Evaluating Estradiol Solubility in PSAs: A Robust Method for examining Crystallinity in Transdermal Drug Delivery Systems

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Background: Transdermal drug delivery systems (TDDS) are commonly prescribed in hormone replacement therapy. Pressure sensitive adhesives (PSAs), a class of polymeric materials used in TDDS, can bond with surfaces on the application of light pressure thereby eliminating the need for heat or solvents. The solubility and crystallisation properties of the active pharmaceutical ingredient (API) in the adhesive are critical quality attributes of drug-in-adhesive (DIA) TDDS. Traditional microscopy approaches to determine API solubility in PSAs, however, have several limitations, including variable patch depth and drying times. The objective of this work was to explore a novel, high-throughput method as a more reliable alternative to microscopic slides for investigating the crystallisation of estradiol in various PSAs.

Methods: Using estradiol as a model drug, "mini-patches" which systematically explored different drug loadings were produced using two PSAs, one silicone-based and one polyacrylate-based. Mini-patches were produced in chemically-compatible cyclic olefin copolymer 96-well plates at a fixed patch depth. They were then microscopically examined at various timepoints using a polarised lens to detect crystallisation over an eight-week period. Additionally, replicate patches of each drug concentration were analysed by Differential Scanning Calorimetry (DSC) to detect the thermal signature of crystallised estradiol as a method independent of subjective visual inspection.

Results: Microscopy analysis revealed clear trends in crystallization. In silicone-based PSAs, crystal formation was observed consistently at estradiol loadings of 1% and above from the earliest time points. In contrast, polyacrylate-based PSAs showed delayed crystallisation, with visible crystals forming at 5% loading on day 0, and at 1% by week four. DSC thermograms from silicone samples exhibited a distinct endothermic peak corresponding to estradiol's melting point (178–180°C) was detected at concentrations exceeding 3% w/w, aligning with visible crystal formation. However, in polyacrylate samples, DSC failed to detect any crystallisation, even at drug loadings where microscopy showed clear crystal presence.

Conclusions: This study presents an alternative streamlined method for assessing estradiol solubility in PSAs, providing a standardised approach to preformulation of DIA systems. Further work will focus on the use of alternative methods of crystallisation detection in mini patch samples such as XRPD.