

Poster Presentation

MS107.P02

Polymorphic stability of progesterone under stress conditions

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Progesterone (PRG) is an essential hormone in regulating the female reproductive system. It is used in gynecology, including contraception, medical abortion, and treatment of conditions related to endometrial and myometrial growth [1]. This drug exhibits two different crystal structures: forms 1 (PRG-1) and 2 (PRG-2); both with equal pharmacological effects. PRG-2 is the metastable form and it is 1.1 kcal/mol less stable than PRG-1 [2]. Polymorphic instability occurs when a metastable solid form (PRG-2) transforms into the most thermodynamically stable (PRG-1) [3]. It is well-known the therapeutic efficacy of a drug substance or drug product can be altered by its polymorphic or chemical transformation [4]. In order to study the polymorphic stability both polymorphs, PRG-1 and PRG-2, were placed under the same mechanical, thermal and high humidity stress conditions. X-ray powder diffraction (XRPD) analysis showed PRG-2 maintained its crystal structure after 3 months of exposure to dark storage condition at 40°C/75% relative humidity and 1 month to light. High performance liquid chromatography (HPLC) showed no degradation of PRG-1 and PRG-2. However, mechanical stress (grinding) on PRG-2 produced seeds of PRG-1 that induced its polymorphic transformation (Figure 1A). DSC curve showed endothermic events at 120.7°C corresponding to the melting point of PRG-2 followed by the recrystallization at 123.8 °C of PRG as PRG-1, finally the fusion of PRG-1 at 127.9°C. The Ea average value was higher in PRG-2 than in PRG-1; it suggested PRG-2 is more thermally stable than PRG-1 and, the decomposition behavior is different between these two polymorphs. Degradation products from thermal stability studies were monitored by coupled TGA-FT-IR analyses and different analyses (Table 2 inset in Figure 1). PRG-1 shows a high maximal rate of degradation (T_{dmax}) and initial temperature of thermal decomposition (T_o) compares to PRG-2.

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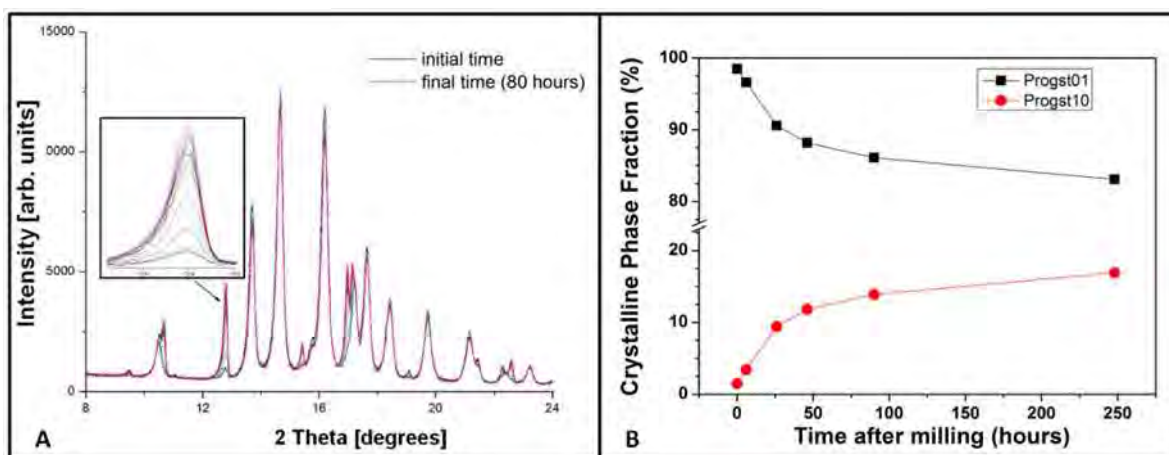


Table 1: Results obtained in TGA analyses

Polymorph	Melting point [°C]	T _{dmax} [°C]	T _o [°C]
PRG-1	120.7	332	288
PRG-2	127.9	305	266

Keywords: progesterone, polymorphic stability, solid-state stress conditions