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Thermal characterization of diltiazem and λ-carrageenan binary systems

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Abstract Interactions between diltiazem hydrochloride (DTZ), an orally active calcium antagonist used in the treatment of angina and hypertension, and lambda carrageenan (λCRG), which has been successfully used in matrix formulations to obtain constant and pH-independent release of basic drugs, were investigated in solid state using differential scanning calorimetry (DSC) and thermogravimetric analysis (TG). The effect of particle size on thermal behaviour of the drug and the polymer was assessed, and the result used to select the most suitable granulometric fractions for the study. Physical mixtures ranging in composition from 3:1 to 0.6:1 (by weight) drug-to-polymer ratios were analyzed as such and after kneading. A stoichiometric ratio of interaction of 1.6:1 (w/w) DTZ:λCRG was found, in agreement with that obtained from dialysis equilibrium studies. All the examined granulometric fractions (<45 μm, 45–75 μm, 75–105 μm and >105 μm) of the interaction product showed similar thermal behaviour.

Keywords Diltiazem hydrochloride · λ-Carrageenan · Differential scanning calorimetry (DSC) · Thermogravimetric analysis (TG)

Introduction

The interaction between drugs and polymeric excipients in sustained release formulations has been subject of an increasing attention in the recent literature. It is well known that strong interactions occur between polyelectrolytes and oppositely charged drugs, which sometimes result in the formation of an insoluble product that makes more efficient the control of drug release [1–6]. Carrageenans [7] are naturally occurring sulphated galactose polymers which may have potential pharmaceutical applications as controlled release excipients [8, 9] that can be employed in formulations based on their interaction with cationic drugs. In particular, as a result of the ionic interaction between lambda carrageenan (λCRG) and a calcium channel blocker with vasodilating activity, diltiazem hydrochloride (DTZ), a slightly soluble complex is obtained, that has been proposed in oral controlled release matrix formulations. The combination of drug displacement by the ions of the medium and complex dissolution from the surface of the matrix resulted in linear drug release over 16–24 h [10, 11].

The interaction between DTZ and λCRG has been previously characterized in solution by means of dialysis equilibrium studies to quantify the binding capacity of λCRG for the drug [12]. Thermal analysis can be a powerful tool to confirm and explain the behaviour of polyelectrolyte–drug interaction products [13–16].

Aim of the present work was to study the interaction between λCRG and DTZ in solid state by means of differential scanning calorimetry (DSC) and thermogravimetric analysis (TG). Since it was demonstrated the relevance of DTZ-λCRG particle size on drug release profiles [17], the effect on thermal behaviour of the sample particle size has been assessed separately on the polymer, on the drug, and on the complex. Complexes prepared with different drug/polymer ratios were studied and compared with the corresponding physical mixtures.

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Experimental

Materials

Diltiazem hydrochloride (Profarmaco, Milan, Italy) (DTZ) and λ-carrageenan Viscarin GP 209 (Prodotti Gianni, Milan, Italy) (λCRG) were individually sieved and the <45 μm, 45–75 μm, 75–105 μm and >105 μm granulometric fractions were collected.

Preparation of DTZ-λCRG binary systems

Physical mixtures of DTZ (<45 μm sieve granulometric fraction) with λCRG (<45 μm sieve granulometric fraction) in the drug-to-polymer 3:1, 1.6:1, 1:1 and 0.6:1 (by weight) ratios were prepared by simple homogenization of the powders in a Turbula mixer for 20 min. Kneaded mixtures were prepared by wetting the physical mixtures in a mortar with the minimum volume (5 mL/1 g) of distilled water and grinding with a pestle to obtain a paste which was then dried at 50 °C in a hot air oven up to constant weight. The interaction product was prepared by mixing the polymer (1.6 g) and the drug (1.0 g) as dry powders, wetting with 15 mL of distilled water and kneading for 20 min. The past was kept in a hot air oven at 50 °C overnight and then washed by centrifugation with portions of 20 mL of distilled water. The solid was dried at 50 °C up to constant weight, manually ground in a mortar with a pestle, sieved and kept in a desiccator over P_2O_5.

Differential scanning calorimetry (DSC)

Temperature and enthalpy values were measured with a Mettler STAR^e system equipped with a DSC821^e Module on 3–5 mg (Mettler M3 Microbalance) samples in uncovered aluminium pans under static air atmosphere. An uncovered empty pan was used as reference. The heating rate was 10 K min^{-1} over the 30–250 °C temperature range. Measurements were made for each sample in triplicate (relative standard deviation ± 5%).

Thermogravimetric analysis (TG)

Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell over the 30–250 °C temperature range under static air atmosphere at a heating rate of 10 K min^{-1} on 7–10 mg samples in uncovered alumina crucibles. Measurements were made for each sample in triplicate (relative standard deviation ± 2.5%).

Preparation of DTZ-λCRG matrix tablets and release test

Tablets (290 mg) of each granulometric fraction of the interaction product were obtained by direct compression, with a Kilian KIS reciprocating tableting machine (Guarnerio and Mantelli, Milan, Italy), equipped with 11 mm convex punches.

The drug release profiles were obtained in an USP 32 apparatus 1 at 100 rpm, 37 °C, in 500 mL of either pH 1.2 simulated gastric fluid (USP 32, without enzymes) or in 0.05 M KH_2PO_4/NaOH pH 6.8 buffer.

The experimental curves were fitted with a Weibull equation by means of non linear fitting programme (Systat Inc., Evanston IL, 1989). The parameter t_d describes the release rate, corresponding to the time at which 63% of the drug has been released from the tablet. The parameter γ is related to the shape of release profiles [18].

Results and discussion

The characterization of the individual components of the binary system DTZ-λCRG is given in Figs. 1 and 2, respectively, taking into account the possible effect of the particle size of the sample on thermal behaviour. The DSC curve of DTZ shows a typical profile of an anhydrous crystalline drug characterized by an endothermic effect due to drug melting ($T_{m,onset} = 210.9 \pm 0.3$ °C, $T_{m,peak} = 216.8 \pm 0.7$ °C, and $\Delta H_m = 97 \pm 2$ J g^{-1}) just before decomposition. A mass loss was recorded in TG curve around 220 °C, corresponding to the decomposition of the sample.

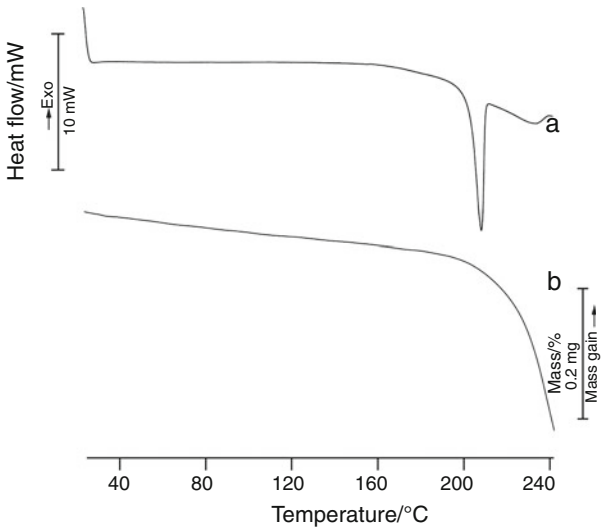

Fig. 1 DSC (*a*) and TG (*b*) curves of diltiazem·HCl

The thermal behaviour was not apparently different for the granulometric fractions tested (<45 μm, 45–75 μm, 75–105 μm and >105 μm), so that only the DSC curve of the <45 μm sieve granulometric fraction is reported in Fig. 1. Thermal behaviour of amorphous λCRG (Fig. 2) shows the presence of loosely bound water (14.1 ± 0.4% as mass fraction by TG) and exothermal decomposition in the 160–220 °C temperature range. A clear influence of the particle size of the sample particularly in terms of the onset and peak temperature of decomposition in DSC and of the inflection point temperature in TG, could be observed, as reported in Table 1. To prepare physical mixtures of DTZ with λCRG, the <45 μm sieve granulometric fraction was used because this fraction showed the sharpest peak, at about 213 °C (Fig. 2, curve *d*), while broader peaks at lower temperatures were recorded for the samples of higher particle size

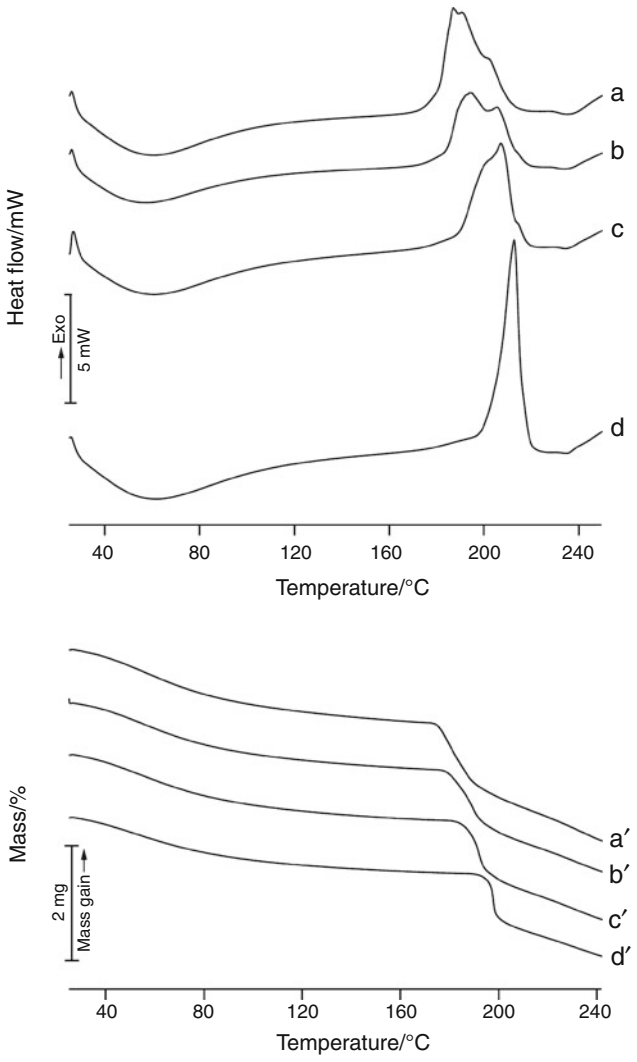

Fig. 2 DSC and TG curves of λ-carrageenan samples of different particle size (>105 μm (*a*, *a′*), 75–105 μm (*b*, *b′*), 45–75 μm (*c*, *c′*) and <45 μm (*d*, *d′*) granulometric fractions)

Table 1 Thermal parameters of λ-carrageenan samples of different particle size

Particle size	T_{onset} (°C)	T_{peak} (°C)	Inflection point by TG (°C)
>105 μm	180.5 ± 0.2	187.2 ± 0.1	179.0 ± 0.5
75–105 μm	183.5 ± 0.3	194.3 ± 0.2	189.5 ± 0.4
45–75 μm	188.4 ± 0.1	207.4 ± 0.1	191.8 ± 0.4
<45 μm	204.1 ± 0.3	213.1 ± 0.2	197.7 ± 0.3

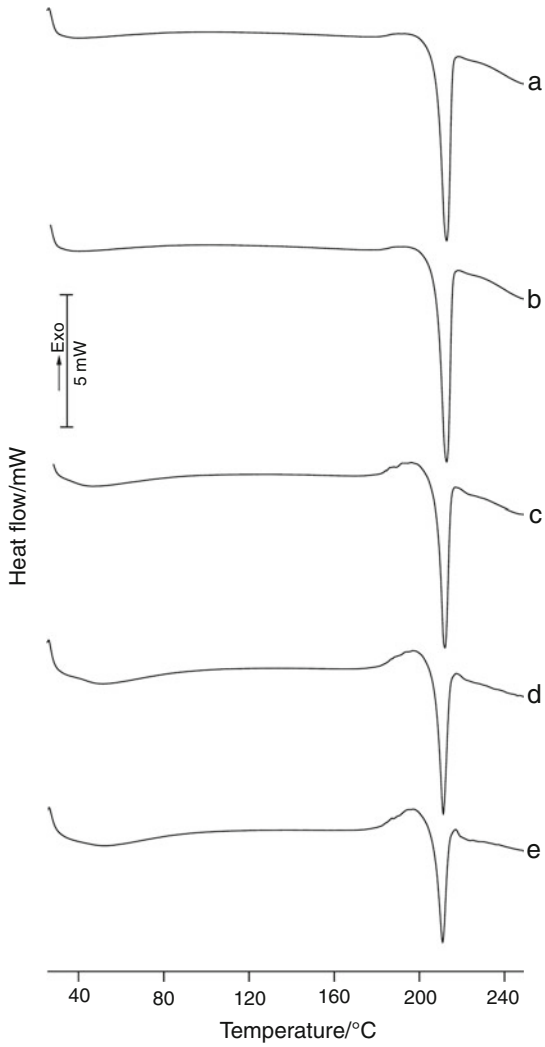

Fig. 3 DSC curves of diltiazem·HCl and λ-carrageenan physical mixtures at different drug to polymer weight ratio (6:1 (*a*), 4.5:1 (*b*), 3:1 (*c*), 2:1 (*d*), 1.6:1 (*e*))

dimensions. The inflection point temperature in TG curves shifts to higher temperature with the decrease of particle size dimensions, probably due to the increase of the temperature decomposition in DSC curves.

Figure 3 illustrates the DSC curves of physical mixtures at various drug-to-polymer weight ratios (6:1, 4.5:1, 3:1,

Table 2 Fusion enthalpy per unit mass of DTZ in various physical mixtures with λCRG

DTZ:λCRG (w/w)	6:1	4.5:1	3:1	2:1	1.6:1	1:0
$\Delta H_{m,DTZ}$ (J g^{-1})	97 ± 2	89 ± 3	81 ± 2	84 ± 2	81 ± 3	97 ± 2

2:1, 1.6:1) prepared and tested as such. The fusion enthalpy per unit mass of DTZ blended with λCRG was approximately the same of that of the drug alone, in the physical mixtures with higher drug mass ratio (Table 2). The overlapping of the exothermal degradation of the carrier with the endothermal melting of the drug makes it difficult to set with precision the limits of the endothermal effect due to the drug melting, so that the values of melting enthalpy could be not so exactly determined especially in the physical mixtures at higher carrier mass ratio.

The same binary systems subjected to wet grinding (kneaded) were characterized by DSC as shown in Fig. 4. A kneading-induced interaction can be clearly observed as an alteration of the endothermal effect due to drug melting, more or less pronounced depending on the drug to polymer weight ratio. In particular, the endothermal effect became more and more asymmetric with the decrease in drug to carrier weight ratio and disappeared in the system with 2:1 ratio (w/w) and lower values; therefore the interaction's ratio induced by kneading is approximately 2:1 DTZ:λCRG (w/w).

This is in reasonable agreement with the determination of the interaction between DTZ and λCRG determined by means of dialysis equilibrium studies [12]: in this case a stoichiometric ratio of 1.6:1 (w/w) was found.

Three different DTZ:λCRG mixtures, 1.6:1 (w/w) corresponding to the stoichiometric ratio, 3.2:1 (w/w) and 1:1 (w/w) with an excess of drug and an excess of polymer, respectively, were mixed as dry powders, wetted with small volumes of distilled water and kneaded. The products were washed with distilled water by centrifugation. The washing step easily removes the excess of freely soluble DTZ unbound to the polymer, and less easily, the excess of the polymer. If the drug is completely bound to the polymer (as it happens for lower than stoichiometric DTZ-λCRG ratios) it cannot be washed away because the complex is poorly water soluble.

In Fig. 5 are reported the DSC curves of DTZ-λCRG kneaded mixtures, washed before drying, at different drug to polymer weight ratio (1:1 (curve *a*), 1.6:1 (curve *b*) and 3.2:1 (curve *c*)). The DSC curve of the 1.6:1 (w/w) mixture is characterized by a dehydration endothermal effect between room temperature and 125 °C with an associated mass loss of 5.5 ± 0.2% that corresponds to about 14% referred to the polymer alone (TG curve not shown). The absence of the melting peak of DTZ accounted for a non crystalline state of the drug when bound to λCRG, as already demonstrated in a previous our study [12]. The

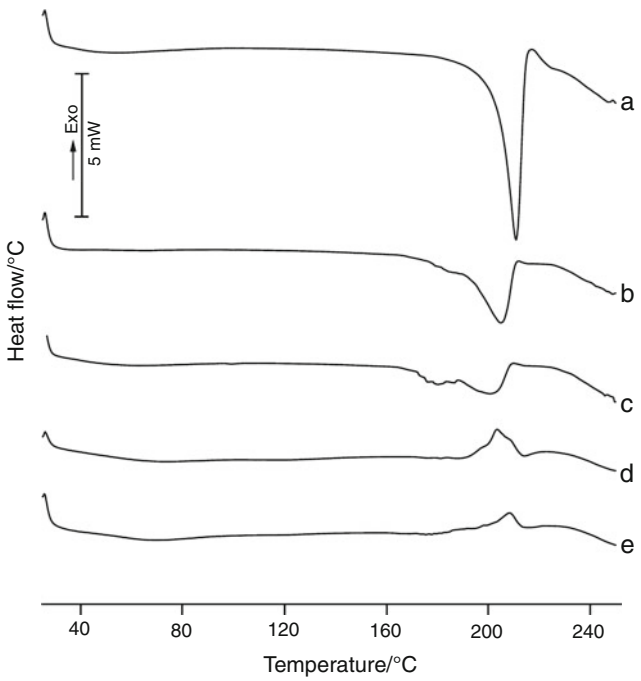

Fig. 4 DSC curves of diltiazem·HCl and λ-carrageenan kneaded mixtures, not washed before drying, at different drug to polymer weight ratio (6:1 (*a*), 4.5:1 (*b*), 3:1 (*c*), 2:1 (*d*), 1.6:1 (*e*))

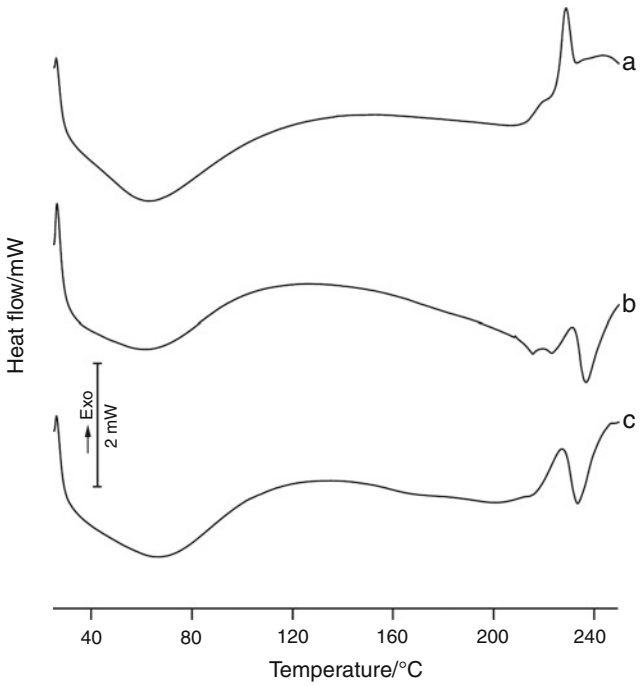

Fig. 5 DSC curves of diltiazem·HCl and λ-carrageenan kneaded mixtures, washed before drying, at different drug to polymer weight ratio (1:1 (*a*), 1.6:1 (*b*), 3.2:1 (*c*))

thermal effects recorded at temperatures >195 °C can be attributed to sample decomposition.

Similar DSC profile was displayed by samples obtained from mixtures at higher drug:polymer weight ratios than the stoichiometric interaction product (3.2:1, w/w) (Fig. 5, curve *c*). In this case, the excess of unbound drug was removed by the washing step. In the case of the 1:1 (w/w) ratio (Fig. 5, curve *a*), in spite of the washing, a polymer excess can be still present as confirmed by the exothermal effect of decomposition that is more pronounced.

As previously done on the pure components, the effect of the particle size on thermal behaviour of the stoichiometric kneaded product (1.6:1, w/w) has been assessed and results are given in Fig. 6. All the examined granulometric fractions

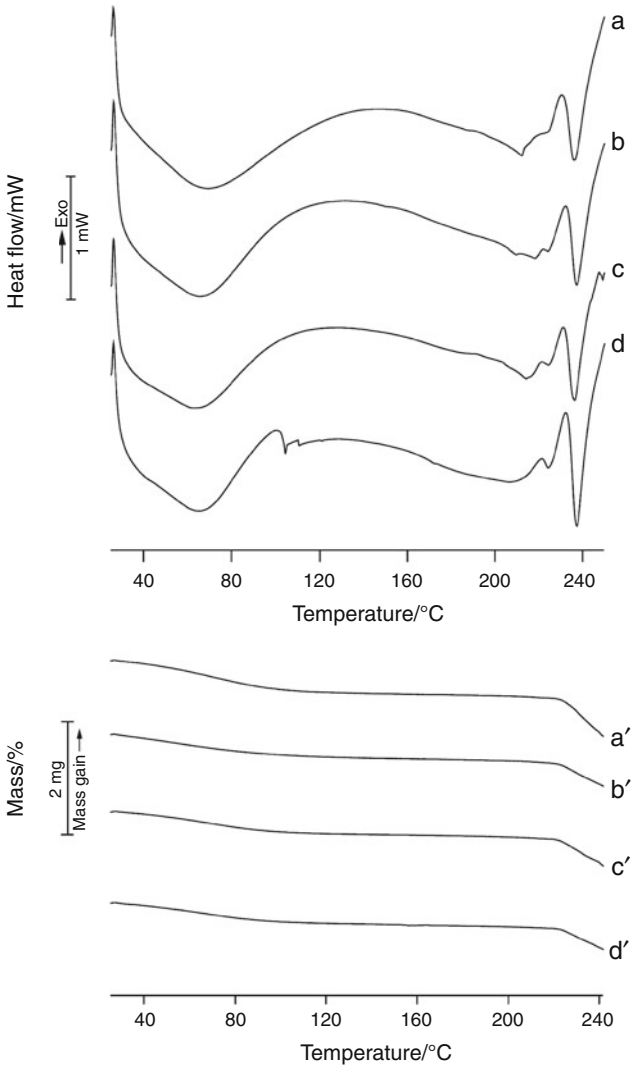

Fig. 6 DSC and TG curves of the diltiazem·HCl-λ-carrageenan 1.6:1 (w/w) interaction product of different particle size (>105 μm (*a*, *a*′), 75–105 μm (*b*, *b*′), 45–75 μm (*c*, *c*′) and <45 μm (*d*, *d*′) granulometric fractions)

Table 3 Parameters of Weibull equation obtained by fitting the drug release curves of tablets based on different drug-complex particle size, both in pH 1.2 and pH 6.8 release buffer

	pH 1.2			pH 6.8		
	t_d (h)	γ	R^2	t_d (h)	γ	R^2
75–105 μm	2.93	1.04	0.999	0.59	1.70	0.994
45–75 μm	15.91	1.01	0.999	8.97	1.00	0.998
<45 μm	15.18	1.09	0.998	11.98	1.13	1.000

(<45 μm, 45–75 μm, 75–105 μm and >105 μm) showed similar thermal behaviour, i.e., a broad endothermal effect in the dehydration region (30–120 °C) due to loosely bound water of the polymer, and endo- exothermal effects in the temperature range 200–240 °C due to sample decomposition.

Table 3 shows the parameters obtained from the fitting of the drug release experimental curves obtained on the matrix tablets prepared with each granulometric fraction of the stoichiometric interaction product. The experimental curves were fitted by mean of a Weibull equation [18].

The particle size of the interaction product strongly influenced the drug release especially when larger size fractions were used (75–105 μm). The difference in release rate became less important between the two fine fractions (45–75 and <45 μm).

Conclusions

Experimental evidence of the interaction between DTZ and λCRG was achieved by thermal analysis (DSC and TG). Consistent quantitative data could not be directly obtained owing to overlapping of drug melting and polymer decomposition with each other in the mixtures. The stoichiometry of interaction could, however, be assessed due to the insolubility of the interaction product and the solubility of the individual components in water. A flat DSC profile in the region of drug melting accounted for a non crystalline state of the interaction product, as confirmed by a previous study. The relative amount of water associated with the polymer in the bound state (by TG) was about the same as in the free state. The thermal stability of λCRG was instead positively influenced by its interaction with DTZ.

Interaction products prepared with different drug-to-polymer weight ratios were studied and compared with the corresponding physical mixtures. No differences could be observed between the behaviour of the different ratios in the physical mixtures. All the examined granulometric fractions (<45 μm, 45–75 μm, 75–105 μm and >105 μm) of the interaction product showed similar thermal behaviour.

The differences in release rate observed when the same granulometric fractions were used to prepare matrix tablets must therefore be explained tacking into account the different behaviour during compaction or during matrix hydration.

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