Thermal properties and eutectic behaviour of dapivirine in combination with steroid hormones and other antiretrovirals

THERMAL PROPERTIES AND EUTECTIC BEHAVIOUR OF DAPIVIRINE IN COMBINATION WITH STEROID HORMONES AND OTHER ANTIRETROVIRALS

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It is well established that the melting point of a drug is inversely proportional to its lipophilicity [e.g. Calpren et al., J Pharm Sci, 83 (1994) 29-33] which, in turn, correlates with its ability to be absorbed in vivo. Therefore, if the melting point of a drug can be reduced without affecting other physicochemical parameters, then drug release and/or absorption may be enhanced. This general principle has been exploited in a number of marketed pharmaceutical products, including the topical anaesthetic cream EMLA® and the contraceptive vaginal ring Nuvaring®. Both products contain two active pharmaceutical ingredients – EMLA® contains a mixture of lidocaine and prilocaine, while Nuvaring® contains levonorgestrel and ethinyl estradiol (Fig. 1). Each drug in these combinations serves to reduce the melting point of the other drug, much in the same way that salt reduces the melting point of water (explaining its use on icy roads). For example, the phase diagram for etonogestrel and ethinyl estradiol shows that the maximum reduction in drug melting point occurs for a 1:1 mixture (Fig. 2).

During the first heating cycle, DPV shows a polymeric transition at 105°C and a crystalline melt at 222°C. Following cooling, a second heat cycle shows a glass transition at 80°C, a recrystallisation process at 160°C and a subsequent crystalline melt at 220°C.

Figure 3. DSC thermogram showing thermal behaviour of DPV alone. During the first heating cycle, DPV shows a polymeric transition at 105°C and a crystalline melt at 222°C. Following cooling, a second heat cycle shows a glass transition at 80°C, a recrystallisation process at 160°C and a subsequent crystalline melt at 220°C.

Figure 4. DSC traces showing thermal behaviour of BPV and LNG mixtures. DPV shows a polymeric transition at 105°C and a melting endotherm at 220°C. All other combinations showed similar thermal behaviour.

Figure 5. Phase diagrams for various dapivirine combinations. A – levonorgestrel (LNG), B – maraviroc (MVC), C – darunavir (DRV), D – 17 beta-estradiol (E2). According to the figures E–H, the eutectic or lowest melting composition is determined as the composition having the highest heat of fusion value for the eutectic melting transition. These eutectic compositions are indicated by a dashed line.