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Microwave Assisted Technology and its Role in Pharma Industry

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ABSTRACT

Energy is the basic source required for carrying out work. Current paper describes a brief review of microwave technique, its use in pharmaceutical sciences. Microwave technique are being a traditional method for drying, synthesizing, preparing, heating, etc . They are also used during organic synthesis. Microwave can be used as cross heating barriers which arrive due to preliminary, insufficient heating of the product resulting in an inappropriate product. The microwave energy ranges from 300MHz to 300GHz which is sufficient enough for heating and drying of pharmaceuticals. Microwave techniques benefits one with time management, high percentage of yield, faster process, clear chemistry.

Keywords: Microwave, drying, heating, application in pharmaceutical sciences

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INTRODUCTION [1,2]

A microwave is a form of electromagnetic radaiation, which falls at the lower band of the electromagnetic spectrum and is define as measurement of frequency as 300 - 300,000 MHz, corresponding to wavelengths of 1 cm - 1m Wavelengths ranging among 1 cm- 25 cm are comprehensively used for RADAR transmissions while remaining wavelength range is used for telecommunications.

Their are two main effects of microwave irradiation on meter which are famed as:

1. Thermal effects resulting from dipolar polarization and ionic conduction.

2. Electrostatic polar effects which lead to dipole-dipole type interactions between the dipolar molecules and the charges in electric field.

In this manner, more polar states appear to be more constant in the electric field. This phenomenon might be the source of precise non-thermal microwave effects.

The electric component causes heating by two mechanisms;

A] Dipolar polarisation

B] Ionic conduction.

Dipolar polarization mechanism

It is a process in which the heat is generated in polar molecules. Dipolar polarization can generate heat by either one or both the following mechanisms:

1. Interaction between polar solvent molecules (water, ethanol, methanol, etc.)

2. Interaction between polar structure molecules (hydrophilic polymer or carriers, etc.)

Ionic Conduction mechanism

Where the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc.) are stimulate through the material under the pressure of the electric field, resulting in a polarization. These generates currents which will cause heating in the sample due to any electrical resistance.

A lot of materials are transparent to microwaves i.e they do not absorb microwave. Examples of such materials are quartz glass and PTFE, which be able to be used as microwave windows. The most important property of microwave fields however is absorption of microwaves by the materials, as materials that absorb microwaves are heated.

The amount of microwave energy absorbed is expressed by the following equation:

$P = 2 \pi f v^2 E0 Er \tan \theta$

Where,

P - The power density of the material = energy absorbed (W/m^3)

f - Frequency (Hz) v - electric field (V/m)

E0 - dielectric permissivity of free space (8.85 x 10-12 F/m)

Er - dielectric constant of the material

tan θ - loss tangent

For a given material and a given electric field, $2 \pi f v^2 E0$ is constant, and the absorbed microwave energy is proportional to the term Er tanθ, called the loss factor. Materials with a elevated loss factor will eagerly absorb microwave radiation, while materials with a little loss factor are either reflecting or transparent for microwave radiation.

MICROWAVE V/S CONVENTIONAL HEATING:[2,3]

Traditional or conductive heating depends upon a thermal energy source directly applied to the reaction vessel. Conductive heating is not so efficient and slow but is broadly applicable and theoretically uncomplicated. Basically, conductive heating gets the chemist where they want to go. However, the inefficiencies of ramping-up to temperature, lack of fine control over the bulk reaction temperature and the time needed for the cooling of the bulk reaction all together impart disadvantages. The key point is that conductive heating of solutions has been the primary means of heating solutions during traditional synthesis chemists' training.

On the contrary, microwave heating can affect remotely, and is a rapid and for most is not therotically uncomplicated. Reaction solutions are heated via the direct coupling of microwave energy with either the solvent or molecular entities in solution followed by rapid loss of the energy in the form of heat. The microwave energy is much less than the usual bond-dissociation energies of typical organic moieties. Because microwaves travel at the speed of light they can be turned off instantly upon reaching the temperature set point of the reaction solution.

To heat efficiently the microwave energy must couple successfully with the reaction solvent of choice. Not all solvents absorb microwave energy equally well. In general solvents are categorised as high, medium or low absorbers and this in part characterises their ability to warm solutions via the absorption of microwave energy. The differential microwave energy absorptive rates for different solvents should not be viewed as a deterrent, as this technique allows for rapid reaction scoping and alternative reaction conditions can be rapidly identified.

ADVANTAGES OF MICROWAVE TECHNIQUES:

1. Rapid heating of large volume.

2. Denial overheating at surface.

3. Effective and rapid process control.

4. High heating efficiency.

5. Environmental heat loss avoided.

6. Energy saving.

7. Lower cost of operating.

8. Uniform heating occurs throughout the material as opposed to surface and conventional heating process.

9. Speed is increased of the process.

10. Desirable chemical and physical effects are produced.

11. Floor space requirements are decreased.

12. Better and more rapid process control is achieved.

13. In some cases selective heating occurs which may considerably increase efficiency and decrease operating cost.

14. High efficiency of heating, reduction in unwanted side reaction (reaction Quenching).

15. Purity in final product.

16. Improve reproducibility.

17. Reduce wastage of heating reaction vessel.

18. Selective heating i.e. heating selectively one reaction component.

19. Eco friendly process.

Disadvantages of Microwave oven method:

1. It is very difficult to set proper temperature for reaction to occur.

2. Microwave method is not applied for heat sensitive materials.

APPLICATION OF MICROWAVE:[4,5,6,7,8,9,10,11,12]

A) Microwave Drying:

In microwave drying the product is exposed to high frequency electromagnetic waves. These high-frequency waves selectively excite the polar molecules (dipoles) and ions, causing them to align themselves with the rapidly changing direction of the electrical. In this process of orientation, adequate heat is generated throughout the material to evaporate moisture from within the mass. This creates a total pressure gradient, which promotes rapid movement of liquid water and water vapour towards the surface of the material, and hence very rapid drying takes place without the need to overheat the atmosphere. In view of the unique mechanism of microwave heating, selective heating is possible during the drying of heterogeneous materials. The rate of energy conversion (from electrically to thermal) and distribution throughout the material is dependent on the electrical (or more specifically dielectric), thermal and physical properties of the material, as well as temperature and moisture content. There are two main mechanisms of this energy conversion: ionic conduction and dipole rotation. The latter will be dominant in most materials, with the former having increased significance in more ionic materials.

Various Types of Microwave assisted Organic Reactions

The microwave-assisted organic reactions have been broadly classified into two categories

1. Microwave-assisted reactions using solvents;

2. Microwave-assisted reactions using solvent-free conditions.

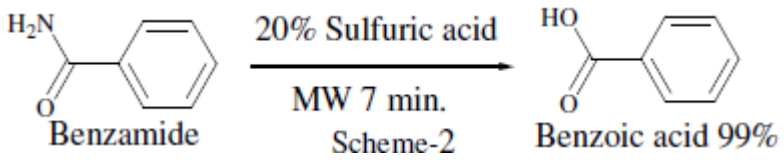
B) Microwave Assisted Reactions using Solvents:

Following are the example of microwave assisted reaction using solvents

a) Hydrolysis

Hydrolysis of benzyl chloride with water in microwave oven gives 97 % yield of benzyl alcohol in 3 min. The usual hydrolysis in normal way takes about 35 min.

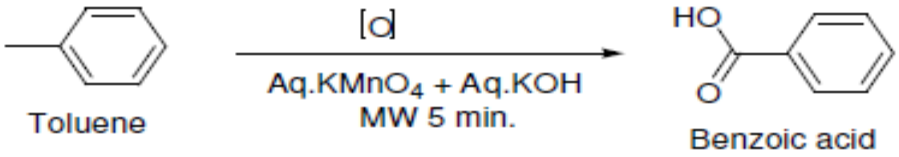
The normal hydrolysis of benzamide takes 1 hr. Conversely, under microwave conditions, the hydrolysis is completed in 7 min giving52 99 % yield of benzoic acid.



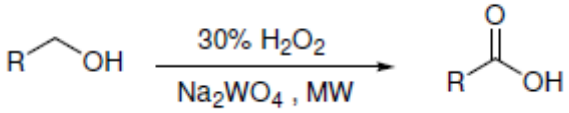
Scheme-2

b) Oxidation

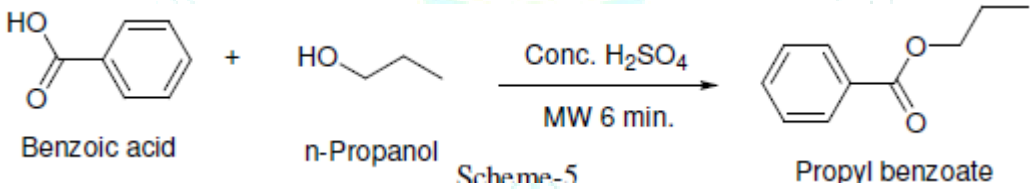
Oxidation52 of toluene with KMnO4 under normal conditions of refluxing takes 10-12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40 %.



A Number of primary alcohols can be oxidized to the corresponding carboxylic acid using sodium



c) A combination of benzoic acid and n- Propanol on heating in a microwave oven for 6 min in presence of catalytic amount of conc. Sulfuric acid gives Propyl benzoate.



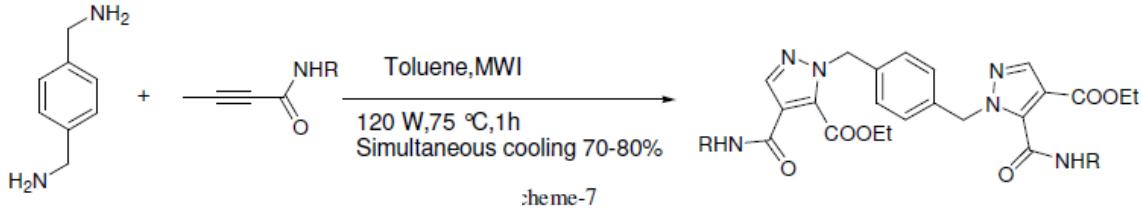
Scheme-5

d). Decarboxylation

Conventional decarboxylation of carboxylic acids involves refluxing in quinoline in presence of copper chromate and the yields are low. However, in the presence of microwaves decarboxylation takes place in much shorter time.

e) Cycloaddition

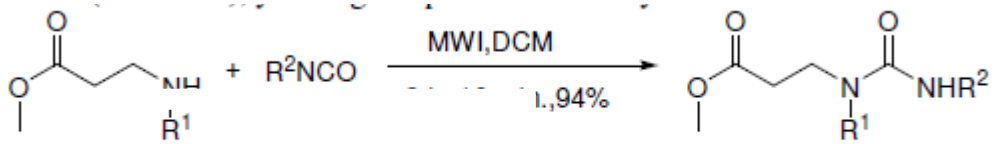
1, 3-Dipolar cycloadditions55 are important reactions in organic synthesis. Cycloaducts were prepared by carrying out the reaction between an azide and a substituted amide in toluene. This reaction was carried out under microwave irradiation at 120 W at 75 °C for 1 h. The product was isolated in 70–80 % yield.



Scheme-7

f) N-Acylations

N-Acylations were carried out using secondary amines and isocyanate in dichloromethane under microwave irradiation (8–10 min), yielding the product in 94% yield.



Scheme-8

Microwave assisted Reactions under Solvent-Free Conditions

Due to the environmental concerns, there has currently been an increasing demand for efficient synthetic processes and solvent-free reactions. Some old and new methodologies are being used to reduce and avoid pollution caused by chemical activities. In this framework, the microwaves have become an

important source of energy in many laboratory procedures. In addition, microwave-assisted solvent free organic synthesis (MASFOS) has been developed as an environmentally friendly process as it combines the selectivity associated with most reactions carried out under microwaves with solvent and waste-free procedures in which organic solvents are avoided throughout all stages. In these environmentally conscious days, the research and development are directed towards devising cleaner processes. Environmental hazards and the successive degradations are instrumental for the quick evolution of green chemistry concept involving benign reagents and conditions.

The MASFOS reactions are of three types:

1. Reactions using neat reactants

2. Reactions using solid-liquid phase transfer catalysis (PTC)

3. Reactions using solid mineral supports.

For carrying out reactions with neat reactants i.e without the use of a solvent or a support (Heterogeneous reactions), at least one of the reactants at the reaction temperature should normally be liquid. In such a set-up, either the solid is partially soluble in the liquid phase or the liquid is adsorbed onto the surface of solid with the reaction occurring at the interface. There is also another possibility, namely that both the reactants are solid. Generally, they melt during the reaction course and then undergo reaction .

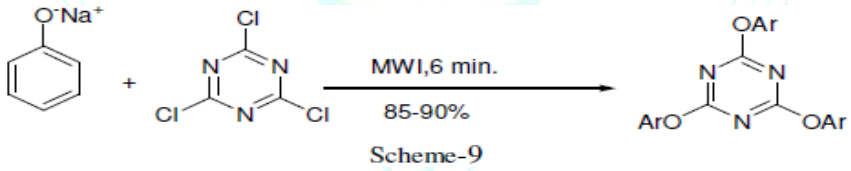
Following are the Examples of Microwaves assisted Reactions with neat reactants-

1. **Aromatic Nucleophilic Substitutions**

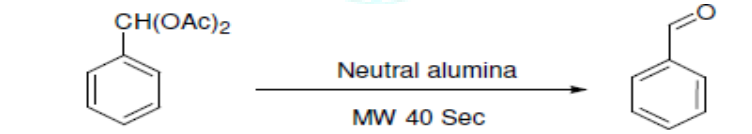
Formations of Substituted Triazines, Aromatic nucleophilic substitutions are carried out using sodium phenoxide and 1, 3, 5-trichlorotriazine under microwave irradiation (6 min). The products, 1, 3, 5-triarlyoxytriazines are obtained in 85–90% yields.

2. Deacetylation

Aldehydes, phenol and alcohols are protected by acetylation. After the reaction, the deacetylation of the product is carried out usually under acidic or basic conditions the process takes long time and the yields are low. Use of microwave irradiation reduces the time of deacetylation and the yields are good.



Scheme-9



Acetic acid acetoxy-phenyl -methyl ester

Benzaldehyde

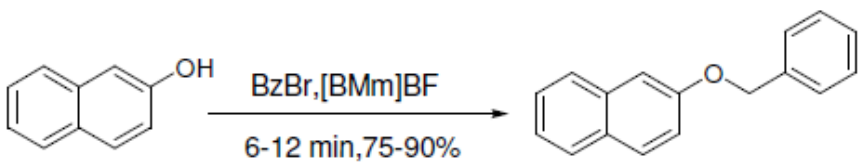
Scheme-10

Microwave assisted Reactions using phase transfer catalysis (PTC):

Solid liquid phase transfer catalysis (PTC) has been described as an efficient method in organic synthesis and is under active examination. This method is specific for anionic reactions as it involves anionic activation. A catalytic amount of a tetralkylammonium salt or a cat ion complexing agent is added to the mixture (in equimolar amounts) of both pure reactants. Reactions occur in the liquid organic phase, which consists here only of the electrophilic R-X. The presence of an additional liquid component is disadvantageous as it induces a dilution of reactants and consequently a decrease in reactivity. The electrophile R-X is hence both the reactant and organic phase for the reaction.

1. O-Alkylation

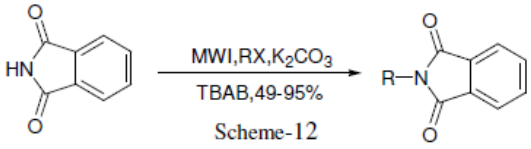
Preparations of ethers were carried out from naphthol using benzyl bromide and 1-butyl-3-methylimidazolium tetrafluoroborate under microwave irradiation (6-12 min) the products were isolated in 75-90% yields.



Scheme-11

2. N-Alkylations

N-Alkylation under microwave irradiation using phase transfer catalysts occupy a unique place in organic chemistry. Bogdal and co-workers reported the synthesis of *N*-alkyl phthalimides using phthalimide, alkyl halides, potassium carbonate and TBAB; giving products in 45–98% yields.

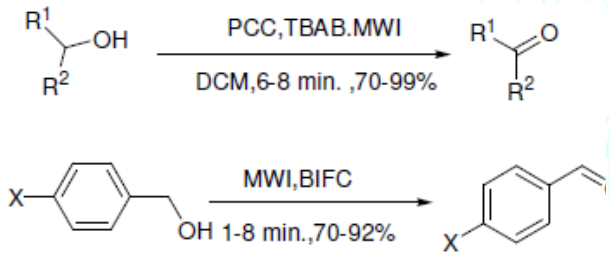


Scheme-12

3. Oxidations

Chakraborty reported the oxidation of secondary alcohol and benzyl alcohols using phase transfer catalysts. Oxidation of secondary alcohols to acetone derivatives was carried out using PCC, tetrabutylammonium bromide and dichloromethane under microwave irradiation (1–8 min), products were

isolated in 70–99% yields. Oxidation of benzyl alcohols was conducted using BIFC under microwave irradiation (1–8 min) yielding benzaldehyde derivatives in 70–92% yields.



Scheme-13

BIONANOCOMPOSITES PREPARATION(BNCS):

A physical blend of drug with natural carriers was prepared by simple blending of drug with carrier in required ratios (drug: carriers) for 10 min. For each sample, a physical mixture of Drug and natural carrier was made by uniform mixing. The weight-to-weight (w/w) ratio of drug to the carrier was taken as per required by ratios keeping amount of mixture constant. Then 4 ml of water was added for each gram of the drug–carrier mixture to make homogeneous slurry (the water was added for hydration of the carrier). A fixed amount of the slurry (5 g) was placed in a glass beaker with a Teflon stirrer (transparent to microwaves) and treated with microwave irradiation for different times at power of 560 W. The temperature of the mixture at the end of treatment was recorded using an inbuilt temperature measurement probe (Table 1). The samples were then ground in a glass mortar and sieved to achieve a particle size of 80–250 mm.

MICROWAVE A GREENER APPROACH:

Recently, there has been a growing interest in the use of microwave technology for organic synthesis. The use of microwave induced heating offers certain advantages, such as shorter reaction times, controlled heating and cooling (by placement of an in-line heat exchanger adjacent to the microwave heating zone or by direct contact between a cold finger and the reaction mixture), and reduction of secondary products . Microwave ovens recommend a clean and sometimes economic substitute to oil baths for many organic reactions. The popularity of microwave heating has been extended to research applications and recently even to academic teaching laboratories. It has been confirmed that microwave heating is helpful in solvent-free reactions as well as in reactions that do not utilize catalysts. In addition, reactions under solvent-free conditions offer the additional advantage of avoiding the use of solvents that can sometimes be expensive, toxic, or difficult to remove and dispose. Recently, the synthesis of analgesic drugs has been engaged to reveal the reward of microwave-assisted synthesis in terms of purity, yield, and reaction time.

CONTROLLED MICROWAVE PROCESSING APPLIED TO PHARMACEUTICAL FORMULATION OF IBUPROFEN:

The apparatus used for the microwave heating comprises a modified domestic microwave oven with a separate magnetron power supply that permits rapid switching to allow pulse-width modulation (duty cycle of 1 s) power control. The oven has shielded inlets to allow access for a fibre optic temperature probe (Luxtron) and a magnetic stirrer, while a PC and bespoke software provide user control of the microwave power and data acquisition. A mode stirrer, consisting of a rotating metal plate within the oven, is used to avoid power 'hot spots' and to aid uniform heating.

MICROWAVE IN HERBAL SYNTHESIS:

The analysis and extraction of plant matrices play an important role in development, modernization and quality control of herbal formulations. With the enhancement in the demand for herbal drugs in the global market, stringent quality control guidelines are been laid down, which the researchers have to follow for herbal formulations. Strict quality control requirements insist faster and improved sample preparation techniques; so that within an approximate time frame results are obtained with investigative experiments and scale up can be attempted. To serve up this reason need for techniques with attributes like efficiency and economy is felt. MAE can prove as a boon to natural product research, if applied to research in discovery of new and effective compounds from plants.

There are very few reports for claim of MAE to herbal drug research. Hence, there is a need to boost the acceptance and utility of this novel extraction technique for its applications in herbal drug industry.

MICROWAVE SYNTHESIS OF NANOCRYSTALLINE ZINC OXIDE:

Nanocrystalline ZnO materials are synthesized using a single-step, microwave-assisted method with zinc acetate as a precursor and 1,4- butanediol as a solvent and promoter under mild conditions. As ready nanocrystalline ZnO has a elevated catalytic activity for the synthesis of propargylamines. This simple method would also be applicable to the synthesis of other functional metal oxide materials.

MICCROWAVE ASSISTED EXTRACTION AND PRESSURISED SOLVENT EXTRACTION:

Microwave assisted extraction and pressurised solvent extraction are emerging as attractive alternatives to conventional extraction methods such as Soxhlet, percolation, digestion, extraction under reflux, sonication and in some cases steam distillation. Initially employed as a digestion method for different sample types such as environmental, biological and geological matrixes, MAE is now widely accepted in analytical laboratories. The main advantage of MAE resides in the performance of the heating source. The high temperatures reached by microwave heating reduces dramatically both the extraction time and

the volume of solvent required. PSE works according to the principle of SLE with elevated temperature and high pressures in order to keep the solvent in a liquid state. Enhanced diffusivity of the solvents leads to an increase in extraction speed and efficiency. With both MAE and PSE, recoveries of analytes and reproducibilities are improved and, therefore, both methods should be considered as interesting alternatives with the limitation that experimental conditions must be chosen in order to avoid possible thermal degradation. Finally the costs of the specialised equipment (especially PSE) may also influence the choice of the extraction technique.

MICROWAVE ASSISTED DIGESTION PROCEDURE FOR TITANIUM DIOXIDE:

The proposed microwave digestion of TiO2/AC photocatalyst is a fast and simple method of sample treatment prior to TiO2 spectrophotometric analysis. This is superior to other procedures because: it is capable of full recovery of TiO2 in much shorter digestion time, no ashing step is required, less chemicals and sample size are required and many samples can be treated simultaneously. Ashing is not necessary because complete recovery is obtained without ashing. The use of sulfuric acid is an appropriate digesting reagent in this procedure, which is capable of dissolution of TiO2 while activated carbon will remain undigested. This is appropriate since this will reduce the complexity of the matrix and thus reduce possible interferences. The % recovery of TiO2 is affected by sample particle size, the presence of a digestion catalyst and the concentration and volume of sulfuric acid. Complete analysis of four samples is possible in 30 min by the use of the proposed microwave procedure.

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