*Journal of Thermal Analysis and Calorimetry, Vol. 89 (2007) 3, 775–781*

# THERMAL STUDIES OF PRE-FORMULATES OF METRONIDAZOLE OBTAINED BY SPRAY DRYING TECHNIQUE

*Antonilêni F. D. Medeiros*[1*], *Ana Flávia O. Santos*[1], *F. S. de Souza*[2], *I. D. B. Júnior*[2], *J. Valdilânio, J. V. V. Procópio*[2], *D. P. de Santana*[1] *and R. O. Macêdo*[2]

[1]Pharmaceutical Sciences Department – Federal University of Pernambuco – UFPE, Prof. Artur de Sá, s/n – University City Zip. 50.740-521, Recife, PE, Brazil
[2]Unified Laboratory of Medicine Development and Assay – LUDEM – Federal University of Paraíba – UFPB, Campus I Zip. 58059-900, João Pessoa – PB - Brazil

Compatibility studies between active drugs and excipients are substantial in the pharmaceutical technology. The objective of the present work was to develop pre-formulated mixtures of metronidazole (MT) obtained by spray drying (SPDR) and their thermoanalytical characterization. Dynamic and isothermal TG, conventional DSC and DSC coupled to a photovisual system were used. DSC experiments with both techniques confirmed the homogeneity of the conventional and pre-formulated mixtures. The TG data made possible the comparison the thermal stability of the different mixtures. Similar thermal stabilities were found of the conventional and pre-formulated mixtures, with slower particles sizes of MT.

***Keywords:*** *metronidazole, spray drying, thermal analysis*

## Introduction

Compatibility studies between active drugs and excipients are the one of the main stages during the development of new formulations [1]. Among different industrial processes spray drying (SPDR) is the most extensively used one that involves formation and drying of particles. It is highly adequate for continuous production of dry solids, in the form of powders, granules or agglomerates from solution, emulsion or suspension [2].

SPDR technique has been used successfully to microencapsulate of bioactive molecules like enzymes, flavors and drugs and also in the preparation of drug release systems with a great variety of biodegradable polymers [3].

Development of solid dosage forms using SPDR compared to conventional techniques presents many advantages like homogeneity, to reduce and make uniform the particles, and to enhance the rate of dissolution and higher drying speed [4]. This way, SPDR technique produces a pharmaceutical product with better quality, reproducibility and thermal stability [5].

Metronidazole drug is an active adversely wide spectrum of parasite and anaerobic bacterium. It is a classic amebicid and fungicide drug with a great use in the slowly developing countries.

One aim of the present study is to enhance the pharmaceutical quality of MT [5–7] as well as to develop its pre-formulated mixtures by SPDR technique and to compare their thermal properties to the conventional mixtures.

## Materials and methods

### *Materials*

Metronidazole (Genix, China), starch (Dinalab, Brazil), colloidal silicon dioxide–Aerosil® (Genix, Germany), croscarmellose sodium (Sweden, Forlab), lactose 80 mesh (Dinalab, China) all in pharmaceutical grade, furthermore deionized water and absolute ethanol were used.

### *Sample preparation and drying conditions of SPDR*

Preparation of conventional and spray dried mixtures have been done using the following procedures:

Ternary conventional mixtures

- Sample A: 1.67 g of MT drug substance, 0.16 g of starch and 0.16 g of Aerosil® powders were homogenized mechanically and put in a dry and clean container.

* Author for correspondence: antonileni@gmail.com, ruiomacedo@yahoo.com.br

*1388–6150/$20.00*

*Akadémiai Kiadó, Budapest, Hungary*
*Springer, Dordrecht, The Netherlands*

- Sample B: 1.43 g of MT drug substance, 0.43 g of sodium croscarmellose and 0.16 g of Aerosil® were homogenized mechanically and put in a dry and clean container.
- Sample C: 1.67 g of MT drug substance, 0.16 g of lactose and 0.16 g of Aerosil® powders were homogenized mechanically and put in a dry and clean container.

Ternary SPDR mixtures

- Solution A: 10.0 g of MT drug substance, 1.0 g of starch and 1.0 g of Aerosil® were homogenized mechanically, then 80 mL of ethanol and later 120 mL of deionized water was added.
- Solution B: 10.0 g of MT drug substance, 3.0 g of croscarmellose and 1.0 g of Aerosil® were homogenized mechanically, followed by the addition of 80 mL of ethanol and later 120 mL of deionized water.
- Solution C: 10.0 g of MT drug substance, 1.0 g of lactose and 1.0 g of Aerosil® were homogenized mechanically, and then 80 mL of ethanol and later 120 mL of deionized water was added.

Samples were dried in a LabPlant model SD-05 SPDR apparatus. The experimental dry conditions were:

- Solution A: internal temperature ($T_{int}$) 100°C, exhaustion temperature ($T_{exa}$) 65°C, rate of liquid feed 5 mL $h^{-1}$.
- Solution B: internal temperature ($T_{int}$) 140°C, exhaustion temperature ($T_{exa}$) 85°C, rate of liquid feed 5 mL $h^{-1}$.
- Solution C: internal temperature ($T_{int}$) 140°C, exhaustion temperature ($T_{exa}$) 75°C, rate of liquid feed 5 mL $h^{-1}$.

Solutions A, B and C were agitated and pre-heated up to approximately 50°C and only then they were pumped through the peristaltic pump of the SpDr system to a nebulization chamber and atomized in a 0.5 mm nozzle followed by the drying process in a co-current system with a pressure of 1.5 bar. Dry particles were collected in a container coupled to cyclone of the SPDR system and then they were put in a dry and clean container to be analyzed later.

## Thermal analysis

DSC curves were obtained at a heating rate of 5°C $min^{-1}$ up to 500°C in nitrogen, flow rate: 50 mL $min^{-1}$. The analyzed sample masses were about 2.0 mg. DSC photovisual data were recorded on a SHIMADZU model DSC-50 calorimeter coupled to a photovisual system [8], model VCC-520 equipped with an OLYMPUS microscope and with a SONY camera. The operation conditions were the same as in case of conventional DSC. The photos were taken by Assimetrix program at real time to observe the variation of phase transitions of the samples. Temperature calibration was done using indium (156.6°C±0.3) and zinc (410.6°C±0.3) as standards. The heat flow signal was calibrated by melting heat of indium (28.59±0.30 J $g^{-1}$).

Thermogravimetric curves were recorded on a Shimadzu apparatus model TGA-50H, calibrated with calcium oxalate monohydrate in nitrogen (flow rate: 50 mL $min^{-1}$) and with synthetic air (flow rate: of 20 mL $min^{-1}$). Dynamic curves were recorded at a heating rate of 10°C $min^{-1}$ up to 900°C. The initial sample masses were 5.0±0.5 mg. Isothermal curves were recorded at 150, 160, 170, 180 and 190°C for 120 min. Thermal curves were analyzed using TASYS software form Shimadzu.

## Results and discussion

No interaction was observed between the MT drug and the excipients. This is evidenced by the melting temperatures (Table 1) of MT in its conventional and pre-formulated mixtures, which was in agreement with the literature values (158–160°C) [9].

A decrease in the enthalpy values of pre-formulates was observed. It can be attributed to the better drug protection effect by the excipients although neither physical nor chemical interactions took place be-

**Table 1** Melting points (*mp*) and enthalpies ($\Delta H$) of MT and in its conventional and pre-formulated mixtures

| Sample | MT | MT/Starch/Aerosil® | MT/Croscarmellose/Aerosil® | MT/Lactose/Aerosil® |
|---|---|---|---|---|
| *mp* conventional mixtures/°C | 159.9 | 160.3 | 160.2 | 169.2 |
| $\Delta H$/J $g^{-1}$ conventional mixtures | –74.5 | –133.5 | –96.4 | –133.5 |
| *mp* pre-formulated mixtures /°C | – | 159.9 (±0.1) | 159.6 (±0.2) | 157.9 (±0.1) |
| $\Delta H$/J $g^{-1}$ pre-formulated mixtures | – | –122.1 (±22.6) | –90.7 (±20.0) | –120.0 (±11.1) |

Results as average ±sd; $n$=3 pre-formulated samples

**Table 2** Representative decomposition stage temperatures and residues of metronidazole (raw material) in the conventional and pre-formulated mixtures prepared by SPDR

| | MT | | MT/Starch/Aerosil® | | | | MT/Croscarmellose/Aerosil® | | | | MT/Lactose/Aerosil® | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Conventional | | Conventional | | Pre–formulated* | | Conventional | | Pre–formulated* | | Conventional | | Pre–formulated* | |
| Temperature/°C | $T_0$ | $T$ | $T_0$ | $T$ | $T_0$ | $T$ | $T_0$ | $T$ | $T_0$ | $T$ | $T_0$ | $T$ | $T_0$ | $T$ |
| 1st stage | 178.3 | 296.0 | 144.1 | 286.1 | 171.8 (±26.8) | 288.00 (±1.0) | 84.0 | 193.4 | 36.8 (±3.8) | 181.0 (±6.9) | 84.4 | 284.5 | 131.1 (±7.4) | 285.8 (±1.1) |
| 2nd stage | 299.0 | 789.8 | 286.1 | 775.8 | 288.0 (±1.0) | 707.3 (±143.7) | 193.4 | 286.4 | 181.0 (±6.9) | 278.8 (±1.3) | 248.5 | 725.8 | 285.8 (±1.1) | 704.5 (±33.4) |
| 3rd stage | – | – | – | – | – | – | 286.4 | 345.9 | 278.8 (±1.3) | 350.1 (±7.5) | – | – | – | – |
| 4th stage | – | – | – | – | – | – | 345.9 | 542.5 | 350.1 (±7.5) | 566.8 (±11.2) | – | – | – | – |
| Residue (%) | 1.4 | | 9.2 | | 11.0 | | 9.9 | | 11.5 | | 6.3 | | 10.8 | |

*average±sd

tween drug and excipients in these mixtures. However, the pre-formulated mixture containing MT/Lactose/Aerosil® showed approximately 12°C decrease in the temperature of the first phase transition process, reducing the value of $\Delta H$. During the preparation of the mixture by spray drying the interaction between MT and lactose could be eliminated as it had been indicated by the melting point of MT in its pre-formulates. This shows a change which is characteristic for lactose, which is the major excipient in the formulation. This theory was confirmed by DSC photovisual (Fig. 1).

Conventional DSC data of the pre-formulated mixtures, MT/Starch/Aerosil®, MT/Croscarmellose/Aerosil®, MT/Lactose/Aerosil® showed small changes in the thermal behaviour, which was not possible to evaluate using only the conventional DSC technique. However, DSC photovisual technique presents itself a more sensitive analytical tool in recognizing the alterations in the thermal behaviour and morphological changes during phase transitions and thermal decomposition processes (Fig. 1).

This shows that process to obtain the pre-formulated mixtures does not change the thermal behaviour of MT drug compared to its correspondent conventional mixtures, except for mixture containing lactose.

Table 2 shows the dynamic TG data with decomposition stages temperatures and residues of metronidazole (raw material), conventional and pre-formulated mixtures via SPDR.

Ozawa's model was used in the kinetic studies to evaluate the thermoanalytical kinetic parameters as activation energy ($E_a$), frequency factor ($A$) and reaction order ($n$). The data collected in Table 3 are evidencing a zero order kinetic behavior of MT with the mean activation enthalpy of 59.3 kJ mol$^{-1}$ (RSD=1.52 kJ mol$^{-1}$), frequency factor ($8.48\cdot10^{-4}$–$8.54\cdot10^{-4}$ min$^{-1}$) at $\alpha_{10}$, $\alpha_{20}$ and $\alpha_{30}$ decomposed fractions (Table 3).

The values of Antoine constants: $A$=5.23662, $B$=1159.34 and $C$=–220.03, in the 446–517 K temperature interval, for vapor pressure curves obtained from methylparaben standard [10] following the Antoine equation ($\log P=A-B(T+C)$) to determine the value of '$k$', and then Langmuir equation, that can be modified to obtain the vapor pressure values of many simple components ($P=[\alpha^{-1}(2\pi R)^{1/2}][(T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)]=k\upsilon$) [11]. It was obtained for methylparaben constant at a heating rate of 10°C written in [12], which was 125413±1.774, and the vapor pressure curves for MT and its conventional and SPDR mixtures were constructed.

It was confirmed that the first mass loss stage is the volatilization of MT and follows zero order kinetics [12]. This could be calculated using methylparaben vapor pressure value determined at a heating rate of 10°C min$^{-1}$, which was 125417±1.774. This value was used to calculate the vapor pressure of MT in each mixture that is presented as the following values for ponderal pressures: 143776.07 and 124558.17 Pa to conventional and pre-formulated mixtures of MT/Starch/Aerosil® respectively, 174197.98 and 88962.27 Pa to conventional and pre-formulated mixtures of MT/Croscarmellose/Aerosil®, respectively; 100210.39 and 93708.44 Pa to conventional and pre-formulated mixtures of MT/Lactose/Aerosil®, respectively.

From the isothermal TG data the rate constants of decomposition kinetics in the studied temperatures were calculated following the Arrhenius equation [13] (Table 3). According to the obtained results the pre-formulated mixtures of MT/Starch/Aerosil®, MT/Croscarmellose/Aerosil® and MT/Lactose/Aerosil® presented similar thermal constants with respect to their correspondent conventional mixtures in the studied temperatures. Conventional granulation processes, using static stream bed drying of pre-formulates, normally increases the particle size distribution to higher ranges compared to SPDR process. In this way granule sizes and homogeneity changes, influencing directly the solubility and dissolution of drug substances in biological fluids. In technological point of view, granulation by SPDR promotes the granulation without affecting the initial particle size and also maintains good particle size homogeneity producing a better reproducibility between batches with regard to the intrinsic characteristics present of the drug in its formulation. So, the SPDR process did not influence the stability of this pre-formulated mixture, while, at the same time the dissolution rate MT was increased by increasing the superficial area of the powder mixtures indicating that SPDR technology is a promising way to develop pharmaceutical products with better biological activity.

**Table 3** Kinetic parameters of MT

| Metronidazole | $\alpha_{10}$ | $\alpha_{20}$ | $\alpha_{30}$ |
|---|---|---|---|
| Activation energy*/ kJ mol$^{-1}$ | 59.3±0.90 | 59.3±0.95 | 59.3±0.87 |
| Variance coefficient/% | 1.524 | 1.596 | 1.470 |
| Frequency factor/ min$^{-1}$ | $8.477\cdot10^4$ | $8.495\cdot10^4$ | $8.538\cdot10^4$ |
| Order | 0 | 0 | 0 |

*average±sd

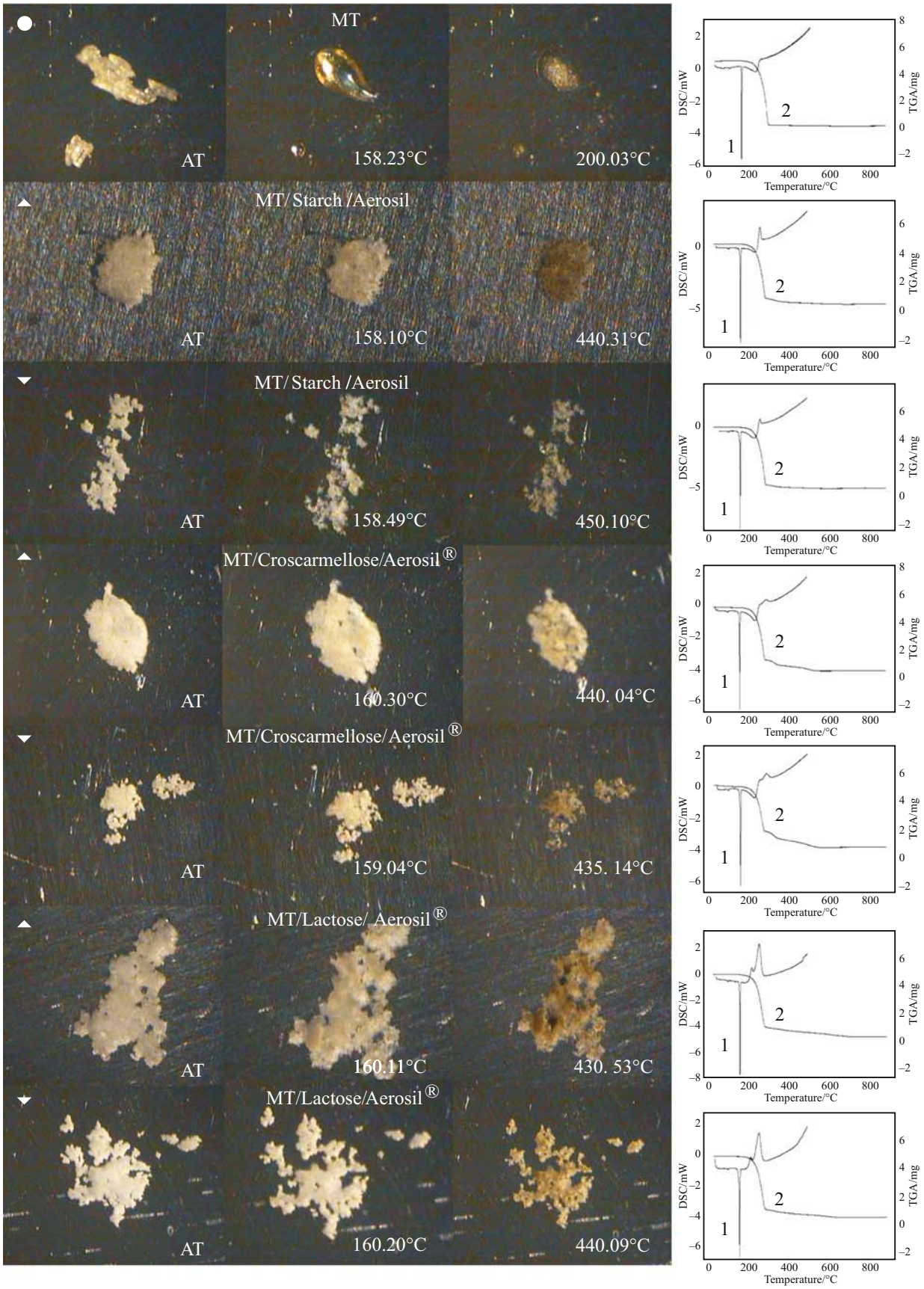


**Fig. 1** Photovisual DSC of MT drug ● – substance and ▲ – its conventional and ▼ – pre-formulated mixtures completed with the 1 – DSC and 2 – TG curves

**Table 4** Rate constants ($k$) of isothermal decomposition of metronidazole (raw material), conventional and Pre-formulated mixtures using SPDR

| Temperature /°C | | 150 | | 160 | | 170 | | 180 | | 190 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Constants | Conventional | Pre-formulated | Conventional | Pre-formulated | Conventional | Pre-formulated | Conventional | Pre-formulated | Conventional | Pre-formulated |
| MT | $k_0$ ($r^2$) | $1.42\cdot10^{-5}$ (–0.9946) | – | $4.76\cdot10^{-5}$ (–0.9992) | – | $1.01\cdot10^{-4}$ (–0.9999) | – | $1.68\cdot10^{-4}$ (–1.000) | – | $2.44\cdot10^{-4}$ (–1.000) | – |
| | $k_1$ ($r^2$) | $2.01\cdot10^{-5}$ (–0.9976) | – | $3.16\cdot10^{-5}$ (–0.9993) | – | $8.43\cdot10^{-5}$ (–0.9998) | – | $2.10\cdot10^{-4}$ (–0.9999) | – | $3.01\cdot10^{-4}$ (–0.9998) | – |
| | $k_2$ ($r^2$) | $1.51\cdot10^{-5}$ (0.9946) | – | $5.95\cdot10^{-5}$ (0.9994) | – | $1.81\cdot10^{-4}$ (0.9998) | – | $9.97\cdot10^{-4}$ (0.9997) | – | $1.33\cdot10^{-3}$ (0.9994) | – |
| MT/Starch/ Aerosil® | $k_0$ ($r^2$) | $2.22\cdot10^{-5}$ (–0.9982) | $2.32\cdot10^{-5}$ (–0.9980) | $5.12\cdot10^{-5}$ (–0.9997) | $4.75\cdot10^{-5}$ (–0.9994) | $9.44\cdot10^{-5}$ (–0.9999) | $1.03\cdot10^{-4}$ (–0.9999) | $1.63\cdot10^{-4}$ (–1.000) | $1.61\cdot10^{-4}$ (–0.9999) | $1.96\cdot10^{-4}$ (–1.000) | $2.14\cdot10^{-4}$ (–1.000) |
| | $k_1$ ($r^2$) | $1.46\cdot10^{-5}$ (–0.9982) | $1.46\cdot10^{-5}$ (–0.9980) | $3.51\cdot10^{-5}$ (–0.9997) | $3.33\cdot10^{-5}$ (–0.9994) | $7.56\cdot10^{-5}$ (–0.9998) | $8.56\cdot10^{-5}$ (–0.9998) | $1.79\cdot10^{-4}$ (–0.9999) | $1.81\cdot10^{-4}$ (–0.9998) | $2.30\cdot10^{-4}$ (–0.9997) | $2.98\cdot10^{-4}$ (–0.9997) |
| | $k_2$ ($r^2$) | $2.44\cdot10^{-5}$ (0.9982) | $2.56\cdot10^{-5}$ (0.9980) | $6.50\cdot10^{-5}$ (0.9996) | $5.91\cdot10^{-5}$ (0.9994) | $1.59\cdot10^{-4}$ (0.9997) | $1.87\cdot10^{-4}$ (0.9997) | $5.33\cdot10^{-4}$ (0.9996) | $5.85\cdot10^{-4}$ (0.9996) | $6.94\cdot10^{-4}$ (0.9991) | $1.17\cdot10^{-3}$ (0.9991) |
| MT/ Croscarmellose/ Aerosil® | $k_0$ ($r^2$) | $2.06\cdot10^{-5}$ (–0.9979) | $2.22\cdot10^{-5}$ (–0.9958) | $4.16\cdot10^{-5}$ (–0.9995) | $5.04\cdot10^{-5}$ (–0.9996) | $9.93\cdot10^{-5}$ (–0.9999) | $1.03\cdot10^{-4}$ (–0.9999) | $1.54\cdot10^{-4}$ (–0.9999) | $1.46\cdot10^{-4}$ (–0.9999) | $1.84\cdot10^{-4}$ (–1.000) | $1.67\cdot10^{-4}$ (–0.9999) |
| | $k_1$ ($r^2$) | $1.28\cdot10^{-5}$ (–0.9979) | $1.45\cdot10^{-5}$ (–0.9957) | $2.90\cdot10^{-5}$ (–0.9995) | $3.67\cdot10^{-5}$ (–0.9996) | $8.26\cdot10^{-5}$ (–0.9999) | $8.79\cdot10^{-5}$ (–0.9998) | $1.55\cdot10^{-4}$ (–0.9998) | $1.43\cdot10^{-4}$ (–0.9998) | $1.99\cdot10^{-4}$ (–0.9998) | $1.76\cdot10^{-4}$ (–0.9995) |
| | $k_2$ ($r^2$) | $2.25\cdot10^{-5}$ (0.9979) | $2.44\cdot10^{-5}$ (0.9956) | $5.04\cdot10^{-5}$ (0.9995) | $6.37\cdot10^{-5}$ (0.9996) | $1.72\cdot10^{-4}$ (0.9998) | $1.83\cdot10^{-4}$ (0.9997) | $4.29\cdot10^{-4}$ (0.9996) | $3.28\cdot10^{-4}$ (0.9995) | $5.33\cdot10^{-4}$ (0.9991) | $3.97\cdot10^{-3}$ (0.9987) |
| MT/Lactose / Aerosil® | $k_0$ ($r^2$) | $2.23\cdot10^{-5}$ (–0.9983) | $2.30\cdot10^{-5}$ (–0.9986) | $4.90\cdot10^{-5}$ (–0.9992) | $4.56\cdot10^{-5}$ (–0.9996) | $9.53\cdot10^{-5}$ (–0.9999) | $8.25\cdot10^{-5}$ (–0.9998) | $1.49\cdot10^{-4}$ (–0.9999) | $1.24\cdot10^{-4}$ (–0.9999) | $2.06\cdot10^{-4}$ (–1.000) | $1.68\cdot10^{-4}$ (–1.0000) |
| | $k_1$ ($r^2$) | $1.46\cdot10^{-5}$ (–0.9983) | $1.50\cdot10^{-5}$ (–0.9986) | $3.42\cdot10^{-5}$ (–0.9991) | $3.20\cdot10^{-5}$ (–0.9995) | $7.69\cdot10^{-5}$ (–0.9998) | $6.38\cdot10^{-5}$ (–0.9997) | $1.48\cdot10^{-4}$ (–0.9998) | $1.09\cdot10^{-4}$ (–0.9999) | $2.63\cdot10^{-4}$ (–0.9997) | $1.76\cdot10^{-4}$ (–0.9999) |
| | $k_2$ ($r^2$) | $2.45\cdot10^{-5}$ (0.9983) | $2.54\cdot10^{-5}$ (0.9986) | $6.16\cdot10^{-5}$ (0.9991) | $5.61\cdot10^{-5}$ (0.9995) | $1.63\cdot10^{-4}$ (0.9998) | $1.25\cdot10^{-4}$ (0.9996) | $4.46\cdot10^{-4}$ (0.9996) | $2.73\cdot10^{-4}$ (0.9998) | $8.91\cdot10^{-4}$ (0.9991) | $5.12\cdot10^{-4}$ (0.9996) |

## Conclusions

Pre-formulates obtained by SPDR presented similar thermal behavior to the corresponding conventional mixtures, except for the mixture that contained lactose.

Kinetic parameters of conventional and pre-formulated mixtures obtained by TG showed the same stability.

Data showed that SPDR technique may be applied in development of pharmaceutical products.

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Received: July 13, 2006
Accepted: May 29, 2007

DOI: 10.1007/s10973-007-7874-5