Solid Modifications in Sidenafil Citrate

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SOLID MODIFICATIONS IN SILDENAFIL CITRATE

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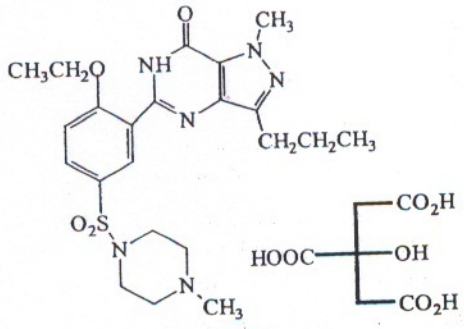
Introduction

Sildenafil citrate is a new drug that has been introduced recently for the treatment of male impotence.



Sildenafil Citrate

This drug was found to inhibit the synthesis of 5-phosphodiesterase enzyme (SPE) that plays an important role in the male erectile function. The clinical use implications of this drug have been the subject of many studies [1,2,3,4]. However, the physico-chemical studies of the drug were not as fortunate as its therapeutic uses, from publications point of view. Among properties required to develop formulations, are the knowledge of crystalline modifications of the drug and the influence of manufacturing and handling on Sildenafil citrate polymorphs.

Experimental Methods

Materials

All chemicals used were of analytical grade.
Sildenafil citrate was provided by the Jordanian Pharmaceutical Manufacturing Co., Naor Jordan. The powder is white and fluffy. When examined under the microscope it exhibits birefringence. The crystals are fine needles with varying lengths. Thermograms of Sildenafil citrate obtained by using 910-S DSC TA instruments (USA) connected to TA 2000 analysis system equipped with Du Pont analysis system (USA). Thermogram shows a single endothermic peak at 197-199°C. and the drug decomposes following melting. Mass spectra q-4s`-NMR, 2-C^{13}-NMR, IR and Elemental analysis were carried out to assure the drug identification.

Preparation of the polymorphic forms

- Preparation of polymorph I

3 to 5 g of Sildenafil citrate were dissolved in 300 ml of boiling water, filtered, concentrated by evaporation and allowed to crystallize at room temperature. Crystals were dried and kept in amber bottles in a dessicator over calcium chloride pellets at room temperature.

- Preparation of polymorph II

1 to 2 g of Sildenafil citrate were dissolved separately in 100 ml of methanol, 500 ml of acetone, 350 ml of ethanol, 300 ml of propylene glycol, 350 ml 1-propanol, 350 ml 2-propanol, 400 ml of isobutanol. The powder was dissolved with the aid of heating and continuous stirring. The solution was concentrated by evaporation and left to cool at room temperature. Crystals appeared within 24-48 hours from preparation. Crystals were collected and stored as described in polymorph I preparation.

- Preparation of polymorph III

1 g of Sildenafil citrate was dissolved in 300 ml of hot ethanol. The hot solution was placed in an ice-making chamber at around -2°C. Crystals appeared within 48-72 hours.

Effect of heating, compression and trituration on different polymorphs

A sample of each polymorph and the reference sample were stored in oven at 65°C for one week.

A sample of each polymorph was compressed into tablets using hydraulic press at 5 and 10 tons. Thermograms of the upper part of the tablet and the lower part were screened using DSC.

The powder was triturated using mortar and pestle for several time intervals. For each time interval 3 samples were screened for any transformation using DSC.

Results and discussion

Three polymorphs were obtained and designated as I with m. p. (198.9-199.5), II with m. p. (194.2-195.3) and III (186.0-189.0).

X-ray powder diffraction, I.R. and DSC-thermograms appear to differentiate between these polymorphs. However, other polymorphic forms appear to exist as a mixture with one or two polymorphs. Those mainly were observed in the crystal obtained by rapid cooling of hot methanol or water solutions or a mixture of both (Figure 1).

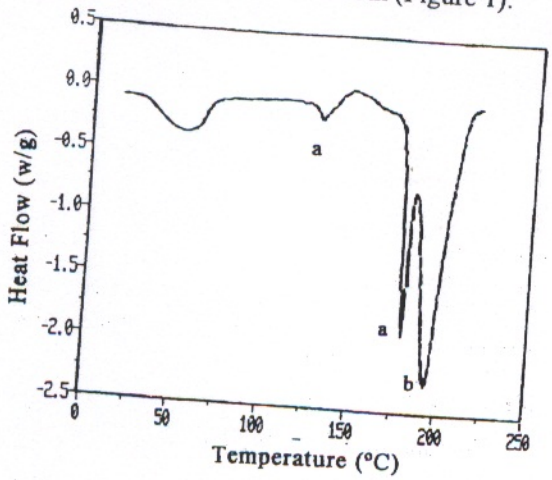


Figure 1: DSC thermogram of Sildenafil citrate powder obtained from rapid cooling of a hot solution of methanol. a: unidentified polymorphs, b: polymorph I.

Storing at 65°C did not show any sign of transformation indicating a reasonable solid state stability when stored at high temperatures. Compression force causes the m. p. of polymorphs I and II to shift to a lower m.p. (188 - 189°C). This indicates that these forms have been transformed to a third form. Such changes are facilitated by compression. However, when compression was applied for different time intervals it did not show any further transformations. This suggests that application of compression when testing the powder for IR must be taken with cautionary measures. Further, compression process must be evaluated when manufacturing tablets. It seems that the process is compression force dependent.

Trituration of polymorphs I, II and III are illustrated in figure 2, which suggests that different polymorphs are liable to transform to polymorph II.

It seems that the application of mechanical force in the form of compression or trituration or milling may result in some kind of transformation as anticipated and this may result in chemical instability as has been reported by Laine et al [5]. The amorphous form can be obtained by freeze-drying.

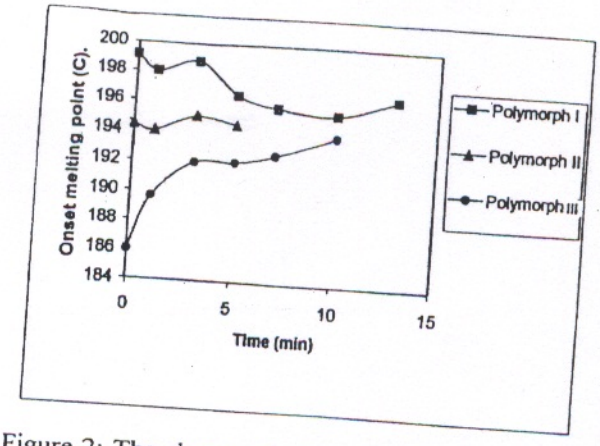


Figure 2: The change of onset of melting point (°C) as a function of trituration time.

Conclusion

Sildenafil citrate exists in 3 polymorphic forms. Other polymorphic forms exist but need to be separated in order to be identified.

Polymorphs are not heat sensitive but sensitive to mechanical force applied in powder processing.

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