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EFFECT OF AGEING ON PROGESTERONE-POLYOXYETHYLENE GLYCOL 6000 DISPERSIONS. X - RAY STUDY

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ABSTRACT

Progesterone solid dispersions in polyoxyéthylene glycol 6000 were prepared by fusion method in order to improve the progesterone wettability and solubility in aqueous body fluids. Its crystalline state after fusion was determined by radiocrystallography on the pure drug and on the solidified melts. It has been established that a slow cooling speed of the melt induced the stable polymorph emergence in the solidified melt (α form). Moreover, X-ray diffraction patterns investigation showed a good physical stability of the preparations after one year storage at room temperature.

INTRODUCTION

Progesterone, progestational hormone used to control habitual abortion showed a very slight water solubility (38 $\mu mol.l^{-1}$, i.e 12 $\mu g.ml^{-1}$ at 37°C) (1) (2) (3) (4), and was known to exist in at least two polymorphic forms in its crystalline state (5) (6) (7).

The alpha form consisted of orthorombic prisms (space group $P\ 2_12_12_1$, a = 12,598 ; b = 13,832 ; c = 10,384 ; m.p. 127-131°C)(8), while the beta form consisted of orthorombic needles (space group $P\ 2_12_12_1$, a = 6,252 ; b = 12,592 ; c = 22,488 ; m.p. 121-123°C)(9). The alpha form was thermodynamically stable, while the beta form was metastable (10).

Because of its limited aqueous solubility in gastrointestinal fluids, clinical treatment with natural progesterone had previously been hampered by the lack of an orally active preparation, but recently, significant absorption has been demonstrated after oral administration of micronized progesterone (11). With this aim in view, we have used solid dispersion technology, methods already employed by numbers of authors for improving the dissolution rate of many poorly water-soluble drugs.

In an earlier study, we have shown, by differential scanning calorimetry, that, according to the manufacturing conditions, progesterone in the solidified melt may occur amorphous or in various crystalline states (12). To avoid problems such as the emergence of metastable forms in the melt or polymorphic transformation during storage, we have established that a slow cooling speed from the molten state in the DSC apparatus, allowed the preparation of the progesterone stable form (alpha form).

The aim of this work was to confirm by radiocrystallography that the fusion and cooling processes in the oil bath lead to the pure alpha form, and to examine the effect of solid dispersions ageing after one year storage at room temperature.

EXPERIMENTAL

Materials

Pure crystallized progesterone (< 200 µm, alpha form) (Laboratoire Besins - Iscovesco, France) and PEG 6000 (Lutrol 6000, BASF) were used without further purification.

Methods

Preparation of solid dispersions

Solid dispersion consisting in mixtures at various concentrations of progesterone in polyoxyethylene glycol 6000 (PEG 6000) were prepared using the fusion method clearly defined by Chiou and Riegelman (13).

The samples, corresponding to a total amount of 5 g, covered the range 2,5% - 75% w/w of progesterone - PEG 6000 ratio. After weighing they were bottled in a screw - capped pyrex glass container and placed for 10 min. in a Turbula mixer. The physical mixture were heated at 130°C in the same container by immersion in an oil bath until completely melted. Fused mixtures were slowly solidified with continuous stirring at a constant 1°C/min. cooling speed in order to achieve the progesterone alpha form in the solidified melt. Then, the solid dispersions were removed from the oil bath and kept for 48 H in a glass dessicator containing anhydrous phosphoric acid. After hardening, the solidified melt was pulverized into a fine powder with a grinding mill and sieved to a particle size range <200 μm. The powders were immediately bottled in a glass container and stored at room temperature until physical measurements could be made.

Pure drug samples were subjected to the same thermal treatment in order to evaluate the fusion and cooling processes influence on the X-ray diffraction patterns.

Two physical mixtures samples (2,5% and 5% w/w progesterone - PEG 6000) were prepared by simple mixing of these last two pure components possessing the same particle size range (< 200 μm) and obtained after fusion and cooling in the oil bath.

X-ray diffraction studies

An X-ray powder diffractometer (CGR theta 60) was used to determine the physical state of progesterone in the solid dispersions.

Powdered samples, pulverized in an agate mortar, were mounted with adhesive paper on a screen sample holder, and the X-ray diffraction patterns were determined using Mo K α_1 radiation (λ = 0,7093 Å) filtered by monochromator (2 θ scan speed 0,5°/min.).

Powedered samples of progesterone, PEG 6000 and physical mixtures (2,5% and 5% w/w) were examined for standards.

RESULTS AND DISCUSSION

The X-ray diffraction patterns of progesterone, PEG 6000, physical mixtures and various solidified melts are illustrated in figures 1 - 5.

The diffraction spectra of progesterone alpha form, before heating and after fusion and monitored cooling, are represented on the figures 1 (a) and 1 (b). On this second spectrum, the large diffuse hump, the weak intensity and the broadenning of the peaks indicate that the progesterone is ill-crystallized. However, progesterone main peaks can be noticed particularly at 6°45 and 8°55 which characterize the alpha form. Additionnally, the lack of metastable progesterone distinctive peaks (at 6°8 and 8°2) indicate that the drug crystallizes only in its stable form (alpha) when prepared according to solidified melts manufacturing conditions.

The X-ray diffraction patterns of PEG 6000 run before and after fusion are shown on figure 2. They are nearly superposable and exhibit two peaks of high intensity (at 9°65 and 11°70), and some peaks of less intensity (7°75, 13°20, 13°50, 13°90) ; the 7°75 peak being strongly reduced after melting.

On figure 3, the two studied physical mixtures spectra possess all the characteristic spectrum lines of PEG 6000, but, in addition, they exhibit two peaks at 6°45 and 8°55, characteristic of progesterone alpha form. Moreover, if the first peak (6°45) is near the limit of detection, the second is clearly detached from the noise. This means that, in spite of its small proportion in the mixture, the crystallized progesterone is detectable.

Figure 4 illustrates the X-ray diffraction patterns examined on freshly prepared solidified melts. On these spectra, for all dis - persions containing more than 10% progesterone, the simultaneous presence of progesterone and PEG 6000 peaks, without new peaks nor peak displacements, demonstrates the existence of a crystalline mixture of the two components. The peaks sharpenning denotes an

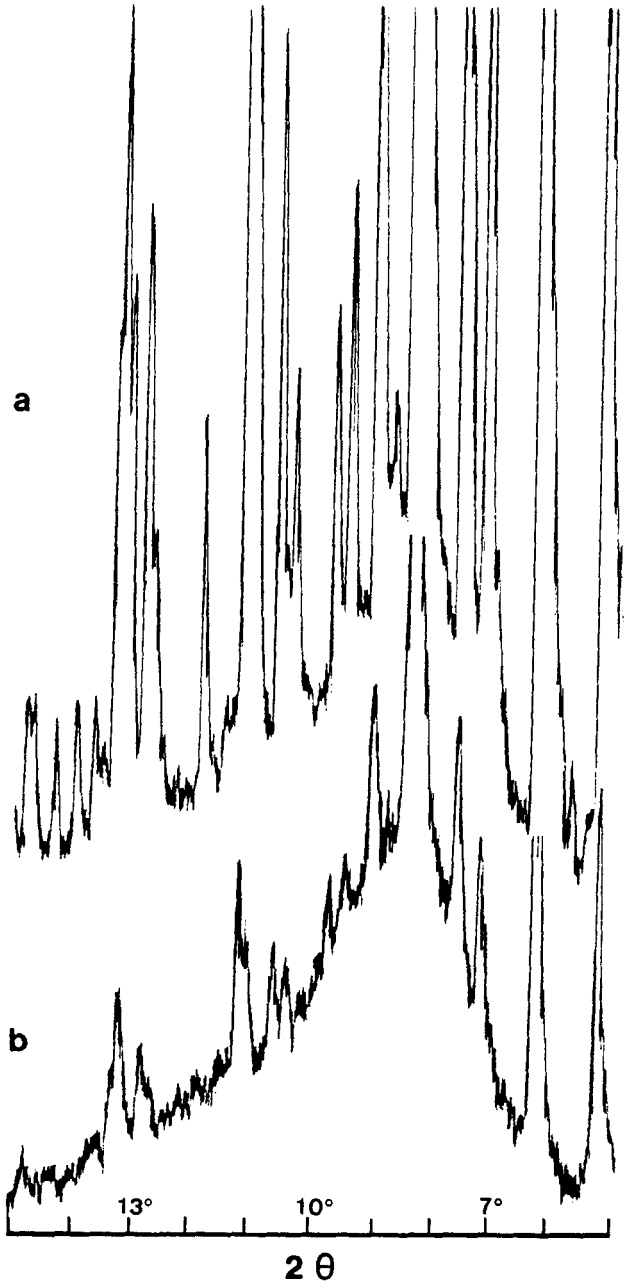

FIGURE I

X-ray diffraction patterns of pure crystallized progesterone alpha form before (a) and after (b) controlled fusion and cooling in the oil bath.

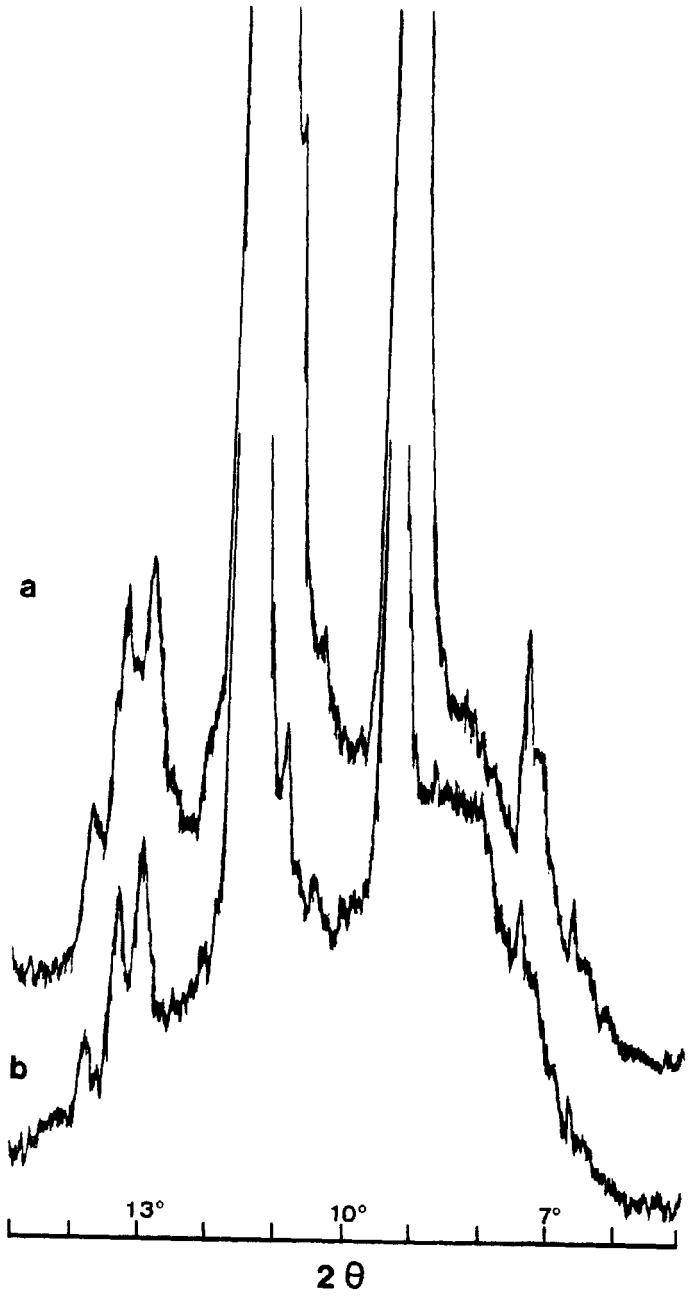

FIGURE 2

X-ray diffraction patterns of pure pulverized PEG 6000 before (a) and after (b) controlled fusion and cooling in the oil bath.

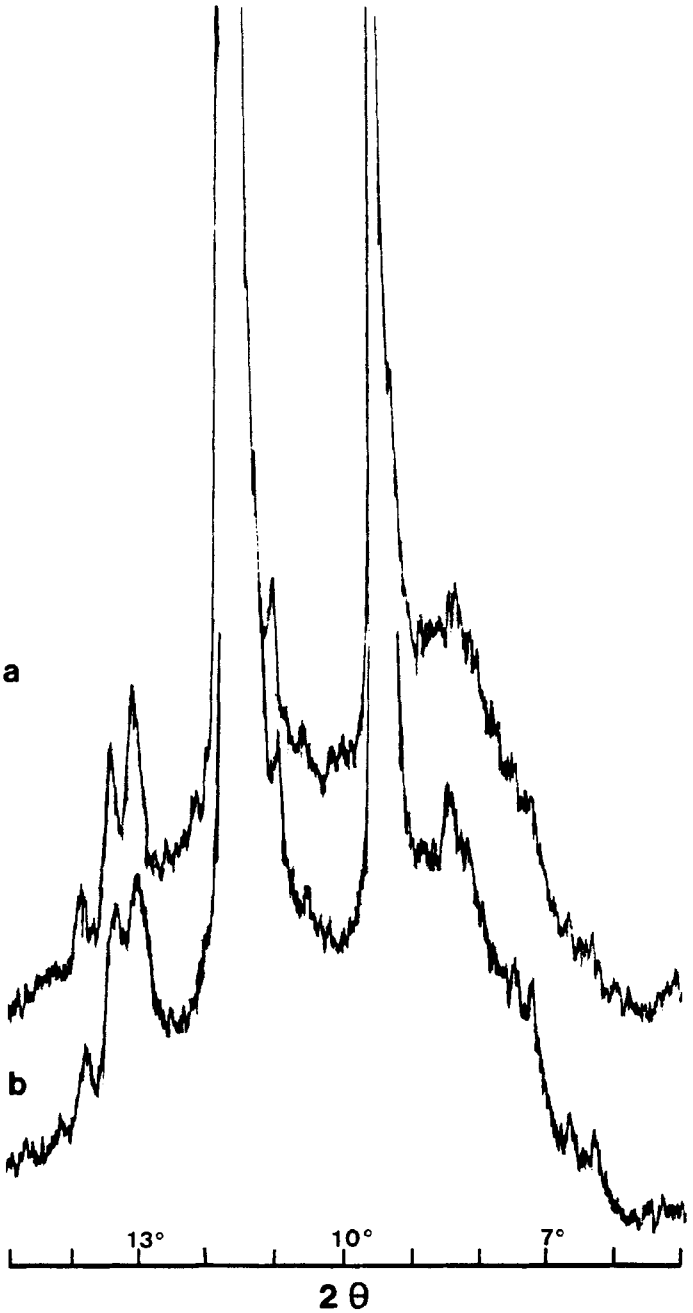

FIGURE 3

X-ray diffraction patterns of two progesterone-PEG 6000 physical mixtures. Key : a = 2,5:97,5 ; b = 5:95 w/w progesterone-PEG 6000.

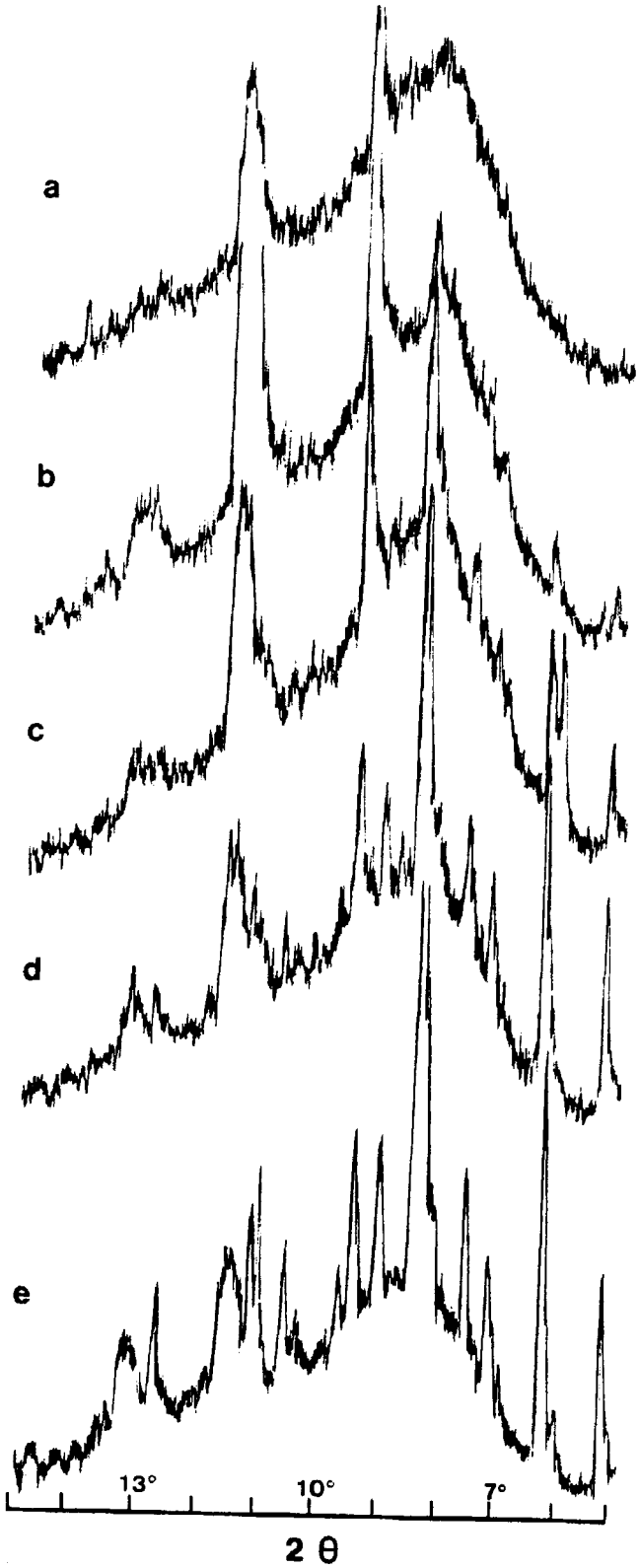

FIG. 4 X-ray diffraction patterns of various progesterone-PEG 6000 freshly prepared solid dispersions. Key: a=2,5:97,5 ; b=10:90 ; c=30:70 ; d=50:50 and e=75:25 w/w progesterone-PEG 6000.

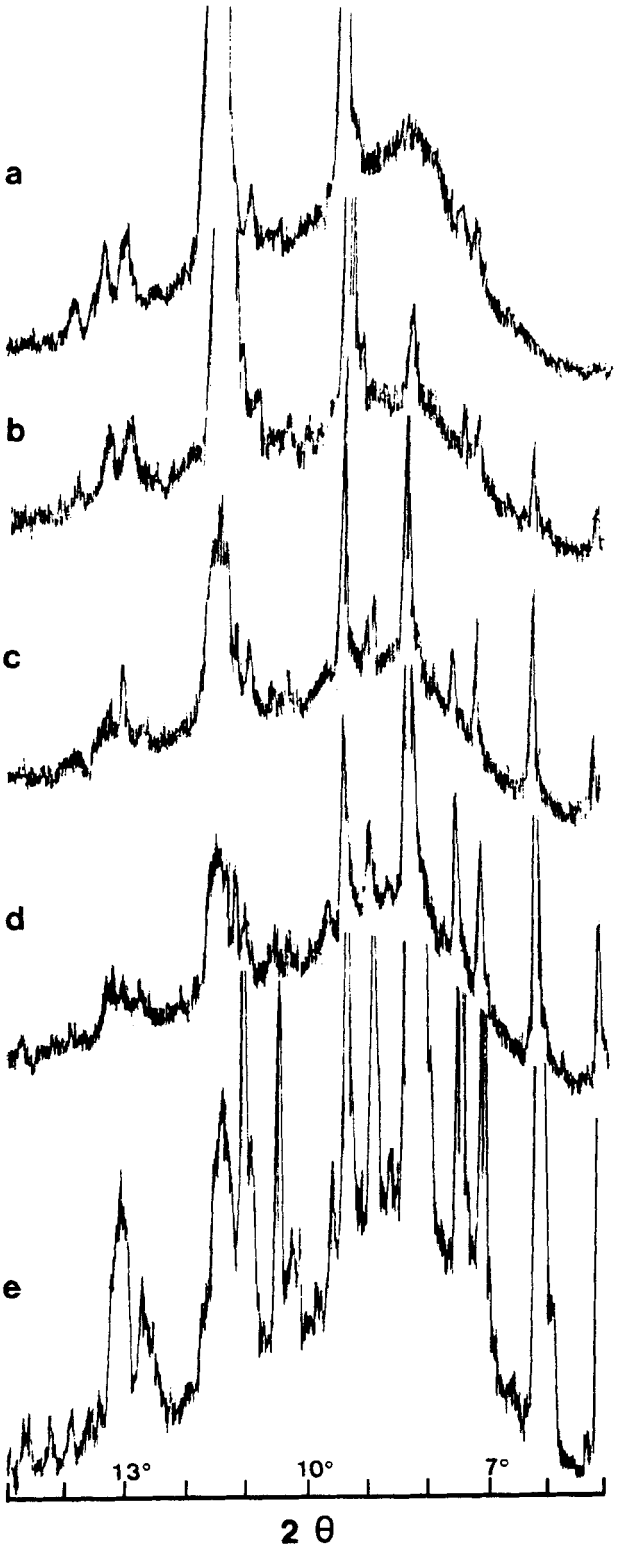

FIG. 5 X-ray diffraction patterns of various progesterone-PEG 6000 solid dispersions after one year storage at room temperature. Key: a=2,5:97,5 ; b=10:90 ; c=30:70 ; d=50:50 and e=75:25 w/w progesterone-PEG 6000.

increase in the crystallinity when the progesterone concentation rises in the solid dispersions. The lack of progesterone characteristic peaks, on the first diffractograms (a) corresponding to 2,5% progesterone - PEG 6000 dispersion (eutectic composition (12)), indicates that progesterone is not crystallized in the melt at this concentration. In this particular case, the lack of displacement of the PEG 6000 peaks leads to the conclusion that an interstitial solid solution has been formed during manufacturing.

In figure 5, the X-ray diffraction patterns run one year later on the same solidified melts, show a slight increase in the progesterone peaks heights with ageing. This phenomenon affects the solid dispersions with high progesterone content and may be attributed to an increase either in the degree of crystallinity or in the size of the progesterone particles. On the contrary, on the first diffractogram which concern the 2,5% solidified mekt, the absence of progesterone characteristic peaks is always observed.

CONCLUSION

The X-ray diffraction spectra show that in solidified melts, the progesterone is always present in its alpha form and does not undergo any structural modification. The presence of the only stable form of progesterone in the dispersions avoids drug polymorphis transformations which might induce modifications in solubility or dissolution kinetic with ageing (14) (15) (16) (17) (18).

The spectra also show a quite good physical stability of the preparations during storage. After 12 months, no important change appears, except for a slight rise of the crystallinity in dispersions containing highest progesterone concentrations. Moreover, the melt with eutetic composition keeps its amorphous state and displays an excellent stability.

However, the stability of solid dispersions has to be estimated by the evolution of dissolution kinetics and studies are in progress in our laboratory in order to confirm these results and to conclude this work.

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