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# Elaboration and thermal study of interactions between cinnarizine and gelucire® 53/10 physical mixtures and solid dispersions

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**Abstract**

This work involves the study of elaboration and thermal characterization of Gelucire® 53/10-cinnarizine (10, 20, 30, 40 and 50% w/w cinnarizine) binary systems (solid dispersions and physical mixtures). The analytical thermal techniques employed, differential scanning calorimetry (DSC) and hot stage microscopy (HSM) have demonstrated the ability of melted Gelucire® 53/10 to dissolve the crystals of cinnarizine. The high solubilizing effect of this vehicle, in comparison with other carriers, may be explained on the basis of its surfactant properties. Only at low drug percentages, can the total dissolution of cinnarizine present in the system be achieved.

*Keywords:* Gelucire® 53/10; Cinnarizine; Solid dispersion; DSC; HSM

Cinnarizine is an antihistaminic and antivasoconstricting agent, with calcium slow channel blocking activity. An important problem associated with the obtention of solid oral dosage forms for this drug has been its poor aqueous solubility and wettability.

The Gelucires® are a family of vehicles derived from hydrogenated food grade oils and fats. These amphophilic excipients have a fatty consistency and can be distinguished by their HLB and their melting point (mp). They are identified by denominations of the form: Gelucire® mp/HLB. The mp varies from 33 to 65°C and the HLB from 1 to 14. The HLB of the excipient has an essential influence on the in vitro release of the active substance. Rapid or sustained release profiles can be obtained by using different Gelucires®. The Gelucires® with low HLB, can be employed to decrease the dissolution rate of drugs (Huet de Barochez et al., 1989; Vila-Jato et al., 1990a, Vila-Jato and Delgado, 1990b) the high HLB ones for fast release (Serajuddin et al., 1988; Smith et al., 1990).

Some authors have indicated that the physical instability of the solid dispersions elaborated with

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Gelucires® are due to changes in the melting properties of Gelucire® and variations in the dissolution rate of incorporated drugs (Mouricout et al., 1990; Sutananta et al., 1993). However, few reports exist in the literature on characterization of these binary systems. The objective of this research work was to characterize Gelucire® 53/10-cinnarizine binary systems by thermal analysis techniques: differential scanning calorimetry (DSC) and hot stage microscopy (HSM).

Cinnarizine was a gift from Lab. Alonga (Madrid, Spain), and Gelucire® 53/10 was supplied by Gattefossé (Paris, France).

Solid dispersions: solid dispersions of Gelucire® 53/10-cinnarizine at different drug proportions 10, 20, 30, 40 and 50% w/w were prepared using the fusion carrier method at 100°C (Ginés et al., 1990). It was only possible to prepare Gelucire® 53/10-cinnarizine solid dispersions up to 50% w/w because of the lack of homogeneity of the solid dispersions above this percentage.

Physical mixtures: the physical mixtures were prepared by simple mixing of the two components previously sieved (100 $\mu$m), in the same proportions of solid dispersions.

Differential scanning calorimetry (DSC): samples were examined using a DSC Mettler FP 85 differential scanning calorimeter. A heating rate of 10°C/min was used from 30 to 300°C in an air atmosphere. Samples of 10 mg were weighed and encapsulated in flat-bottomed aluminum pans of 45-$\mu$l volume with crimped-on lids.

Hot stage microscopy (HSM): physical changes in the samples on heating were monitored using hot stage microscopy (HSM Mettler model FP 82 HT). A little amount of the samples (approximately 0.1 mg), was placed on a glass slide with coverglass and heated at 5°C/min in the range of temperature 30–150°C.

When the drug is added on melted Gelucire® 53/10, we can observe the dissolution of the drug in the carrier. This dissolution process is complete in the systems containing up to 40% w/w drug, and partial in the system with the drug and vehicle in same proportions (50/50% w/w). Consequently, at the elaboration temperature, the binary systems are true solutions or suspensions, respectively.

The DSC thermogram of Gelucire® 53/10 (Fig. 1a), shows a double endothermic peak at 60 and 67°C due to the fusion of the product. It is interesting to point out that a weak inflection on endothermic change in the base line is detected at 190°C in pure Gelucire® 53/10. This effect has

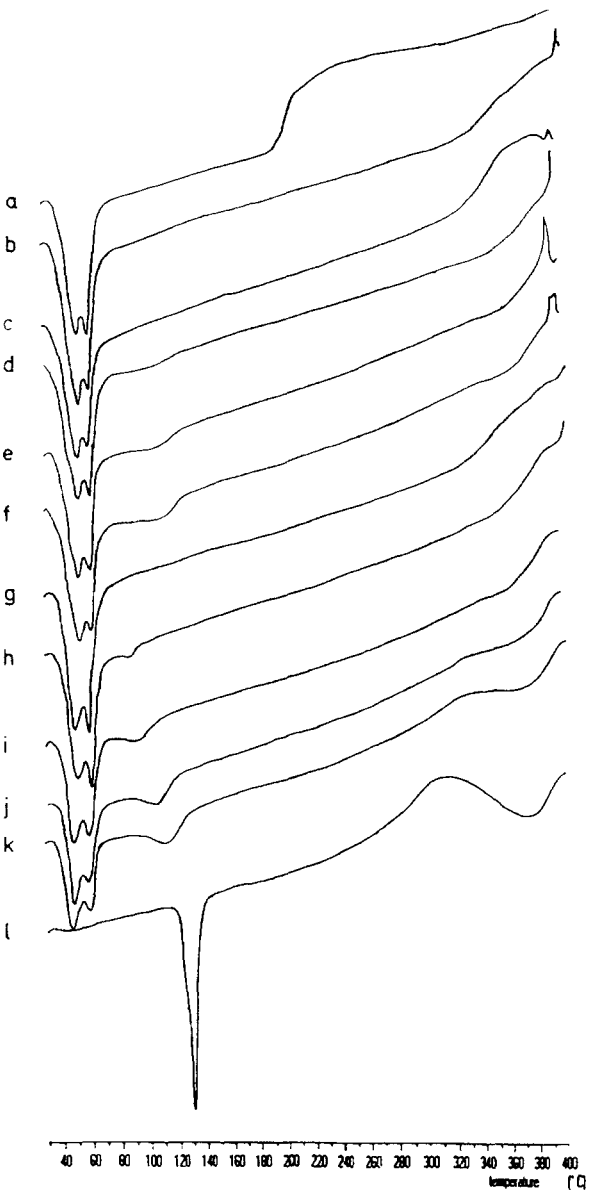


Fig. 1. DSC thermograms of different samples: Gelucire® (a); solid dispersions of 10 (b), 20 (c), 30 (d), 40 (e) and 50% (f); physical mixtures of 10 (g), 20 (h), 30 (i), 40 (j) and 50% (k) and cinnarizine (l).

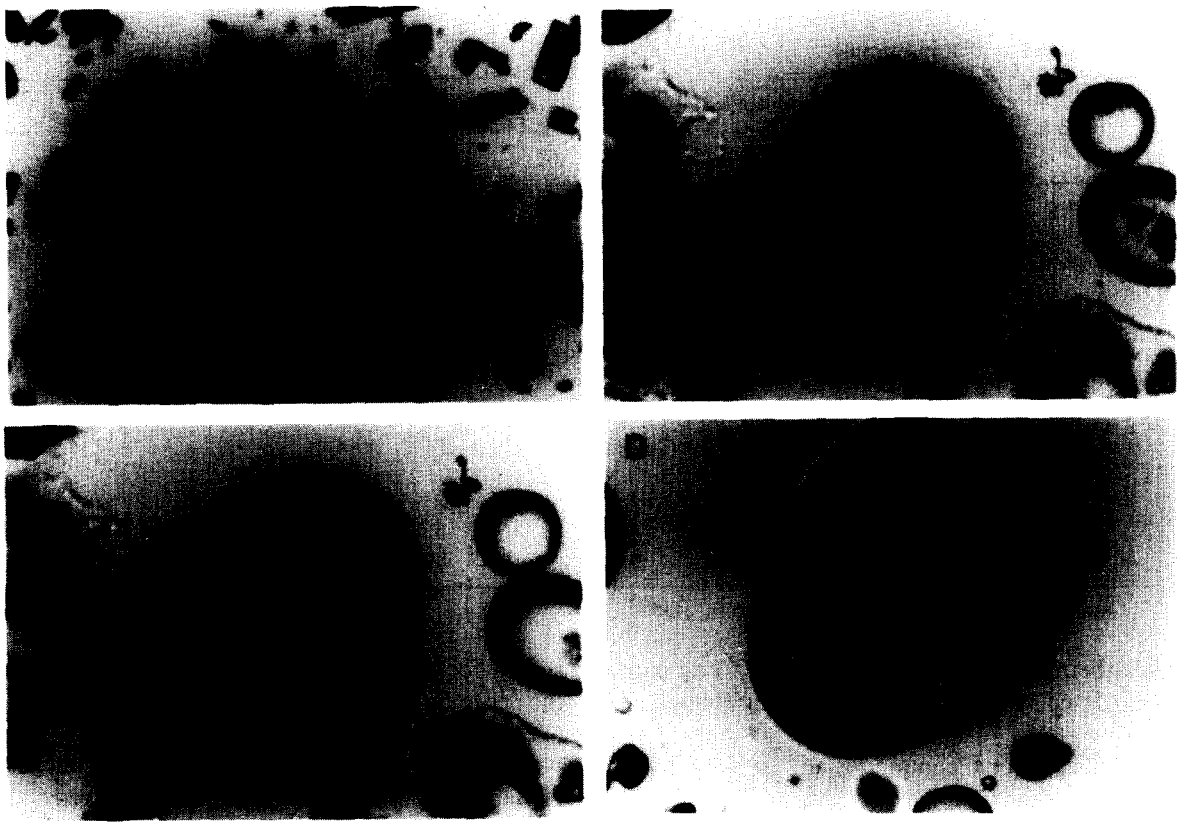

Fig. 2. Micrograph of original cinnarizine particles (a); solid dispersion (10%) at 53 (b) and 70°C (c) and solid dispersion (50%) at 100°C (d).

also been reported by Duclos et al., 1993 with other Gelucires®, and similar results for PEGs 1500, 4000 and 6000 have been reported by Ginés et al., 1993.

Cinnarizine exhibits only a single sharp endothermic peak at 130°C (Fig. 1l). It was followed by an exothermic event, in the range 270–320°C.

The DSC curve for the solid dispersion at 10% in cinnarizine (Fig. 1b) denotes the disappearance of the endothermic melting peak of the drug. In the solid dispersion elaborated with 20% w/w in cinnarizine (Fig. 1c) the first endothermic effect is accompanied with a small endothermic effect close to the principal one. The DSC diagram for solid dispersion elaborated at 30% in cinnarizine (Fig. 1d) exhibits an endothermic effect detected at 100°C. This effect becomes more intense and centered at 110 and 120°C, when the amount of cinnarizine is 40 and 50% w/w, respectively.

Physical mixtures of Gelucire® 53/10-cinnarizine (Fig. 1g–k), showed thermal behaviour in accordance with the observations made during the elaboration of the solid dispersions. The DSC curves of low percentages in cinnarizine (to 30% w/w) exhibit only one endothermic peak corresponding to the melting point of Gelucire® 53/10. The disappearance of the endothermic peak corresponding to the fusion of cinnarizine is due to its solubility at lower concentration in the melted Gelucire® 53/10.

Fig. 2a shows a micrograph corresponding to original cinnarizine particles, as received. The microscopical examination revealed the presence of prismatic crystals with different dimensions and crystalline appearance. After dynamic heating, the drug melts at 120°C, heating to higher temperatures produces a progressive darkening of these vesicles (at 220°C). This fact is in accordance with

Table 1
Thermal evaluation of different samples

| | 1st endothermic effect | | 2nd endothermic effect | |
|---|---|---|---|---|
| | Melting peak (°C) | $\Delta H_f$ (J/g) | Melting peak (°C) | $\Delta H_f$ (J/g) |
| Gelucire® 53/10 | 59.9–67.3 | 180 | - | - |
| Cinnarizine | - | | 136.7 | 96.9 |
| Solid dispersions (%) | | | | |
| 10 | 58.3–67.3 | 178 | - | - |
| 20 | 57.1–67.0 | 167 | 91.6 | 4.3 |
| 30 | 55.4–65.6 | 119 | 101.3 | 11.2 |
| 40 | 54.4–63.7 | 111 | 108.2 | 20.1 |
| 50 | 53.4–63.4 | 102 | 115.6 | 28.8 |
| Physical mixtures (%) | | | | |
| 10 | 62.3–68.6 | 214 | - | - |
| 20 | 61.4–69.2 | 178 | - | - |
| 30 | 61.1–68.3 | 177 | - | - |
| 40 | 60.3–67.4 | 159 | 109.7 | 13.4 |
| 50 | 59.8–66.6 | 144 | 115.8 | 17.1 |

the exothermal effect registered by DSC and can be associated to the beginning of drug degradation.

Solid dispersions containing up to 40% w/w cinnarizine show similar behaviour on HSM. Only micrographs of solid dispersion 10% w/w cinnarizine are shown. Initially, the identification of drug particles in the solid dispersion was not possible by optical microscopy. After heating to 53°C, the Gelucire® 53/10 melts and the crystalline particles of cinnarizine can be easily detected by microscopic observation (Fig. 2b). It is important to note that the drug exists as microcrystalline particles after its processing in solid dispersions in contrast with the pure drug (see Fig. 2a).

The heating to higher temperatures (Fig. 2c) produces a partial dissolution of the crystals entrapped inside the liquid vesicles. We must point out that temperatures at which the dissolution process is total are at 80, 90, 100 and 110°C for the solid dispersions containing 10, 20, 30 and 40% w/w cinnarizine, respectively.

For solid dispersion with 50% w/w drug, after fusion of the vehicle, two drug crystal types are observed (Fig. 2d). They are microcrystals similar to those of solid dispersions and others, but with larger particle sizes, comparable with those observed for pure drug. The dissolution process of the drug in the melted carrier first affects the microcrystals, the total disappearance of which occurs before 100°C. In a second step, between 100 and 115°C, larger crystals are dissolved.

The former results may be explained on the basis that, at high drug ratios (50% w/w), the drug solubilization during the elaboration of solid dispersions is partial, and an excess of drug remains unaltered.

In these systems, the dissolution process of cinnarizine occurs at a wider range of temperatures, because the drug is present as large crystals and, hence, its dissolution process is slower. This different behaviour Table 1 between the solid dispersions and physical mixtures also would explain the evolution observed in heat fusion values as a function of cinnarizine content in these systems.

The higher fusion enthalpies of solid dispersions respecting physical mixtures can be explained as an effect of the elevated energy level consumed by the simultaneous dissolution process of a large number of microcrystals. This wide absorption of energy in a narrow temperature range is readily detectable by the DSC apparatus. On the contrary, for physical mixtures, the increase of this temperature range to reach fusion of

the bigger crystals is not with in the scope of the apparatus, thus displaying less peak enthalpies.

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