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POLYMORPHISM OF PROGESTERONE
Influence of the carrier and of the solid dispersion manufacturing processes. A calorimetric and radiocrystallographic study

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Solid dispersions are used in pharmaceutical technology in order to improve solubility and/or dissolution kinetics of poorly water soluble drugs [1, 2, 3]. A preliminary study concerning progesterone structure after melting revealed the existence of a drug polymorphism after cooling, and gave the opportunity to specify the manufacturing conditions in order to obtain the stable form of this hormone [4]. In this work, two different types of progesterone solid dispersion have been compared. The first one is obtained by a slow cooling rate of the drug in the presence of polyoxyethylene glycol 6000 and the second one after quenching in the presence of saccharose distearate.

DSC and radiocrystallographic studies of the solid dispersions served to specify the nature of the compounds obtained and to characterize the physical structure of the hormone in the solidified melts.

Introduction

In order to increase dissolution and oral absorption of progesterone, a poorly water soluble drug [5], we used solid dispersions technology. Two types of hydrophilic carrier (polyoxyethylene glycol 6000 and saccharose distearate in correlation with two types of manufacturing processes (slow cooling rate and quenching) were compared.

Preparation of solid dispersions and methods

The solid dispersions were prepared using the fusion method [1]. Physical mixtures, containing various proportions of progesterone in the hydrophilic

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carrier (10:90, 20:80, 30:70 and 50:50 *w/w*), were heated with continuous stirring in an oil bath at 130° until completely melted. When the liquid was homogeneous, it was:

– slowly solidified with a continuous stirring at a constant 1 deg/min cooling rate for the progesterone-PEG 6000 comelts.

– quenched by steeping in a 2:1 mixture of ice and NaCl, for the progesterone saccharose distearate comelts.

After solidification, the comelts were kept for 48 h in a glass dessiccator and, after hardening, pulverized and sieved to a particle size range <200 μm.

Thermal analysis was carried out with a differential scanning calorimetry analyser (DSC 4, Perkin–Elmer). The heating rate was 10 deg/min and the samples weight was about 5 mg. Calibration was achieved with Indium as reference material.

An X-ray powder diffractometer (CGR Theta 60) was used to determine the physical state of the solid dispersions. Powder samples, pulverized in an agate mortar, were maintained with adhesive paper on a screen sample

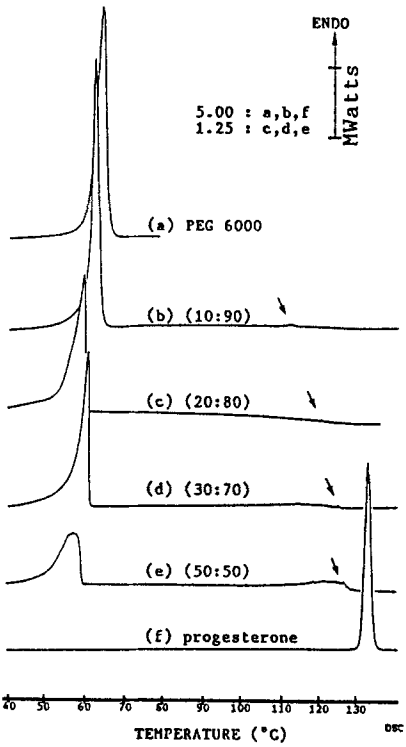

Fig. 1 DSC curves of Progesterone / Polyoxyethylene glycol 6000 solid dispersions

holder and the X-ray diffraction patterns were determined using Mo K_{α_1} radiation ($\lambda = 0.7093$ Å) filtered by monochromator (2θ scan speed $= 0.5$ deg/min).

Thermal analysis

Progesterone / Polyoxyethylene glycol 6000 solid dispersions (Fig. 1)

– the first curve (*a*) corresponds to the fusion of the pure PEG 6000 (peak from 55 to 65°).
– on the other curves (*b*), (*c*), (*d*) and (*e*), the excess of progesterone in the comelts is revealed by a secondary endothermic peak shifting towards the higher temperature with the increasing concentration of the drug in the comelts.

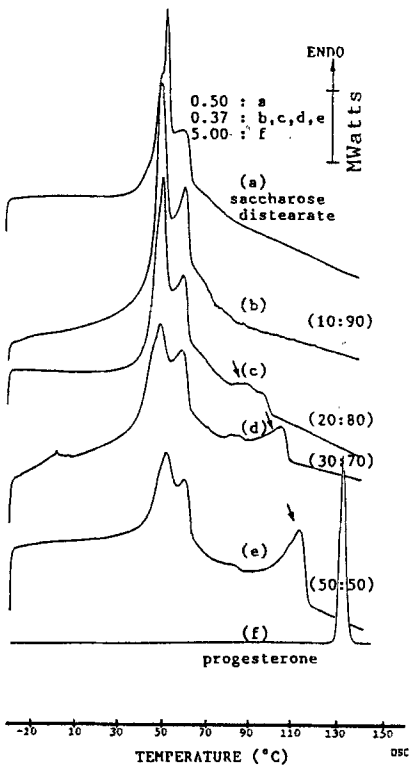

Fig. 2 DSC curves of Progesterone / Saccharose distearate solid dispersions

– the curve (*f*) exhibits a peak at 130° corresponding to the fusion of the pure progesterone.

Progesterone / Saccharose distearate solid dispersions (Fig. 2)

– the upper curve (*a*) exhibits three peaks between 40° and 70° corresponding to the fusion of the pure saccharose distearate.
– the additional peaks on curves (*b*), (*c*), (*d*) and (*e*) display the fusion of the excess of progesterone in the comelts.
– the last curve (*f*) corresponds to the fusion of pure progesterone with a peak at 130°.

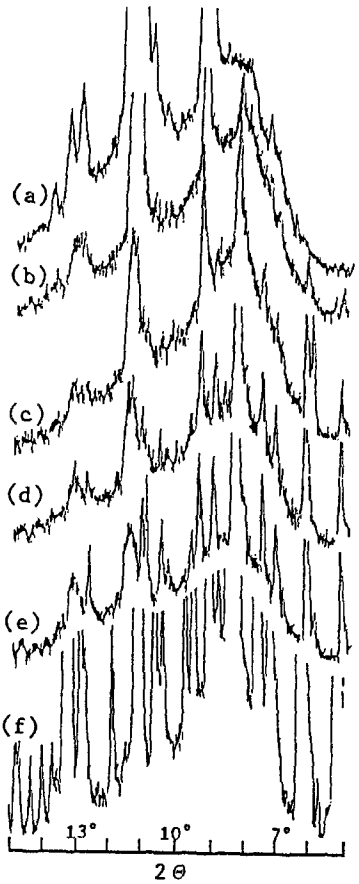

Fig. 3 Diffractograms of Progesterone / Polyoxyethylene glycol 6000 solid dispersions

X-ray diffraction studies

Progesterone / Polyoxyethylene glycol 6000 solid dispersions (Fig. 3)

– the upper diffractogram displays and characteristic spectrum lines of the pure PEG 6000 at 9°65, 11°75 and 13°2.
– whatever the comelts composition (*b*), (*c*), (*d*) and (*e*), the characteristic spectrum lines of the carrier are observed in all the diagram. Furthermore, the spectra show a broad diffuse peak between 7° and 10° which converts into peaks (characteristic of the progesterone α form), when the drug concentration increases in the solid dispersion (peaks at 8°55 and 6°45).
– the lower diffractogram corresponds to the pure progesterone α form, with a characteristic peak at 8°55.

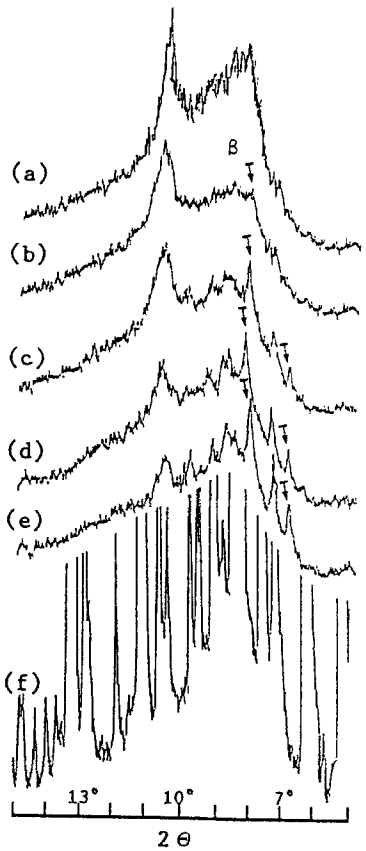

Fig. 4 Diffractograms of Progesterone / Saccharose distearate solid dispersions

Progesterone / Saccharose distearate solid dispersions (Fig. 4)

– the upper (*a*) and the lower (*f*) curves correspond to the pure components. The main peaks are $10^{\circ}7$ for the saccharose distearate and $8^{\circ}55$ and $6^{\circ}45$ for the progesterone.
– diffractogram (*b*) consists of the saccharose distearate spectrum lines and a broad diffuse peak between 7° and 10° which denotes the presence of progesterone in an ill-crystallized state.
– the diffractograms (*c*), (*d*) and (*e*) reveal the saccharose distearate spectrum lines and furthermore the broad peak between 7° and 10° is overlapped with three discrete peak, increasing with the progesterone concentration, which is the proof of the presence of the metastable β–form of progesterone. Moreover, there is no detectable peak at $8^{\circ}55$ which would belong to the α-form of progesterone.

Conclusion

Thermal analysis studies lead us to conclude that we are in presence of a solid dispersion in which the active drug is dispersed in a microparticular state or even in a molecular state within the hydrophilic matrix.

Additionally, according to the methods of preparation, we can observe, by X-ray studies, the characteristic lines of the progesterone α form when the cooling rate is <1 deg/min. On the contrary, the characteristic β spectrum lines appear with quenching >10 deg/min.

The presence of progesterone in its metastable form could induce drug polymorphism transformation with ageing. So, storage studies, at different temperatures, are actually in progress in our laboratory in order to examine the physical structure of the drug in the comelts.

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Zusammenfassung – Dispersionen werden in der pharmazeutischen Technologie angewendet zur Erhöhung der Bioverfügbarkeit schlecht wasserlöslicher Wirksubstanzen. In einer Voruntersuchung konnte durch Schmelzen von Progesteron gezeigt werden, dass polymorphe Formen existieren. Unterschiedliche Progesteronpräparate wurden durch Mischungen einerseits mit Polyethylenglykol 6000 und andererseits mit Saccharosedistearat hergestellt, wobei verschiedene Erstarrungsprozesse angewendet wurden.

Die Methoden der DSC und der Röntgendiffraktion wurden zur Charakterisierung der erhaltenen Festkörper eingesetzt.