



Review Article

MICROWAVE AND ITS ROLE IN PHARMACEUTICAL SECTOR: A REVIEW

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ABSTRACT

Energy is supplied directly to the material by an electromagnetic field in the processing of microwave. Due to this rapid heating takes place throughout the material thickness with reduced thermal gradients. Volumetric heating can also reduce processing times and save energy. The microwave field and the dielectric response of a material govern its ability to heat with microwave energy. Knowledge of electromagnetic theory and dielectric response is necessary to optimize the processing of materials through microwave heating. The fundamentals of electromagnetic theory, dielectric response, microwave and its advantages, especially applications of microwave in Pharmaceutical, are reviewed in this article.

Keywords: electromagnetic, conduction, microwave, microwave.

INTRODUCTION

Microwaves are a form of electromagnetic energy with frequencies between 300 MHz and 300 GHz, generated by magnetrons under the combined force of an electric and a magnetic field perpendicular to each other (figure 1) corresponding to wavelengths of 1 cm to 1 m. In the electromagnetic spectrum they fall between radio waves and optical waves. For domestic, scientific, medical and industrial purposes two frequencies are allocated that do not interfere with communications frequencies: 915 MHz and 2450 MHz. In the pharmaceutical industry the most common frequency used is 2450 MHz, because of the advantages this frequency offers in conjunction with vacuum.^{1, 2}

Waves are generally of two types

- 1) Electromagnetic waves.
- 2) Mechanical waves.

Both these types of waves transport energy from source to receiver. Microwave is a type of electromagnetic wave

whose wavelength range falls in between Radio waves & Infrared waves.

Microwave refers to the use of electromagnetic waves of certain frequencies to generate heat in a material. Microwave is apparently heading for exhibiting good potential in the field of Pharmaceutical industry. The heating produced by Microwave fields are reflected off metals, which they do not heat. For this reason metals are used as conduits for the microwaves, or wave-guides, and as walls for a microwave oven.² As pharmaceutical equipment is manufactured from stainless steel, the vacuum chamber acts as confinement for the microwaves by reflecting them back into the chamber.

Many materials are transparent to microwaves and do not heat either. Examples of such materials are quartz glass and PTFE, which can be used as microwave windows. The most important property of microwave fields however is absorption of microwaves by the materials, as materials that

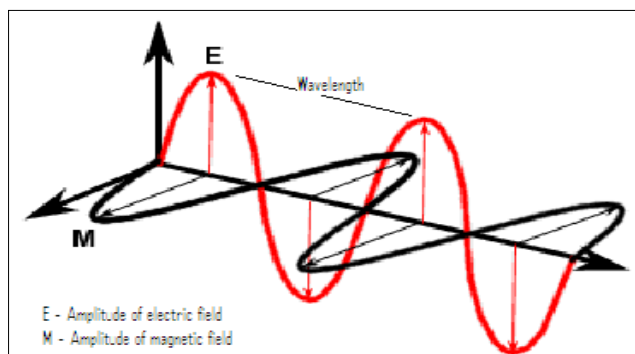


Fig.1. Electromagnetic wave in free space

absorb microwaves are heated. Microwave heating is a direct method of heating. In the rapidly alternating electric field generated by microwaves, polar materials orient and reorient themselves according to the direction of the field. The rapid changes in the field – at 2450 MHz, the orientation of the field changes 2450 million times per second – cause rapid reorientation of the molecules, resulting in friction and heat creation (figure 2). When considering material will behave once exposed to microwave heating, a critical factor is the material's dielectric properties. This is the ability to form a dipole when exposed to an electric field. The operation of microwave heating can be explained simply in terms of two mechanisms: Ohmic and Frictional heating. In ohmic heating (conductance), which particularly applies to solids, the alternating electric field of the microwave (E) causes movement of charged carriers, like electrons within the solid. This movement creates a current which produces heat through any electrical resistance of the solid (dielectric properties). In frictional heating (dipolar polarization), which practically applies to polar liquids such as water or ethanol, the permanent dipoles attempt to track the alternating electric field of the microwave. At microwave frequencies, the molecules can't quite track the rapidly alternating field and the resultant 'jostling' produces heat and the liquid heats up.^{3,4}

This type of heating is instantaneous, uniform and penetrating throughout the material, which is a great advantage for the processing of pharmaceutical compounds. As already mentioned above, different materials have different properties when exposed to microwaves, related to the extent of absorption of the microwaves.

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

$$P = 2 \pi f v^2 E_0 E_r \tan \theta$$

Where,

P - The power density of the material = energy absorbed (W/m³)

f - Frequency (Hz)

v - electric field (V/m)

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

E_r - dielectric constant of the material

tan θ - loss tangent

For a given material and a given electric field, $2 \pi f v^2 E_0$ is constant, and the absorbed microwave energy is proportional to the term $E_r \tan \theta$, called the loss factor. Materials with a high loss factor will readily absorb microwave energy, while materials with a low loss factor are either reflecting or transparent for microwave energy.⁵

Microwave oven

Microwave is not a form of heat, but a form of energy which manifests as heat through its interaction with materials.

The basic mechanisms observed in microwave assisted synthesis are

Dipolar polarization

Conduction.

Interfacial polarization.

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.)

Conduction mechanism

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

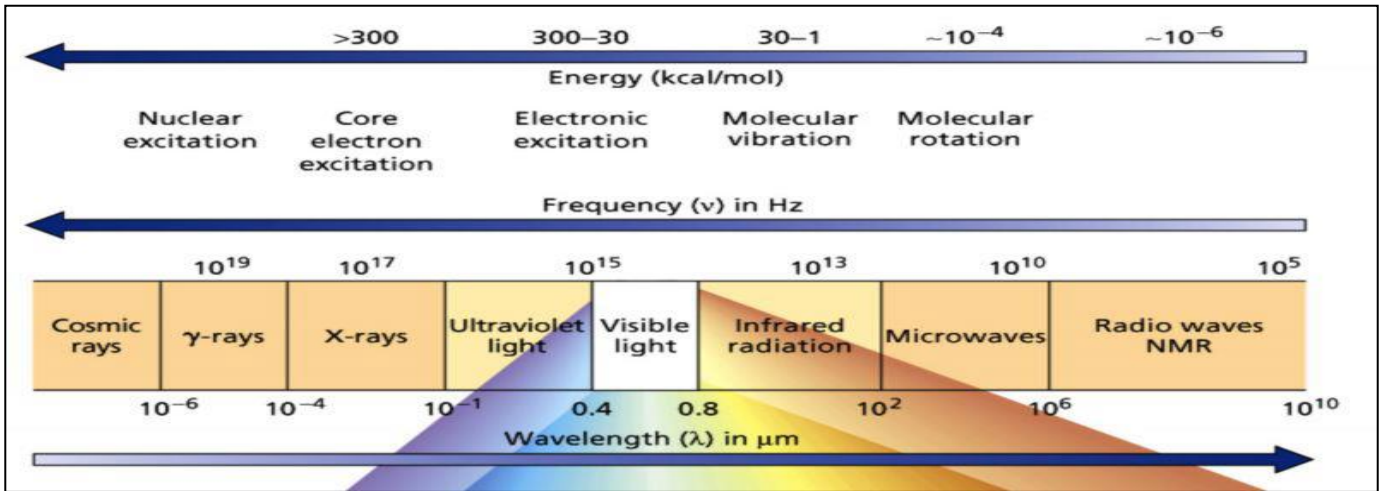


Fig.2. Range of frequencies of electromagnetic radiation

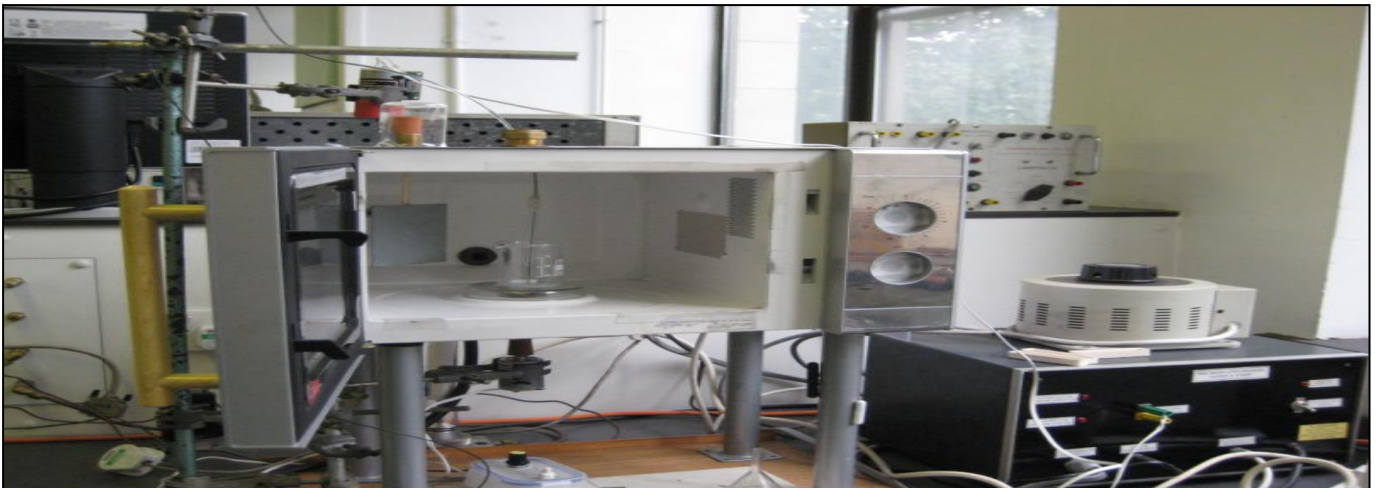


Fig3: Microwave oven & control unit

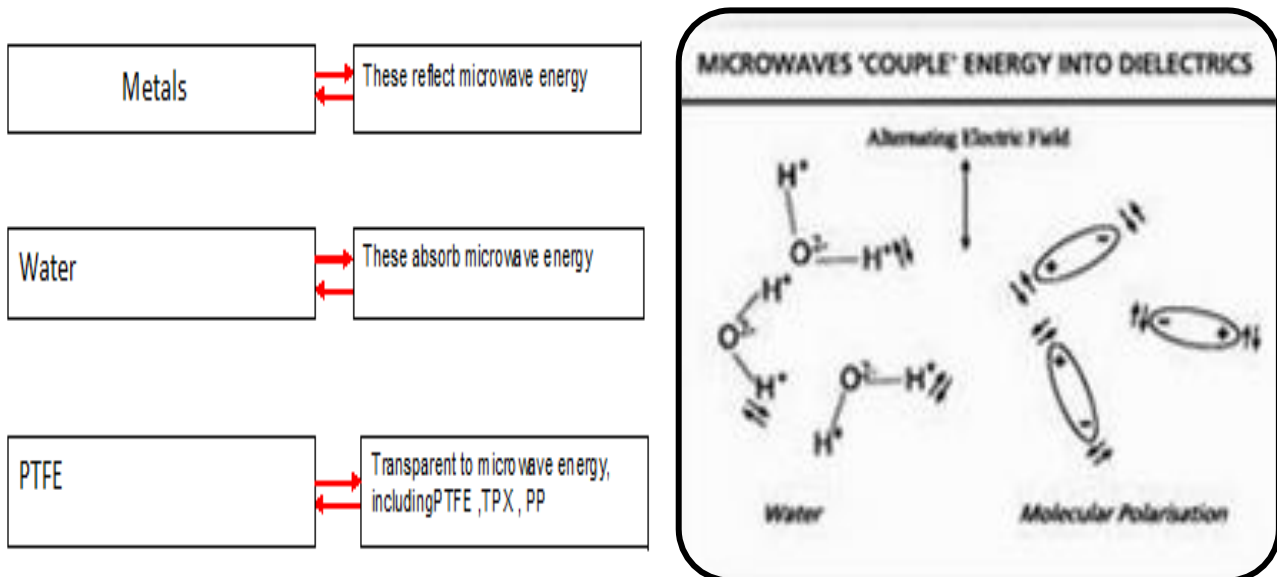


Fig.4. Di-pole rotation in a microwave field

Table: 1 Loss factors of commonly used ingredients for pharmaceutical formulations

Commonly used excipients			Commonly used solvent	
1	Maize starch	0.41	Methanol	13.6
2	Avicel	0.15	Water	12.0
3	Carbonate	0.08	Ethanol	8.6
4	Mannitol	0.06	Isopropranol	2.9
5	Calcium phosphate	0.03	Acetone	1.25
6	Calcium carbonate	0.06	Ice	0.003
7	Lactose	0.048		

Table: 2 Difference between Conventional and Microwave assisted heating

S. no	Conventional heating	Microwave heating
1	Heating mechanism involve- conduction	Heating mechanism involve- dielectric polarization and conduction
2	By thermal or electric source heating take place.	By electromagnetic wave heating take place.

Interfacial polarization

This mechanism can be considered as a combination of the conduction and dipolar polarization effects. It is important 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 discovery applications because it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. The physicochemical properties of excipients can be specifically modified by microwave to provide the intended release properties of drugs in dosage form development. MW heating with the benefits of differential temperature measurement to give a sensitive means of probing the thermal properties of materials as a function of temperature is developed by Parkes et al.

In recent years, the microwave is utilized to process drug delivery system such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, and tablet and film coat. Practically, the microwave could induce drying, can change drug release properties by polymeric cross linkages and drug-polymer interaction, and also improve drug dissolution via modifying the structure of drug crystallites.

The use of microwave opens a new route to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms. It provides the intended release characteristics of drugs in dosage forms without the need for excessive heat, lengthy process and/or toxic reactants.

Advantages of Microwave oven method

1. Rapid volumetric heating.
2. No overheating at surface.
3. Better and rapid process control.
4. High heating efficiency.
5. Environmental heat loss can be avoided.
6. Energy saving.
7. Low operating cost.
8. Uniform heating occurs throughout the material as opposed to surface and conventional heating process.
9. Process speed is increased.
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 certain cases selective heating occurs which may significantly 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.^{2,6,1}

Disadvantages of Microwave oven method:

1. It is very difficult to set proper temperature for reaction to occur.
2. Microwave oven method cannot be applied for heat sensitive materials

Recently, microwave heating has emerged as a powerful technique to promote a variety of pharmaceutical processes related to drying, chemical reaction, sterilization etc.

Material used in Pharmaceutical Production:

The materials commonly used in pharmaceutical production (Table I), microwave energy is very well suited for drying of pharmaceutical formulations. The liquids most frequently used for wet granulation (water, alcohol ...) have much higher loss factors than the other standard ingredients for a wet granulation (lactose, corn starch ...), leading to higher absorption of microwave energy and thus preferential heating of the liquids.

For many Excipients these properties used tables and monographs ⁷

An important fact about the loss factor is that it changes with the temperature of the product. This phenomenon is related to the relaxation frequency of materials. The relaxation frequency is the time required for build-up and decay of the order induced by an electric field. This frequency increases with the temperature of the material. As the efficiency, or the amount of energy converted into heat by each cycle of dipole rotation, is optimum when the microwave frequency coincides with the relaxation frequency, the amount of microwaves absorbed by a material – and thus the loss factor – will differ with the temperature of the material. The loss factor of water decreases with increasing temperature. The reason for this is that at room temperature, the relaxation frequency of the small water molecules is already larger than the microwave frequency, and with increasing temperature it moves further from the microwave frequency, resulting in a lower absorption of microwave energy.

For larger molecules however, the relaxation frequency at room temperature is often lower than the microwave frequency, and with increasing temperature it moves closer to the microwave frequency, resulting in more energy conversion. This increased absorption of microwave energy will result in an increased temperature, which in its turn will again lead to increased absorption. This phenomenon is called thermal run-away, and is illustrated in figure 4. As most pharmaceutical processes are executed at a temperature lower than the critical temperature of the most common pharmaceutical ingredients and the modern microwave dryers are executed with accurate product temperature control, the risk of encountering thermal run-away in a pharmaceutical process is minimal.⁸

Microwave is apparently heating for exhibiting good potential in the field of Pharmaceutical industry. The heating produced by Microwave, have been found to be superior to the conventional in numerous situations described in table 1. Although microwave technology has been in use from long time, its application in the pharmaceutical industry is relatively recent. Single Pot Processors equipped with microwave drying were only introduced 15 years ago. The properties of microwaves however make them very well suited to dry pharmaceutical formulations in a fast and elegant way. The modern microwave drying systems are all equipped with the necessary safety measures to ensure completely safe processing for both operator and product. Nevertheless, careful design of the process parameters is necessary to obtain optimal results from the microwave technology in pharmaceutical production having several advantages microwave is emerging as need of the day. It has shown definite benefits over conventional ways of heating in thawing, drying, sterilization, and production of sustained release dosage units etc.

Knowledge available for safe & efficacious use of Microwave energy is growing day by day. In the recent years, the use of microwaves has become very attractive in organic chemistry. In fact with respect to Conventional heating i.e. Conduction, Convection and Radiation with Infrared light, microwave irradiation offers several advantage such as rapid volumetric heating, no overheating at the surface, addressable heating, energy saving and low operating cost. Hence microwave, when used with certain

precaution, is a promising energy for pharmaceutical discipline. It can be concluded that microwave energy will have an enhanced and prominent role to play in pharmaceutical industry.

The Advantages of Microwave drying technique are –

1. Microwaves systems are more compact, requiring a smaller equipment space or footprint.
2. Microwaves generate higher power densities, enabling increased production speeds and decreased production costs.
3. To standardize the drying process for pharmaceutical granulations by microwave technique and compare the present release of drug obtained by microwave technique with other drying technique.
4. Environmental heat loss is save
5. Reduction in unwanted side reaction
6. Desirable chemical and physical effects are produced.
7. Improve reproducibility
8. Uniform drying.
9. Efficient drying.
10. Easily controllable.
11. Detection of end point of drying possible.
12. Dust free.
13. Easily cleanable.
14. Purity in final products.^{2,9}

Application of Microwave in Pharmaceutical

Microwave used in pharmaceutical dosage form development:

Application of microwave to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres¹⁰, nanomatrix¹¹, solid dispersion¹², controlled release tablets formulation¹³ and tablet film coating¹⁴. The microwave could induce drying, polymeric cross linkages as well as drug-polymer interaction, and modify the structure of drug crystallites via its effects of heating and/or electromagnetic field on the dosage forms¹⁴. The use of microwave opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process or toxic reactants. Alternatively, the microwave can be utilized to process excipients prior to their use in the formulation of drug delivery systems¹⁵. The

intended release characteristics of drugs in dosage forms can be met through modifying the physicochemical properties of excipients using the microwave. A new microwave assisted method was used to prepare magnetic Fe₃O₄ particles and magnetic bovine albumin microsphere.^{16,17}

Wong used microwave-treated water to increase the dissolution propensity of both hydrophilic and hydrophobic free drugs and drugs encapsulated in calcium cross linked alginate beads.¹³The first report to use microwave heating in the cross-linking of pharmaceutical carriers was made by Teng and Groves, who produced thermally denatured protein matrices useful as controlled-release systems.^{13,18}Kerc describe the method in which physical mixture of both felodipine drug and porous amorphous silicon dioxide carrier is subjected to microwave treatment at 500 W for different periods of time, between 5 and 15 min. The drug release propensity is higher in samples subjected to microwave irradiation for a longer period of time. The drug release propensity of microwave-treated physical mixture is greatly higher than those of pure drug, physical mixtures which are untreated by microwave or treated by vacuum at 100°C, or obtained using solvent deposition method. These observations are described to a reduction in the level of crystallinity of drug following its treatment by microwave in the form of a physical mixture.

Moneghini et al. prepared microwave activated solid dispersion systems in different ratios of Ibuprofen to PVP/VA 64 or HP-β-CD by irradiating these physical mixtures to microwave at 600W for 6 and 15 min. These activated systems were able to remarkably increase the dissolution profile of poorly soluble drug.¹⁹The microwave has also been utilized to produce solid dispersion using the concept of hybrid heating. Low loss pharmaceutical materials have a poor electro-thermal coupling capacity with microwave. They are difficult to be heated by microwave at room temperature. Nevertheless, they could absorb the microwave energy upon preheating to a suitable temperature and beyond which they will couple with the microwave. Using a high loss reactor, the reactor could absorb the microwave energy readily at a low temperature, convert the energy to heat, and transfer the heat to the low loss pharmaceutical materials by diffusion which in turn promotes the coupling capacity of processing mass with microwave. The solid

dispersion prepared thus far via hybrid heating includes nano matrix with nanocrystal and molecular clusters of drug embedded in the core, and microcrystals of drug adhered onto the surfaces of matrix. This in turn is envisaged to enhance the dissolution propensity of water-insoluble drugs.¹¹

Microwave has been utilized to design controlled-release alginate, alginate-chitosan, pectinate-chitosan and poly (methyl vinyl ether- co-maleic acid) beads. ^{20,21,15} The drug release characteristics of these beads were dependent on the propensity of polymer-polymer and drug-polymer interaction brought about by microwave. The microwave has also been investigated as the alternative mode to crosslink gelatin matrix which is available as microspheres suspended in a polar acetone. It is found that only a short span of 10 min is required for effective crosslinking of gelatin microspheres by microwave unlike when thermal denaturation method is used. ^{10,22,23} Skin treatment by microwave followed by solid pectin film loaded with sulphanilamide and oleic acid result in permeation of all drug molecules that are released from film.²⁴

Effect on Tablet and Film Coating:

The use of microwave has a strong implication in design of sustained-release drug delivery system 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 polymer coat is commonly introduced to the tablet from aqueous solution or suspension of polymer. The drying of polymer coat can be effected by microwave and/or hot air. The film coat dried using microwave is more elastic, has more tensile strength than oven or air dried films and faster rate of drying, but possesses slightly lower level of tensile strength than that dried using hot air current.¹⁴

The matrix tablets prepared from microwave-treated Ispaghula husk swell considerably and do not erode during the in vitro dissolution testing. ²⁵

Semisolid formulation

In semisolid formulation, microwave heating technology help to improve the microbiological and rheological qualities of Jelly, body lotion, ointment.

The ointments prepared at various uncontrolled and controlled temperatures when evaluated for organoleptic, microbiological & rheological qualities however did not show

any significant difference in comparison with traditional method during manufacturing. It's any significant difference, but the method is useful for producing good quality stable product.

Drying of Granules:

Many studies have been published in the meantime showing no difference in either stability or physicochemical properties of granules dried with microwave-vacuum processing, compared to other drying methods such as traydrying or fluid bed drying. As microwaves are nonionizing and do not possess the necessary amount of energy required for the formation of free radicals or the liberation of bound water, there are no conditions created during microwave drying that foster product instability. ^{26,27}

The design of a microwave drying process however still requires the careful consideration of the different parameters involved and their interaction to arrive at an optimal result. One of the most important interactions that need to be taken into account is the interaction between the pressure in the bowl and the microwave level. As explained above, the risk of electric breakdown increases when the pressure in the bowl decreases. However, when a higher pressure is used for the process, the evaporation temperature of the granulation liquid is also higher, leading to the fact that in the initial phase of the drying process, the microwave energy will most likely be used to heat up the product instead of for evaporation. Depending on the temperature sensitivity of the product, an optimal balance between pressure and microwave level needs to be determined. To avoid any adverse effects of the use of microwaves outside the practical range of pressures, most manufacturers of microwave single pot processors have restricted the pressure range in which microwaves can be activated to 30 –100 mbara. Vacuum and microwave power levels are also important in relation to the porosity of the granules. As microwaves are instant and penetrating, granulation liquid inside of the granules can evaporate immediately after the microwaves are switched on. If the evaporation rate exceeds the migration rate of the vapour towards the granule surface, a pressure build-up inside of the granule can occur, possibly leading to explosion of the granules and creation of fines ²⁸. Lowering the microwave power level or increasing the working pressure may

eliminate this effect. Other parameters to consider are the method and frequency of agitation of the product.

Agitating the product is necessary to ensure an even power distribution throughout the product bed. Too much agitation can however lead to attrition of the granules and creation of fines. For this reason, very low mixer speed and the possibility for intermittent mixing are available for all single pot processors.^{29,30}

Drying of Granules: Approval of US-FDA for acceptability of Microwave technology in Pharmaceutical industry, the fact that many drugs, manufactured with microwave-vacuum processing, have been approved by the FDA and other regulatory bodies world-wide without requiring additional stability or analytical testing apart from that normally required for other manufacturing methods; corroborates the safety of using microwaves for drying pharmaceutical formulations. It also refutes the fear of many companies that in case of a change of the manufacturing process to microwave drying the regulatory bodies would require extensive validation, stability and analytical data. A conversion from an approved manufacturing process to a microwave drying process for an immediate release solid oral dosage form in the US is governed by the FDA's SUPAC IR Guidance document, just like any other change in such a manufacturing process. In 1992, a survey was done by Robin and colleagues of 8 European regulatory bodies to determine the implications of converting an approved fluid bed drying process to a microwave drying process. None of the agencies required more data than could be expected for similar types of manufacturing changes (change in process or equipment). Most of the agencies required only process validation data, and 3 suggested limited stability data (up to 6 months of accelerated data).^{31,7}

CONCLUSION:

In recent years, the use of microwave has become very attractive in the Pharmaceutical Field. Several advantages of microwave like rapid volumetric heating, no overheating at surface, better and rapid process control, high heating efficiency, environmental heat loss can be avoided, energy saving, low operating cost and many more advantages. Microwave also used in Pharmaceutical drying that can change the drug release properties by polymeric cross linkages and drug interaction improves drug dissolution via

modifying the structure of drug crystallites of microwave to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, controlled release tablets formulation and tablet film coating. The use of microwave opens a new route to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms.

REFERENCES