

## Microwave Drying

**Microwave drying is an accepted drying method for pharmaceutical formulations, which is nonetheless still relatively unknown to some. This paper attempts to give an overview of the most important aspects of microwaves and their relevance to pharmaceutical processing.**

First a brief history of the use of microwaves in the pharmaceutical industry is given. Some theoretical background on microwave properties is discussed to provide a better insight into the reasons for the use of microwaves and for the existence of certain safety measures. Also the design of the currently available single pot processors equipped with microwave drying is briefly discussed. Finally some considerations related to the process itself, such as parameter design, stability and regulatory concerns, are addressed.

### History

The first applications of microwave energy for heating and drying date back to the nineteen-thirties (1). The development of the magnetron during the Second World War presented a challenge to the engineering and scientific world to develop industrial applications for this technology. During the decades that followed major developments in the design of magnetrons and extensive investigation of material properties have led to the adoption of microwave applications in several industry sectors, such as the food, rubber, ceramics, paper and other industries (2). Also medical applications for microwaves were developed as early as the nineteen-fifties (3) (4).

Compared to other industry sectors, the pharmaceutical industry has been a late adopter of microwave technology. Only in 1979 the initial concept of combining microwave and vacuum was proposed by ICI, and the first static-bowl microwave-dryer prototypes were developed in collaboration with T.K.Fielder. In the same year, Dr. Schwabe and IMI developed a microwave vacuum belt dryer for drying plant extracts (5).

Although the static microwave dryer proved the potential qualities of microwave drying for the pharmaceutical industry, problems such as caking and local overheating led to the development of agitated microwave dryers in the mid-eighties and the first combined high-shear granulator-microwave dryer (Spectrum) was introduced by T.K.Fielder in 1987 (5) (6), followed by Collette N.V. in 1989 with the Vactron.

The interest in microwave technology was very high, as demonstrated by the fact that as early as 1989, an FDA workshop was held on which 4 major American pharmaceutical companies presented their experiences with the technology to more than 100 FDA staff, and AAPS dedicated a symposium to this new technology at their Annual Meeting (7). During the next decade, microwave drying has gained a strong foothold in pharmaceutical production – although the adoption of the technology has proceeded more slowly than first anticipated – and currently more than 100 microwave dryers are in use at pharmaceutical companies worldwide to manufacture a variety of drugs, of which many are approved by the FDA (5).

## Theory of 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: 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 (8).

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. 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 absorb microwaves are heated (9).

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 is a great advantage for the processing of pharmaceutical compounds (9).

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 (10):

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

Where P = the power density of the material = energy absorbed (W/m<sup>3</sup>)

f = frequency (Hz)

v = electric field (V/m)

E<sub>0</sub> = dielectric permittivity of free space (8.85 x 10<sup>-12</sup> F/m)

E<sub>r</sub> = dielectric constant of the material

tan δ = loss tangent

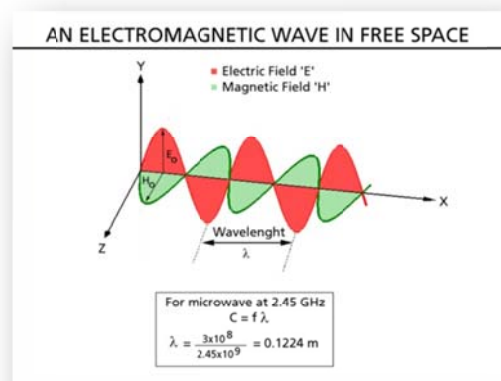


Figure 1: an electromagnetic wave in free space

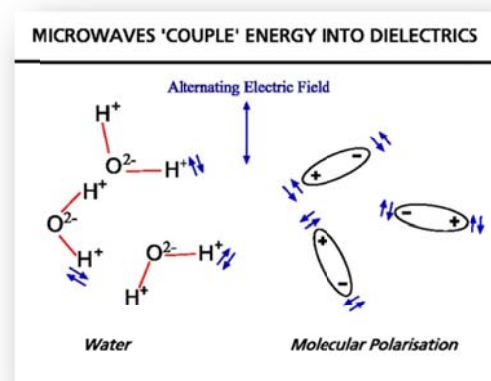


Figure 2: Di-pole rotation in a microwave field

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  $E_r \tan \delta$ , 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.

Given the characteristics of 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 materials these properties have been investigated and are published in tables and monographs (11).

**Table I: Loss factors of commonly used ingredients for pharmaceutical formulations**

Commonly used excipients		Commonly used solvents	
Maize starch	0.41	Methanol	13.6
Avicel	0.15	Water	12.0
Carbonate	0.08	Ethanol	8.6
Manitol	0.06	Isopropanol	2.9
Calcium Phosphate	0.06	Acetone	1.25
Calcium Carbonate	0.03	(Ice	0.003)
Lactose	0.048		
(Polypropylene	0.0027)		
(Teflon	0.0003)		

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. In figure 3, the change in loss factor with the temperature of some food products is illustrated.

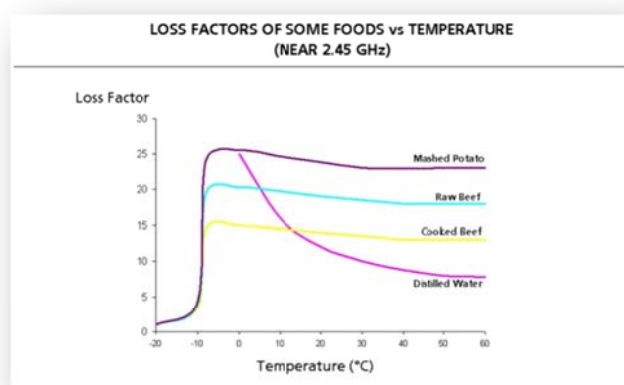


Figure 3: Loss factor vs. Temperature

As can be seen in figure 3, 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 (2) (9).

Another important characteristic of microwaves, especially related to the combination with vacuum drying is the breakdown electric field of gases. This characteristic is the electric field at which a discharge of the gas will take place. At atmospheric pressures, the risk of a breakdown is low, because the high frequency breakdown electric field is high. When the pressure is reduced, the breakdown electric field is significantly lowered, thereby increasing the risk for a breakdown.

A discharge of the gas can be observed as a glow or arc, and is disadvantageous because of possible damage to the product or the equipment and because it represents loss of power (2). In modern microwave dryers, many precautions have been taken to avoid such discharges (see next paragraph).

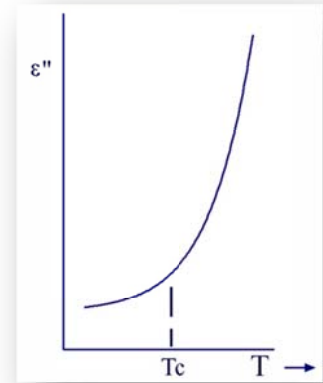


Figure 4: Thermal run-away phenomenon

## Microwave Drying Systems

Although microwaves are used in different types of equipment – for example microwave vacuum belt dryers (5) – this paper will only discuss the so-called Single-Pot systems, or high shear granulator-dryers, equipped with microwave drying capacity.

Magnetrons are the source of microwave energy and have either a fixed output or a variable output.

Fixed output magnetrons regulate the forwarded power to the processing vessel by cycling on and off. Usually they have a low power and several magnetrons are mounted on the lid of the bowl to allow step-wise control of the microwave input into the product.

Variable output magnetrons control power directly by adjusting wattage and usually have a higher output level. They are located in a separate area and the microwaves are guided to the processing vessel by wave-guides. This setup allows easier access for servicing, but requires proper tuning of the wave-guides to avoid reflection of microwaves to the magnetron.

As magnetrons generate heat, they have to be cooled using either air or water. The latter is the most efficient way of cooling magnetrons given the greater heat capacity (8).

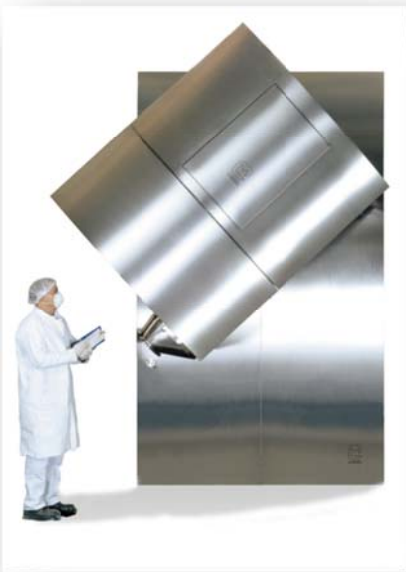


Figure 5: Top drive Single Pot Processor: UltimaPro™ 600 (GEA Pharma Systems nv)

Modern microwave dryers are equipped with several features to ensure safe operation of the system for the operator, the product and the equipment.

All microwave equipment has to comply with the guidelines for microwave leakage specified by the Center for Devices and Radiological Health within the FDA and by the American National Standards Institute (12) (13), which is 5-mW/cm<sup>2</sup> maximum exposure at a distance of 5 cm from any surface of the microwave cavity and at a frequency of 2450 MHz. The equipment manufacturers include safety features such as microwave chokes and conductive seals into the design of microwave processors to avoid any microwave leakage from the vessel.

In addition to these features to avoid leakage, the available microwave systems are designed with safety interlocks to avoid accidental exposure. For example, microwaves can only be activated when the process vessel is operating under vacuum and all bowl openings are sealed off.

Early reports on experiments with the prototypes of microwave dryers often reported problems with temperature control of the product, arcing, local overheating and even burning of the product. These problems were mainly related to design issues or lack of experience with microwave drying.

All modern microwave dryers have an optimized design for microwave drying – for example, sharp edges and loose contacts between metal parts are avoided, because discharges could occur there. Also the control systems have been optimized to include different process controls, such as temperature control, microwave reflection control and arc detection. Important parameters such as forwarded power, reflected power, product temperature, energy added, etc. can be monitored in real-time and maximum limits can be set to control the process.

Finally, to avoid local overheating of the product the possibility to mix at low speed, or to use a swinging bowl to move the product is offered.

## Process Considerations

Directly connected to the early observations mentioned in the previous paragraph came also the concerns about a possible influence of microwave drying on the granule characteristics and stability of the product.

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 (8) (14) (15) (16) (17).

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 (8).

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 (18), 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) (19).

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. 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. As an alternative to using the mixer arm to agitate the product, the use of a swinging bowl is offered by GEA Pharma Systems nv in their UltimaPro™ range.

Finally, the control of the jacket temperature during microwave drying can have an important impact on the yield of the process. As the microwaves supply most of the energy needed for drying, the heated jacket of the bowl does not need to act as an energy source. Therefore, its temperature can be controlled to a temperature slightly above or below the product temperature to avoid caking of the product.

Endpoint control of the drying process is another important aspect of the microwave drying process. All microwave dryers offer the possibility to use product temperature as endpoint for microwave drying. Product temperature is a good indicator for the end of the drying process if the formulation contains ingredients with a relatively high loss factor such as cornstarch. However, if the formulation contains only ingredients with a low loss factor (for example lactose), product temperature will rise very slowly, and over-drying could occur if the endpoint of drying is only based on product temperature. In those cases, the amount of reflected power gives a good additional indication for the endpoint, as reflected power will increase towards the end of the process, because less microwave energy is absorbed into the product. Additionally, the UltimaPro™ of GEA Pharma Systems nv is equipped with a calibrated power measurement (forwarded and reflected) allowing the calculation of the exact amount of energy added to the product. This amount of energy added can then be used as a validated endpoint for drying if a known amount of liquid has to be evaporated.

## Conclusions

Although microwave technology has been around since the Second World War, 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 make them however 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.

For more detailed and extensive background about the theory of microwaves and its industrial applications, I refer to the book "Industrial Microwave Heating" by A.C. Metaxas and R.J. Meredith (2).

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