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Research paper

Practical method for choosing diluent that ensures the best temperature uniformity in the case of pharmaceutical microwave vacuum drying of a heat sensitive product

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Abstract

Microwave vacuum drying is getting more and more popular thanks to its known advantageous and unique features, but its non-uniform electric field can cause nonhomogeneous temperature distribution in the workload. The origin and effect of a generated hot-spot is influenced by the electromagnetic and thermodynamic features of the microwave system and the workload. In the case of single/one pot technology, the geometry and the construction of the microwave cavity is primarily designed for high-shear granulation. As for the workload, its composition has first-order effect on the electric field pattern. The aim of our study is to present a rational decision procedure based on basic practical experiments and the elaborated '3D layered thermography' technique to make it possible to choose the most suitable diluent to formulate a heat sensitive active pharmaceutical ingredient given its stability due to temperature distribution within the workload. Comparing two commonly used diluents, namely microcrystalline cellulose and corn starch, it was found that in the case of different actives with different acceptable temperature limits different diluents are recommended. Drying of a composition consists of an active ingredient characterized by a temperature limit of 70 °C. Using corn starch is safer when the workload is less endangered than when using microcrystalline cellulose. Above this temperature limit microcrystalline cellulose becomes beneficial.

Keywords: High shear granulation; Microwave vacuum drying; Thermography; Temperature distribution; Hot-spot; Heat sensitive

1. Introduction

The aims of pharmaceutical formulation are to determine what type of excipients guarantee the medical effect of the active ingredient, and to specify the suitable steps and parameters of production. If there is wet granulation and hence drying is required for formulation of a heat sensitive active, than vacuum drying is advised, especially single/one pot technology (Fig. 1). Single/one pot technology means that the granulation and the consecutive drying step takes place in the same equipment without interruption of the process.

Vacuum drying is a time-consuming operation, thus, additional transfer of energy is beneficial. Microwave is highly recommended. The benefits and drawbacks of microwave vacuum drying in the pharmaceutical industry have been well known for decades. In spite of the fact that dielectric drying offers unique advantages [1,2], the biggest resistance to its widespread use may be the confirmed non-uniformity of the electromagnetic field (E-field), which results in nonhomogeneous temperature distribution [3,4]. The origin and effect of a generated hot-spot is influenced by the electromagnetic and thermodynamic features of the microwave system and the workload.

In case of single/one pot technology, the geometry and the construction of the microwave cavity is primarily designed for high-sheer granulation. As for the workload,

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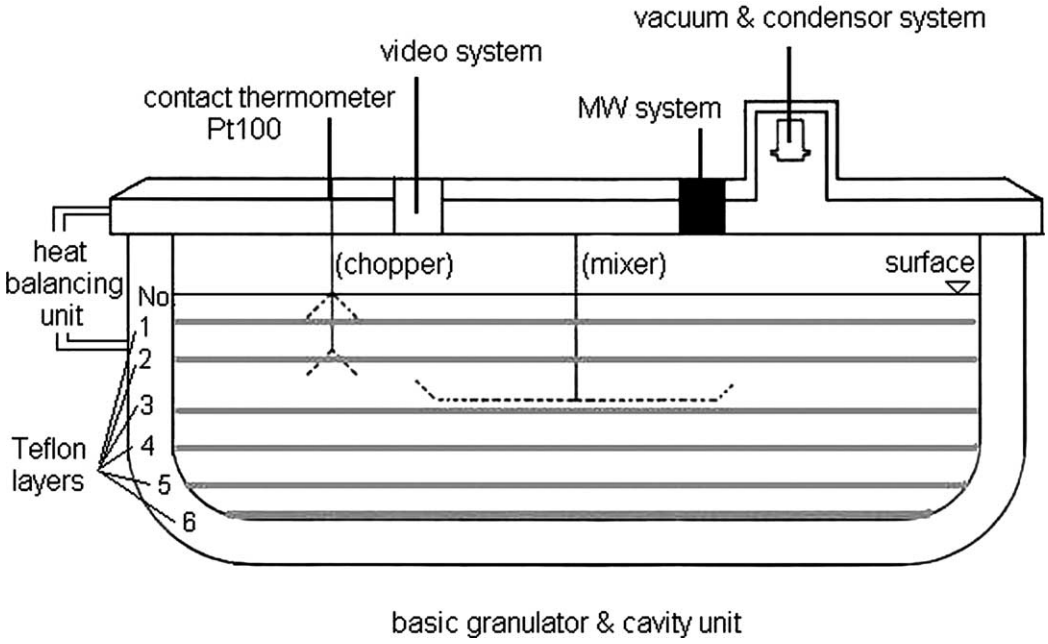

Fig. 1. Single/one pot apparatus with teflon layers.

namely the composition has first-order effect on the E-field pattern, thus, there is uniformity of generated heat. Dielectric drying can be risky if the microwave energy absorption capability (characterised by the loss factor, the ability of a material to dissipate electrical energy into heat) of a diluent is smaller than that of the active pharmaceutical ingredient. In such a case the temperature of the active rises faster (microwave selectivity) and may reach an undesirable temperature, where it may decompose or change. In-process monitoring of the temperature of the active ingredient is not possible because of the complex pharmaceutical composition, not to mention the single/one pot technology, where microwaves may be used. To avoid the undesirable unequal temperature distribution there are several possible solutions, e.g. intensification of the mixer motion, and/or reduction of the microwave power. The former would change the grain-size distribution unacceptably, while the latter would considerably increase the process time. As a result of experimental process optimization the best uniformity and highest acceptable power density as well as the shortest drying time are sought, without any corresponding damage of the workload.

The dielectric and thermal properties of a complex pharmaceutical composition are rarely known, and moreover change during drying, which makes accurate mathematical modelling rather uncertain. For that very reason preliminary tests must never be neglected. This paper focuses on macroscopic temperature distribution, and not on the molecular/microscopic level [5].

The aim of our study is to present a rational decision procedure based on basic practical experiments and the elaborated '3D layered thermography' technique to make it possible to choose the most suitable diluent to formulate a heat sensitive active ingredient considering its stability based on acceptable temperature distribution within the workload.

1.1. Nonhomogeneity of microwaves

Field concentration of standing waves or close proximity to the power-feed-point can cause non-uniform distribution of the microwave field [6]. Many factors influence the uniformity of the E-field. They can be divided roughly into two groups, cavity effects (design limitation, location of the microwave inlet point, shape of the cavity, hanging parts such as spray gun, mixer, chopper, thermometer etc.) and workload interactions (loss factor, penetration depth and thickness of the workload, particle's features, etc.), that are different from product to product and from equipment to equipment.

From the cavity point of view inter alia 'mechanical moving mode stirrers' or 'waveguide rotating joints' or simple agitation of the workload are used to assure more uniform E-field distribution, and thus, heating. Adequate homogeneity can be achieved, e.g. in a developed microwave applicator, as characterised by its cylindrical shape and adjusted with several magnetrons [7]. In the case of special pharmaceutical microwave assisted single/one pot equipment, the geometry of the cavity is first of all developed for granulation and not for perfect E-field distribution. The number and position of magnetrons is very restricted. Agitation of the workload is preferred, although it cannot ensure perfect homogeneity, and endangers the grain size distribution.

As for the workload effect on the E-field homogeneity it is the dielectric properties of the components, which

determine this. The components characterised by greater loss factor (and smaller heat capacity) become warmer more readily, resulting in temperature variances within the workload [4]. These differences can be compensated for via mechanical agitation to a certain degree, but its prevention is the most desirable, and thus, choosing suitable excipients is absolutely essential.

1.2. Theoretical models of microwave nonhomogeneity

An inherent deficiency of dielectric drying—especially of microwave aided vacuum drying—is that there is no common method to control, nor to properly monitor, the E-field distribution and its effect after starting the microwave treatment. With the help of mathematical models based on Maxwell's equations the theoretical electric and magnetic field configuration within the product can be calculated [8,9] even in 3D [10,11], if the configuration of the cavity, the dielectric properties of the workload and the granule's geometry, etc. are exactly known. The following dielectric heating equation is generally used to calculate the dissipated microwave power density (P_d, W/m^3) [4,9]:

$$P_d = 2\pi f \varepsilon_0 \varepsilon'' E_i^2 \tag{1}$$

where f = microwave frequency (Hz); ε_0 = free-space or absolute permittivity of vacuum, 8.854 10^{-12} 9(F/m); ε'' = loss factor of the dielectric material (dimensionless); E_i = electric-field strength within the dielectric (V/m)

The different loss factors in case of different materials result in different penetration depths (D_p, m) [2] causing different temperature distribution.

$$D_p = \frac{\lambda_0}{2\pi\left(2\varepsilon'\right)^{0.5}} \left\{ \left[1 + \left(\frac{\varepsilon''}{\varepsilon'} \right)^2 \right]^{0.5} - 1 \right\}^{-0.5} \tag{2}$$

where λ_o = wave length in free space (m); ε' = dielectric constant (dimensionless) and; ε'' = loss factor of the dielectric material (dimensionless)The calculations involve difficulties especially in the case of pharmaceutical compositions. The workload consists of several ingredients characterised by different and often unknown dielectric and thermal properties that are furthermore changing continuously during the drying process. For that reason, up to now experimental tests can never be omitted.

The internal energy (U, J) of the product being dried in microwave oven changes with the absorbed (dissipated) microwave energy (E_d, J). Based on the first law of thermodynamics, temperature is considered as an indicator of E-field. The change in the internal energy can be expressed by the following relations:

$$\Delta U = \sum Q - \sum W \tag{3}$$

$$\Delta U = Q_{\text{solvent}(t_{\text{start}} \to t_{\text{BP}})} + Q_{\text{steam}(t_{\text{BP}} \to t_{\text{end}})} + Q_{\text{solid}(t_{\text{start}} \to t_{\text{end}})} - W_{\text{volum}} + W_{\text{evap}} \tag{4}$$

$$\Delta U = c_{\text{solvent}} m_{\text{solvent}} \Delta T_{(t_{\text{start}} \to t_{\text{BP}})} + c_{\text{steam}} m_{\text{steam}} \Delta T_{(t_{\text{BP}} \to t_{\text{end}})} + c_{\text{solid}} m_{\text{solid}} \Delta T_{(t_{\text{start}} \to t_{\text{end}})} - p\Delta V + L_V m_{\text{solvent}} \tag{5}$$

The energy dissipation of the steam, which is actually present in the cavity is negligible due to its small amount. There is no remarkable volumetric work ($\Delta V \approx 0$).

$$\Delta U = c_{\text{solvent}} m_{\text{solvent}} \Delta T_{(t_{\mathbf{start}} \to t_{\mathbf{BP}})} + c_{\text{solid}} m_{\text{solid}} \Delta T_{(t_{\text{start}} \to t_{\text{end}})} + L_V m_{\text{solvent}} \tag{6}$$

where Q = quantity of heat (J); W = work (J); $Q_{\text{xx}(t_{\text{yy}} \to t_{\text{zz}})}$ = quantity of heat of the indicated material in the given temperature range (J); W_{volume} = volumetric work (J); W_{evap} = evaporation work (J); c_{xx} = specific heat capacity of the indicated material (J/kg K); m_{xx} = mass of the indicated material (kg); $\Delta T_{(t_{\text{yy}} \to t_{\text{zz}})}$ = temperature difference between the indexed events (K); L_v = heat of vaporization (J/kg)

The energy dissipation of the steam, which is present in the cavity, is considered negligible due to its small amount ($m_{\text{steam}} \approx 1$g). There is no volumetric work ($\Delta V \approx 0$). The change in the internal energy during microwave drying can be calculated on the basis of the dissipated microwave power (P_d, W) and the microwave treatment time (t, s).

$$\Delta U = E_d = P_d t \tag{7}$$

Microwaves are not forms of heat, but rather forms of energy that are manifested as heat through their interaction with materials. There is a two-step energy conversion: electric field is converted to induced ordered kinetic energy, witch in turn is converted to disordered kinetic energy, at witch point it may be regarded as heat within the material.

For experimental determination of the dissipated microwave power ($P_{d,}$ W), a special instrumental set-up is required to measure the magnetron output power (P_m, W) the reflected power (P_r, W) and all the losses that are evolved in the set-up (e.g. losses by the direction coupling, by fitting attenuation, etc.). Based on the measured reflected microwave power, the dissipated microwave power can be calculated by the following equation [12]:

$$P_d = P_m - BP_r \tag{8}$$

where B comprises the different attenuations and losses (dimensionless).

In accordance with the aforementioned, it can be stated that the change in the product temperature is proportional to the change in the internal energy of the material and to the dissipated power, thus, to the electric-field strength, within the dielectric, so it is suitable for process monitoring

(when W_{volume}, W_{evap} and Q_{steam} are neglected because ΔV, $m_{solvent \rightarrow steam}$ and m_{steam} are very small values).

Theoretical models are always limited by generalization and simplification. Calculations consider the workload homogeneous from dielectric, thermal and other points of view although this is not generally the case. Especially when drying complex pharmaceutical compositions, the workload may consist of several ingredients, characterised by different and often unknown dielectric and thermal properties. Moreover these are continuously changing during a drying process, not only in time but also in 3D, and depending on many factors (e.g. moisture content and temperature). For that very reason, experimental tests are much more reliable.

1.3. Thermography

Among the neither perturbing, nor intrusive temperature-monitoring alternatives, infrared imaging is known as one of the most promising. Thermal imaging relies on the fact that all bodies emit electromagnetic radiation due to electronic oscillation and the radiated energy is proportional to the objects' temperature. The advantage of IR monitoring is that it does not disturb the drying, and a huge quantity of data can be recorded digitally and displayed instantly [13]. The limitation of IR monitoring is that it provides information exclusively about the monitored surface. Ohlsson et al. made cross sections of solid objects and used thermal imaging to get a 3D map about its temperature distribution [14].

2. Materials and methods

Microcrystalline cellulose (MCC), lactose, potato starch, corn starch (CS), calcium hydrogen phosphate, calcium carbonate and mannitol as diluents are commonly used in the pharmaceutical industry. The dielectric property (loss factor) might be known in the case of excipients (Fig. 2) but hardly in the case of an active pharmaceutical ingredient. For that very reason, the following simple pre-test was carried out to compare the relative microwave absorption feature of the active with that of diluents. The same mass (10–10 g) of each material was filled into a Teflon cylinder, tapped to an equal volume, placed in the middle of the rotating plate into the cavity and treated under the same microwave conditions (Whirlpool MD112 household oven, 750 W, 2450 MHz, atmospheric pressure). The measured temperature change refers to the relative microwave absorption capability of the material if the heat capacities are considered equal (Fig. 2) [15].

The diluents characterised by lower temperature rise, thus, microwave absorption capability of other than the active ingredient are less suitable for microwave assisted drying. In this case the active particles would primarily absorb the energy during drying, so its temperature would rise more rapidly and may reach an undesirable temperature. According to this preliminary test MCC and CS are considered to be more suitable. Both of them are characterized by relatively high temperature rise (in harmony with their water contents, thus, dielectric properties found in the literature [16]), and so the risk of unnoticeable dielectric overheating of an active is smaller if the drying is fast enough. In this case the active particles might be heated primarily via conduction. To avoid the development of an overheated area the prevention of unequal temperature distribution is absolutely essential. As for the pharmaceutical workload the selection of the adequate diluent is elementary.

Not all of the effects that influence the E-filed distribution (such as e.g. microwave inlet position, or geometry of the granulator) can be eliminated, although

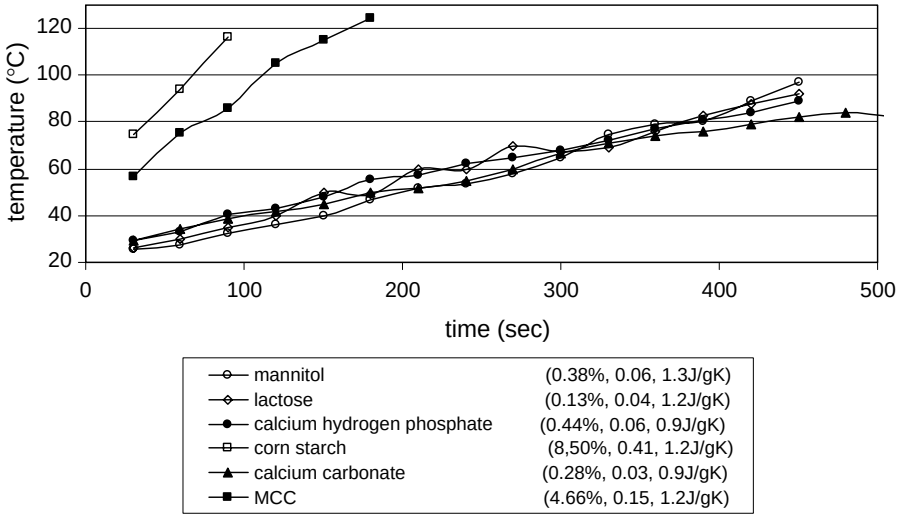

Fig. 2. Temperature of different materials against the radiation time (measured moisture content, wet weight based, LOD% /80 °C, 10 min., Mettler Toledo HR73 moisture analyzer/, loss factor (16) and specific heat capacities [15]) ($n = 3$).

they may be lessened and borne in mind in the case of process engineering. Our aim has been to elaborate a technique that is usable in everyday formulation R&D to select the most adequate diluent (excipients) that assures the best homogeneous heat distribution on the one hand to lessen the risk of hot-spot formation and on the other hand to reduce the drying time.

In our experiments the comparable analysed workloads were, during the pre-tests, short listed diluents, namely CS from Roquette GmbH and MCC (Vivapur 101) from Merck (JRS). It is desirable for the loss factors of the chosen materials to be similar but higher than that of the given active pharmaceutical ingredient. (If an excipient is characterized by much higher loss factor then temperature nonhomogeneity would also exist.)

2.1. The elaborated '3D layered thermography' mapping method

Teflon (PTFE) disks of 1 cm thickness are used to divide the workload consisting of CS or MCC horizontally into six layers of 2 cm thickness. Teflon is used as it is practically transparent for microwave. Between the layers tiny Teflon distance pieces assure an even density and thickness of the material, because it is known that the loss factor depends on the characteristic bulk density [17]. The change of the dielectric and thermodynamic properties of a diluent also depend on the moisture content. During the drying process the initial temperature was 25 °C, the moisture content was 13% (wet weight based) in case of CS and 4% in case of MCC. The changes of thermodynamic [18–20] and dielectric properties [21,22] are not significant due to its minimal values.

Each experiment was carried out three times so as to be suitable for statistical evaluation and comparison. The horizontally divided steady-state workloads (6.3 kg, 2/3 of the total capacity) were heated by microwave at 1.2 kW under a pressure of 50 ± 5 mbar in a single pot system (Fig. 1) (Collette Ultima 25 l, Collette NV, Belgium). Initially, the temperatures of the double-jacket of the cavity and the workloads were tempered at 25 ± 1 °C. The temperature of the condenser was controlled at 6 ± 1 °C during the drying processes. Circulation in the cooling system was stopped, thus, the double-jacket was heated up exclusively by thermal conduction. After 25 min of microwave radiation all the six layers (CS or MCC) were monitored one by one by an infrared camera (AGA782 Infrared Imaging System, Infrared System AB, Sweden). The sensitivity of the temperature determination was 0.2 °C. The snapshots were taken within 1 min of the microwave being switched off. Transient IR snapshots [23] prove that the temperature decrease between the end of the microwave treatment and the taking of the thermograms is negligible (ΔT_{max} found 1–2 °C) (Fig. 3).

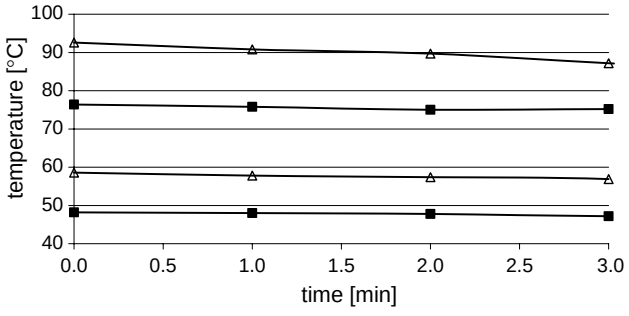

Fig. 3. Transient temperature of CS (Δ)and MCC (■) at different initial temperatures (long-wave emission constants are 0.95) ($n = 3$).

3. Results and discussion

Thermal imaging offers immediate 2D visual information. The colours of the thermocartograms refer to the temperature of the area, in accordance with the given colour scale, which makes qualitative analysis possible (Fig. 4). Hotter areas are seen directly under the microwave inlet window. The asymmetrical temperature pattern on the surface is the consequence of the microwave inlet position and the vertical temperature decrease is in agreement with the penetration depth concepts [2].

To get more detailed 3D information about the temperature distribution of the workloads the obtained thermocartograms are evaluated with the undermentioned 'layered thermography' technique (Table 1, Fig. 5 and Fig. 6). One layer is represented by some 24,000 pixels in the thermocartograms. One pixel corresponds to 1.2 mm^2 of the corn starch layer.

The mass ($m_{n_x i_y}$, kg) of bulk characterised by a chosen temperature range (i_y: $i_{25–30}\ldots i_{95–100}$) in a layer ($n_x$: $n_1\ldots n_6$) can be calculated by the camera-detected surface area ($A_{n_x i_y}$, m^2) (the sum of the surfaces according to the number of the pixels), the known thickness ($d_{n_x} = d =$ constant, 0.02 m) and the density ($\rho_{n_x} = \rho \sim$ constant, ~ 560 kg/m^3) of the product layer. Based on preliminary tests, the vertical temperature difference within a layer of 0.02 m thickness was never greater than 1–2 °C, thus, the temperature of the whole amount under a given surface can be characterised by the surface temperature. The distance pieces ensure the permanent thickness of the product layers and the loss of mass is negligible due to its small amount ($\Delta m < 10\%$ both in case of MCC and CS, according to thermal gravimetric analysis from 25 to 100 °C), which is why density is considered constant within the workload.

$$m_{n_x i_y} \cong A_{n_x i_y} d\rho \tag{9}$$

The percentage of the material amount ($m^*_{n_x i_y}$, %/°C) characterized by an i_y temperature range within the n_x layer can be calculated from the mass in question ($m_{n_x i_y}$, kg) and the mass of the entire layer (m_{n_x}, kg) (in other words from the number of pixels in question and the total number

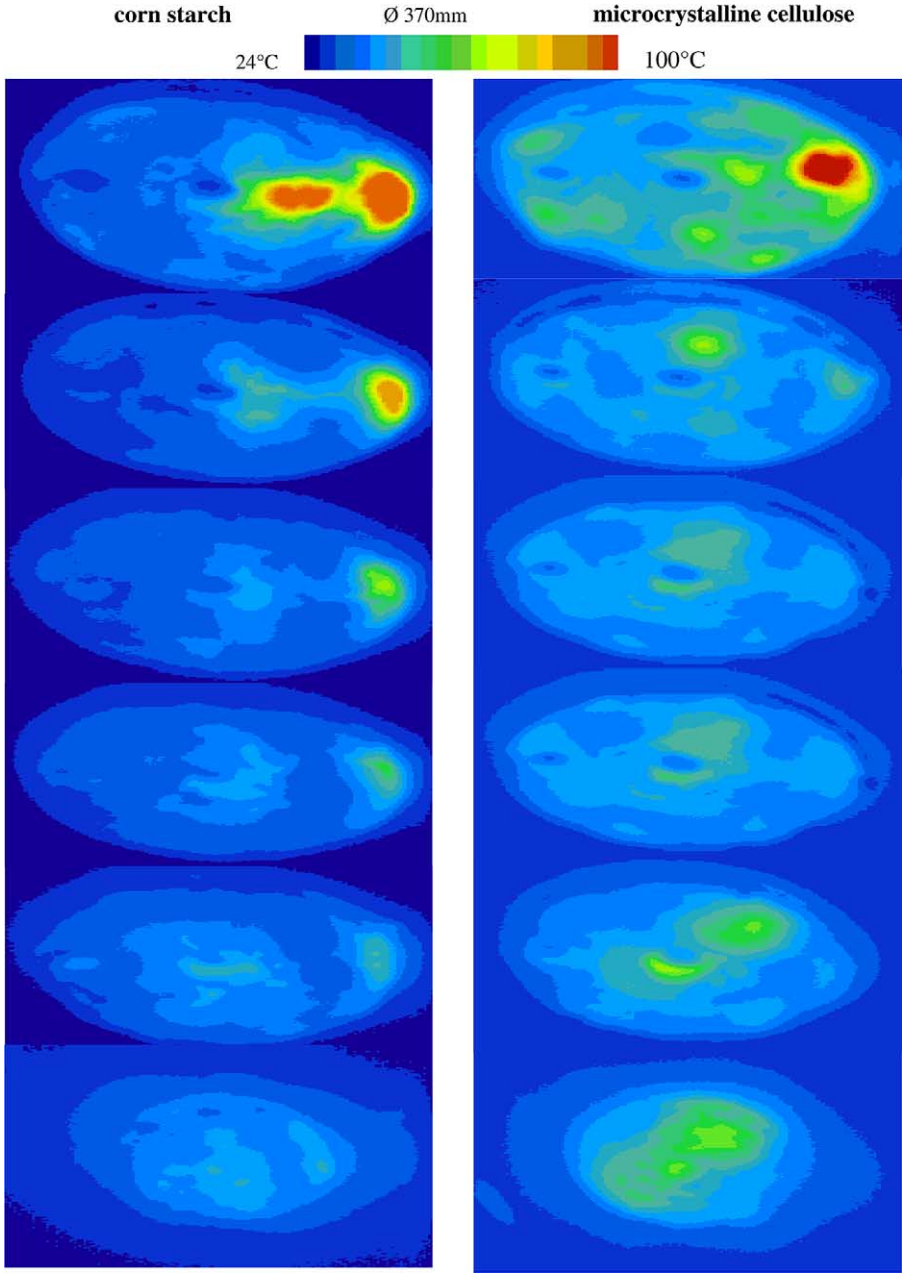

Fig. 4. 2D thermocartograms of the 6 layers of MCC and CS as workload

of pixels in the entire layer):

$$m^*_{n_x i_y} = \frac{m_{n_x i_y}}{m_{n_x}} \times 100 \tag{10}$$

The percentage of the total material ($M^*_{i_y}$, %/°C) characterized by an i_y temperature range within the whole workload (M, %) is:

$$M^*_{i_y} = \frac{M_{i_y}}{M} \times 100 \tag{11}$$

The average temperature of the n_x layer ($\overline{T}_{n_x}$, °C) can be calculated from the percentage of the material characterized by an i_y temperature range within the n_x layer ($m^*_{n_x i_y}$, %/°C) multiplied by the mean temperature of the incidental i_y temperature range ($T_{\overline{i_y}}$, °C).

$$\overline{T}_{n_x} = \sum \frac{(m^*_{n_x i_y} \times T_{\overline{i_y}})}{100} \tag{12}$$

Statistical test (analysis of variance) proves the reproducibility of the parallel experiments because there were not significant differences ($P > 0.05$), which makes qualitative analysis possible.

In formulating of any active pharmaceutical ingredient it is beneficial to keep the product temperature low, while most decompositions are faster at higher temperature. Drying of compositions containing a heat-sensitive essential

Table 1
The quantitative evaluation of the temperature distribution based on "layered thermography". Three replications were used to generate each data and analysis of variance proves the reproducibility, $p > 0.05$. (data of MCC are bold and italic) (where: n_x = number of a layer; T_{i_y} = temperature range [°C]; $M^*_{i_y}$ = percent of the total material in the i_y temperature range within the whole workload [%/°C]; $m^*_{n_x i_y}$ = percent of the material in the i_y temperature range within the n_x layer [%/°C]; $\overline{T}_{n_x}$ = average temperature of the n_x layer [°C]; $\overline{T}$ = average temperature of the total workload [°C])

Layer No. [n_x]	1	2	3	4	5	6	$M^*_{i_y}$ [%/°C]
T_{i_y} [°C]	$M^*_{n_x} i_y$ [%/°C]						
20–25	16.3	3.2	–	–	–	–	3.2
	5.5	–	–	–	–	–	0.9
25–30	21.9	33.9	37.3	34.9	31.3	13.9	28.9
	12.2	26.5	5.4	17.0	15.7	–	12.8
30–35	19.9	39.1	39.1	37.7	34.9	39.1	34.9
	23.4	15.4	35.4	30.1	24.2	28.2	26.1
35–40	20.7	10.5	18.0	20.7	26.4	38.3	22.4
	9.1	21.1	20.7	19.4	20.2	18.6	18.2
40–45	6.1	7.2	3.1	5.0	5.7	8.6	5.9
	19.0	25.0	28.1	20.1	17.9	15.2	20.9
45–50	3.2	3.5	0.7	1.0	1.8	–	1.7
	13.2	7.9	6.5	8.9	11.9	8.8	9.5
50–55	2.2	0.7	0.5	0.5	–	–	0.6
	5.5	2.0	3.7	3.3	4.8	12.3	5.3
55–60	1.6	0.6	0.5	0.2	–	–	0.4
	6.3	1.0	0.1	1.3	3.2	10.0	3.7
60–65	1.4	0.4	0.6	–	–	–	0.4
	1.7	0.8	–	–	1.8	6.4	1.8
65–70	1.2	0.3	0.1	–	–	–	0.2
	1.3	0.3	–	–	0.4	0.3	0.4
70–75	1.0	0.2	–	–	–	–	0.2
	0.6	–	–	–	–	–	0.1
75–80	0.8	0.2	–	–	–	–	0.2
	0.6	–	–	–	–	–	0.1
80–85	0.6	0.2	–	–	–	–	0.1
	0.6	–	–	–	–	–	0.1
85–90	0.6	0.4	–	–	–	–	0.2
	0.4	–	–	–	–	–	0.1
90–95	0.6	–	–	–	–	–	0.1
	0.4	–	–	–	–	–	0.1
95–100	2.1	–	–	–	–	–	0.4
	0.3	–	–	–	–	–	0.1
$\bar{T}_{n_x}$ [°C]	36.7	33.2	32.4	32.6	33.1	34.6	33.7
	40.8	36.9	37.8	36.9	38.7	43.3	39.1

active such as vitamins (e.g. vitamin B, C, D, retinol and β-carotene), antibiotics (e.g. ampicillin trihydrate, benzylpenicillin, phenoxymethylpenicillin, amoxicillin) and many other drugs (acetylsalicylic acid, ergometrine, methylergometrine, and tetracycline) [24,25] is not only beneficial but indispensable to ensure that the least part of the bulk exceeds the actual safety temperature limit (depending on the active). CS and MCC as the chosen diluents were compared according to some given temperature limits (30, 40, 50, 60, 70, 80 and 90 °C) from the temperature distribution point of view.

Based on the graphs (Fig. 7) it can be stated that the usage of CS as diluent is safer up to the critical temperature limit of 70 °C. In this case the proportion of the endangered workload is less than when using MCC in the used single pot unit under the used drying parameters. Dielectric drying of a composition consists of an active characterized by higher critical temperature; it seems that the usage of MCC is more suitable. It is obvious that a decrease in exposed microwave power reduces the ratio of the critical workload, but on the other hand it radically increases procedure time. According to the above process the selection of the most suitable diluent makes it possible to achive the shortest drying time without endangering the active compound.

The novelty of the elaborated '3D layered thermography' method is that the heat distribution can be mapped and evaluated even quantitatively in case of a complex pharmaceutical composition characterised by unknown and continuously changing dielectric and thermal properties. The presented technique offers information about the temperature distribution of a bulk workload in a simple way. It makes it possible to compare the amount of generated heat and its distribution in the case of different diluents (excipients and composition) to select the best ones to formulate a given active pharmaceutical ingredient. Based on the confirmed reproducibility, it makes both qualitative and quantitative modelling possible.

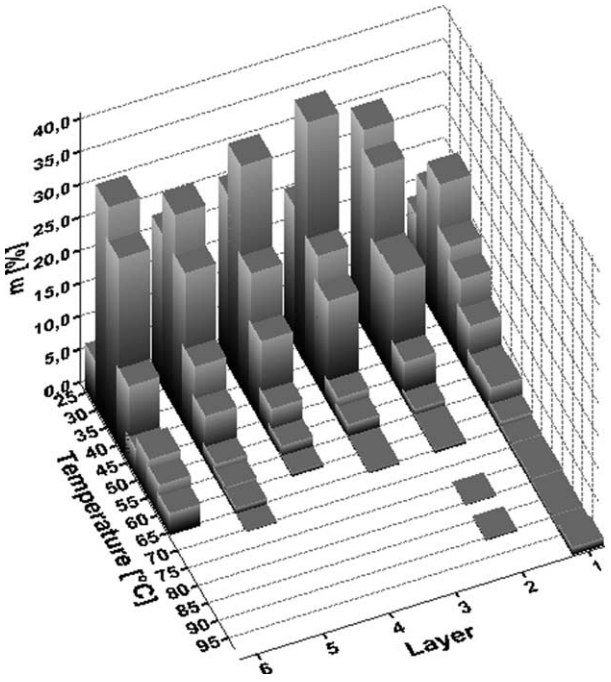

Fig. 5. The different layers of CS are characterized by different temperature distributions ($n=3$; $P>0.05$) (where: $m^*_{n_x i_y}$ = percent of the material in the i_y temperature range within the n_x layer (%/°C)) See data in Table 1.

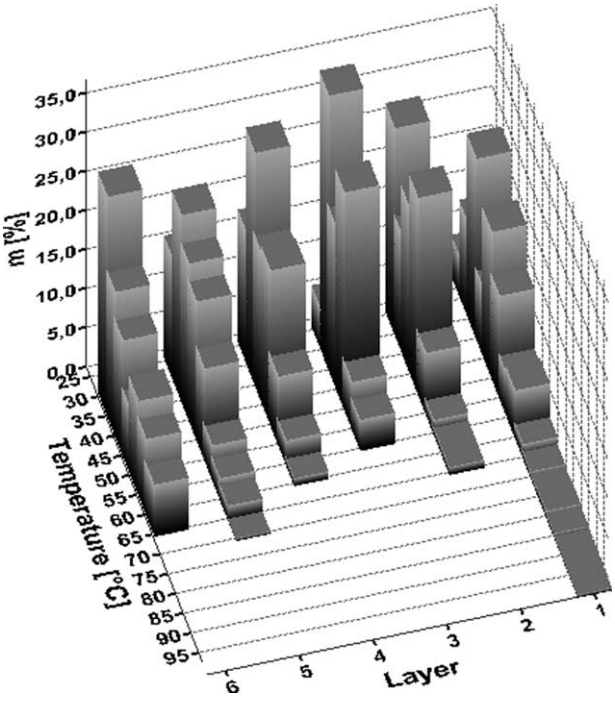

Fig. 6. The different layers of MCC are characterized by different temperature distributions ($n=3$; $P>0.05$) (where: $m^*_{n_x i_y}$ = percent of the material in the i_y temperature range within the n_x layer (%/°C)) See data in Table 1.

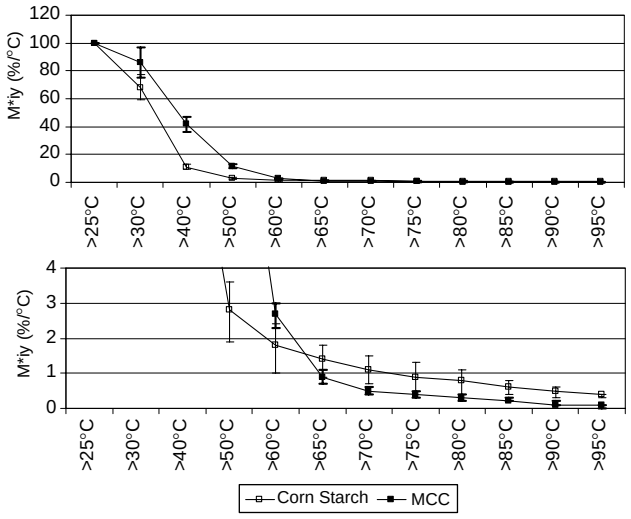

Fig. 7. The percent of the cumulative endangered workloads depending on actual temperature limits after a given drying time (25 min) ($n=3$; $P>0.05$) (where: $M^*_{i_y}$ = percent of the total material in the i_y temperature range within the whole workload (%/°C)). See data in Table 1.

4. Conclusions

An aim of formulation R&D is to choose those excipients which assure appropriate stability given the production method, to guarantee the medical effect until the end of shelf life. In the case of microwave assisted vacuum drying the most imperceptible risk is the formation of overheated areas. The possibility of monitoring temperature during a running process is functionally very limited, due to granulation in a single/one pot equipment, thus, prevention of any damage of the workload is absolutely essential.

How to select a suitable diluent that assures the most homogeneous and acceptable temperature and microwave energy distribution in the case of a given pharmaceutical active is not obvious. The dielectric and thermal properties of a complex pharmaceutical composition are hardly known, and moreover are changing during the process, and, therefore, preliminary tests must never be omitted.

The elaborated '3D layered thermography' technique provides reliable, reproducible and quantifiable information about temperature distribution, even in the case of a bulk workload. Moreover the quantitative evaluation allows us to determine the amount of the workload characterised by any optional temperature range. This advantage of the new method makes it possible to select the best diluent, which is characterised by the smallest over-temperature ratio (best temperature homogeneity), in the case of dielectric drying of any heat sensitive composition.

The presented '3D layered thermography' method and train of thought can be used in everyday practice in the case of any kind of dielectric equipment and workloads to stud temperature distribution as it develops, even quantitatively.

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