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RESEARCH PAPERS

SINGLE-STEP GRANULATION METHOD WITH MICROWAVES: PRELIMINARY STUDIES AND PILOT SCALE RESULTS

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ABSTRACT

Common pharmaceutical excipients and compounds were dried either by a simple convection method or by a combined convection and microwave method in a static bed or by a combined microwave and vacuum method in a mixed bed. A simple placebo granulation was dried by an exclusive vacuum method and by a combined microwave and vacuum method in a mixed bed. The results were compared.

INTRODUCTION

Due to environmental restrictions or economical reasons (1), there is a big need in the field of pharmaceutical production for adequate technologies. Particularly in the field of drying pharmaceutical granules cost reduction and ecologically accepted technologies are required which are able to guarantee a high level of quality and security. A better alternative for the established technologies of tray drying and fluid bed drying seems to be the single-step-granulation technology where dry mixing, granulating and drying steps are performed in a single vessel without any refilling or transportation process in between and without any risk of cross contamination. The purpose of this study was to find out whether a microwave drying method is satisfactory in this respect and whether it is able to meet the criteria of a universally applicable production method.

MATERIAL AND METHODS

As preliminary studies drying experiments were carried out with single excipients as lactose monohydrate (L), corn starch (S) or calcium hydrogenphosphate (C) and with the following placebo formulation.

Lactose monohydrate	60.0%
Corn starch	32.0%
Corn starch, soluble (for granulating solution)	4.5%
Silicium dioxide	3.2%
Magnesium stearate (for final blending)	0.3%
Purified water	25.5%

For the preliminary trials a Heraeus MUT 6060 (Heraeus, D-63450 Hanau) microwave dryer was used. In this dryer only static drying was possible and the wetted samples had to be prepared outside the dryer. The power supply for microwave drying was an ON/OFF-type magnetron. For less than maximum input calculated ON/OFF-intervals must be controlled exactly. Alternatively the MUT 6060 equipment can be used solely as a convection dryer or as a combined convection-microwave-dryer.

For the wetting of the excipients a planetary mixer (Erweka, D-63150 Heusenstamm was used. The wetted samples were passed through a 0.2 mm sieve and filled into a flat glass tray. In order to minimize undesirable material effects the same container was always used.

For temperature measurement during drying the MUT 6060 was provided with a PT 100 thermocouple probe well placed in the material to be dried. Loss on drying was determined by simple weighing of the samples after certain drying times.

The pilot scale experiments were carried out in a Collette Vactron 75 (Machines Collette, B-2160 Wommelgem) single-step-granulator. Granulating of the placebo formulation was standardized by an end point detection system based upon power measurement. During the drying step the pressure inside the vessel, the temperature of the material and the value of the electric field were registered. The moisture content of the batch was determined by a Mettler infrared balance (Mettler GmbH, D-35396 Giessen).

In order to simulate caking conditions different compounded granules containing model drugs were irradiated with microwaves in the MUT 6060. Quality control analyses were done by means of HPLC and DSC.

RESULTS AND DISCUSSION

Static drying of pharmaceutical excipients in the MUT 6060

During the first trials with the MUT 6060 equipment effects like overheating and even burning of the product could be observed frequently. Therefore an indirect quantitative method was applied to find out whether the electric field inside the applicator was homogeneous or not. According to Figure 1 nine glass containers

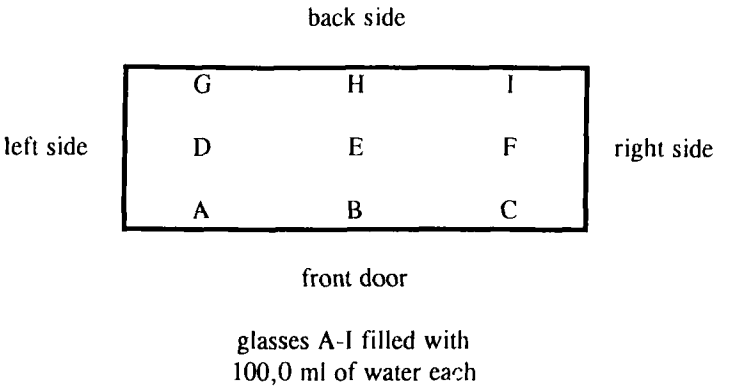


FIGURE 1: Cross-sectional view of the MUT 6060 microwave dryer

each of them filled with 100 ml of water were placed on the bottom of the applicator. By measuring the temperature of the water it could be proved that different amounts of microwave energy were absorbed by the water depending on the position of the glasses (Figure 2). As the results of this simple trial were reproducible, it can be concluded that the electric field and the distribution of the microwaves inside the dryer cavity were not homogeneous.

After adjustment of the power input device it was finally possible to utilize a small but relatively homogeneous area in the middle of the applicator for further trials.

As a result it was found that there was no possibility of drying the organic substances L and C without overheating and thermal damage. Therefore intermittent application of microwave was necessary, and the maximum temperature inside the material was limited to 70°C.

The different drying behaviour of the excipients was due to their different dielectric losses (S: $\varepsilon'' = 0.41$; L: $\varepsilon'' = 0.02$; C: $\varepsilon'' = 0.06$) on the one hand and due to their different sorption characteristics on the other hand (C and L belong to the low hygroscopic class I, while S belongs to the high hygroscopic class III) (2,3,4).

The excipient S tended to heat up itself by absorption and had better binding properties for moisture (Figure 5), whereas L (Figure 4) and especially C (Figure 3) could be dried more easily and with less risk of overheating. They did not absorb too much microwave energy, but they gave back the bound water more readily than S. The inorganic substance C could even be dried with permanent microwave power input (Figure 3, C4). Obviously there is a big difference between exclusive convection drying and combined microwave and convection drying.

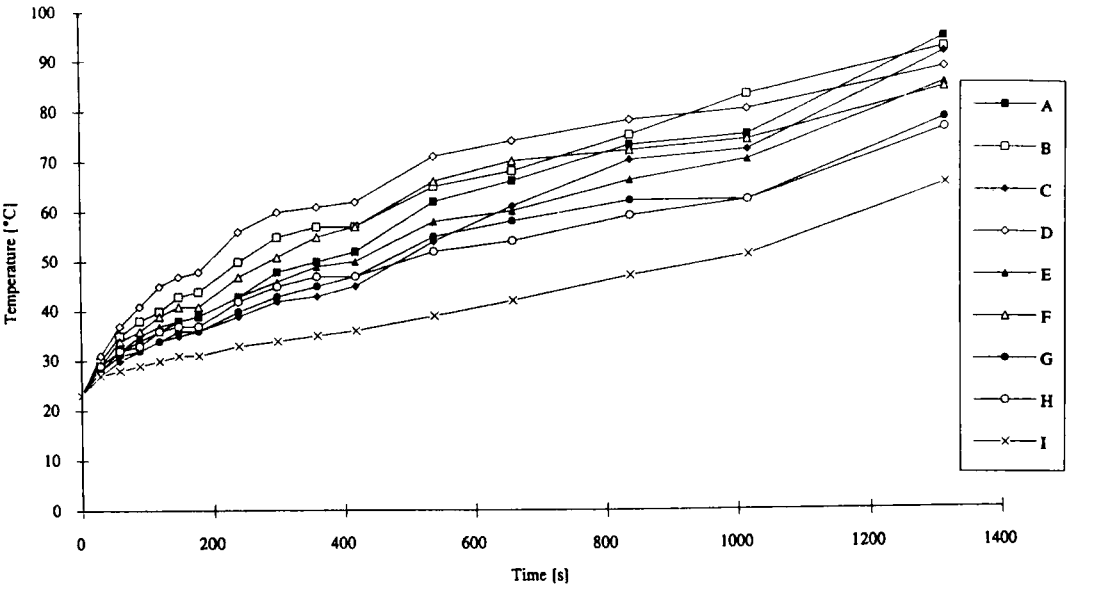


FIGURE 2: Temperature curves of water samples irradiated with full microwave power (720 W)

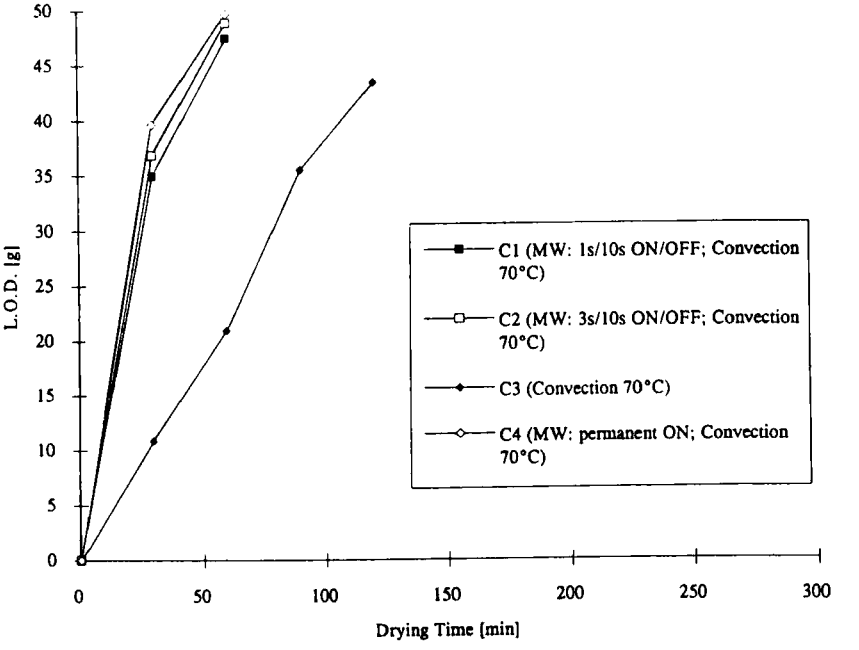


FIGURE 3: Drying curves of calcium hydrogenphosphate samples

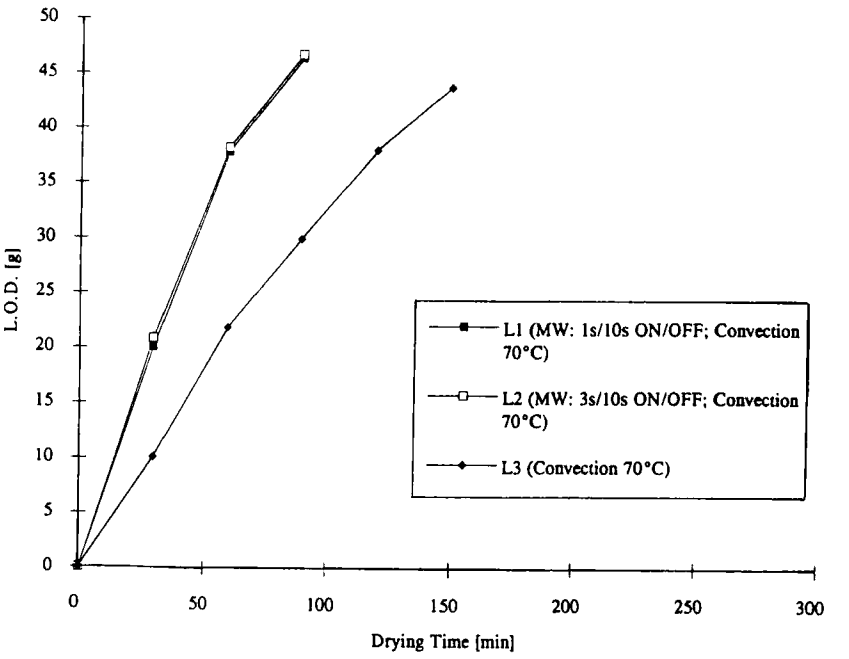


FIGURE 4: Drying curves of lactose monohydrate samples

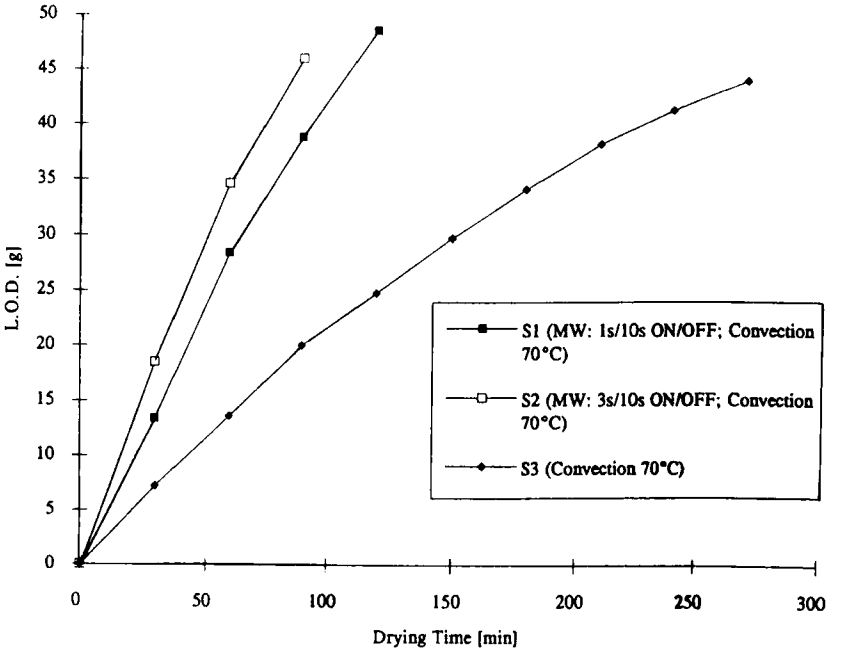


FIGURE 5: Drying curves of corn starch samples

Dynamic drying of pharmaceutical excipients in the Vactron 75

Dynamic instead of static drying processes were the main differences between the preceding trials and the following series. This was realized by suitable action of the impeller blades and additional vacuum and conduction drying elements.

In this process the dielectric behaviour of the materials played a predominant role. Substances like S with a rather high dielectric loss showed a continuous increase of temperature because not only the moisture but also the excipient itself absorbed considerable amounts of microwave energy (Figure 6). For the same reason the values of the electric field strength were almost constant. Both experimental batches were dried with the same microwave power input of 1 kW. They showed a satisfactory reproducibility.

A totally opposite behaviour could be observed in drying L with a different power input of 1 kW (Figure 7: L 310127) and 3 kW (L 310128). While the temperature curves showed almost no increase during drying, the E-field strength increased steeply when the endpoint of drying was reached. This is the point when all the free water has evaporated. In this case E-field measurement could be used for end point detection in drying, because a significant change can be easily observed. In trial L 310128 the excess of microwave energy induced an automatic reduction of power input by 20% whenever the limit of 40 kV/m was exceeded as indicated by the arrows in Figure 7.
As the excess of power input was too high in trial L 310128 arcing resulted, because the critical field strength for breakdown phenomena was reached (5). The reason for this excess and for the arcing was an interruption after 30 minutes and the restart with 100% = 3 kW power input (6,7).

Dynamic drying of placebo granules in the Vactron 75

In order to get reference values two placebo batches were dried with the same jacket temperature but different vacuum stages. Even with a very low pressure of 2 mbar inside the vessel a residual moisture of 3.6% resulted after five hours of drying in trial E 300122. Drying at 30 mbar ended as well at 3.6% after six hours (Figure 8).

Finally trials were done by additionally activated microwave functions. In all these trials the pressure inside the vessel showed 30 mbar and the microwave power input was at 3 kW. Three of the trials were carried out at a jacket temperature of 60°C, one trial with a reduced temperature of 45°C (Figure 9). All trials with the higher jacket temperatures reached a residual moisture of 2.5±0.1% after 90 minutes, thus proving satisfactory reproducibility. In order to reach the same moisture contents of 2.5% with a lower jacket temperature of 45°C two hours of drying were necessary. Comparing for example trial E 300121 (Figure 8) without and trial E 280121 (Figure 9) with microwave input the difference in drying times was significant.

Additionally the E-field and temperature measurement were evaluated in order to find out whether they were suitable methods for end point detection in

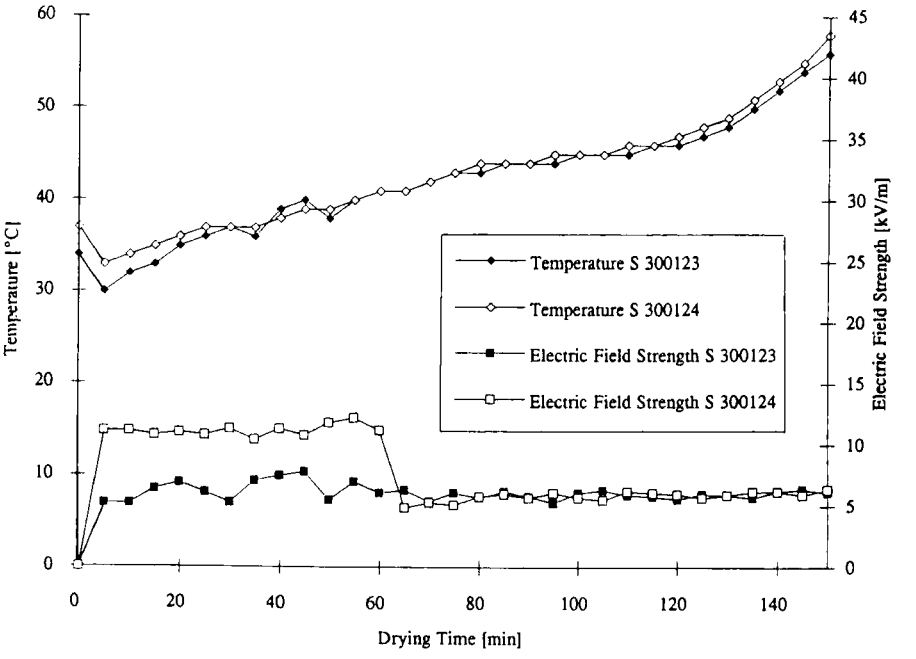


FIGURE 6: Temperature and E-field curves of corn starch samples

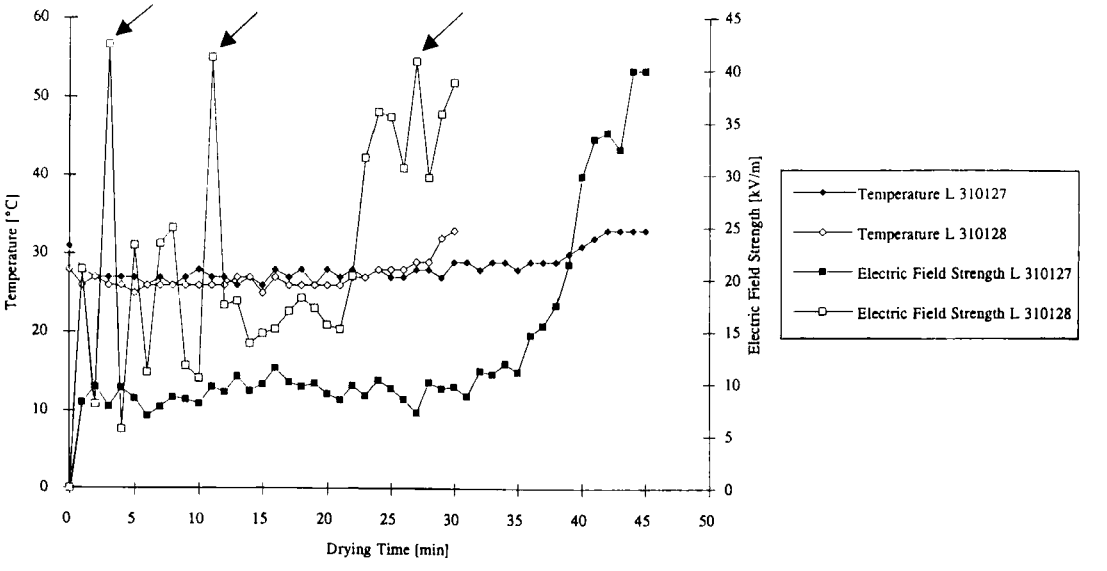


FIGURE 7: Temperature and E-field curves of lactose monohydrate samples

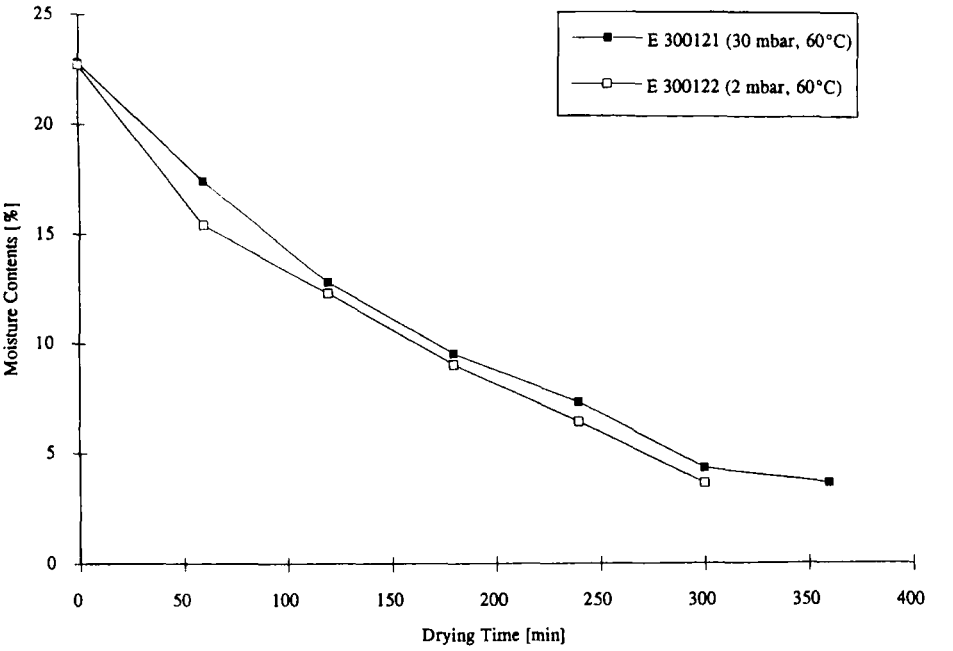


FIGURE 8: Drying of placebo granules by a combined contact and vacuum method

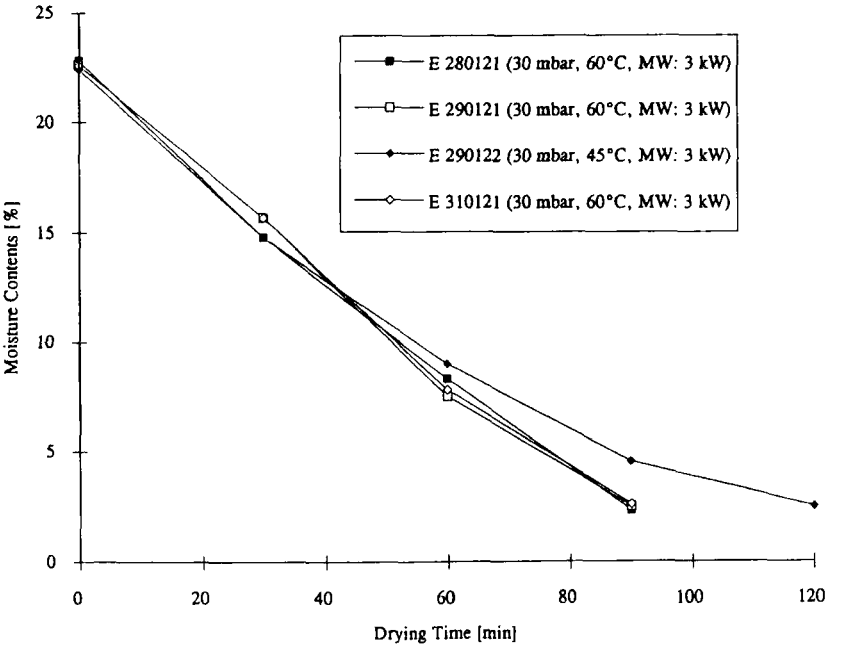


FIGURE 9: Drying of placebo granules by a combined contact, vacuum and microwave method

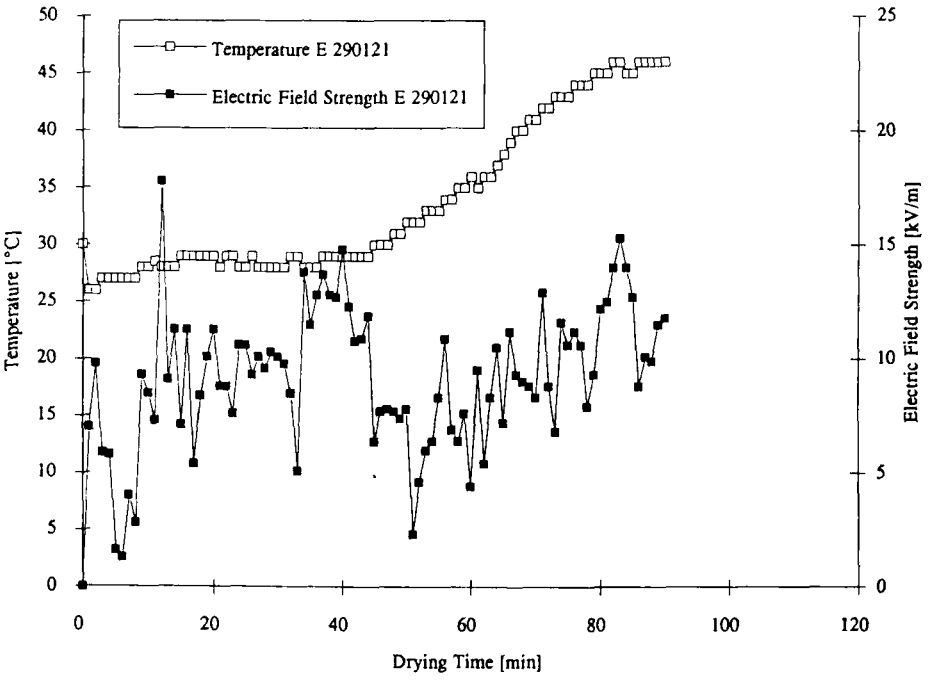


FIGURE 10: Temperature and E-field curves of placebo batch E 290121

drying pharmaceutical granules. In Figure 10 and Figure 11 the values of the two trials E 290121 and E 310121 are given. The corresponding temperature curves were in good agreement. The curves of the electric field strength however were of totally different appearance and could therefore not be interpreted.

An additional aspect of E-field measurement is the fact, that it is obviously not able to prevent microwave induced damage to the product. In one of the trials there was sticking of wet product at the zone indicated by X-X-X in Figure 12. Due to the high moisture content in this immobile area there was high absorption and as a consequence local overheating and thermal runaway effect took place (5). As the absorptive behaviour of the overheated and partly burned material was still sufficient and maybe even better than that of intact product, the E-field sensor could not react. In this way the burned area could expand until it reached the point of temperature measurement (Figure 12, 3).

Obviously caking or sticking on the walls of a microwave based dynamic dryer is a severe problem because inhomogeneities of the electric field can then no longer be compensated for by the mixing action of the impeller. The situation is comparable to a static dryer, where site and intensity of local overheating, thermal runaway effect and their undesirable consequences are not calculable.

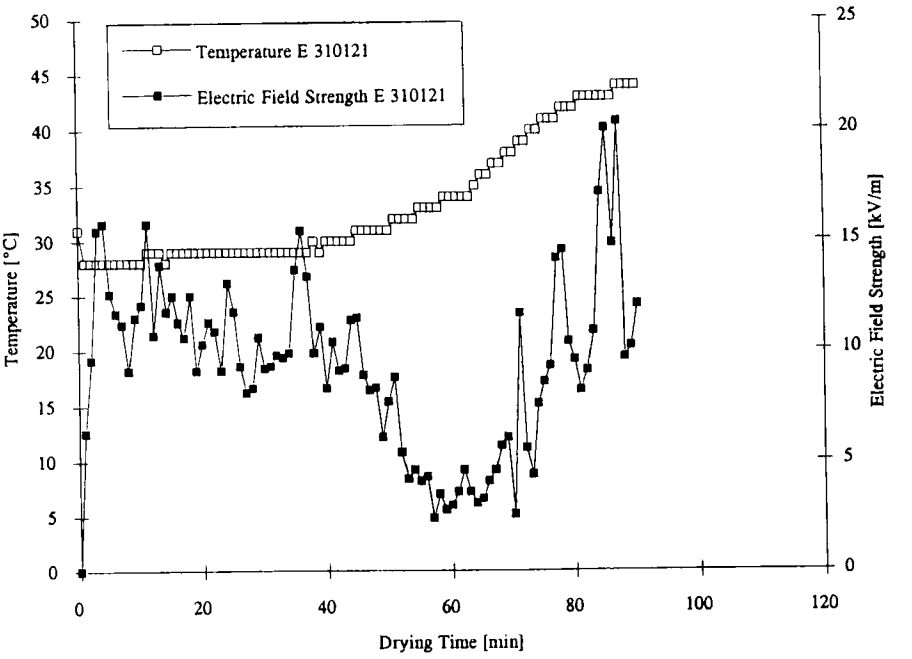
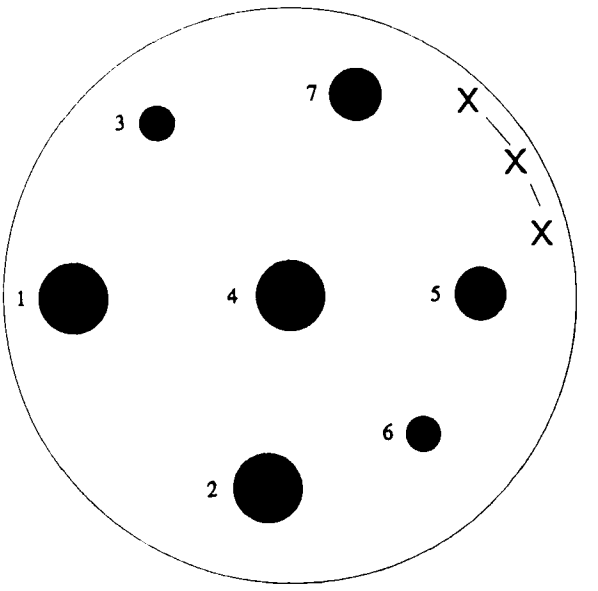


FIGURE 11: Temperature and E-field curves of placebo batch E 310121



1 Microwave Entry
2 E-Field Sensor
3 IR-Sensor for Temperature Measurement
4 Impeller Shaft
5 Chopper Shaft
6 Binder Addition
7 Vacuum Connection, Dust Filter
X Zone of Caking

FIGURE 12: Cross-sectional view on the mixer lid

Table 1

Irradiation Time [s]			0	10	30	60	120	360
	Method	Detection Limit [%]	Disintegration Products [%]					
Product A	HPLC	0,1	---	---	---	---	---	20
Product B	HPLC	0,1	---	---	---	---	---	---
Product C	HPLC	0,1	---	---	---	---	---	4,0
Product D	HPLC	0,1	---	---	---	---	---	---
Product E	DSC	0,2	---	---	---	---	---	---
Product F	DSC	0,3	---	---	---	---	---	---
Product G	HPLC	0,1	---	---	---	---	0,5	0,5
Product H	HPLC	0,2	---	---	---	---	---	---
Product I	HPLC	0,1	---	---	---	---	---	---
Product J	HPLC	0,15	---	---	---	---	---	---

In order to find out how stable different granules were under caking conditions, samples were irradiated in the MUT 6060 unit for defined periods of time (Table 1).

The active ingredients of ten products were analysed, possible decomposition products of excipients were not investigated. Product A and C showed remarkable amounts of decomposition products. The determination of product G showed decomposition products, which are still unknown.

CONCLUSION

Microwave drying is an elegant, effective and quick method for drying pharmaceuticals. The inherent risk of this technology is especially due to the fact that there is no adequate and reliable method to control the microwaves after they have entered the drying cavity. Therefore compensatory mechanisms, such as satisfactory mixing of the batches are necessary. The reason is to avoid the coincidence of concentrated microwave radiation on the one hand, and immobilized stationary granules on the other hand. Furthermore microwave drying can not generally be recommended for all active substances or excipients, because the thermosensitive and dielectric attitudes of some substances enhance the risk of unacceptable thermic damage. Some devices in microwave equipment such as arc detectors or electric field sensors effectively protect the magnetrons from reflection damage, but are not able to prevent damage to the product (5).

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