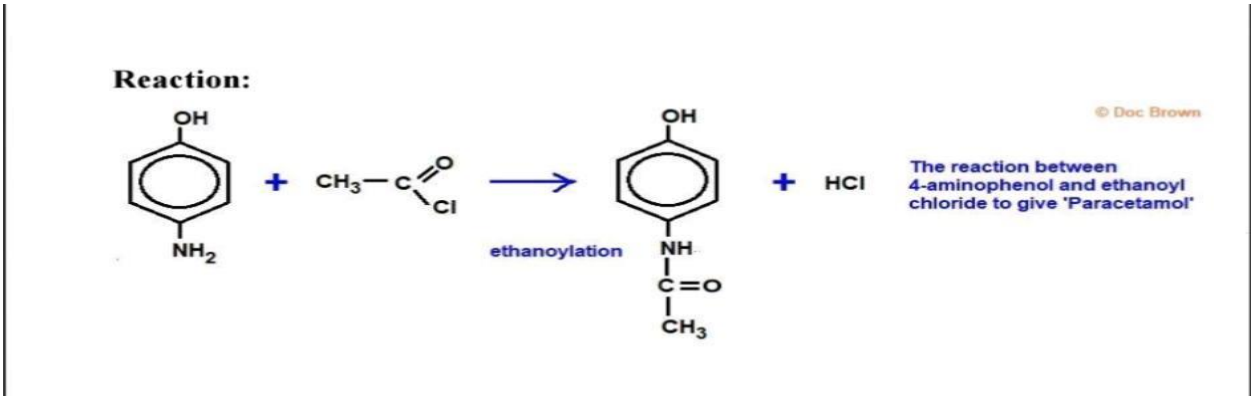


Figure No.3: Applications of microwave assisted synthesis

Reaction

P-aminophenol **Acetyl chloride** **Paracetamol**



Experimental Work

Synthesis of paracetamol (microwave oven) Procedure

Mix in 2 ml of pure acetyl chloride and add approximately 2 grams para–amino phenol to a beaker.

Cover the mouth of a tripod beaker and place it in ice in an oven at 100 W for 3 min, or at varying power levels (30% likely below level3), 70°C, for five min.

A 4-minute period at a temperature of 90°C is also acceptable. Allow the contents of the flask to cool completely before pouring into a beaker I filled with 30 ml of cold water and stirring with ice chips.

To obtain the unrefined product, it is passed through a Büchner funnel using suction and washed with cold water.

Then, dry it either by placing it between the filter paper folds and air-drying or by using an electric oven on 100°C.

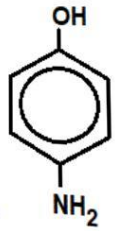
Recrystallization can be achieved by dissolving the crude product in 70% (v/v) ethanol and heating it to 60°C, followed by adding 1 g of powdered animal charcoal to remove the yellow or orange stain.

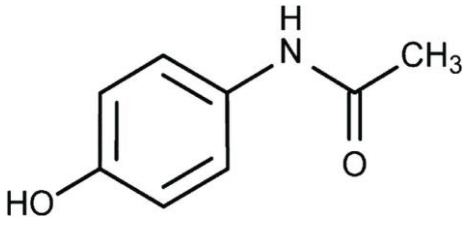
Ensure that the filtrate is concentrated and thoroughly cleaned over a water bath [26]

Calculation

Here limiting reagent is p-aminophenol; hence yield should be calculated from its amount taken.

P-aminophenol **Paracetamol**





C6H7NO
= 12× 6 +7×1+14×1+16×1.
= 109 g/mole.

C8H9NO2
=12×8+1×9+14×1+16×2
= 151g/mole

109g P-aminophenol=151g of paracetamol

2 g P-aminophenol=X g of paracetamol

Theoretical yield = 151×2÷109×X

Theoretical yield = 2.77 g

Practical yield = 2 g

Percentage Yield = (Practical Yield)/(Theoretical Yield) x 100

= 2/2.77×100

=72%

Figure No.4 Product of Paracetamol

Uses

It is a potent pain reliever for antipyretic purposes. Increased pain threshold and activation of the hypothalamic thermoregulatory center are responsible for the antipyretic effect and analgesic effect, respectively.

Moreover, it has been demonstrated to be advantageous in conditions characterized by pain, discomfort and fever, such as colds and other viral infections.

It has been shown to be useful in reducing pain associated with various forms of arthritis and rheumatoid diseases, as well as headaches, dysmenorrhea's, muscle discomfort [27]

Physico-chemical characteristics

Appearance white amorphous powder

Melting point :169°C

UV Experimental Work:

UV characterization of paracetamol in accordance with concentration involves using UV-visible spectroscopy to analyse how the absorbance of light changes with varying concentrations of paracetamol in solution. Here's how it typically works: UV characterization of paracetamol involves establishing a calibration curve relating absorbance to concentration using UV-Vis spectroscopy, which allows for accurate determination of paracetamol concentrations in solutions.

UV characterization Procedure

Preparation of standard solution

10 mg drug was dissolved in 15 ml methanol and was shaken well.

Then 85 ml water was added to it to adjust the volume up to 100 ml (100 ppm). From that 5 ml was taken and volume was adjusted up to 50 ml with

Preparation of test solution

20 tablets were weighed and powdered. Powdered tablet equivalent to 100 mg of paracetamol was weighed and taken into 100 ml volumetric flask then 15 ml of methanol was added and shaken well to dissolve it after that 85 ml of water was added to adjust the volume up to 100 ml. From that 1 ml of solution was withdrawn and taken in 100 ml volumetric flask. The volume was adjusted with diluent up to 100 ml.

Calibration Curve

Measure the Absorbance of Standard Solutions: Set the UV-Vis spectrophotometer to the wavelength where paracetamol derivative has its maximum absorbance (usually around 230nm).

Zero the Spectrophotometer: Use a blank solution (solvent only) to zero the spectrophotometer.

Record the Absorbance: Measure and record the absorbance of each standard solution at the determined wavelength.

Plot the Calibration Curve: Plot a graph of absorbance versus concentration for the standard solutions. The plot should be a straight line (Beer's Law plot). [28,29]

RESULT

Sr. no	Observation	As per IP	Result
1	Colour	White	Whitish blue
2	Appearance	White amorphous powder	White amorphous powder
3	State	Solid	Solid
4	Solubility	Soluble in water	Soluble in water
5	Odour	Odourless	Odourless
6	Melting point	168°C	168°C

Table No.1.: Evaluation Test

IDENTIFICATION TEST

Basic tests for pharmaceutical substances

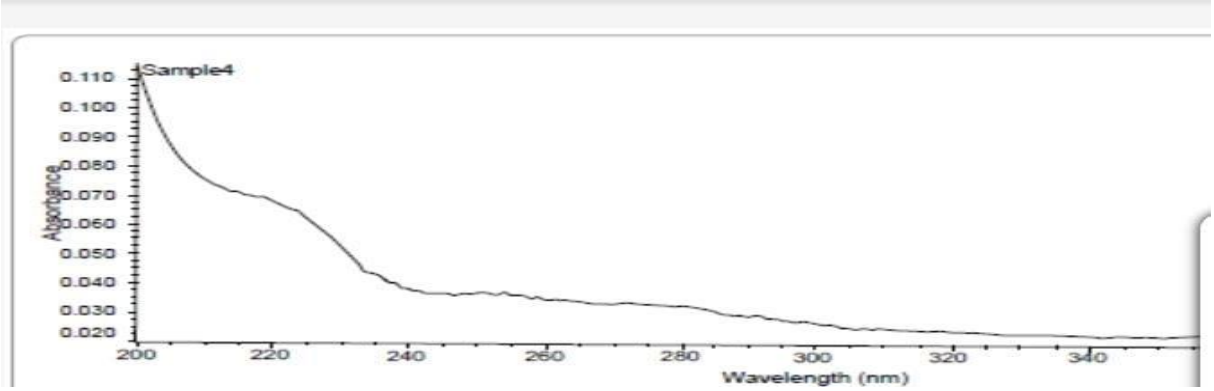
Sr No	Test	Observation	Inference
1	Test 1: Dissolve 0.1 g paracetamol in 10 ml water Add 0.05 ml ferric chloride solution.	Violet blue colour is produced	Test is positive
2	Test 2: Boil 0.1 g of paracetamol with 1 ml HCl for 3 min. Add 10 ml water & cool, no ppt produced. Add 0.05 ml 0.1N potassium dichromate.	A violet colour slowly develops which don't become red	Test is positive

Table No.2.: Identification Test

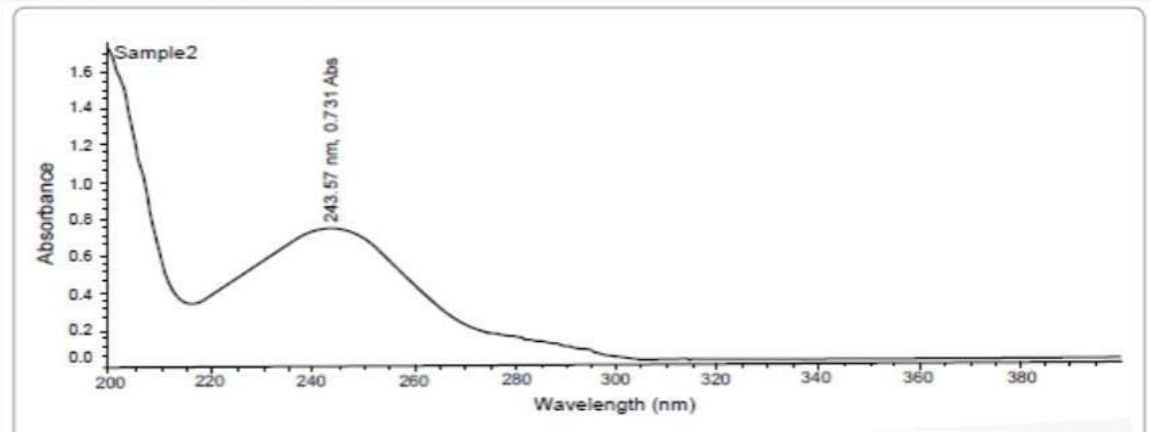
UV CHARACTERIZATION

Sr No	Concentration	Absorbance	Wavelength
1	0.2 ml	1.7	243nm
2	0.4 ml	0.11	221nm
3	0.6 ml	1.6	240nm
4	0.8ml	1.6	240nm
5	1 ml	0.006	218nm

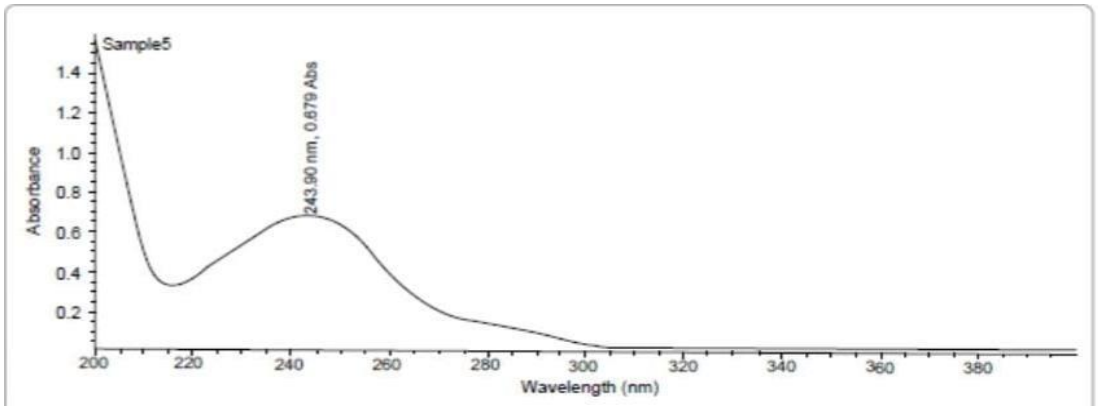
Table No.3.: UV Spectroscopy Characterization



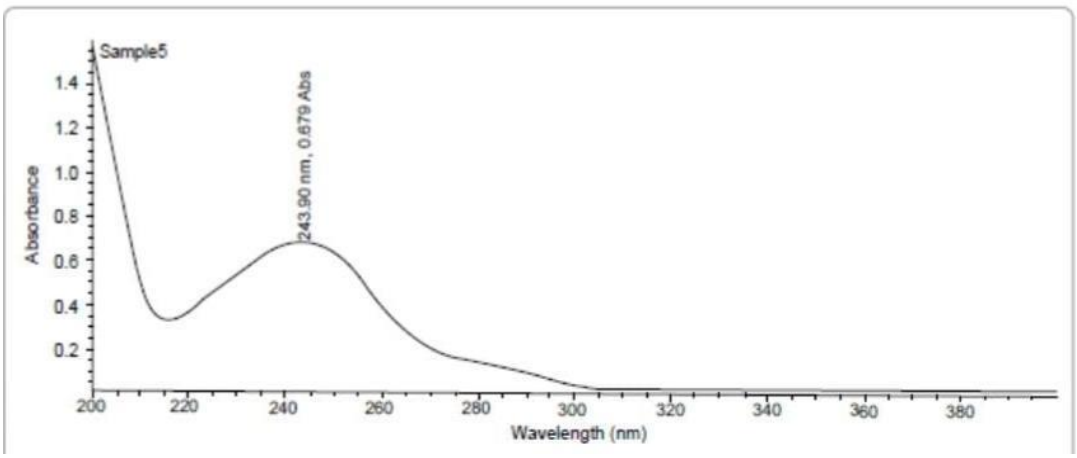
Graph No.1:0.2 ug/ml Concentration of Sample



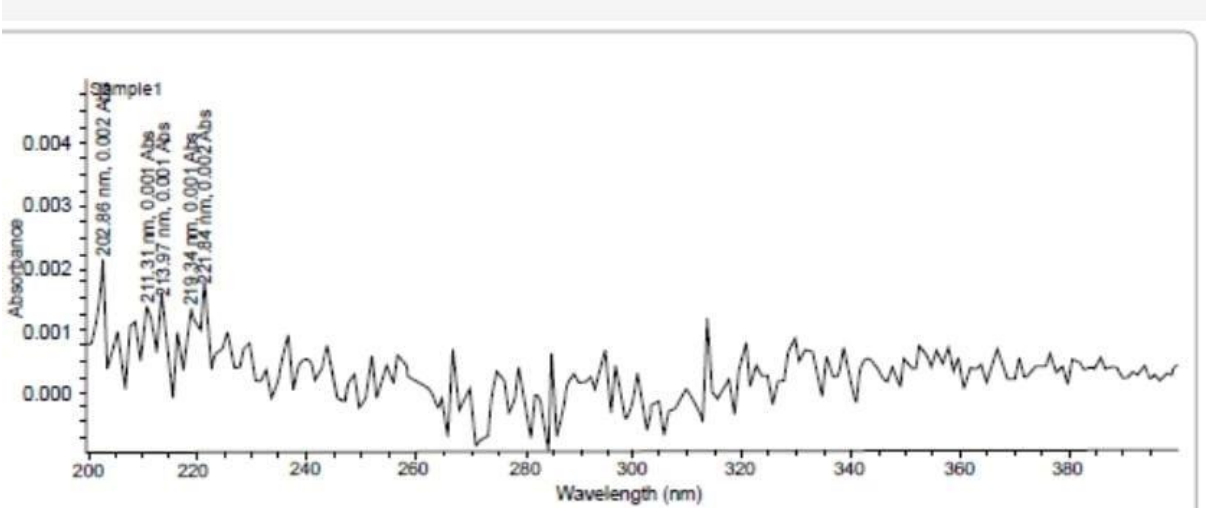
Graph No.2:0.4 ug/ml Concentration of Sample



GraphNo.3:0.6 ug/ml Concentration of Sample



GraphNo.4:0.8 ug/ml Concentration of Sample



GraphNo.5:1 ug/ml Concentration of Sample

DISCUSSION

Microwave-assisted synthesis of paracetamol from p-aminophenol using acetyl chloride offers a modern and efficient approach to producing this widely used pharmaceutical compound. The method leverages the advantages of microwave irradiation to achieve faster reaction rates, higher yields, and potentially greater purity of the final product compared to traditional synthesis methods. This makes it a promising technique for both research and industrial applications in pharmaceutical manufacturing

CONCLUSION

The convenience of synthesis in green chemistry is due to the use of microwaves. Microwave irradiation is an effective way to use it as the heat source of chemical synthesis, significantly shortening the reaction times of many synthetically useful chemical transformations. To enhance the technology, it is necessary to replace traditional microwave ovens with devices that produce precise measurements and pose minimal safety risks.

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