

Single-Pot Systems for Drying Pharmaceutical Granules



This paper reviews single-pot systems for the production of solid dosage drugs in the pharmaceutical industry. A discussion of the underlying physics is followed by a detailed review of the drying processes. The paper concludes by a comparison of the different techniques based on published data.

by Harald Stahl

The number of single-pot systems used for the production of granules for solid drugs is increasing continuously worldwide. Even if 'single-pot system' has now become an accepted term, it may be helpful to specify, though, that the single-pot system referred to in this paper always consists of a mixer/granulator and a dryer incorporated in one vessel. A typical single-pot system is shown by Figure 1.

The first single-pot units were mixer/granulators retrofitted for vacuum drying. The energy needed for drying was provided by heated jacket water. However, the single-pot system was only accepted by the pharmaceutical industry when drying times were reduced dramatically by microwave (1987) [1] or by gas (1989) [2] assistance.

A number of different reasons exist why single-pot technology is selected for the production of granules:

- The yield of modern production-scale single-pot systems is far in excess of 99% [3].
- Organic solvents can be recovered relatively easily, as it is only necessary to treat the pure solvent vapour rather than a large air flow with a small organic solvent concentration as in the case of the fluidized bed process. As the granules are dried in a vacuum atmosphere containing practically no oxygen, the explosion risk is also reduced substantially.
- Where highly active substances are handled, the one-pot process allows a relatively easy protection of the environment because of the fully contained design and the integrated cleaning-in-place systems.
- One-pot units can be used for the aseptic production of granules since the process is fully contained and an additional sterilizing-in-place system can be installed [4].

Granulation in a one-pot system is the same as in a conventional mixer/granulator. The conventional unit then discharges the moist granules into a stand-alone dryer. Frequently, a sizing mill is interfaced to break down large granules which are difficult to dry. As milling cannot be integrated into the one-pot process, potential oversize particles are an essential consideration with respect to drying.

Drying

Different drying processes have been used in one-pot systems. These processes and their limits are discussed below.

Pure Vacuum Drying. In pure vacuum drying, the most simple and oldest alternative, the energy needed for drying is provided by heated jacket water. Since most substances for pharmaceutical applications are sensitive to high temperatures, the maximum inside wall temperature of the vessel is limited. As the thermal conductivity of the granules is relatively low, they must be moved during drying to absorb the heat necessary for the evaporation of the solvent from the vessel wall. Since the granules are porous, thermal conductivity decreases as the vacuum pressure drops and drying progresses [5] [6]. This effect can only be accommodated by more mechanical mixing which results in a partial mechanical destruction of the granules.

Gas-Assisted Drying. Due to the problems discussed, unassisted vacuum drying is only in exceptional cases suited for the production of drug granules. To accelerate drying, gas can be injected into the process. Equipment manufacturers use different systems [4]. The first single-pot units designed for gas-assisted vacuum drying were introduced by Zanchetta & C. SRL in 1989 [2]. All gas systems presently on the market are designed for bottom-entry gas injection. The gas rises through the granule bed and is exhausted together with the evaporated liquid through the cover of the pot. Necessarily, this vacuum unit and the associated organic solvent condenser must be larger than a vacuum unit built for unassisted vacuum drying or microwave drying. Most of the energy required for evaporation is still transferred into the pot across the wall of the vessel, as discussed in [7]. In the Zanchetta Roto P 50 unit (50L), for example, the gas flow rate is 16 m³/hr. If the gas is injected at a temperature of 60°C and the gas cools to 20°C as it passes through the moist granules, the energy input is 640 kJ. If this heat were exclusively available for the evaporation of water and did not heat the product, it would be sufficient to evaporate approx. 250ml of water per hour. The gas flow rate in pots marketed by other manufacturers is still lower [8]. According to [8], gas throughput in the GP 65 unit (65L) is no more than 2 m³/hr.

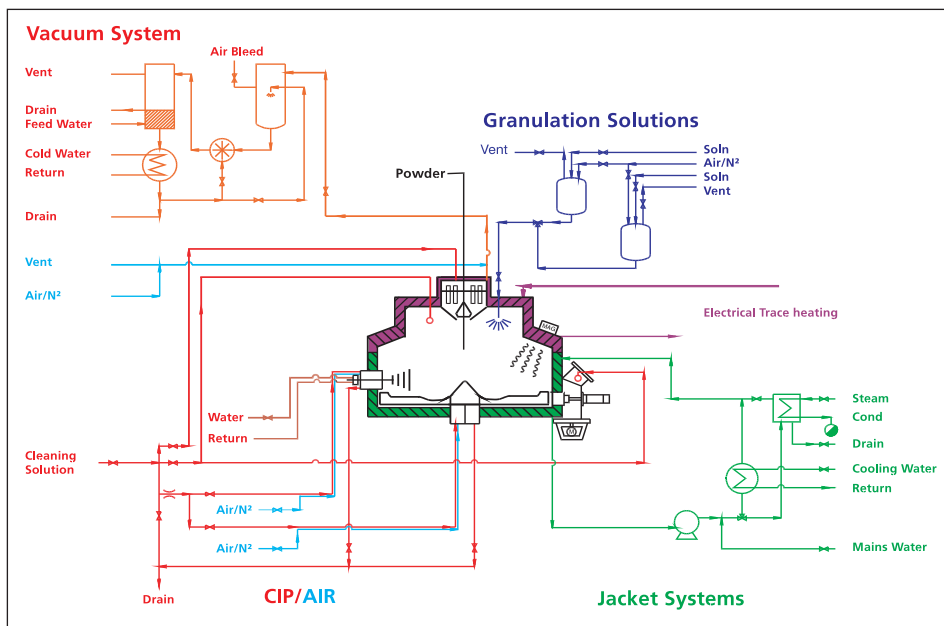


Figure 1: Typical single-pot system.

The substantial reduction in drying time measured in gas-assisted drying system tests is for this reason merely to a very small degree due to the additional energy input, but mainly attributable to the largely improved heat transfer between the vessel wall and the product [9]. Finally, solvent vapour transportation from the granule bed to the vacuum pump is increased by the gas flowing through the vessel.

Microwave Drying

History. The first microwave heating and drying applications date back to the thirties [10]. However, it took the development of powerful microwave generators (magnetrons) in the fifties for microwave drying to make real progress mainly in the food industry [11] [12]. Microwave applications in medicine were also developed during the fifties [13] [14]. In the pharmaceutical industry, microwave systems were first used in 1979. ICI and T.K. Fielder developed together a static microwave vacuum dryer. Dr. Wilmar Schwabe and IMI [17] built a microwave vacuum belt dryer for drying plant extracts in the same year.

The first single-pot system using microwave-assisted drying was marketed by T.K. Fielder in 1987. By 1992, some twenty pharmaceutical companies around the world had already installed forty microwave systems [18]. As early as in 1989, four of the largest American pharmaceutical companies presented stability data at a meeting with over 100 FDA representatives and demonstrated that the decomposition products of microwave drying do not differ from those of conventional drying [30]. At present, some 100 microwave units are in operation around the world and manufacture approx. 35 different drugs mostly approved by FDA [4].

Physical Background. Microwaves are electromagnetic waves generated usually by magnetrons under the combined force of an electric and a magnetic field [10]. All single-pot systems use microwaves of a frequency of 2,450 Mhz equivalent to a wave length of 12.2 cm [31]. In physical terms, the product to be dried is a dielectric material exposed to a microwave field. The material and the field interact by polarization which produces a relative displacement of positive and negative bound charges in the dielectric. A distinction must be made between the displacement polarization of charged particles and the orientation polarization of particles which have permanent or induced dipole moments.

Materials behave very differently in the presence of microwaves. This behaviour is described by the complex dielectric constant. If polarization was frictionless (real part of the dielectric constant), the process would only produce a charge difference without heating the product. However, if the motion of the molecules results in friction, electric energy is needed to overcome the friction, causing product heating. This process is expressed by the imaginary part of the dielectric constant referred to as the dielectric loss factor. These properties are known for most materials and have been published in tables and in monographs [29]. This paper will therefore not specify material properties, but discuss some of the general knowledge on the interaction between microwaves and materials:

- The interaction between inorganic materials and microwaves is normally very weak. The loss factor of silica glass is, for example, 0.0002. An empty cup is, for instance, hardly heated in a residential microwave appliance.

- Water of crystallization cannot be stimulated by microwaves, because the lattice prevents motion and therefore orientation polarization.
- Homopolar liquids do not interact with microwaves, either, because they do not have any dipole moments. The loss factor of cyclohexane is, for example, 0.0004.
- The interaction between polar liquids and microwaves is particularly strong, as the loss factor of ethanol of 8.6 shows.
- The behaviour of organic solids varies. The loss factor of PTFE is, for example, 0.0002, while the loss factor of lactose is 0.02.
- The loss factor of a homogeneous mixture of two substances is always between the loss factors of the two pure substances. Methods of calculating these factors are, for example, given by [21] [22].
- Heterogeneous mixtures of a solid and a polar liquid, such as moist oversize granules, absorb microwave energy particularly strongly where the moisture content is high since the loss factor of the liquid is substantially higher than that of the solid. The residual moisture content is therefore uniform [1] [23] [24].
- Microwaves of a wave length of 12.2cm penetrate a product, depending on residual moisture, by between several centimeters (very moist) and several metres (dry). For this reason, little product motion is required during drying.
- As regards pharmaceutical substances, the experience of microwave drying has in many cases been good, as the number of approved drugs shows. Nevertheless, the fitness of each new formulation (in particular, if it contains a new substance) for microwave drying must be tested. Even if it is unlikely that a substance cannot be dried by microwaves [25] [26], such tests are, in fact, necessary, as the relationship between the complex dielectric constant and temperature and moisture content is different for every substance.

Process. Figure 2 shows a typical microwave-assisted vacuum drying process. Following granulation (stage 1), the moist granules are dried. In stage 2, the pressure is decreased to a vacuum of normally between 40 and 80 mbar absolute. As the pressure decreases, liquid evaporates and the product temperature falls. To accelerate drying, microwave energy is radiated into the pot when the vacuum pressure has been reached (stage 3). Energy input depends on the product temperature. Ideally, the microwave energy only serves to evaporate liquid without heating the product. As the moisture content of the product

decreases, the temperature of the product will rise (stage 4).

Energy input is decreased by the control system. As the temperature of the product rises above a limit temperature because the residual moisture content is low (stage 5), the microwave system is stopped. The granules will normally be sufficiently dry. If the residual moisture concentration is too high, drying continues at a reduced vacuum pressure without microwave assistance (stage 6).

If total drying time is not particularly critical, the temperature of the vessel wall can be controlled to be only slightly (approx. 1°C) above the product temperature. This mode of operation prevents energy input across the wall of the pot, but also avoids deposits on the vessel wall. The energy needed for drying is in this case exclusively provided by the microwave system.

radiation is monochromatic, a polychromatic frequency spectrum is used for infrared radiation because of the type of the radiation source [5] [7]. The radiation energy stimulates intramolecular vibrations. Infrared absorption depends for this reason very much on the composition of the material including the moisture level near the surface, since every molecule will only absorb energy at a characteristic wave length. This effect is, for example, used in infrared spectroscopy to identify molecules.

Process. A 50L dryer combining jacket heating, gas assistance and infrared heating is described in [7]. A 400L vessel is also discussed in [2] [7]. Fundamentally, the dryer is of the gas-assisted type, as discussed above. To accelerate drying, infrared energy is radiated into the pot through the cover. Since the surface temperature of the radiation source is as high as 1,000°C, it must be isolated from the pot itself by a silica glass window. However, as silica glass is not

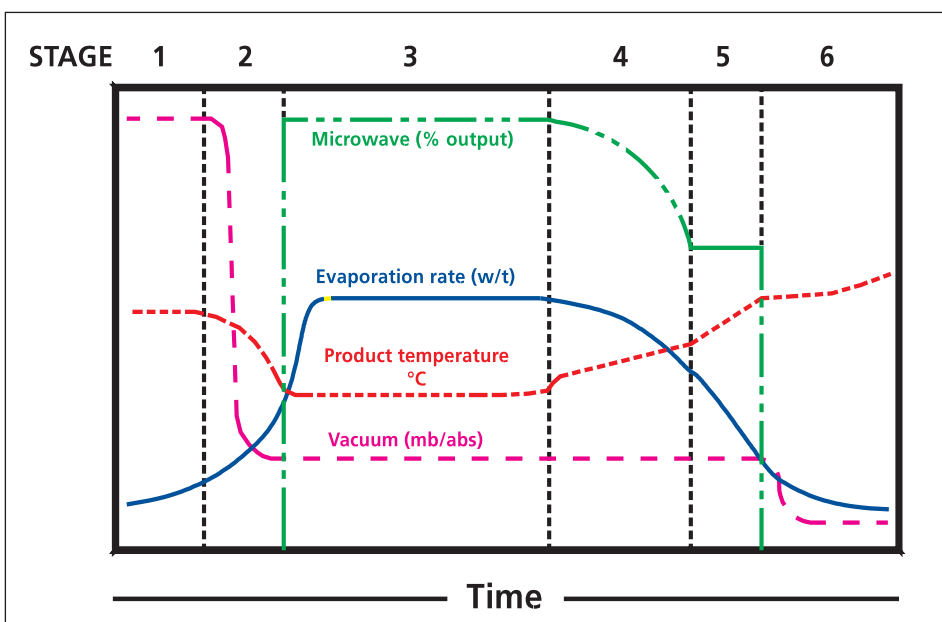


Figure 2: Typical microwave-assisted vacuum drying process. Duration usually between 45 and 120 min.

Infrared Drying

A gas-assisted system equipped with an infrared dryer was proposed by [7] [2] as an alternative to microwave drying. Papers on infrared drying without gas assistance have not been published to-date.

Physical Background. Like microwave drying, infrared drying uses electromagnetic waves. Infrared waves are, however, four to five orders of size shorter than microwaves. For this reason, the behavior of material exposed to infrared radiation is fundamentally different. Whereas microwaves penetrate deeply into the material because of their relatively long wave length and transfer energy selectively to the moisture, infrared radiation which has a substantially higher energy content interacts mainly with the surface and the near-surface area of the material [5]. While microwave

completely translucent to infrared radiation, the silica glass becomes very hot. The silica glass is therefore purged with cold air, because the risk of igniting dust on the glass would otherwise be too great. Unfortunately, no clear data on infrared radiation levels are given in [7] for the 50L pot. The dissertation only mentions an absorbed radiation level of $3 \times 250 \text{ W}$ for one of the radiators used. No absorbed or emitted radiation levels are given for the other radiators. The enhancement of the gas-assisted process by infrared energy is only discussed by a comparison of the moisture content-versus-time curves. In the 400L scale configuration described in [7], the infrared energy did not reduce the drying time required by the gas-assisted process without infrared radiation enhancement. The data in [2] do not allow a quantitative analysis.

Comparison of Drying Methods

The different drying techniques are compared below both for pilot-scale and full-scale units. This comparison is based on water, as the heat of evaporation of water is particularly high. The heat of vaporization of other liquids used in pharmaceutical production processes is substantially lower as table 1. [27].

Liquid	Boiling temp.(°C)	Heat of evaporation (kJ/kg)
Water	100	2257
Ethanol	78.3	846
Isopropanol	82.3	670
Acetone	56.2	523
Methylene chloride	40.1	329
Chloroform	61.2	254

Table 1: Boiling temperature and heat of evaporation of various liquids.

Prior to a discussion of the drying times achieved by the different processes, it is helpful to consider the mechanism involved in the removal of water from granules. As thermal energy is transferred into the pot after granulation, the energy will have the following three effects:

- Increase in granule temperature
- Increase in water temperature
- Water evaporation

In the case of a mixture consisting of 20 kg of solid matter of a typical specific heat of 1.25 kJ/(kgK) and 3 kg of water, for example, energy requirements are as follows:

- Increase in granule temperature from 20 to 40 °C = 500 kJ
- Increase in water temperature from 20 to 40 °C = 250 kJ
- Water evaporation = 6.770 kJ

The data demonstrate that the drying capacity of such a system is reasonably described by the water evaporation capacity. This conclusion is important, as residual moisture levels and product end temperatures differ in the cases discussed below.

Pilot-Scale Drying. Pilot-scale 50 - 70L units are offered by all manufacturers of single-pot systems. Depending on the manufacturer, drying is by one or several of the drying processes discussed in this paper. Results have been published by a number of authors [7] [8] [18] [25] [26] [28] for individual processes or for several processes which were compared. These results are largely in agreement with each other. The moisture concentration-versus-drying time curves in Fig. 3 [8] are typical of the different drying techniques.

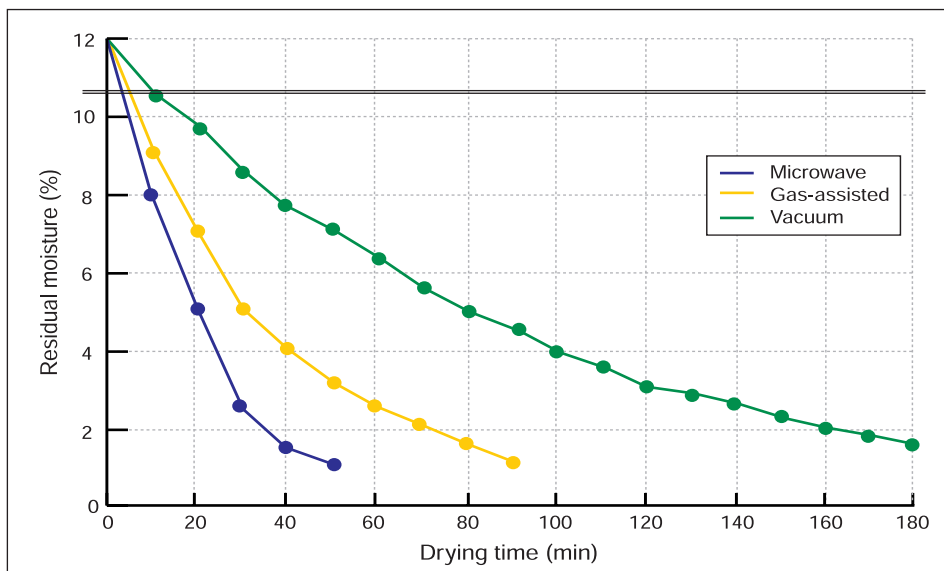


Figure 3: Typical pilot-scale moisture versus drying time curves.

Even at the pilot scale, the drying time needed for unassisted vacuum drying is unacceptably long in particular in the case of temperature sensitive substances, because the maximum vessel wall temperature is limited. Drying can be accelerated by passing gas through the pot, but again, the maximum wall temperature is a limiting factor. These limitations do not exist in microwave drying where the wall can be kept at a temperature similar to the product temperature to avoid caking, condensation and fouling. For water and a vacuum pressure of 40 mbar absolute, this temperature is approx. 31°C as long as the residual moisture content of the product is sufficiently high. As drying continues, the residual moisture concentration becomes too low for the entire microwave energy to be used for evaporation as discussed above and the product begins to heat up. This temperature rise is normally limited by a reduction of energy input per unit time. If the product is not yet sufficiently dry, when the maximum product temperature is reached and the microwave dryer is stopped, the process must be completed by pure vacuum drying. However, unlike straight-forward vacuum drying or gas-assisted vacuum drying, vacuum drying following the use of microwave energy benefits from the hot temperature of the product, as the heat stored by the product is available for evaporation.

As discussed, single-pot processes do not allow the destruction of oversize granules by a sizing mill as in a process where the moist granules from the mixer granulator are transferred to a fluidized-bed dryer. If such oversize particles exist, microwave drying is the only process which achieves a homogeneous residual moisture level, because moisture absorbs more microwave energy than the dry granules.

The correlation between the drying time and the fill level of a 80L single-pot unit is discussed

in [35]. The paper shows that this correlation is non-linear if no microwave energy is used.

Scale-up and Production-Scale Drying. The capacity of a full-scale production-type unit may be up to 2,000L. Drying in such single-pot systems has been discussed by different authors [18] [26] [32] [33].

In [18], a 65L and a 1,200L vessel featuring microwave drying are compared. In the 65L pot, 15 kg of solid matter granulated with 4 kg of water was dried in 90 minutes. The same time was sufficient to dry 210 kg of solid matter granulated with 60 kg of water in the 1,200L vessel. Microwave energy input was 1.8 kWh at the 65L scale and 27 kWh at the 1,200L scale. Temperature measurements in the 1,200L vessel made at different points and at different times of the drying cycle confirmed that temperature has very evenly distributed in the product and in good agreement with the temperature readout of the integrated temperature sensor. The paper also mentions that lumping may occur when hot product is discharged from the pot. Product cooling using a cooling fluid circulating through the jacket would be too slow because of the small size of the wall surface by comparison with the product volume handled. The paper suggests the addition of 60 kg of dry ice which reduces the temperature of the product by 20°C in 7 minutes.

Upscaling from 75L to 600L and 1,200L is discussed in [32] for a moisture-sensitive formulation requiring a reduction of the moisture content to less than 0.2%. Using microwave energy, 15 kg of the substance could be dried in an average 40 to 45 minutes in the 75L pot. The drying time was the same for 300 kg of substance in a 600L vessel, while 50 to 55 minutes were needed to dry 600 kg in a 1,200L pot. Without microwave assistance, scale-up from 75L to 600L trebled the drying time.

Evaporation rates are given in [26] for different formulations and different size pots. In 50L and 70L units, gas-accelerated drying achieved rates of 1.3 to 1.6 kg of water per hour. These rates were more than doubled by the use of microwave energy. The paper does not mention any substance quantities but merely the average water concentration of 25% after granulation. These pilot-scale evaporation rates are compared by the paper with 600L pot microwave and 400L pot gas-assisted drying data for the same formulations. Microwave drying achieved an evaporation rate of between 20 and 30 litres of water per hour and resulted in a drying time of approx. 90 minutes or less for all formulations. Gas-assisted drying only allowed evaporation rates between 6 and 10 litres per hour and required drying times of up to 5 hours.

Regulatory Considerations

Stability Data. Data for product storage over a period of up to twelve months were published in [26]. In most cases, decomposition product concentrations were lower for microwave-dried formulations than for the formulations made using conventional or gas-assisted drying. In one case only, a slightly increased decomposition product concentration was found for the microwave-dried formulation. In all cases, the products were well within the approved specifications after twelve months of storage at 40°C.

Other authors [30] [36] [37] [38] [39] also reported that single-pot microwave-assisted drying produces no more and no different decomposition products than tray of fluidized-bed dryers.

Product deterioration due to decomposition or burning as a result of microwave drying occasionally mentioned in literature [7] [26] [40] [41] is practically always do to operator errors such as agitators which are not switched on or incorrect process data such as high microwave energy input or inappropriate vacuum pressure. In all cases, these errors resulted in product deterioration due to local or global overheating.

Approval

In [42], the authors report that most of eight European drug approval agencies merely required process validation data when the process for the production of an approved substance was changed from fluidized-bed drying to single-pot microwave drying. Three agencies required additional six-month stability data.

The FDA assesses the changeover from one drying process to another process [33]

according to [43] and imposes for a changeover to microwave drying no other requirements than for a changeover to any other drying process.

No special requirements for the approval of drugs dried by microwave energy have been reported since 1990.

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