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Role of Microwave in Pharmaceutical Sciences

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Abstract

Microwave chemical synthesis has become a method of choice for chemists through out many industries. The technology allows the synthesis to be done faster and cleaner with reduced solvent consumption as a "greener" process. Due to mass heating effect much faster temperature increase can be obtained depending upon microwave power. A variety of organic reactions can be done faster and with higher yield with microwave assistance. It allows less byproducts, high purity, selective heating, low energy input, green solvent, less solvent usage and software supported experiment documentation. Many active pharmaceutical agents(API) have synthesized using microwave assistance. For example, Trimethoprim, Albuterol and oxaprozin etc. In the synthesis of Albuterol, the different steps require prolonged heating. With microwave heating the rate of reaction and yields are significantly increased.

Keywords: *Microwave synthesis, drug discovery, pharmaceutical science.*

Introduction

Recently Microwave has shown a great potential in the field of pharmaceutical science. It has facilitated the drug discovery process and synthesis of many new chemical entities. A microwave is a form of electromagnetic energy which falls at the lower end of the electromagnetic spectrum between infrared and radio waves region with frequencies between 300MHz and 300GHz, corresponding to wavelengths of 1cm to 1m[1]+(Adam,2003).It is a form of energy which manifests as heat through its interaction with materials. The mechanisms in microwave assisted synthesis are dipolar polarization, conduction and interfacial polarization (wani et al,2014)Dipolar polarization is a process in which the heat is generated in polar molecules by interaction between polar solvent molecules (water, ethanol, methanol etc.) and interaction between polar structure molecules (hydrophilic polymer or carriers, etc.). When the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc.) are moved through the material under the influence of electric field, resulting in a polarization. These induced currents cause heating in the sample due to electrical resistance. Interfacial polarization can be considered as a combination of the conduction and dipolar polarization effects. It is significant for heating systems that comprise a conducting material dispersed in a non-conducting material. Microwave assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug development process as it dramatically reduces reactions times form days or hours to minutes or even seconds.

Advantages (Himanshu et l,2014: Honda et al,1998: Gedye et al,1986: Owivediet al, 2009)

- Uniform heating occurs throughout the material as opposed to surface and conventional heating process.
- Rapid volumetric heating.
- Desirable chemical and physical effects are produced.
- Floor space requirements are decreased.
- Better and rapid process control.
- High efficiency of heating, reduction in unwanted side reaction
- Low operating cost.
- Energy saving.
- Environmental heat loss can be avoided.
- Purity in final product.
- Improved reproducibility.
- Reduced wastage of heating reaction vessel.
- Selective heating i.e. heating selectively one reaction component.
- Superheating: conventional heating is done from outside, therefore the core of solvent may be as much as 5°C cooler than the edge, while in microwave, the core is 5°C hotter than outside, because of surface cooling, therefore in microwave, we can raise the boiling point of solvent by as much as 5°C, an effect known as super heating.

Disadvantages (Wani et al,2014)

- It is very difficult to set proper temperature for reaction to occur.
- It cannot be applied for heat sensitive materials.

Microwave synthesis in Drug discovery Hong Liu and Zhang,2011

In Molecular Imaging: In preclinical drug discovery, molecular imaging can help validate drug targets in assays of disease and select lead molecules in the chemistry optimization phase. For this radio-labelled pharmaceuticals are needed. Microwave technology can address the challenges of the rapid labelling of radiopharmaceuticals (Tones & lu,2008)

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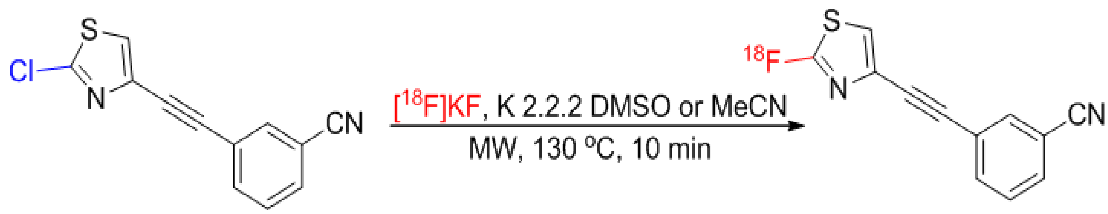
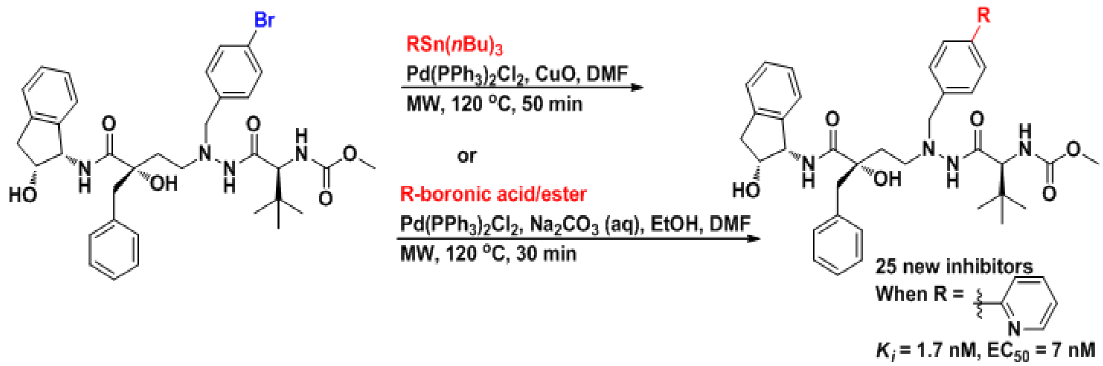


Sch-1.Microwave assisted rapid labelling of PET (Simeon et al, 2011)

Lead generation and optimisation: Microwave irradiation was used to accelerate a key step in optimisation of new potent HIV-1 protease inhibitors. With microwave enhancement, target compounds were synthesized using Stille or Suzuki cross couplings at 120°C for 30-50 min. all with retained (S)-configuration at quaternary carbon.



Sch-2. Microwave assisted Rapid synthesis of Target compounds (Hong Liu & Zhang, 2011)

Microwave combined with click chemistry: Simone R.D. et al., 2011, introduced microwave irradiation in 1,3-dipolar addition reaction (Click reaction) and after subsequent Suzuki cross coupling reaction, generated a library and provided a faster way to obtain desired final products in satisfactory yields. Biological evaluation of these compounds disclosed three new potential anti-inflammatory drugs.

Microwave combined with solid supported combinatorial chemistry: Microwave enhanced chemistry is ideally suited for combinatorial chemistry in drug discovery to rapid and automated preparation of a large number of compounds for optimization to new therapeutic agent. For example, Murray et al adapted Microwave irradiation to solid phase synthesis of β- peptides combinatorial library via a split-and – mix approach, which significantly reduced synthesis time and amounts of reagents (Murray et al,2011)

Microwave combined with soluble polymer supported combinatorial chemistry: Microwave heating has also been shown to significantly benefit the polymer-supported combinatorial chemistry. For example the synthesis of indoline substituted nitrobenzene on a polyethylene glycol (PEG) support and its further elaboration to structurally diverse benzene fused pyrazino/ diazepino indoles is recently disclosed (Liu et al, 2011)

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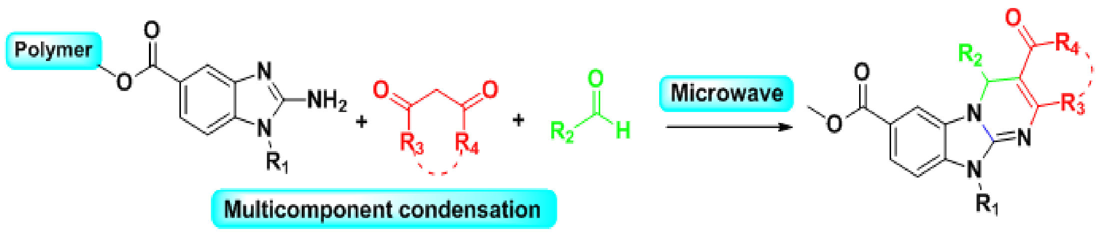
Microwave combined with MCR and parallel synthesis: In parallel synthesis, a highly reactive intermediate via a series of simple steps is usually synthesized and subsequently subject to a number of different reagents generating a library of compounds. Zhou et al. demonstrated the efficiency of library synthesis involving a multi component reaction, microwave heating and flourous separation in constructing four diversity points 1,4-benzodiazepine-2,5-diones (BZDs) library via a Ugi/de-Boc/cyclization/Suzuki strategy (Zhou et al, 2010)

Microwave combined with MCR and soluble polymer supported combinatorial chemistry: Microwave irradiation greatly accelerates the rate of all reactions while polymer support facilitates purifications by simple precipitation technique. This strategy dramatically increases the efficiency of the overall multistep synthesis(Hsiao et al,2010)



Sch-3. Multidisciplinary Synthetic approach for Rapid access of Molecules (Hsiao et al,2010)

Microwave for drug extraction: Microwave assisted extraction (Himanshuet al, 2010) (MAE) technique offers high and fast extraction of active constituents with less solvent consumption and protection for thermolabile constituents. MAE technique has been used to optimise the extraction of mucilages and pectins from different plant sources(Shrishailappa et al , 2009). Mattina et al have applied microwave assisted extraction to obtain taxanes from *Taxus* biomass (Mattina et al, 1997)

Advanced Microwave extraction system: The ETHIOS 1 is built to offer the highest performance and best safety features in the industry; it offers fast vessel heating together with homogenous microwave distribution through the cavity.

Microwave digestion: It is one of the standard sample preparation procedures for elemental determination in analytical chemistry. The great advantage of using a microwave field is the speed of heating the sample and the acid solution.

Microwave in synthetic chemistry: A common theme throughout all the phases of drug discovery process is speed. Greater speed provides a competitive advantage and allows for more expensive and limited sources, faster exploration of structure activity relationships(SARs), enhanced delineation of intellectual property and more timely delivery of crucially needed medicines. Kidwai[17] et al. have shown microwaves to be effective in the synthesis of the novel antibacterial β-lactams, quinolines and cephalosporin. Microwave irradiation has been applied for the synthesis of inhibitors of malarial proteases plasmapsin I and II.

Microwave in drying and sterilization: Microwave drying shortens drying times, reduce drying defects, increase the potential for product innovation and provide a seamless integration into automated manufacturing systems. Due to combination of vacuum and microwave heating, Pharma-Micro- a rotary vacuum microwave dryer and sterilizer, provide high quality drying and sterilization of any substances and materials at relatively low temperatures avoiding conventional drying problems.

Microwave thawing: One of the methods for thawing is the use of microwave. Stability of majority of drugs remains unaffected except for some preparations, thus providing criticism for microwave thawing.

Microwave used in pharmaceutical dosage development: The use of microwave has a strong implication in design of sustained release drug delivery systems such as matrix and coated tablet. The drug release property of a tablet is modified by the addition of a polymeric coat onto the matrix. The drying of the polymeric coat can be affected by microwave. The microwave dried film coat is more elastic, has more tensile strength than oven or air dried films and dry faster but possesses slightly low level of tensile strength than that dried using hot air current. Microwave is also being used to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, controlled released tablets formulation and tablet film coating (Himanshu et al, 2010)

Microwave in cancer therapy: The microwaves are also being used in the new technique of heat and kill cells containing high amounts of water and ions, or electrically charged atoms. Side effects appear to be minimal. This is known as microwave thermotherapy or microwave therapy to kill cancer cells(Science daily, 2007)

Conclusion

Microwave heating has gained a widespread acceptance both within academia and industry and blossomed into a useful technique in organic synthesis and drug discovery and development. With the rapidly expanding numbers of published examples and the readily available tips and tools that accompany commercial instrumentation the leap from traditional conditions to microwave heating is far less daunting. It also testifies to the growing popularity of microwave irradiation as an accepted tool in laboratories. The results show that microwave irradiation is more than just a method for performing reactions in a shorter time. The most interesting and spectacular results are yet to come. With its wide range of advantages, the use of microwave open new route to control the physicochemical properties and drug delivery profiles of pharmaceutical, dosage forms.

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