



ISSN: 0975-766X
CODEN: IJPTFI
Research Article

**Available Online through
www.ijptonline.com**

**MICROWAVE: AN EMERGING TREND IN PHARMACEUTICAL PROCESSES AND
FORMULATIONS**

Bonde MN*¹, Sohani AC¹, Daud AS¹, Sapkal NP²

¹ Zim Laboratories Ltd., Nagpur, India-441 501.

²Gurunanak College of Pharmacy, Nari, Nagpur-26.

Email: minalbonde@zimlab.in

Received on 29-09-2011

Accepted on 17-10-2011

Abstract

Microwave, which has achieved popularity in the kitchen, packaged good, also has an enormous potential in pharmaceutical manufacturing. Microwave technology has a great excellence and use in pharmaceutical industry. A revolutionary microwave processing technology using 915 MHz microwave energy has been approved by US Food and Drug Administration. This technology eliminates food pathogen and microorganism in just five to eight minutes and produces safe product with much higher quality than conventionally processed products. Being focused to pharmaceutical industries, the microwave heating has been used now-a-days in applications of Drying, Thawing, Sterilization, Drug Extraction, Chemical Synthesis, Hydro distillation etc. It's applications have been found to be extended in Preparation of Solid Dispersions, Coating of Tablets, Drying of Granules, Semisolid Formulations like Ointments, Cream, lotions etc. In today's competitive era microwave is one of the major tool for the rapid lead generation and optimization through which medicinal chemist will be able to deliver critically needed new chemical entities and candidate drug. The use of microwave open new route to control the physiochemical properties and drug delivery profiles of pharmaceutical dosage forms. This article is an attempt to review the involvement of application of microwave technology in the pharmaceutical process as well as pharmaceutical dosage form.

Introduction

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

Waves are generally of two types 1) Electromagnetic waves. 2) Mechanical waves.

The main point of differentiation between Electromagnetic and Mechanical waves is that Electromagnetic waves do not require a medium for transportation, as required by Mechanical waves. Both these types of waves transport energy from source to receiver [1]. Microwave is a type of electromagnetic wave whose wavelength range falls in between Radio waves & Infrared waves. Microwave is generally used for drying & thawing, but now its use has been extended to, Sterilization, Drug Extraction, Chemical Synthesis, Hydro distillation etc. applications have been found to be extended in preparation of pharmaceutically accepted Dosage forms.

Certain frequencies have been allocated by the Federal Communications Commission (FCC) for the purpose of heating. Typically, Microwave food processing uses the 2 frequencies of 2450 and 915 MHz Of these two, the 2450 MHz frequency is used for home ovens, and both are used in industrial heating. It is worthwhile to note that outside of the United States, frequencies of 433.92, 896 and 2375 MHz are also used. The frequencies applicable to industrial, scientific, medical & domestic uses for heating purpose lie between 9.15 MHz to 2.45 GHz.

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, 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. Figure 1 & Figure 2 shows the Electromagnetic spectrum & Energy transfer comparison of Convectional heating with that of Microwave heating.

Fig 1. Electromagnetic spectrum.

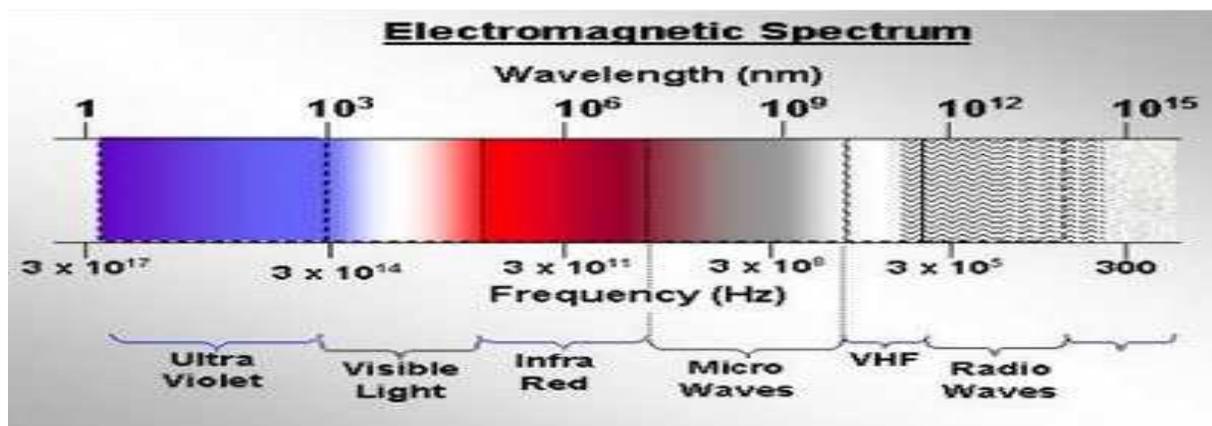


Fig 2. Energy transfer comparison.



Table.1. Difference between Conventional and Microwave assisted heating.

Conventional	Microwave
Reaction mixture heating proceeds from a surface usually inside surface of reaction vessels	Reaction mixture heating proceeds directly inside mixture
The vessel should be in physical contact with surface source that is at a higher temp.	No need of physical contact of reaction with the higher temperature source.
By thermal or electric source heating take place.	By electromagnetic wave heating take place.
Heating mechanism involve – Conduction	Heating mechanism involve-dielectric polarization & conduction
All the compound in mixture are heated equally	In microwave, specific component can be heated specifically
Heating rate is less	Heating rate is several fold high

US FDA APPROVED MICROWAVE STERILIZATION PROCESS

A revolutionary thermal processing technology using 915 MHz microwave energy has been approved by US Food and Drug Administration (FDA). The outcome results in food with a longer shelf life as well as better flavor and nutritional value compared to more traditional food-processing methods. This is the first time that the FDA has approved the use of microwave energy for producing pre-packaged, low-acid foods– hence it has been come up as a major milestone that clears the way for its commercialization”.

Since the introduction to industrial microwave ovens in the late 1940s, the food industry and US Army have shown strong interest in exploiting the rapid heating capability of microwaves to improve the quality of canned food. The technical issue has always been ensuring uniform and reproducible heat treatment. The technology immerses packaged food in pressurized hot water while simultaneously heating it with microwaves at a frequency of 915 MHz — a frequency which penetrates food more deeply than the 2450 MHz used in home microwave ovens. This combination eliminates food pathogens and spoilage microorganisms in just five to eight minutes and produces safe products with much higher quality than conventionally processed products. It is a heat process, which does not create any chemicals or any residues that are harmful to humans. The new processes for producing shelf-stable, low-acid foods must pass rigorous reviews by FDA to ensure that the technology is scientifically

sound and the products will be safe. As the FDA has approved first microwave sterilization in food products, therefore in the next few years it will gain a great potential in pharmaceutical industry. The superiority of microwave lies in the uniform and efficient heating and at times in localized and focused heating and at times in localized and focused heating. Through the exhaustive search of literature it could be concluded that microwave, when used with certain precaution, is a promising energy in pharmacy.

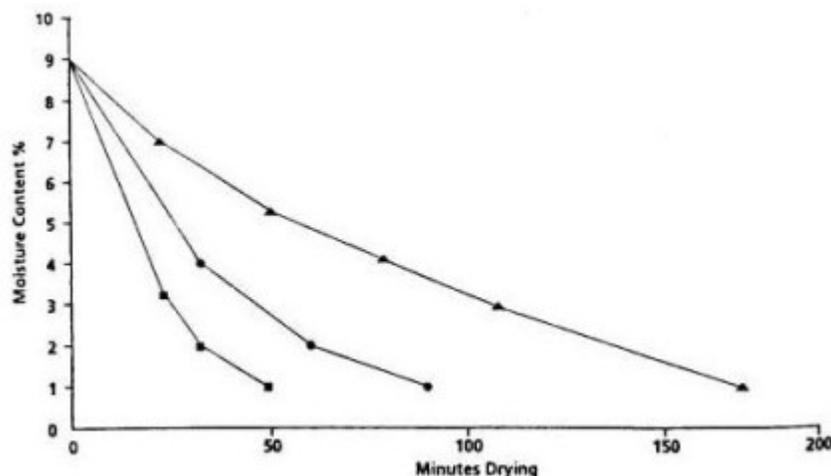
APPLICATIONS OF MICROWAVE TECHNOLOGY IN THE PHARMACEUTICAL PROCESSES

1. Microwave Drying

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). 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 i.e.: 915 MHz and 2450 MHz. In the pharmaceutical industry the most common frequency used is 2450 MHz, because of the advantages which this frequency offers in conjunction with vacuum. Microwave fields are reflected off metals, which they do not heat. For this reason metals are used as conductors for the microwaves, or wave-guides, and or as wall for a microwave oven. 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 get heated either. Examples of such materials are quartz glass and PTFE, which can be used as microwave windows.

The most important property of microwave field is absorption of microwaves by the materials, as materials that absorb microwaves get 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). This type of heating is instantaneous, uniform and penetrating throughout the material, which has a great advantage for the

processing of pharmaceutical compounds. Microwave has wide application in industry for drying purpose as it possesses advantage over other drying procedure.



Graph1: Comparison of Drying curves for different modes of Drying.

- --- Microwave
- --- Vacuum with air
- ▲ --- Vacuum only

The above graphical representation depicts the advantage of microwave drying over other drying mode. This is due to the ability of water and most of the industrial solvents which absorb microwave energy more rapidly than solids causing the effective heating; leading to evaporation. It is mainly used to remove water or polar organic solvents from heat sensitive powders; granules bulk drugs, pastes and slurries etc. [2] Microwave equipments are also used to measure the moisture content in the pharmaceuticals [3]. Online moisture can be detected for microwave vacuum dryer using near Infrared Spectroscopy (NIS), though only if the moisture content of product is 6% or less. Thus, drying can be made continuous process with precise control of moisture. [4]

Advantages of a microwave dryer includes

- 1) Uniform drying.
- 2) Efficient drying.
- 3) Easily controllable.
- 4) Detection of end point of drying possible.

- 5) Dust free.
- 6) Easily cleanable.

Disadvantages

- 1) Not suitable for materials with high loss factor & high solubility
- 2) Vacuum is required for reasonable drying.

2. Microwave sterilization

There is great utilization & significance of a new method i.e., microwave sterilization in Pharmaceutical industry [5], [6]. The sterilization is brought about by microwave dielectric heating effect. Microwave sterilization is now utilized for sterilization of heat labile drugs where a high temperature is generated for sterilization in a shorter period of time. That creates a possibility of making the process continuous. Such a process can benefit the industry due to its economy & lesser production time. The efficiency of Microwave Sterilizer was put to test via sterilization of two heat labile drugs, Ascorbic acid & Pyridoxamine phosphate, both in solution form. The result showed that though reduction of bio-burden was equal to that of autoclaving, autoclaved drugs showed certain deteriorations in quality, which was not observed in microwave sterilized drugs. The validation requirement of microbicidal suitability of microwave created a need to find out biological indicator for microwave sterilization. Sasaki and the co-workers showed that sterilization effect of microwave is due to Production of heat and there is no other non-thermal mechanism. This suggested that spores of *Bacillus Stearothermophilus* are an appropriate biological indicator in validation of microwave sterilization.[7]

Sterilization of vials was not affected regardless of its position in the sterilizer thus indicating uniform heating ability of the microwave. A Continuous Microwave Sterilizer (CMWS) has been developed [8]. The high temperature and short time sterilization by microwave heating in a CMWS were evaluated. *Bacillus stearothermophilus* spores were used as biological indicator. The lethal effect of microwave sterilizer was equal to that of Autoclave.

Pharma-Micro is a rotary Vacuum microwave dryer and sterilizer. Due to combination of Vacuum and microwave heating, Pharma-Micro provides high level of drying and sterilization at relatively low temperature avoiding conventional drying problems which are like:

- Change of composition and structure of material
- Undesired sintering, agglomeration and induratio.
- Contamination of the products with combustion products of gas or oil

The advantages of Pharma-Micro are as follows:[9]

- Deep drying of products can be done at relatively low temperatures
- Speeding up the drying process in 10-15 times
- Decreasing of power consumption in 20- 100 times
- Selective elimination of water without other components decomposition
- Avoidance of agglomeration
- Simultaneous low temperature sterilization
- Ecologically clean drying process

3. Microwave Thawing

Thawing is process where freeze stored drugs brought to normal Physiological temperature before administration especially if an injection. One of the methods for thawing is the use of microwave. Stability of majority of drug preparation was unaffected except for some preparations, thus providing criticism for microwave thawing [10]. The stability of many drugs both physical and chemical was not affected after microwave thawing [11-16]. Microwave thawing reduced process cost as well as preparation time. G. J.Sewell, A. J. Palmer & P. J. Tidy showed the effect of infusion volume, infusion load size and microwave power on rate of thawing. Frozen infusions of 100-500 ml volume were thawed evenly and reproducibly without overheating. Linear relationships were demonstrated for microwave power output and thawing rate and for infusion load size and thawing time. It was noted that these relationships enable predetermination of microwave thawing times. On the basis of the

results, guidelines for this system were developed [17]. Microwave thawing also caused about 10% reductions in microbial count. Cloxacillin sodium, Flucloxacillin Sodium and Ticarcillin disodium were reconstituted in 0.9% sodium chloride and in 5% Dextrose solutions, stored frozen for up to 9 months, and stability of the antibiotics were assayed following microwave thawing. All of them retained at least 90% of their original potency throughout the study period. However, Cloxacillin and Flucloxacillin in 5% dextrose showed a yellow discoloration after 6 months' storage. It was suggested that these 2 formulations not be stored for more than 3 months before use.[18]

Certain formulations showed undesired effects when processed through microwaves

1. The stability of Intravenous Augment in (Amoxicillin sodium and Clavulanate potassium) in a range of a vehicle was investigated. Aqueous solutions frozen at -20°C and thawed by microwave radiation lost more activity than those stored at 25°C [19].
2. Intravenous Adriamycin (Doxorubicin hydrochloride) could not be thawed with microwave as it got overheated leading to decomposition of the drug [20].
3. Thawing frozen solutions in a microwave oven adversely affected the stability of Cefuroxime sodium (Zinacef) in aqueous solutions, with or without phosphate buffer, and in 5% dextrose and 0.9% sodium chloride injections. Local sequestration of the antibiotic during freezing and that of heating rapidly to boiling may be the possible reason for degradation during microwave radiation [21].

4. Drug extractions

Microwave-Assisted Extraction (MAE) has been a developing extraction technique for the isolation of semi-volatile organic compounds from solid matrices. With MAE, the sample is placed in an open vessel and heated by microwave energy, using a microwave absorbing solvent. The hallmark feature of MAE is accelerated dissolution kinetics as a result of the relatively high extraction temperature. Microwave-assisted extraction (MAE) is a relatively new extraction technique which utilizes microwave energy to heat the solvent and the sample to increase the mass transfer rate of the solutes from the sample matrix into the solvent. Many reports have been published on the application of microwaves for extracting Pesticide/Insecticide residues and Herbicides from the samples. MAE

technique has also been used to extract contaminants present in the environmental samples. The usage of microwaves for extracting Phyto-constituents is still in infancy[22].

Advantages of MAE:

- High and fast extraction ability with less solvent consumption.
- Thermo labile constituents can be protected

5. Microwave-assisted organic synthesis (MAOS)

Microwave-assisted organic synthesis (MAOS) is clearly a method by which the laboratory chemist can achieve goals in a fraction of time as compared to traditional conductive heating methods. Reaction times in the best cases have been reduced from hours or days to minutes. From the standpoint of synthesis chemistry, the use of microwaves as an energy source to heat reaction solutions has been shown to provide the following advantages:

- Broad applicability – few limitations as compared to types of synthesis chemistry
- Increased reaction rates – 1,000-fold in best cases.
- Used to accelerate chemistries in both solution and solid-phase reactions.
- Improved product yields.
- Moderately scalable (sub-milligram to multigram quantities).
- Can be conducted in either open or closed vessels.
- Access to synthetic transformations which is not achievable via conductive heating.
- Broad dynamic temperature range (-45°C to 300°C).
- Green chemistry – reactions in supercritical water or solvent-less reactions.
- Can be used to accelerate the synthesis of peptides.
- Controlled method of heating.
- Rapid reaction optimization.

One might conclude that reduced reaction times and many of the other advantages offered by microwaves as an energy source confer increased productivity and ultimately enhanced efficiency.[23]

6. Microwave-assisted Hydrodistillation

The ability of microwave radiation to heat solid material effectively can also be used for obtaining essential oils. Thus, the herb is placed in a microwave cavity and irradiated with microwaves. This process yields essential oils consisting of relatively low volatile fractions as compared to hydrodistillation. For instance, in coriander oil, the percentage of tetradecanoic and hexadecanoic acid increased whereas that of linalool decreased. This is possibly due to the poor stability of linalool, a tertiary alcohol. Dill seed oil obtained by microwave-assisted hydrodistillation (MWAHD) contained greater quantities of compounds with higher boiling points and lesser quantities of compounds of lower stability. These and other findings indicate that MWAHD is better for extracting stable, high-boiling point components, whereas it is not suitable for recovering chemically unstable compounds [24-28].

APPLICATION OF MICROWAVE IN PHARMACEUTICAL DOSAGE FORM DEVELOPMENT

Microwaves in preparation of Solid Dispersion

The poor dissolution characteristic of relatively insoluble drugs is the rate limiting step in the absorption of a drug from a solid dosage form. In recent years there is a rising interest to design solid dispersion whereby one or more active ingredients are embedded in an inert solid matrix by the melting, solvent or melting-solvent method [29-31]. The dissolution of poor water soluble drugs can be greatly enhanced through reducing the particle size and/or crystallinity of drug during the preparation of solid dispersion. Preparation of solid dispersion by melting method involves heat, which may lead to decomposition or evaporation of the drug particles and/ or matrix former. Alternatively, solvent method demands a high operating cost for solvent, flame proof facilities, solvent removal and recovery system. The environmental problem of the use of organic solvent is also the problem of major concern. Also physicochemical stability and dissolution properties of these prepared solid dispersion are affected appreciably by the storage conditions [32]. Recently, Kerc et al. [33], Bergese et al. [34], and Moneghini et al. have explored the usefulness of microwave as the alternative mode of preparation for solid dispersions. Kerc et al. 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 tendency is higher in samples subjected to microwave irradiation for a longer period of time. The drug release tendency of microwave-treated physical mixture is greatly higher than those of

1. Pure drug,
2. Physical mixtures which are untreated by microwave or treated by vacuum at 100°C,
3. Or obtained using solvent deposition method.

These observations are attributed to a reduction in the level of crystallinity of drug following its treatment by microwave in the form of a physical mixture. Similarly 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 600 W for 6 and 15 min. These activated systems were able to remarkably increase the dissolution profile of poorly soluble Ibuprofen [35].

In another study by Bergese et al., the microwave has also been utilized to produce solid dispersion using the concept of hybrid heating. Low loss pharmaceutical materials have a poor electrothermal 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 nanomatrix with nanocrystals and molecular clusters of drug embedded in the core, and microcrystals of drug adhered onto the surfaces of matrix. This in turn is envisage to enhance the dissolution tendency of water-insoluble drugs.

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. Ispaghula husk, the dried seed coats of *Plantago ovata*, has been employed in the manufacture of

matrix tablet. But the poor gel forming tendency and formation of soft tablet limits its use. Also modification of Ispaghula husk by hot air oven treatment does not appear to be able to induce rigid gel formation. Also prolong heating may degrade polymer and thus the network of polysaccharide needed to sustain the release of drug is lost. Treatment of Ispaghula husk by microwave has shown to introduce superior swelling and rigid gel formation properties to the husk, in both distilled water and simulated gastric fluid (pH 1.2). The matrix tablets prepared from microwave-treated Ispaghula husk swell considerably and do not erode during the in vitro dissolution testing [37]. 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 [38].

Drying of Granules

Many studies have been published in the mean time showing no difference in either stability or physicochemical properties of granules dried with microwave-vacuum processing, compared to other drying methods such as tray drying 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 [39-41].

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 vapor 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 [42-43]. 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 speeds and the possibility for intermittent mixing are available for all single pot processors [44-46].

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 [47-53]).

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.

Although there isn't exists any significant difference, but the method is useful for producing good quality stable product [54].

Apart from the above mentioned applications microwave can be applied for packages of pharmaceutical products and also it is useful to sterilize heat sensitive nutrients such as vitamins, flavor, carbohydrate (preferably lactose), lipids, protein, minerals and vitamins [55]. In recent years, the microwave is utilized to process drug delivery system such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, tablet and film coat [56-57]. 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 [58]. It provides the intended release characteristics of drugs in dosage forms without the need for excessive heat, lengthy process and/or toxic reactants [59].

DISADVANTAGES OF MICROWAVE TECHNIQUE RELATED TO SCALE UP

The most disadvantageous thing regarding microwaves, especially for drug discovery industry, is scalability. Scaling up syntheses from gram quantities to kilograms is essential for drug development, as this is a discouraging bottleneck for present-day process chemists. Many milligram- and gram-scale syntheses cannot be replicated, or

even attempted for safety reasons, on larger scales. Microwave technology provides the possibility that the same chemistries used in the initial route can be safely scaled up, enabling chemists to spend their valuable time creating novel synthetic methods, not recreating them. Currently there are no documented published examples of the use of microwave technology for organic synthesis on a production scale level. So, the scalability of microwave reactions still requires more development, especially in the technology and engineering field. Till now, there are a limited number of studies which focus on the effects of microwave on the physicochemical properties of excipients and drugs, as well as, the drug release properties of the formed products. The data of microwave influence on effect of loss factor, thermal conductivity, electrical conductivity, specific heat, moisture content, porosity, size, shape, temperature and other physicochemical attributes of pharmaceutical formulations on drug release are lacking.

So it is therefore imperative to conduct research for the need to scale up syntheses from gram quantities to kilogram and to further understand the mechanism of action of microwave in modifying the drug release properties of dosage forms, as well as, to justify the advantages of microwave for use in processing of drug delivery systems.

Conclusion

Although microwave technology has been around a long time, its application in the pharmaceutical industry is relatively recent. On the other hand, its acceptance and evolution are progressing at developing rate. The modern microwave drying systems are all equipped with the necessary safety measures to ensure completely safe processing for both operator and product. However, careful design of the process parameters is necessary to obtain optimal results from the microwave technology in pharmaceutical production. The main advantages of Microwave assisted techniques are faster and cleaner procedure, higher yields, development of new pathways and green chemistry. In past, microwaves were often used only when all other options to perform a particular reaction had failed or when exceedingly long reactions times or high temperature were required to complete a reaction. This practice is now slowly changing and because of the growing availability of microwave reactors in many academic and industrial laboratories, routine synthetic transformations are now being carried out by microwave irradiation. As US Food and Drug Administration have given authorization to use microwave technology in favor of the food

industries, an attempt could be made for the acceptance and approval of proposal for utilization of microwave technology in pharmaceutical industries. Thus it can be rightly said that Microwave is emerging as a promising tool in pharmaceutical processes and formulations.

References

1. Goaez PW. The New Encyclopedia Britannica, Britannica Inc., 15th Ed. vol 18, USA, 1985. P. 299.
2. Waldron MS. Microwave vacuum drying of pharmaceuticals: Development of a process. *Pharm. Eng* 1998; 8:9-13.
3. Bremecker KB. Moisture Content Measurement in Pharmaceutical Products by Microwaves. *Pharm. Ind* 1983; 45 (1): 78 – 81.
4. White JG. On Line Moisture Detection for a Microwave Vacuum Dryer. *Pharm. Res.* 11 (5) 728-732.
5. Sasaki K, Fukumura M and Miyake Y. Application of high frequency wave (microwave) Sterilization to Pharmaceutical preparations. *Eur. J. Parenter. Sci* 1998; 3(3): 73 – 84.
6. Sasaki K, Honda W, Ohsawa S, Miyake Y and Kawashima Y. Study of microwave sterilizer for injection ampoules. Part 4 Application to sterilization of thermally liable drug solutions *Arch. Pract. Pharm. Yakuzaigaku* 1998; 58 (3): 125 –135.
7. Sasaki K, Mori Y, Honda W, Miyake Y. Selection of biological indicator for validating microwave heating sterilization. *PDA J Pharm Sci Technol.*1998; 52 (Mar-April): 60 – 65.
8. Sasaki K, Honda W, Iijima K et al. Microwave continuous sterilization of injection ampoules. *J. Pharm. Sci* 1998; 50, 172.
9. <http://www.microwavetec.com/pharmamicro.php>, year 2009 dated 10/09/2011, at time 12:45 pm
10. Thomas PH, Tredree RL, Barnett MI. Preliminary studies on the freezing and thawing of intravenous solutions. *Br. J. Intravenous. Ther.* 1998; 4: 14-21.
11. Hecq JD, Evrard JM, Gillet P, Briquet C. Stability of injectable drugs stored in the freezer & thawed by microwave: actualization in 1996”, *Pharmakon* 1996; 106: 83 –92.

12. Moon YS, Chung KC, Chin A, Gill MA. Stability of Piperacillin sodium-tazobactam sodium in polypropylene syringes and polyvinyl chloride minibags. *Am. J. Health. Syst. Pharm.* 1995; 52: 999 –1001.
13. Sewell GJ, Palmer AG. Chemical and physical stability of three intravenous infusions subjected to frozen storage and microwave thawing. *Int. J. Pharm.* 1991; 72: 57 – 63.
14. Stolk LM, Fruijtjer A, Umans R. Stability after freezing and thawing of solutions of Mitomycin C in plastic minibags for Intravesical use. *Pharm Weekbl Sci.* 1986; 98: 286 –288.
15. Keusters L, Stolk LML, Umans R and Van Asten P. Stability of solutions of doxorubicin and epirubicin in plastic minibags for Intravesical use after storage at -20DGC and thawing by microwave radiation. *Pharm Weekbl Sci.* 1986; 8: 194 –197.
16. Ausman RK, Holmes CJ, Walter CW and Kundsinn RB. Application of a freeze-microwave thaw technique to central admixture services. *Drug Intell Clin Pharm.* 1980; 14: 284 –287.
17. Sewell GJ, Palmer AJ, Tidy PJ. Characterization of a frozen storage-microwave thawing system for intravenous infusions. *Int. J. Pharm.* 1991; 70: 119 –127.
18. Sanburg AL, Lyndon RC, Sunderland B. Effects of freezing, long term storage and microwave thawing on the stability of three antibiotics reconstituted in minibags. *Aust. J. Hosp. Pharm.* 1987; 17: 31-34.
19. Ashwin J, Lynn B, Taskis CB. Stability and administration of intravenous Augmentin. *Pharm. J.* 1987; 24:116 —118.
20. Williamson M, Luce JK. Microwave thawing of doxorubicin hydrochloride admixtures not recommended. *Am. J. Hosp. Pharm.* 1987; 44: 505 -- 510.
21. Gupta VD and Stewart KW. Stability of Cefuroxime sodium in some aqueous buffered solutions and intravenous admixtures. *J. Clin. Hosp. Pharm.* 1986; 11: 47—54.
22. Tabor E, Norton R. Freezing and rapid thawing of antibiotic admixture. *Am. J. Hosp. Pharm.* 1985; 42: 1507—1508.

23. Devgun N, Nanda A, Ansari SH. THE PHARMA REVIEW - SEPTEMBER 2009; Microwave-Assisted Extraction – A Promising Extraction Technique for Natural Products.
24. Microwave/microwave-assisted-synthesis-in-the-pharmaceutical-industry-a-current-perspective-and-future-prospectsummer-06.html by Dr Richard W. Wagner, summer 2006.
25. Golmakani M., Rezaei K. Comparison of microwave-assisted hydrodistillation with the traditional hydrodistillation method in the extraction of essential oils from *Thymus vulgaris* L. Food Chemistry, 2008a; 109: 925-930.
26. Golmakani M., Rezaei K. Microwave-assisted hydrodistillation of essential oil from *Zataria multiflora* Boiss. European Journal of Lipid Science and Technology. 2008b; 110: 448-454.
27. Barnhardt EK, Hargett WP, Thoma JE. Method and instrument for low temperature microwave assisted organic chemical synthesis. (February 2006): EP 1627681.
28. Murray JK, Farooqi, B, Sadowsky JD, Scalf M, Freund WA, Smith LM, Chen J. Gellman, S. H. J. Amer. Chem. Soc. 2005: 127; 13271.
29. Huang J, Wigent RJ, Bentzley CM. Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. Int J Pharm. 2006; 319:44-54.
30. Kim EJ, Chun MK, Jang JS. Preparation of a solid dispersion of felodipine using a solvent wetting method. Eur J Pharm Biopharm 2006; 64:200-205.
31. Gupta MK, Boner RH, Goldman D et al. Mechanism for Further Enhancement in Drug Dissolution from Solid-Dispersion Granules upon Storage. Pharm Dev Technol 2002; 7(1):103-112.
32. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002; 231:131-144.
33. Kerc J, Srcic S, Kofler B. Alternative solvent-free preparation method for Felodipine surface solid dispersion. Drug Dev Ind Pharm 1998; 24(4): 359-363.

34. Bergese P, Colombo I, Gervasoni D, Depero LE. Microwave generated nanocomposites for making insoluble drugs soluble. *Mater Sci Eng C* 2003; 23:791-795.
35. Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersions containing Ibuprofen. *Int J Pharm* 2008; 361:125-130.
36. Gohel, MC, Patel KV. Formulation Optimization of Diltiazem Hydrochloride Matrix Tablets Containing Modified Ispaghula Husk Using Factorial Design. *Drug Dev Ind Pharm* 1997; 23(11):1055-1061.
37. Gohel, MC, Patel KV. Formulation Optimization of Diltiazem Hydrochloride Matrix Tablets Containing Modified Ispaghula Husk Using Factorial Design. *Drug Dev Ind Pharm* 1997; 23(11):1055-1061.
38. Joshi HN, Kral MA, Topp EM. Microwave drying of aqueous tablet film coatings: a study on free films. *Int J Pharm* 1989; 51:19-25.
39. Doelling MK, Nash RA. The development of a microwave Fluid Bed Processor. II. Drying A.R. Tapas et al /*Int.J. PharmTech Res.*2009,1(4) 1049 Performance and microwave physical characteristics of Typical Pharmaceutical granulations. *Pharm Res* 1992; 9(11):1493-1501.
40. Duschler G, Carius W, Bauer KH. Single-Step Granulation Method with Microwaves: Preliminary Studies and Pilot Scale Results. *Drug Dev Ind Pharm* 1995; 21(14):1599-1610.
41. Stahl H, Van Vaerenbergh G. Single-pot processing. In: Parikh DM (Ed.), *Handbook of Pharmaceutical Granulation Technology*. London: Taylor and Francis Group; 2005, 311-331.
42. Jones PL, Rowley AT. Dielectric drying. *Dry Technol.* 1996; 14:1063-1098.
43. Sanga E, Mujumdar AS, Raghavan GSV. Microwave drying: principles and application. In: Mujumdar AS, Suvachittanont S (Eds.), *Developments in Drying*. Bangkok: Kasetsart University Press; 2000; 112-141.
44. Jansen W, Van der Wekken B. Modelling of dielectrically assisted drying. *J Microwave Power EE.* 1991; 26:227-236.
45. McLoughlin CM, McMinn WA, Magee TRA. Microwave drying of pharmaceutical powders. *Food Bioprod Process* 2000; 78:90-96.

46. C. M. Doyle and M. J. Cliff. Microwave drying for highly active pharmaceutical granules. *Manuf. Chem.* 1987; 32: 23 – 25.
47. Garcia TP, Lucisano JL. Single-Pot Processing. *Handbook of Pharmaceutical Granulation Technology*, Parikh, D.M., Ed.; *Drugs and the Pharmaceutical Sciences*; Marcel Dekker: New York, 1997; Vol. 81: 303-331.
48. Krieger B, Allen RD. Industrial Microwave Technology, joint paper presented at the Annual Meeting of the Rubber Division of the American Chemical Society.
49. Waldron MS. Microwave Vacuum Drying of Pharmaceuticals: the development of a process. *Pharm. Eng.* 1988; 8: 9.
50. Wade A. *Handbook of Pharmaceutical Excipients*, The Pharmaceutical Press, Washington, 1994.
51. Performance standards for microwave and radiofrequency emitting products, 21 CFR Part 1030, Washington, DC: General Services Administration, 1 April 1988, 461-464.
52. Electromagnetic fields, safety levels with respect to human exposure to radiofrequency, ANSI C.95.1-1982; American National Standards Institute, New York , 1982, 9-10.
53. Mandal TK. Evaluation of microwave drying for pharmaceutical granulations. *Drug Dev. Ind. Pharm.* 1995; 21: 1683.
54. Moll F and Maue R. Preparation of ointments with microwaves: does the use of microwaves produce the same quality? *Deutsche Apotheker Zeitung* 1988; 128 (Sep 15): 1871—1873.
55. Cross GA, Fung DY. The effect of microwaves on nutrient value of foods. *Crit Rev Food Sci Nutr.* 1982; 16(4):355-81.
56. Babincova M, Microwave controlled drug release from Magnetoliposomes, *Pharmazie* 1995; 50 : 702 –703.
57. Babincova M. Targeting and controlled release of drugs using Magnetoliposomes. *Ceska. Slov. Farm.* 1999; 48 (1): 27-29.
58. Wong TW, Chan LW, Kho SB, Heng PWS. Aging and microwave effects on alginate/chitosan matrices. *J Control Release* 2005; 104:461-475.

59. Tapas AR, Magar DD, Kawtikwar PS, Sakarkar DM, Kakde RB. Microwaves in drug discovery and development: A Review International Journal of PharmTech Research. 2009; 1 (4): 1039-1050.

Corresponding Author:

Bonde MN*

Email: minalbonde@zimlab.in