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Reverse Engineering of Nexplanon® Contraceptive Implant: Physicochemical Properties and In Vitro Drug Release

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PURPOSE

Nexplanon® is a long-acting implant inserted subdermally to release etonogestrel and prevent pregnancy for up to 3 years.
The implant is a non-biodegradable and flexible rod composed of a solid ethylene vinyl acetate copolymer (EVA) core imbedded with etonogestrel and barium sulfate. Surrounding the core is a rate-controlling EVA membrane (named as "skin"). Composition of Nexplanon® is listed in **Table 1** [1]. The implant is manufactured using a co-extrusion process [2] and development of this process was discussed in another poster [3]. The goals of this study are:

- To characterize key physicochemical properties of Nexplanon®.
- To study drug release mechanisms of Nexplanon®.
- To correlate drug release mechanisms with structural properties.

OBJECTIVE(S)

- To determine thickness of the rate-controlling membrane.
- To characterize implant surface morphology.
- To study solid state properties of etonogestrel and barium sulfate in Nexplanon®.
- To apply mathematic models to understand mechanisms of drug release through two ends/skin and correlate them with physicochemical properties of Nexplanon®.

METHOD(S)

Characterization of physicochemical properties:

Property	Images were analyzed using ImageJ 3
Skin thickness	100 um thick cross section was prepared using cryo-microtome and analyzed using light microscope.
Surface morphology	Nexplanon® was sputter-coated with gold for 60 s at 40 mA and analyzed using scanning electron microscope (SEM).
Etonogestrel	• Particle size: Nexplanon® was heated to 150 °C, smeared into a glass slide and analyzed using a hot-stage polarized light microscope. • Solid state property: Nexplanon® was heated to 250 °C under Nitrogen purging condition using a Differential scanning calorimetry (DSC).
Barium sulfate	Nexplanon® was heated to 1000 °C at 20 °C/min using a thermogravimetric analyzers (TGA). The residue was then analyzed using SEM.

Characterization of drug release properties:

- In-vitro drug release through the skin, the two ends and whole implant were tested in deionized water at 37 °C in a shaker at 150 rpm.
- To test release through only the skin or the two ends, either the ends or the skin was sealed using etonogestrel-impermeable Loctite® 4011 glue, respectively.
- Etonogestrel was assayed using a reverse-phase HPLC method with UV detection.

Analysis of acquired data:

- All data were processed, fitted and plotted using Excel.

RESULT(S)

Figure 1. Cross section and surface morphology of of Nexplanon®.

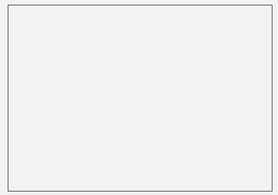


Figure 2. characterization of etonogestrel and barium sulfate.

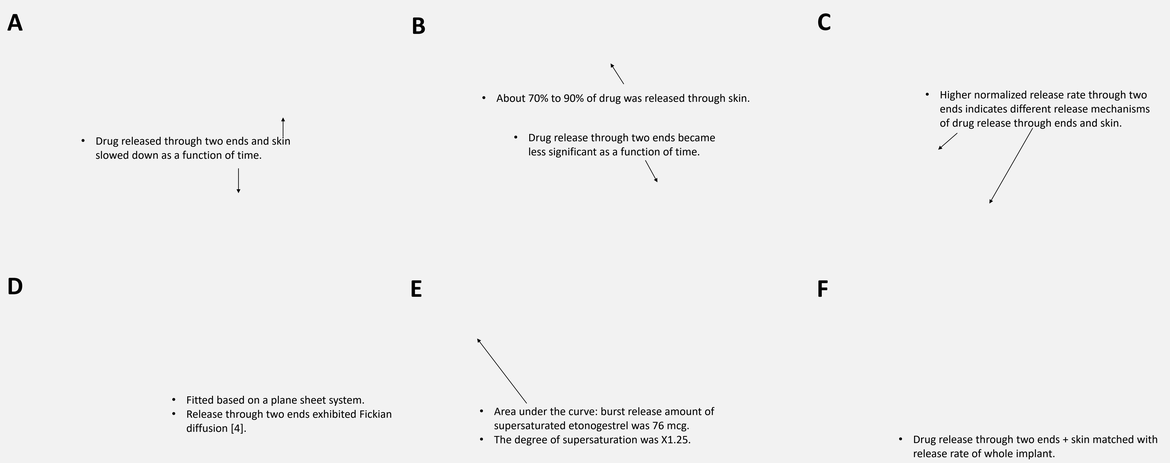
Figure 3. DSC thermogram of Nexplanon® and etonogestrel.

The onset temperature of melting of etonogestrel in Nexplanon® was lower than neat etonogestrel, indicating etonogestrel was partially dissolved in EVA 28.

Table 1. Composition of Nexplanon® [2].

Table 2. Dimension of Nexplanon®.

Figure 5. In-vitro dissolution testing and modelling of drug release mechanisms.



CONCLUSION(S)

Implant structure:

- The thickness of the rate-controlling membrane was 61.0 μm (**Table 2**).
- The surface of the implant skin was free of drug crystals (**Figure 1**).
- The two ends were not covered by the membrane and dispersed with etonogestrel particles (**Figure 1**).

Properties of etonogestrel and barium sulfate:

- The d90 of etonogestrel was 11.9 μm and the d90 of barium sulfate was 3.0 μm (**Figure 2**).
- 99.5% of etonogestrel was at crystalline state (**Figure 2, 3**). 0.5% was at solubilized state (of which 0.1% was supersaturated) (**Figure 5E**).

Drug release mechanisms:

- Drug released through two ends by dissolution and diffusion in EVA 28 matrix (**Figure 5D**).
- Drug released through skin by diffusion in EVA 15 membrane (**Figure 5E)**.
- About 1.2 mg of burst released etonogestrel was observed at the first 15 days due to the presence of supersaturation of etonogestrel and exposed ends (**Figure 5F**).
- Drug was predominantly (70% to 90%) released through skin (**Figure 5B**).
- The apparent release rate through skin was faster than through two ends (**Figure 5A**) due to the 40 times larger surface area of skin compared to two ends (**Table 2**).
- The release rate per unit area through two ends was faster than through skin, indicating faster release mechanism through two ends than skin (**Figure 5C**).
- The total release rate of two ends + skin matched well with release rate of whole implant (unsealed).

REFERENCE

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