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THERMAL STABILITY OF PARACETAMOL AND ITS PRE-FORMULATES OBTAINED BY SPRAY DRYING

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Stability of drugs and products has a great practical interest, which is facing to strict regulation. Thermal studies, besides the determination of the thermal properties of the investigated product allow the verification of possible interactions between the drug substances and excipients. The objective of this work was to obtain solid pre-formulates of paracetamol (PC) by spray drying (SPDR), as well as to investigate their thermal behavior. Dynamic and isotherm TG, conventional DSC and DSC-photovisual coupled methods were used to characterize the conventional and pre-formulated mixtures obtained by SPDR. The results of both DSC investigations showed slight alterations in melting temperatures, which suggests incompatibilities. The TG decomposition data of the mixtures evidenced that the dry process via SPDR leads to stability enhancement of the pre-formulated mixtures.

Keywords: *paracetamol, spray drying, thermal analysis*

Introduction

Modern thermoanalytical, as well as emerging technologies, providing information on the calorimetric, microscopic and spectrophotometric properties are powerful analytical tools for the pharmaceutical development [1–4].

Thermogravimetry is used to determine the stability and decomposition kinetic of a solid medicine, helps in the life-time prediction of the pharmaceutical forms from the degradation rate. Such techniques are fast enough to make quick studies during the technological development and one can obtain information on the quality of the formulations [3, 5].

SPDR is more commonly used to produce finely divided powders, granules, agglomerates, products for encapsulation, to cover, to reduce the particles and provide a more homogeneous particle size distribution [6].

The objective of the present work was to develop solid pre-formulated mixtures of paracetamol (PC) by SPDR as well as to evaluate their stability and thermal properties.

Experimental

Materials

Pharmaceutical grade of PC (Dinalab, batch: 0310005, Brazil), starch (Dinalab, Brazil), colloidal silicon dioxide – Aerosil® (Genix, Germany), croscarmellose sodium (Sweden, batch: 8642100, Forlab), lactose 80 mesh (Dinalab, batch: 0145, China), polyvinylpyrrolidone (PVP) (Palmares, batch: 030000233-78, Brazil), deionized water were used in our experiments.

Sample preparation and spray-drying conditions

Preparation of conventional and SPDR mixtures obeyed the following procedures:

Conventional mixtures

- Sample A: 1.592 g of PC drug substance, 0.159 g of starch, 0.09 g of PVP and 0.159 g of Aerosil®, powders were homogenized and put in a dry and clean container.
- Sample B: 0.926 g of PC drug substance, 0.926 g of croscarmellose sodium, 0.055 g of PVP and 0.093 g of Aerosil®, powders were homogenized and put in a dry and clean container.

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- Sample C: 0.926 g of PC drug substance, 0.926 g of lactose, 0.055 of PVP and 0.093 g of Aerosil®, powders were homogenized and put in a dry and clean container.

SPDR mixtures

- Solution A: 10.0 g of PC drug substance, 10.0 g of starch, 0.6 g of PVP and 1.0 g of Aerosil®, powders were homogenized and added 200 mL of deionized water.
- Solution B: 10.0 g of PC drug substance, 10.0 g of croscarmellose sodium, 0.6 g of PVP and 1.0 g of Aerosil®, powders were homogenized and added 200 mL of deionized water.
- Solution C: 10.0 g of PC drug substance, 10.0 g of lactose, 0.6 g of PVP and 1.0 g of Aerosil®, powders were homogenized and added 200 mL of deionized water.

Samples were dried in a SpDr apparatus from LabPlant (UK) model SD-05. The experimental dry conditions were:

- Solution A: internal temperature (T_{int}) 100°C, due to gelatinization point in the case of starch, exhaustion temperature (T_{exa}) 65°C, feed rate of liquid was approximately 250 mL h^{-1}.
- Solution B: internal temperature (T_{int}) 145°C, exhaustion temperature (T_{exa}) 85°C, feed rate of liquid was approximately 250 mL h^{-1}.
- Solution C: internal temperature (T_{int}) 145°C, exhaustion temperature (T_{exa}) 75°C, feed rate of liquid was approximately 250 mL h^{-1}.

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

Thermal analysis

The calorimetric curves of conventional and SPDR mixtures were recorded using Shimadzu (USA) model DSC-50 calorimeter, calibrated with standard indium under the same conditions as the samples were measured. The DSC curves were recorded at a heating rate of 5°C min^{-1} from ambient up to 500°C in nitrogen (50 mL min^{-1}). The initial sample mass was about 2.0 mg. The photovisual data were recorded applying a Shimadzu (USA) model DSC-50 calorimeter coupled to a model VCC-520 photovisual system connected to an Olympus microscope (USA) and to a Sony (USA) camera in nitrogen (50 mL min^{-1}) from ambient up to 500°C. The photovisual system was connected to a computer using Assimetrix software, through which the images of the samples were visualized at real time. Pictures were recorded according to their DSC curves observing the phase transition of the samples. Thermogravimetric curves were recorded in a Shimadzu (USA) model TGA-50H apparatus calibrated with calcium oxalate monohydrate (the experimental conditions: dynamic and isotherm curves in nitrogen (50 mL min^{-1}) and in synthetic air (20 mL min^{-1})). Isothermal curves were recorded at 160, 170, 180 and 190°C for 120 min. The dynamic TG curves were recorded at a heating rate of 10°C min^{-1} from ambient up to 900°C. The initial sample mass was 5.0±0.5 mg. Thermoanalytical data were analyzed using Tasys software from Shimadzu. Vapor pressures of the pure PC, its conventional mixtures and spray-dried preformulates were calculated from the constant of methylparaben [7] using the Langmuir equation.

Results and discussion

According to literature, the pure PC melts between 168–172°C [8]. The obtained temperature data for the pure PC and its conventional mixtures showed a good correlation to the literature data. However, the spray-dried mixtures showed a slight reduction to the literature ones. In case of the preformulated mixtures with starch or croscarmellose, there was an increase in the activation energy (E_a), which was not observed in the preformulated mixture with lactose. SPDR technology produces particles with reduced size, which leads to an enhancement of superficial area of these particles. This could be responsible for the changes in melting enthalpy of the preformulated mixtures of PC (Table 1).

In the preformulated mixtures, besides the particle size reduction (data are not available) and the uniform distribution of pure PC, the reduction of the melting temperature was also observed.

The alterations in the melting temperatures of the preformulated mixtures showed by conventional DSC were visually followed, too. The photovisual DSC showed slight changes in the color of the mixtures in the respective melting temperatures (Fig. 1), evidencing the fusion of pure PC, while the excipients remained in solid phase denying the interaction between the drug substance and excipient.

Table 2 shows the dynamic TG data with the decomposition stage temperatures and residues of pure PC (raw material) and the conventional and SPDR preformulated mixtures.

Table 1 Melting points values (*m.p.*) on DSC and activation energies (E_a) for PC drug substance and its conventional and pre-formulated mixtures

Sample	PC	PC/Starch/Aerosil®	PC/Croscarmellose/Aerosil®	PC/Lactose/Aerosil®
m.p. conventional mixture/°C	170	169	169	168
E_a conventional mixture/J g^{-1}	–152.0	–78.8	–70.4	–48.6
m.p. pre-formulated mixture/°C	–	168±0.2	167.9±0.5	166.53±0.43
E_a pre-formulated mixture/J g^{-1}	–	–112.61±4.5	–99.7±19.0	–48.7±14

Results as average ±*sd*; *n*=3

Ozawa model was used in the kinetic studies with determining the kinetic parameters (activation energy, E_a; frequency factor, *A*; reaction order, *n*). Data showed in Table 3 are evidencing a zero order kinetic behavior of the pure PC (E_a: 74.07–74.25 kJ mol^{-1}; rsd 1.76 kJ mol^{-1}, frequency factor $1.047 \cdot 10^6$–$1.085 \cdot 10^6$ min^{-1} in the α_{10}, α_{20} and α_{30} decomposed fractions, Table 3).

Using the calculated values the Antoine constants: *A*=5.23662; *B*=1159.34 and *C*=–220.03 in the 446–517 K temperature interval according to the pressure curves obtained to the standard methylparaben [9] following the Antoine equation ($\log P = A - B/(T+C)$) to determine the value of '*k*', and consequently the Langmuir equation that may be modified to obtain the vapor pressure values of many simple components ($P=[\alpha^{-1}(2\pi R)^{1/2}][(T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)]=k\upsilon$) [10]. Applying the constant for methylparaben at 10°C min^{-1} heating rate (125413±1.774 [7]), the vapor pressure curves for PC and its conventional and pre-formulated mixtures were constructed. The constant determined for methylparaben was used to calculate the average vapor pressure for pure PC and for PC in each mixture. The obtained values were: 94043.51 and 128019.77 Pa for conventional and pre-formulated mixtures of PC/Starch/Aerosil®, 122259.80 and 131316.69 Pa for conventional and pre-formulated mixtures of PC/Croscarmellose/Aerosil® and 87502.90 and 137722.16 Pa for conventional and pre-formulated mixtures of

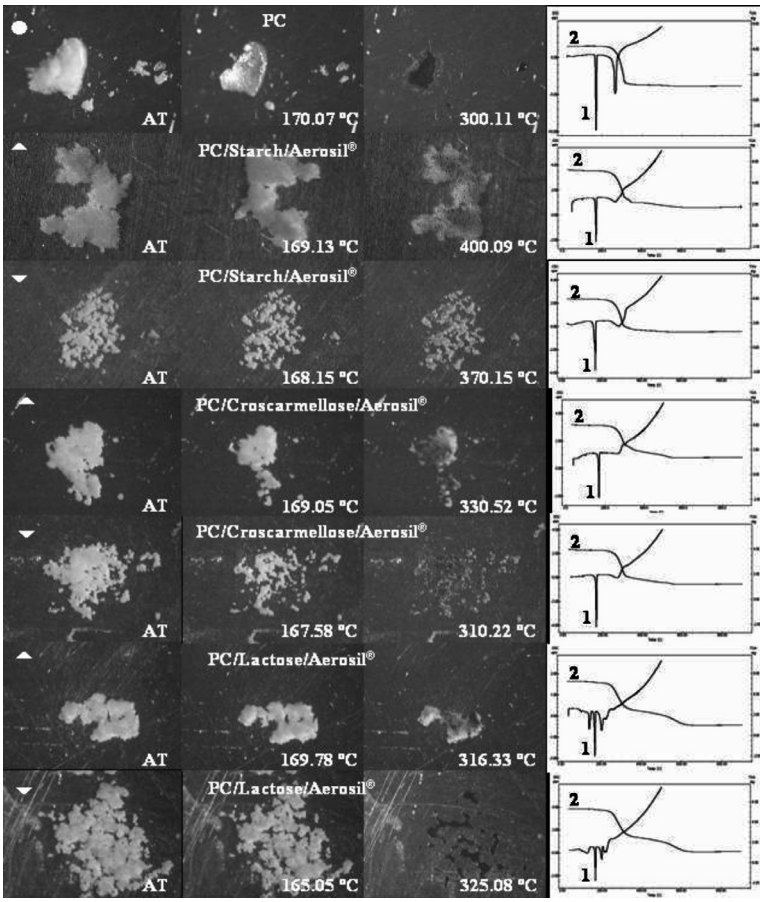

Fig. 1 DSC-photovisual images of ○ – pure PC, △ – conventional and ▽ – pre-formulated mixtures of PC and the corresponding 1 – DSC and 2 – TG curves

Table 2 Decomposition stage temperatures and residues of pure paracetamol and its conventional and spray-dried preformulate mixtures

	PC		PC/Starch/Aerosil®				PC/Croscarmellose/Aerosil®				PC/Lactose/Aerosil®			
	drug substance		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	188	317	187	307	187±7.2	308±1.7	193	302	189±5.9	311±1.6	152	315	124±3.3	295±9.6
2nd stage	323	582	312	590	314±2.7	538±8.7	314	549	318±2.1	561±13.5	334	654	310±12.8	695±40.1
Residue/%	4.2		20.1		16.5±1.8		17.5		12.7±0.5		11.3		7.6±0.1	

*average±*sd*; *n*=3

Table 3 Kinetic parameters of pure PC

Paracetamol	α_{10}	α_{20}	α_{30}
Activation energy*/kJ mol^{-1}	74.07±1.706	74.10±1.299	74.25±0.904
Variance coefficient/%	2.303	1.753	1.217
Frequency factor/min^{-1}	$1.047 \cdot 10^6$	$1.057 \cdot 10^6$	$1.085 \cdot 10^6$
Order	0	0	0

*average±*sd*; *n*=3

Table 4 Rate constants (k) for isothermal decomposition of pure PC and its conventional and spray-dried mixtures

Sample	Constant	Temperature/°C							
		160		170		180		190	
		conventional	pre-formulated	conventional	pre-formulated	conventional	pre-formulated	conventional	pre-formulated
PC	k_0/r^2	$2.37\cdot10^{-6}$ (–0.9354)	–	$4.83\cdot10^{-6}$ (–0.9721)	–	$1.05\cdot10^{-5}$ (–0.9926)	–	$1.90\cdot10^{-5}$ (–0.9982)	–
	k_1/r^2	$1.42\cdot10^{-6}$ (–0.9354)	–	$2.91\cdot10^{-6}$ (–0.9720)	–	$6.65\cdot10^{-6}$ (–0.9926)	–	$1.19\cdot10^{-5}$ (–0.9982)	–
	k_2/r^2	$2.40\cdot10^{-5}$ (0.9354)	–	$4.92\cdot10^{-6}$ (0.9720)	–	$1.10\cdot10^{-5}$ (0.9926)	–	$2.06\cdot10^{-5}$ (0.9982)	–
PC/Starch/Aerosil®	k_0/r^2	$5.71\cdot10^{-6}$ (–0.9823)	$2.67\cdot10^{-6}$ (–0.9397)	$1.31\cdot10^{-5}$ (–0.9940)	$5.29\cdot10^{-6}$ (–0.9843)	$2.52\cdot10^{-5}$ (–0.9988)	$1.13\cdot10^{-5}$ (–0.9942)	$5.05\cdot10^{-5}$ (–0.9996)	$2.15\cdot10^{-5}$ (–0.9983)
	k_1/r^2	$3.43\cdot10^{-6}$ (–0.9823)	$1.59\cdot10^{-6}$ (–0.9397)	$8.35\cdot10^{-6}$ (–0.9940)	$3.17\cdot10^{-6}$ (–0.9843)	$1.61\cdot10^{-5}$ (–0.9988)	$6.96\cdot10^{-6}$ (–0.9942)	$3.43\cdot10^{-5}$ (–0.9996)	$1.36\cdot10^{-5}$ (–0..9983)
	k_2/r^2	$5.84\cdot10^{-6}$ (0.9823)	$2.69\cdot10^{-6}$ (0.9397)	$1.39\cdot10^{-5}$ (0.9939)	$5.41\cdot10^{-6}$ (0.9843)	$2.81\cdot10^{-5}$ (0.9988)	$1.19\cdot10^{-5}$ (0.9943)	$6.37\cdot10^{-5}$ (0.9997)	$2.36\cdot10^{-5}$ (0.9983)
PC/Croscarmellose/Aerosil®	k_0/r^2	$6.12\cdot10^{-6}$ (–0.9886)	$2.47\cdot10^{-6}$ (–0.9272)	$1.27\cdot10^{-5}$ (–0.9950)	$5.83\cdot10^{-6}$ (–0.9797)	$2.38\cdot10^{-5}$ (–0.9962)	$1.29\cdot10^{-5}$ (–0.9943)	$4.53\cdot10^{-5}$ (–0.9994)	$1.92\cdot10^{-5}$ (–0.9958)
	k_1/r^2	$3.80\cdot10^{-6}$ (–0.9886)	$1.45\cdot10^{-6}$ (–0.9272)	$7.89\cdot10^{-6}$ (–0.9950)	$3.52\cdot10^{-6}$ (–0.9796)	$1.53\cdot10^{-5}$ (–0.9963)	$8.17\cdot10^{-6}$ (–0.9943)	$3.15\cdot10^{-5}$ (–0.9994)	$1.22\cdot10^{-5}$ (–0.9958)
	k_2/r^2	$6.27\cdot10^{-6}$ (0.9886)	$2.49\cdot10^{-6}$ (0.9273)	$1.34\cdot10^{-5}$ (0.9950)	$5.97\cdot10^{-6}$ (0.9796)	$2.64\cdot10^{-5}$ (0.9964)	$1.36\cdot10^{-5}$ (0.9943)	$5.57\cdot10^{-5}$ (0.9994)	$2.09\cdot10^{-5}$ (0.9957)
PC/Lactose/Aerosil®	k_0/r^2	$5.77\cdot10^{-6}$ (–0.9724)	$2.86\cdot10^{-6}$ (–0.9365)	$1.19\cdot10^{-5}$ (–0.9957)	$7.11\cdot10^{-6}$ (–0.9893)	$2.25\cdot10^{-5}$ (–0.9986)	$1.42\cdot10^{-5}$ (–0.9946)	$4.48\cdot10^{-5}$ (–0.9970)	$2.85\cdot10^{-5}$ (–0.9989)
	k_1/r^2	$3.63\cdot10^{-6}$ (–0.9724)	$1.72\cdot10^{-6}$ (–0.9365)	$7.28\cdot10^{-6}$ (–0.9957)	$4.37\cdot10^{-6}$ (–0.9894)	$1.40\cdot10^{-5}$ (–0.9986)	$8.79\cdot10^{-6}$ (–0.9946)	$3.40\cdot10^{-5}$ (–0.9972)	$1.81\cdot10^{-5}$ (–0.9989)
	k_2/r^2	$5.91\cdot10^{-6}$ (0.9725)	$2.90\cdot10^{-6}$ (–0.9365)	$1.25\cdot10^{-5}$ (0.9957)	$7.32\cdot10^{-6}$ (0.9894)	$2.49\cdot10^{-4}$ (0.9986)	$1.51\cdot10^{-5}$ (0.9946)	$6.01\cdot10^{-5}$ (0.9973)	$3.22\cdot10^{-5}$ (0.9989)

PC/Lactose/Aerosil®; respectively. So, it could be confirmed that the first mass loss stage obeys a zero order kinetic suggesting that the mass loss is caused by the volatilization of PC.

From the isotherm TG data of PC and its correspondent conventional and pre-formulated mixtures the rate constants for the decomposition in the studied temperature range were calculated according to the Arrhenius model (Table 4). The obtained results showed that the rate constants for the pre-formulated mixtures are lower than the corresponding rate constants for the conventional mixtures indicating that the spray-drying made the mixtures more stable.

Conclusions

According to the results of kinetic analysis the pre-formulates of PC obtained by spray-drying were found more stable than its respective conventional mixtures.

Association of methodologies like thermal analysis and spray-drying made possible to evaluate stability and uniformity of the analyzed solid products.

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