International Journal of Pharmacy and Pharmaceutical Science

ISSN Print: 2664-7222
ISSN Online: 2664-7230
IJPPS 2024; 6(2): 149-156
www.pharmacyjournal.org
Received: 06-08-2024
Accepted: 15-09-2024

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Microwave assisted synthesis: An eco-friendly green chemistry approach of drug synthesis

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DOI: https://doi.org/10.33545/26647222.2024.v6.i2b.135

Abstract
One of the main disadvantages of Pharmaceutical Industries utilizing conventional method of Drug Synthesis is utilization of large amount of energy and producing multiple by-products. Modern approaches of synthetic chemistry focus on minimizing the utilization of the energy and reducing Carbon foot-print which in turn reduces the environmental burden. This is technically called Green Synthesis. There are multiple principles of Green Chemistry which streamlines the synthesis process to emphasize sustainability. Microwave based synthesis, flow reactors, ultrasonic wave assisted synthesis are among three major pillars of Pharmaceutical Green Chemistry. This chapter focusses on Microwave based synthesis as a major approach to reduce the carbon footprints in Pharmaceutical Industries. The reduction in energy consumption is mainly due to three major principles, namely dipolar polarization, ionic conduction and dielectric loss. This results in rapid heating by synthetic microwave ovens. In-spite of all these advantages, close monitoring of the synthesis is often practicable because local hot and cold spot formation leads to explosion of volatile solvents. Multiple drug moieties like quinolines, paracetamol, aspirin, dihydropyridines can be synthesized by this method in Pharmaceutical Industries.

Keywords: Microwave assisted synthesis, green chemistry, sustainable chemistry, paracetamol synthesis, phenytoin

Introduction

In today's world, the primary focus of nearly all the researchers and scientists is to reduce the environmental impact and protect the natural resources from depleting [1]. Natural resources are of mainly of two broad categories, namely renewable sources like air, water, wind and non-renewable resources like coal, petroleum, natural gas [2, 3]. It is high time when the non-renewable natural resources are restricted from permanent depletion and to prevent its excessive usage and wastage indiscriminately [3, 4].
Pharmaceutical Industries, especially the Research and Development and Drug synthesis aims at synthesizing desired drug moieties or complex organic moieties in the laboratory. It aims in use of several chemical and huge time to synthesize the desired product, that too in a quite low yield. This method of synthesis is called conventional mode of synthesis [5,6]. Considering the environmental aspect, the conventional mode of chemical moiety synthesis is often quite hazardous and have negative impact on the environment. The main disadvantages are [6]:

1. Long synthetic step increases energy requirement.
2. Hazardous starting material.
3. Complex and toxic by-product formation.
4. Reduced yield of the product.
5. Complex procedure of synthesis.
6. Increases Carbon footprint.

These limitations are encompassed in the principles of Green Chemistry. One of the main approach of introducing Green Chemistry in Pharmaceutical industries is usage of microwave radiations to perform the chemical synthesis to reduce the negative impact on the environment.

Green Chemistry

Green Chemistry as the term suggest is comprised of two main words, Green and Chemistry. Green represents eco-friendly or environment friendly and Chemistry represents any chemical synthesis or complex synthetic steps [7]. Thus, encompassing both the words, Green Chemistry can be stated as any synthetic procedure of large complex molecules, which aims at reducing the energy consumption and increasing the yield of the products. Listed below are the main aim of Green Chemistry [8].

a) It eliminates the use and generation of toxic chemical
b) Reduces energy consumption
c) Synthesize chemicals of higher yield
d) High purity product synthesizes
e) Use of safer reactants

Principles of Green Chemistry

The concept of Green Chemistry is described by twelve main principles namely [9-11]:

a) Reducing waste generation
b) Increase atom economy
c) Use of less hazardous chemical for synthesis
d) Synthesis of safer products
e) Use of safer solvent and auxillaries
f) High energy efficiency
g) Using renewable feedstocks
h) Reduction in additional steps
i) Using catalysts
j) Biodegradable product design
k) Real time monitoring for pollution prevention
l) Accident prevention

Reducing waste generation [12, 13]

According to Green Chemistry, it is better to prevent generation of waste than to clean it, so it prevents generation of waste and follows Zero-waste technology. Waste product of one system can be utilized as raw material of other. The waste generation is determined by E-factor. Environmental factor (E factor) = $\frac{Mass\ of\ waste}{Mass\ of\ product}$. Lower E value, better the synthetic route and less the waste generation. It aims in design of routes that reduces number of side-products. Fig 1 represents two distinct methods of synthesis of benzyl alcohol from benzaldehyde. The second process has lower E value and hence is more preferred.

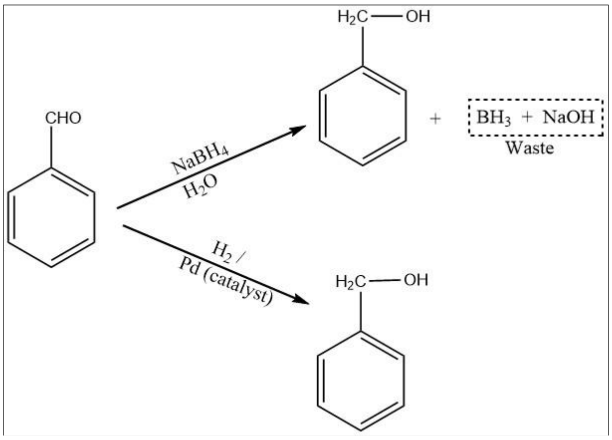

Fig 1: Synthesis of benzyl alcohol from benzaldehyde

Increase in atom economy [14-16]

Green Chemistry emphasize on maximizing incorporation of all reactants to final product. This increases the atom economy. Atom Economy is measure of atoms present in the starting material to the atoms present in final product. $AE = \frac{mass\ of\ atoms\ in\ desired\ product}{mass\ of\ reactants} \times 100\%$. Lower atom economy signifies More by-product and More waste. Thus, more hazardous chemical production occurs. Higher atom economy is preferred. AE is better measure of reaction efficiency than yield. Example: BHC process of ibuprofen synthesis is preferred over Boot's synthesis [16]. It is represented in Fig 2.

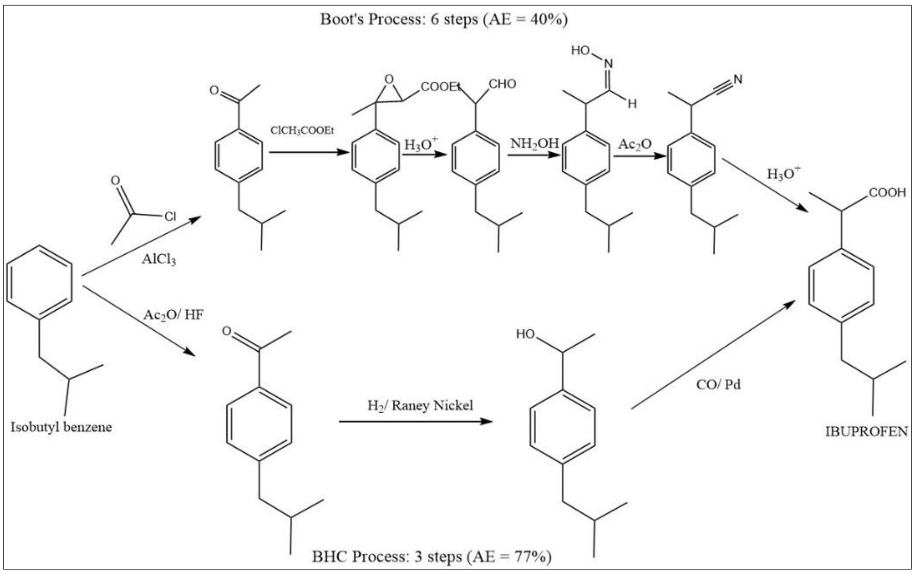

Fig 2: Two major approaches of synthesis of Ibuprofen

Use of less hazardous chemical for synthesis

Another aim of Green Chemistry is 'Production and synthesis of chemicals from compounds that have less toxicity'. Prevents use of reagents that are toxic. 'Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.' It emphasizes on use of sustainable, nontoxic chemical [17]

1. **Example:** The use of a very poisonous gas, carbonyl chloride, is replaced by the use of less hazardous diphenyl carbonate in the synthesis of the polycarbonate, bisphenol A. It is represented in Fig 3 [18, 19].

2. **Example:** Benzene was used to prepare adipic acid. It is VOC and is carcinogenic. It is replaced with glucose in adipic acid synthesis.

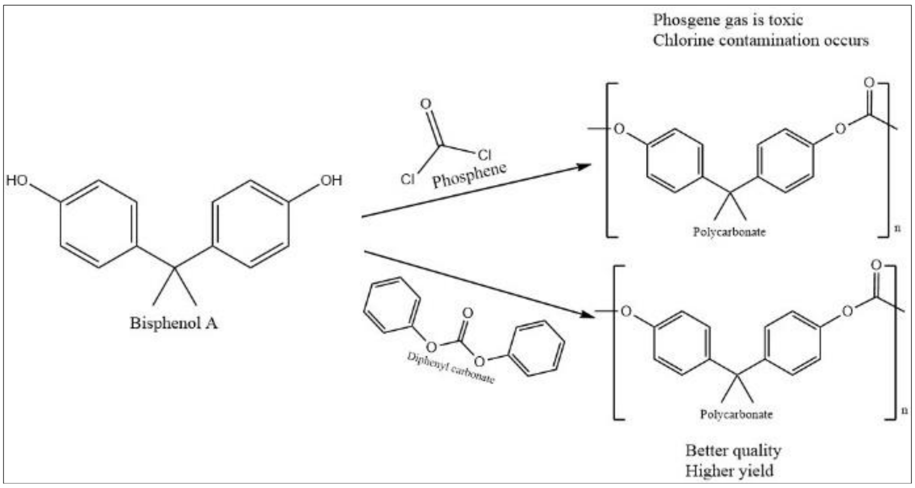

Fig 3: Synthesis of bisphenol A in two distinct methods

Synthesis of safer products [9, 20]

The fourth principle of Green Chemistry emphasizes on the products formed. It states that 'wherever practicable, the products that are synthesized should have negligible or no toxic effect on human health.' It modifies the reaction strategy but preserve efficiency of the compound without any toxicity and make optimum relationship between toxicity and efficacy of the molecule. It designs of safer chemical mainly require knowledge of how molecules act in body.

Example: Pesticides are generally toxic. So, synthesis of pest specific pesticide is done. Tributyl tin oxide was replaced with DCOI as anti-foulant in ships as represented in Fig 4.

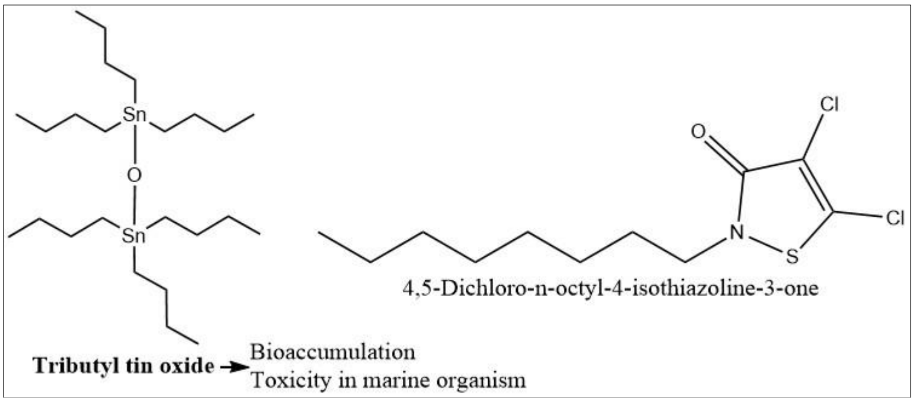

Fig 4: Anti-foulant in ships based on Green Chemistry

Use of safer solvent and auxillaries

The term safer solvent and auxiliaries encompass any compound that directly is not involved in chemical reaction but is required. Solvents often are volatile organic compounds (VOC) and causes environmental and health hazards and toxicity [21]. The role of solvent is to dissolve the chemical reactant and break bonds to form the new product. Solvents are of three categories [22]:

1. Preferred: Water, ethanol, glycerol
2. Usable: Cyclohexane, heptane, toluene,
3. Unusable: Pentane, diethyl ether (low flash point), chloroform benzene (category 1 carcinogen, toxic), Carbon tetrachloride (category 3 carcinogen, toxic, ozone depletory)

Green Solvent are the solvent which are used with a goal to reduce toxicity of the environment imparted by solvents used in chemical synthesis [23]. This include any solvent that satisfy the following criteria [24, 25]

1. Human safe,
2. less toxic,
3. biodegradable;
4. understood environmental fate;
5. high yield

Example: Water, Methanol, Acetone, Ethanol [26, 27]

High energy efficiency [9, 28]

High energy requirement produces negative environmental effects. Energy requirements should be minimized. Such process should be planned that uses minimum energy for reaction to complete. Since energy source is non-renewable, energy utilization should be limited. Moderate and ambient temperature requiring reactions should be encouraged.

Different approaches or reducing the energy requirement are:

(a) Reflux under heat which increases the vapour pressure causing faster reactions
(b) Reuse of waste heat for heating other medium
(c) Use of microwave based heating than conventional heating
(d) Preference for photochemical reactions (solar radiations)

Using renewable feedstock [9, 10]

A raw material or feedstock should be renewable in nature. Non-renewable sources of starting reagents like petroleum source based reagents should be discouraged. These being non-renewable depletes over time. Fossil resources are not renewed in a time and will unable to fulfill growing demand over time. So, renewable sources of feed stocks should be used. It includes [29, 30]:

Biomass: Biomass produced is 180 billion metric ton/ year but only 4% is used. These biomasses can be used for organic synthesis.

1. **Carbohydrate:** Sucrose, glucose, cellulose can be processed
2. **Lignin:** Nature's richest source of aromatic carbon. Used in polymers, adhesives, production of phenolic chemicals.
3. **Fats, protein, terpenes:** Converted into polymers, lubricants, and detergents.
4. **Bio-diesel:** Alternate to petroleum for transportation
5. **Bio based plastics:** Polylactic acid – made from corn and potato stocks

Example

a) Green synthesis of adipic acid from glucose
b) Synthesis of furfural from biomass

Reduction in additional steps [9]

The reaction procedure which increases number of steps should not be practiced until necessary. Use of protecting group leads to use of deprotection and adds on to the number of addition steps. Thus, use of derivatives causes additional steps which forms additional by-product and additional waste. This reduces atom economy. Simple reaction is encouraged. As given in Figure 2, BHC process have less number of steps and derivatives while synthesis of Ibuprofen and hence is encouraged

Using catalyst

Catalyst are the substances that increase the rate of reaction. In green chemistry, catalyst are important because [31-32]:

a) Increases reaction rate
b) Requires less heating or energy. Thus, increases energy efficiency
c) 100% AE as catalysts are fully recovered
d) Increases yield of the synthesis
e) Reduced production of by-products are catalysts are specific
f) Reduces number of steps of reaction

Biodegradable product design [9]

The main aim of Green Chemistry is not to use renewable sources for synthesis, since it depletes natural resources, similarly the product synthesized should be biodegradable. With time it should be degraded in nature without causing any toxicity. Plastics cause bioaccumulation while pesticides like DDT also accumulates, antibiotics build up in our water bodies. The products should be so designed that it degrade with time by action of water, light or microorganism to harmless degraded derivatives.

Real time monitoring for pollution control [9, 10]

The analysis of the reaction procedure with time should be established. Thus, further on repeating reaction, steps in each case can be monitored. It aims at developing analytical procedure for in-process monitoring and control. This will prevent any unknown accidents or waste generation. Proper planning for the reaction will also increase the atom economy with minimum energy resource.

Accident prevention [9, 10]

Substances or reagent chosen should have low inclination of explosion or catching fire. This can prevent accidents to occur, which will create higher waste. Volatility and flammability of Gas> non-volatile liquid> solid. Using solid reagents generally reduce accident chances. Highly exothermic reactions causing toxic fume release should be discouraged.

Microwave Assisted Synthesis

Microwaves are electromagnetic radiations that have wavelength shorter than radio waves but longer than infrared radiation [33].

1. **Wavelength of Microwave:** 1 mm – 1 m.
2. **Frequency of Microwave:** 300 mHz – 300 GHz.
3. **Frequency used:** 2.45 GHz – Others used in RADAR and other communication.

Ultraviolet rays have wavelength much shorter than Microwaves, but are not used. UV rays are absorbed by the sample and the same frequency is emitted out without any heating. But Microwave radiation causes energy transfer and heating. Thus, microwave radiations are used [33].

Microwave based chemical reaction is a type of green synthesis chemistry, which utilizes the following:

1. Increases energy efficiency because of faster reaction which reduces energy consumption
2. Uses solvent free or green solvent synthesis focusing use of safe solvent and auxiliaries
3. Minimize number of by-product emphasizing on reducing waste value

Mechanisms of heating [34 – 36]

Microwave assisted synthesis mainly follows three methods of heating. These are:

Dipolar Polarization

Microwaves are electromagnetic waves (oscillating). This method is applicable for polar molecule. The main action of heating is, microwave have alternate crest and trough, with the crest and trough the solvent molecule tries to align with wave and thus, rotates the polar molecule. Molecules rotated in contact and causes inter-molecular friction. Thus, it generates heat.

- For wavelength < Microwave: Higher frequency of oscillation: Unable to rotate the molecule with alternate crest and trough. So, energy absorbed then released
- For wavelength > Microwave: Lower frequency, which causes delayed crest and trough and hence forms less rotation. This causes less friction and insufficient heating.

The process of dipolar polarization is illustrated in Fig 5.

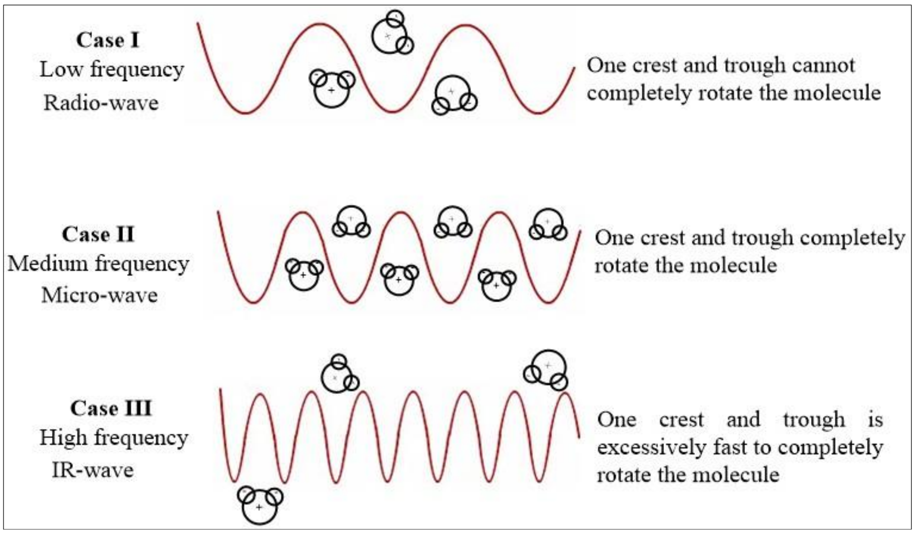

Fig 5: Dipolar Polarization

Ionic conduction

This method is applicable for free ions. Microwave radiation are oscillating waves with alternate crest and wave. Thus, ions tries to align with waves and in response to aligning, undergoes to and fro motion of ion which causes vibration and collision. This results in friction and heat generation

Dielectric Loss

Molecules absorb electromagnetic radiation and thus move to excited state. The molecule remains in excited state for a certain time and then release energy by thermal deactivation. Then it moves back to ground state and emits energy in form of heat.

Distinction with conventional heating [36, 37]

Conventional heating occurs by contact of heating vessel with the heating source.

Conducting vessel comes in contact of heat source. This in turn heats the container and conduct heat to solution. Thus, finally it heats the solution. The following are the properties of conventional heating

- Reaction vessel is heated first
- Outside – in type heating
- 10% heat transfer from each stage (container to solution)
- Higher energy loss
- Higher energy consumption
- Higher reaction time

Microwave heating uses microwave radiation proof vessel, which is transparent over microwave radiation

Microwave radiation penetrates through vessel. It causes dipolar polarization/ ionic conduction of the solvent and reagent and causes localized super heating and transfers the heat to the solution

- Heating based on molecular vibration and rotation
- The sample and solvent is heated first
- Inside – out type heating
- No loss of energy during heat transfer
- More efficiency

There is one major limitation of microwave-based synthesis [38, 39]:

Microwave radiations meets at one point and heats the solvent. This causes localized hotspot. Heat from hot spot transmit to the areas of cold spot and hence causes irregular heating. Solvent with low vapour pressure hence gets heated at a point at high rate which causes explosion.

Types of Solvent Free Microwaved based synthesis

Due to chances of solvent explosion, solvent free synthesis is often encouraged. The reagent themselves react to form product. This eliminates the hazards, volatility, explosive chance of solvent. Due to uncontrolled reaction conditions involving volatile reactants and/or solvents is eliminated

The types are [40]:

1. Reactions using at least one liquid polar reagent: Nucleophilic substitution of trichloro triazine
2. Reaction using supported reagent in dry media: Deacetylation of benzaldehyde diacetate
3. Reaction using phase transfer catalyst
4. Advantages of solvent free synthesis are [40]:
5. Radiation directly absorbed by substrate
6. More energy efficiency
7. More rapid reaction
8. No chance of explosion by VOCs
9. Enhances selectivity of reaction

Pharmaceutical Application of Microwave Synthesis

Multiple drug moiety is now synthesized by microwave methods in place of conventional method. Though there is difficulty in scaling up, but major approaches are been incorporated to avoid the problem of scaling from lab to industrial scale. Research and development team utilizes conventional method of synthesizing drugs during initial phase. This synthesis is being modified in the bench scale to

Green Chemistry principle to increase the efficiency of energy and increase renewability. Multiple drug can be synthesized by Microwave synthetic method, but only few are represented in this chapter.

Phenytoin, which is a hydantoin derivative acts as a CNS depressant can be synthesized in both of the ways. Conventional synthesis employs ethanol as the solvent while microwave assisted synthesis does not use any solvent. Instead, microwave synthesis uses aqueous solvent for synthesis. The two hours reflux step is reduced to almost to ten minutes in case of microwave-based synthesis [41]. This is illustrated in Fig 6A.

Aspirin, an non-selective NSAID can be synthesized in both the ways. In conventional method, aspirin is synthesized by utilizing acetic anhydride and salicylic acid. Reflux of one hour is done using concentrated sulphuric acid as a solvent. The microwave method is a faster approach of only seven minutes. At power of 175 watt, at aqueous medium, it forms aspirin. The percentage yield increased upto 30% in case of microwave method of synthesis [42]. The methods are represented in Fig 6B.

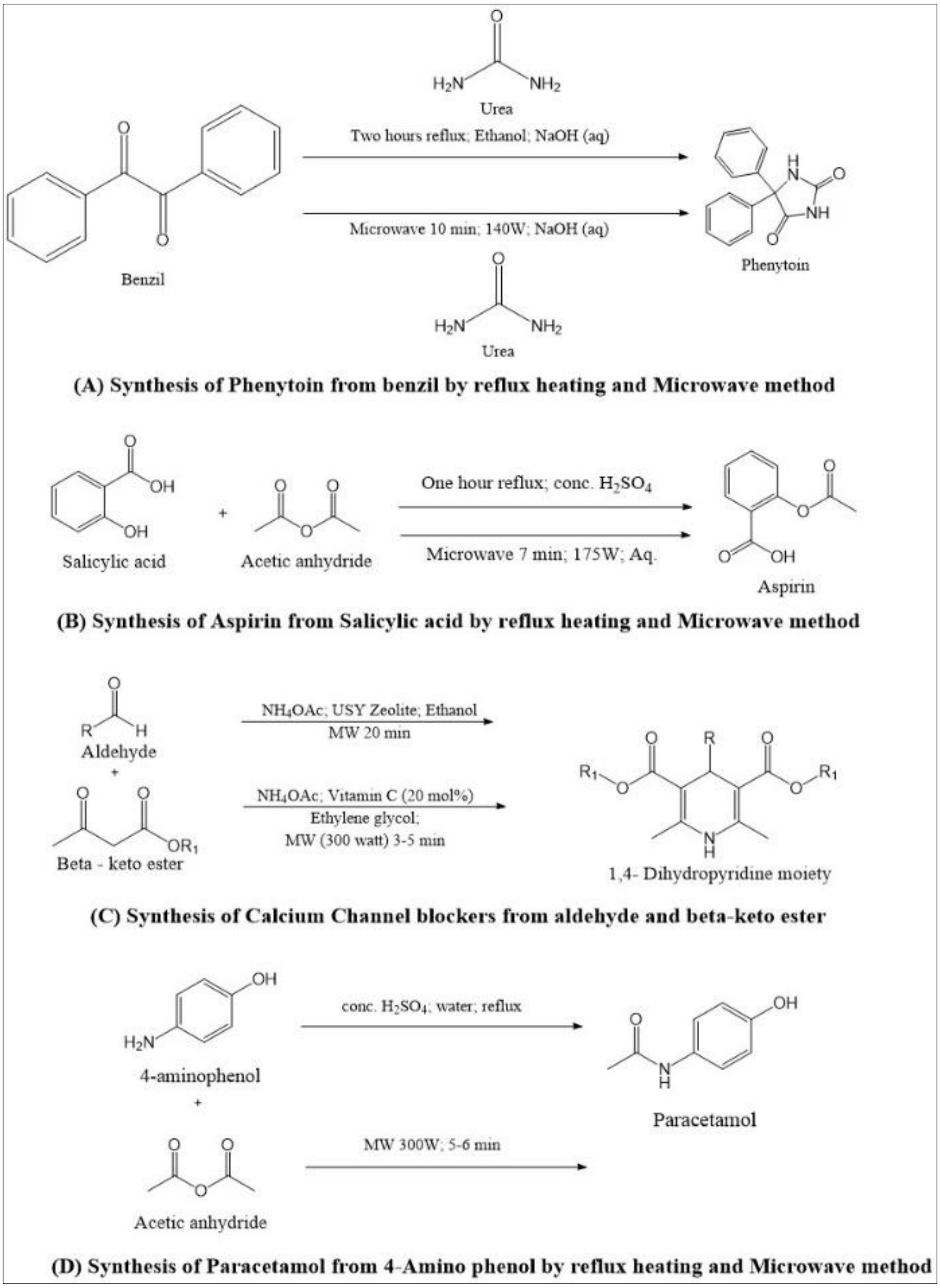

Fig 6: Examples of Pharmaceutical API synthesis by Microwave Synthesis

1,4-Dihydropyridines which are used as Calcium channel blockers and anti-hypertensive agents can be synthesized by Microwave based method. This complex method of synthesis can be performed by two ways, which both requires aldehyde and β −ketoester as its starting material. The two methods are distinctive due to the difference in the reaction conditions and solvents used [43, 44]. These routes are illustrated in Fig 6C.

a) Method 1 utilizes ammonium acetate and zeolite with ethanol for the reaction to happen and hence is a solvent free method of synthesis, where the reaction is supported on an adsorbent media. The reaction is accomplished in just 20 minutes
b) Method 2 is more energy efficient as it takes only 3-5 minutes microwave radiation. It also occurs in presence of ammonium acetate, but the catalyst required is Vitamin C. Ethylene glycol is used in this reaction.

Nifedipine, Nimodipine and other Calcium Channel Blockers are synthesized in this method.

Paracetamol is a commonly used Non-Steroidal Anti-Inflammatory Drug available as Over the Counter. Paracetamol is conventionally synthesized from p-nitro phenol in two step method [45].

The first step reduces p-nitro phenol to p-amino phenol by reducing agents like sodium borohydride. This step is followed by reacting it with acetic anhydride. Since product of one step is the reactant of next step, the product yield is more. In case of Microwave synthesis, p-amino phenol is subjected to acetic acid and microwaved for about 5-6 minute to form the product, paracetamol and is illustrated in Fig 6D.

Conclusion

Green Chemistry is also called sustainable Chemistry because of its aim to prevent excessive depletion of natural resources and reduce Carbon footprint. Microwave is used to reduce the energy consumption for heating and increasing the product yield. Microwave routes of synthesis of multiple Pharmaceutical drugs has been established and several routes of synthesis of several other complex organic molecules are yet to be developed.

Acknowledgments

We sincerely acknowledge Guru Nanak Institute of Pharmaceutical Science and Technology for giving us the opportunity to write the review paper.

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