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RESEARCH PAPER

The Theoretical Basis for Scaling-Up by the Use of the Method of Microwave Granulation

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ABSTRACT

For the scaling-up achieved by the use of the method of wet microwave granulation based on calculations, there is a need for an exact mathematical description for the relationship between the dose of radiation and the resultant effect. By assessing the physical, physical-chemical, and chemical factors, we may conclude that, by the gross kinetic evaluation of the change in the enthalpy and the loss of humidity, there is a possible solution for the mathematical description of the single-step, single-pot granulation from the practical aspect of finding ways to scale-up. This paper overviews the experiments performed in a laboratory-size microwave vacuum granulator in testing two different granules with respect to composition and permittivity and presents the evaluation of the experimental data.
Key Words: *Microwave granulation; Scaling-up; Theoretical basis.*

INTRODUCTION

The scaling-up in wet granulation by the use of microwave devices used for drug manufacturing requires new aspects from the methodological approach with respect to the batch-size changing from a few hundred grams to reaching the range of about a couple of hundred kilograms. The main reason for this is that, during the traditional method, the procedures requiring considerable heat and mechanical energy, such as weighing, powder mixing, wetting, molding-mixing, granulation, drying, regranulation, and so on, follow each other consecutively in different equipment; in the microwave granulator, the greatest amount of substantial changes derived from the most important mechanical and heat energies occur in a complex way in a single piece of closed equipment as a result of simultaneous radiation and mixing.

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Evidently, the energy transfer of the high-frequency electromagnetic radiation does not exclusively result in the evaporation of the solvent. The absorption of the radiation will result in several transformations of the multicomponent granules, depending on their physical properties. It may induce several physical changes (e.g., changes of the temperature, phase of the substance, grain size, specific surface area, solid-state structure, induced electrodynamic nature, etc.), chemical bond alterations (covalent, ionic, ligation, and van der Waals [and even metallic] bond changes), as well as modifications requiring mechanical energy.

Several scientists have already dealt with the development of microwave granulation and the scale-up methods in industrial production. Among other things, they have investigated in detail the feasibility of the new technology and the possibility for scalability (1); they have arrived at important conclusions through the factorial analysis of the most important practical parameters and simulation experiments (2). Other scientists have mainly studied the details of the drying operation of the method (3). We can come across the highlights of the benefits of rendering the new technology in the professional literature (4).

Due to the fact that there is lack of data in the literature regarding the basic relationship between dose of radiation and effect that may be applied for cases of scaling-up by microwave granulation, we conducted experiments with a laboratory-size device. Our intention was to elaborate a mathematical description that is suitable for the gross evaluation of the new technological method, as well as for planning the scaling-up.

Physical Characteristics of the Microwave Device and the Mechanism of the Energy Transfer

In our case, the radiation source of the closed-system microwave granulator was 2.45 GHz; thus, its wavelength was 12.2 cm. Therefore, the maximum and minimum field force of the radiation energy displays sinusoid changes in distances of 6.11 cm in the irradiated space between stationary waves. It is possible to integrate the inhomogeneous dispersion of radiation energy by selecting optimal mass (volume) of the granules depending on the geometrical size of the device given and by determining the appropriate intensity for mixing, thus making the applied radiation virtually homogeneous in the equipment.

The pharmaceutical granulate compositions are generally multicomponent dielectric items that are ready to absorb energy by different mechanisms when exposed to radio-frequency irradiation. Since the electrophysical properties, which affect the capability of some of the components to absorb the microwave radiation, are dependent on the frequency of radiation, the heat, the time exposed to radiation, and the chemiabsorptional interactions potentially occurring on the surface of the components, and they also change during the period of irradiation. Therefore, it is impossible to calculate the total power of the energy required for the theoretical description of scale-up by summarizing the basic mechanisms related to each component.

Ever since the time of introducing the molecular electrostatic maps (MEPs)—calculated by the van der Waals surface of a molecule (5)—to theoretical chemistry, they have successfully been used in several areas for interpreting processes occurring on the surface of molecules (6). The gradient of MEP, ''the molecular electrostatic space,'' is another important quantity of electromagnetic radiation from the aspect of energy transfer and reflects the strength of the interaction with the pointlike dipole (7). By recognizing the characteristics of the substance resulting from the chemical structure, understanding the mechanism of microwave granulation has also become easier.

It is a fact based on experience that only polar substances are able to absorb microwave radiation. Substances that are apolar in nature allow the transit of radiation without its loss. Since the diplomomentum of a substance quantitatively reflects its polarity, which is also related to the permittivity, polarizability, and conductivity of the substance, these electrophysical properties play a decisive role in different mechanisms of microwave energy transfer processes that require varying levels of activation energy.

We are acquainted with the fact that a fraction of the nominal power W of the microwave radiation is absorbed W_{abs} and another fraction is reflected W_{ref}. Their ratio is the induced absorbability coefficient α:

$$\alpha = W_{abs}/W \quad (1)$$

The value of α ranges from 0 to 1, depending on the overall electrodynamic physical properties of the multicomponent granule.

Two different mechanisms play a role in the absorption of microwave radiation. The inductive effect results in reversible electron-, ion-, orientational-, deforming dielectric polarization in the granule containing solid and liquid components during the period of irradiation, which enhances the ability to absorb radiation. The heat effect shows correlation with the multicomponent granule's ad-

ditive or nonadditive polarity and its induced polarity, the high-frequency radiation-loss factor $tg\delta$, and the complex dielectric loss of the substance.

According to Debye's theory, the heat effect can mainly be traced to the production of heat due to the very intensive friction of molecules in the high-frequency field force. Beside this, it is also known that those electrons of susceptible molecules that can be mobilized may be activated to higher energy levels followed by dynamic reorganization; during this period, the substance emits the absorbed surplus energy to its environment in the form of heat [or light (8), but not in the case of medicinal products]. These mechanisms, which are represented by the ''microwave quantum'' from spectroscopy (9), appear to have an insignificant role with regard to the complete energy transfer due to the minimal amounts ($J \cdot mol^{-1}$) involved. In spite of this, we cannot rule out the possibility that, in the case of a multicomponent system, they could still play a significant role in its incalculable nonadditive physical character.

Normally, the pharmaceutical use of the microwave technique can be classified into two possible fields, depending on the power of the radiation source: the ''small energy'' (~mW) moisture analyzing method or the ''high-energy'' applications suitable for granulation. In the case of the latter, the energy transfer leading to significant changes takes place within the granule's chemical solid-state structure, and those beneficial effects can be utilized in a complex way in single-pot procedures.

Theoretical Basis for the Mathematical Description of Microwave Granulation

Due to physical considerations, the energy transfer's dose through the variable power W and time t exposed to radiation may be adjusted according to the following formula:

$$D_{abs} = W_{abs} \times t \quad (2)$$

where D_{abs} is the absorbed dose of radiation, t indicates time in minutes, and W_{abs} is the absorbed power, that is, the difference between the nominal power W and the reflected power:

$$W_{abs} = W - W_{ref} \quad (3)$$

From the methodological aspect, the scale-up is based on the quantitative description of the absorbed dose of radiation and the related ''effect,'' the measurable ''changes.''

The effect of radiation can be characterized by two significant changes:

$D_{abs} \rightarrow$ Loss of water

which is a parameter that can be measured easily, and it may be expressed by the reduction ($\Delta\%$) of the initial water content of the wetted granules. The other possible parameter is

$D_{abs} \rightarrow$ Change in the heat energy

Due to the fact that microwave radiation generates several exothermic and endothermic transformations, their enthalpy balance can be characterized exclusively by a specific (J/kg) value in a gross form on the basis of the change of heat in the irradiated substance. Nevertheless, it is possible to adjust the energy balance of gross processes resulting in heat production due to the microwave radiation by applying the calculable evaporation heat energy used for wet granulation.

EXPERIMENTAL

Samples

The subject of our experiments was the investigation of two different role model granules with compositions that had different mass-proportional additive permeability values even when calculated from the individual components (Table 1).

Granulation Method

We performed the experiments using a Pro-C-epT (Zelzate, Belgium) Mi-Mi-Pro laboratory-size microwave granulator. We performed the homogenization of the components poured into the device, filling an opti-

Table 1

Experimental Samples

Sample	Weight (g)
Lactose granules	
Lactose (Ph.Hg. 7)	90.0
Microcrystalline cellulose (Ph.Hg. 7)	70.0
Pregelatinized starch (USP 18)	30.0
Purified water (Ph.Eur. 3)	35.0
Mass of batch	225.0
Calcium citrate granules	
Calcium citrate (USP 18)	400.0
Pregelatinized starch (USP 18)	20.0
Purified water (Ph.Eur 3)	100.0
Mass of batch	520.0

Table 2

Data from Lactose Granulation Trials

	W													
	50		100		150		200		250		300		350	
Min	°C	%	°C	%	°C	%	°C	%	°C	%	°C	%	°C	%
0	24.4	0	22.8	0	27.2	0	26.5	0	27.0	0	30.0	0	27.7	0
5					27.2	2.1	26.5	2.6	29.5	4.0	30.0	5.0	30.0	5.5
10	24.4	1.2	29.9	1.7	27.2	4.5	26.5	6.2	31.3	8.5	33.5	10.0	36.0	11.1
15					30.0	6.7	33.0	9.2	35.9	11.2	46.0	12.3	56.0	13.2
20	24.7	3.8	30.2	5.4	33.4	9.0	38.0	11.4	47.5	12.8	59.0	13.7	64.7	13.8
25					38.0	10.7	45.0	12.8	57.0	13.8				
30	24.6	5.3	30.7	8.6	36.0	11.9	53.0	13.5						
35					39.0	12.7								
40	24.4	7.6	36.0	11.3	42.0	13.2								
50	24.6	10.0	41.5	12.3										
60	25.0	11.3												
70	24.6	11.6												
W_{abs}	19.8% ± 6.5%		59.0% ± 2.9%		82.0% ± 9.2%		125.4% ± 6.9%		165.1% ± 2.4%		199.3% ± 6.3%		256.7% ± 2.2%	

mal volume, at an impeller speed of 500 (±10) rpm, at 200 (±5) rpm while wetting, and at 700 (±5) rpm while molding-mixing. During the wetting and the molding-pulverizing operations, we also set in action the pulverizer at 2000 rpm and 200 rpm, respectively. The rate of water uptake was 30 ml/min. We applied a vacuum effect of 50 (±10) mbar in the drying phase. Throughout the whole process, the device continuously stored the temperature of the granulate and the nominal and reflected microwave power values in its memory unit.

Determining the Humidity Content

We measured the amount of water collected in the condenser during the process of vacuum drying. Also, in the case of the experiment with the lactose granule, we also took samples during the manufacturing procedure to determine the exact values, and we measured the remaining water content with a Mettler HR 73 Halogen-type quick-tester (Mettler Toledo, Greifensee, Switzerland).

X-Ray Diffraction Surveys

The recording of the diagrams was achieved using a Philips PW 1840 X-ray diffractometer to apply CuK_α radiation with an excitation of 30 kV and 30 mA.

RESULTS

Table 2 shows the data for lactose samples after they were irradiated by a nominal power of 50–350 W for 5–70 minutes. Shown are the changes in the temperature (°C) and water content $(\Delta\%)_t$ with respect to time, as well as data on the absorbed power W_{abs}. Table 3 shows similar data for the calcium citrate samples.

We performed X-ray diffraction examinations in the case of the calcium citrate samples. Table 4 shows data for the initial powder mixture (I), the data for samples containing 19.23% added water (II), and the powder diagram of samples exposed to 450 W of radiation for 30 min (III).

The standard deviation that characterizes the experiments had a maximum value of $(\Delta\%)t = 13.29\%$ (±0.69%) ($n = 11$) in the case of the lactose sample, evidently lower than the initial $(\Delta\%)_{max} = 15.56\%$ due to the vacuum-system; nevertheless, it can be reproduced in good quality. The maximum $(\Delta\%)_t = 17.00\%$ (±0.9%) ($n = 6$) in the case of the calcium citrate sample, which is still lower than the initial $(\Delta\%)_{max} = 19.23\%$; it can also be reproduced in good quality. For each exper-

Table 3

Data from Calcium Citrate Granulation Trials

	W					
	200		250		300	
Min	°C	%	°C	%	°C	%
0	21.5	0	22.4	0	23.8	0
5			23.9	0.7	27.5	1.0
10	24.5	1.5	24.4	2.6	27.7	3.7
15			24.4	4.8	27.4	6.2
20	25.0	4.7	24.9	6.7	27.7	8.6
			24.9	8.6	27.4	10.8
30	25.0	8.2	24.9	10.5	27.2	12.8
35			24.9	11.9	27.7	14.4
40	25.5	11.3	25.4	13.3	29.2	15.5
45			25.4	14.6	32.6	16.2
50	26.0	13.8	26.9	15.6	34.8	16.5
60	27.5	15.4	29.4	16.3		
70	31.0	16.3				
W_{abs}	19.8% ± 6.5%		59.0% ± 2.9%		82.9% ± 9.2%	

Table 4

Data from X-Ray Diffractograms of Calcium Citrate Samples

I		II		III	
dĂ	I/I_0	*dĂ*	I/I_0	*dĂ*	I/I_0
17.77	18.6	23.08	100.0	26.2	100.0
5.11	45.2	15.04	81.7	7.73	48.2
3.93	100.0	7.70	50.7	5.13	52.2
2.61	50.0	6.28	27.1	3.88	79.0
2.39	34.4	5.08	65.3	2.59	32.4
		4.30	16.9		
		3.91	89.3		
		2.59	33.1		

iment, we indicated in Tables 2 and 3 the values of W_{abs} standard deviation ($n = 12$).

DISCUSSION

Relationship Between the Dose of Radiation and the Loss of Water

Figure 1 demonstrates the values of the absorbed dose of radiation D_{abs} and the related values of the loss of water, excluding the 50-W values with the lactose granule. In the case of the calcium citrate experiment, the graph constructed on the basis of the 200-, 250-, and 300-W values is typical for the relationship existing between dose and effect. The data on lactose display a linear relationship up to the point of the 2600 D_{abs} value, which has a regression coefficient of .9832 ($n = 21$), with its ''rise of a curve'' being .0047, so

$$(\Delta\%)_t = .0047 \cdot D_{abs} \quad (4)$$

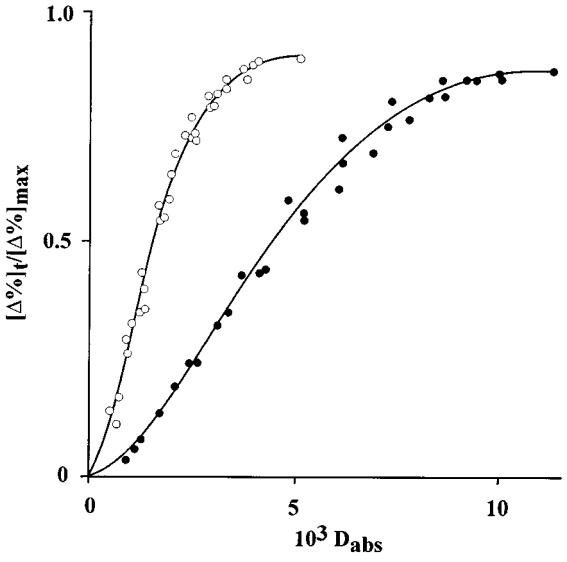

Figure 1. Effect of microwave radiation on loss of water of ○, lactose trials and ●, calcium citrate trials.

Based on these, we are able to calculate the two most important operating parameters—time and the dose of radiation—required for the scale-up method.

Let us suppose that, in the case of the lactose experiment, the water content was found to be optimal during preformulation, which could otherwise be arbitrarily adjusted; for example, we wish to have a 4% water content, and to achieve that, the amount of the loss of water has to be $15.56 - 4 = 11.56\%$ according to the calculation. The radiation effect required has to be calculated according to formula 4:

$$D_{abs} = \frac{11.56}{.0047} = 2460$$

which is the dose of absorbed radiation that is required. On the basis of this, a whole series of exposure periods and the related W_{abs} values can be derived by the application of formula 2, as in the given example:

Minutes	1	10	20	30
W_{abs}	2447	244.7	122.4	81.6

During the granulation procedure, the adjustable nominal power of the device (with respect to the composition of the granule) multiplied by the predetermined induced absorbability coefficient α according to formula 1; we achieved a nominal power value that corresponds to the W_{abs} value required for performing the process.

Dose of Radiation and the Kinetics of the Loss of Water

Considering the data of Table 2, the loss of water appears to correspond to a zero-order kinetics process with respect to time; therefore, we can state that

$$\frac{d(\Delta\%)_t}{dt} = k$$

on the basis of which the loss of water at time t is calculable by the following formula:

$$(\Delta\%)_t = k \cdot t \tag{5}$$

Based on the experimental data, we observed the following rate constants (k $\Delta\% \cdot \text{min}^{-1}$) at the individual nominal irradiation levels:

W	50	100	150	200	300	350
k	0.213	0.353	0.377	0.606	0.800	1.11

The logarithm of the rate constants plotted against the reciprocal value of the corresponding W_{abs} value displays the Arrhenius-like relationship shown in Fig. 2.

Figure 2 clearly shows that the increase of the radiation power above the radiation level of 50 and 100 W shows irregularity, which implies that greater radiation power is able to stimulate radiation-absorbing mechanisms that require higher activation energy, too. This fact is supported by the observation that, on the basis of the increasing temperature of the product due to the effect of the radiation power, the activation energy calculated by the Clausius-Clapeyron equation for the two segments of the graph resulted in specific values of 12.9 and 42.7 (±13.3%) kJ in the 50–100 W and 150–350 W ranges, respectively.

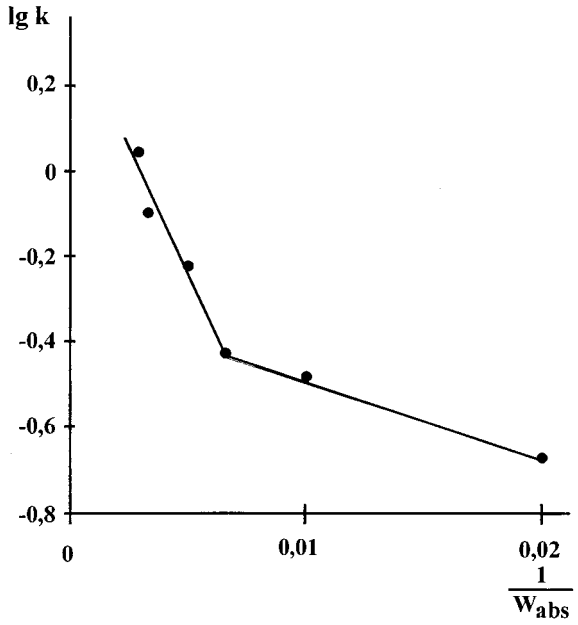

Figure 2. Arrhenius-type graphical relationship.

In the granulate, the added water binds at different energy levels, and the total mass of the water A gets converted to vapor phase B when exposed to radiation; thereafter, the mass of the condensed water C becomes measurable. The following consecutive process is represented by k_1 and k_2 rate constants for the transport of water in the microwave granulator:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Apparently, we can state for the two zero-order kinetic processes that

$$dA/dt = k_1 \cdot t \text{ and } dC/dt = k_2 \cdot t$$

based on this, the solution for scaling-up in the case when $k_1 > k_2$

$$A_t = A - [t \cdot (k_1 - k_2) + C_t]$$

The values of k_1 and k_2 are mainly determined by the power of the radiation and the difference in the temperature between the substance and the condenser. It is possible to calculate the mass of water that remains in the granules A_t and the amount that collects in the condenser C_t at a given time t on the basis of the mathematical description of the consecutive process. Relying on these findings, we are able to control the scale-up procedure even during the process on line; furthermore, the manufacturing process may even be automated.

Dose of Radiation and the Kinetics of the Change in the Heat Energy

During the process of microwave granulation, the temperature of the irradiated sample (for example, in the case of the 50-W lactose experiment) remained practically unchanged, yet in other cases, it showed an increase with respect to time, which is demonstrated by Fig. 3.

The changes in the temperature accompanying the process depend on the state of balance existing between the exothermic ↔ endothermic reactions. The endothermic evaporation heat of water in the temperature range 20°C–70°C (calculated by the Clausius-Clapeyron equation) is 43.3 (±0.97%) kJ/mol, through which the heat energy content of the irradiated sample (calculated by the

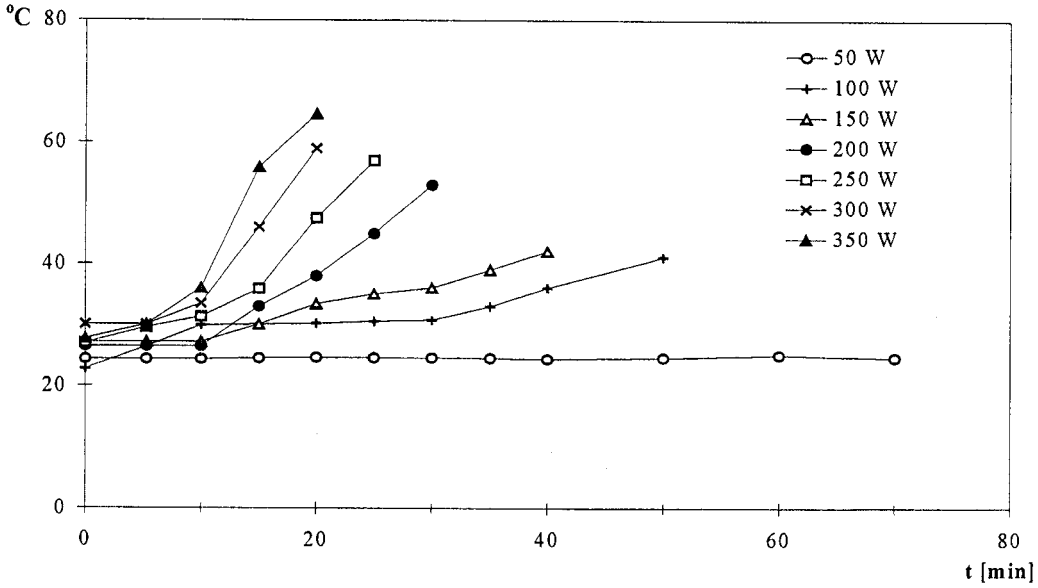

Figure 3. Change of temperature of lactose granulation trials.

temperature and mass of the sample) can be corrected for every given time *t*. In such a way, the change in the heat energy ΔkJ/kg (compared to the initial value) in the irradiated substance can be used for reaction-kinetic analysis in relation to time. For the sake of demonstration, we will put forth the 350-W values of the lactose experiment:

Minutes	0	5	10	15	20
ΔkJ/kg	0	14	58	122	205
$(\Delta kJ/kg)^{1/2}$	0	3.7	7.6	11.0	14.3

Figure 4 shows the reaction-kinetic function of these data and has a regression coefficient of 0.9994, which results in a good quality linear line. Based on this, we can state that the gross microwave energy transfer appears to follow a procedure of half-order kinetics.

As mentioned in the Introduction, radiation generates several reversible alterations. In Fig. 1, we can see that the steepness of the linear segments of the ''dose → effect'' functions of the lactose and calcium citrate samples displays significant variations. The regression coefficient of calcium citrate is 0.9921 ($n = 21$), and its ''rise of a curve'' is 0.0022, compared to which the rise of a curve of lactose is 2.14 times greater. Due to physical considerations, we can conclude that this value is determined by the nonadditive permittivity of the multicomponent system, as well as its other combined electrophysical properties. These nonadditive properties may not be arrived at by taking all the individual properties of the components into account with respect to their mass ratio. Among others, using the literary data ε′ and ε″ (10) on the 42 different pharmaceutical substances, including water, the calculated permittivity of the two examined samples hardly showed a difference compared to the 2.14 times greater value from the experimental work. It appears that this experimental method will even be suitable for numerically expressing the nonadditive permittivity of multicomponent systems.

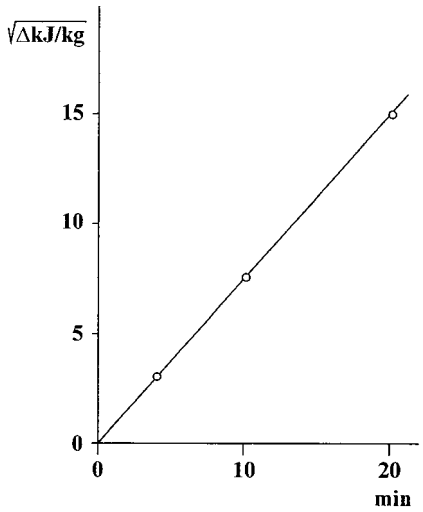

Figure 4. Graphical demonstration of half-order reaction kinetic experience.

Based on the X-ray diffraction surveys, we can also state, for the calcium citrate experiments, that the solid-state structure of the mixture (I), the wetted sample (II), and the sample that had been exposed to radiation went through a significant change. Such a so-called heteromorphic solid-state alteration (11) can also be achieved through heat treatment in the case of calcium citrate, which proved to be beneficial with regard to tablet production technologies and its in vitro biopharmaceutical property and to the quality of the calcium citrate tablet in general (12).

CONCLUSION

It is possible to elaborate numerical data for the scale-up of microwave wet granulation in Mi-Mi-Pro laboratory equipment by the systematic examination of the dose of radiation and the quantitative effect related to it. The loss of water can be described by the absorbed dose of radiation and the principles of consecutive reaction kinetics. The analysis of the heat effect of radiation will provide further useful information determined by the balance of physical, physical-chemical, and chemical exothermic and endothermic reactions. Apparently, the gross change in the heat energy can be described by a principle of half-order kinetics. Based on experience, the potential solid-state alteration, which mainly turns out to be reversible, of the irradiated substance can be detected by an X-ray diffraction method. Such a so-called heteromorphic alteration, like the one observed in the case of the quality of the calcium citrate tablet, proved to be beneficial.

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