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Development of a coextrusion process to prepare etonogestrel long-acting implant

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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 coaxial rod comprised of a solid ethylene vinyl acetate copolymer (EVA) core surrounded by a concentric EVA membrane (named as 'skin').The core is imbedded with etonogestrel and barium sulfate. Reverse engineering of Nexplanon® is discussed in another poster [1]. The implant is manufactured by a coextrusion process [2]. We developed a coextrusion process to prepare etonogestrel implant modelled after Nexplanon®. The goals of this work were:

- Apply processing control strategies to prepare prototype implant modelled after Nexplanon®.
- Characterize key quality attributes of prepared implants and correlate them with processing parameters.

METHOD(S)

Processing parameters	Control strategy	Affected quality attributes
Core materials feed rate	• Powder blend was extruded, pelletized and mixed with lubricant. • 1.34 kg/hour was kept using a gravimetric lost-in-weight feeder.	• Core and skin mass ratio • Skin thickness
Skin material feed rate	• Flood-fed feeding mechanism was applied. • 0.16 kg/hour was controlled by screw rpm.	
Core materials mixing	• Core materials were double-extruded using TSE. • 3 kneading zones were applied.	• Drug particles distribution • Drug content uniformity in core
Core materials inlet die pressure	• A gear pump was placed between TSE and co-axial die to stabilize pressure.	• Precision of diameter
Skin material inlet die pressure	• A single-screw extruder was used to feed skin material.	
Draw down of molten strand	• Total output rate was fixed at 1.5 kg/hour: 0.16 kg/hour for skin, 1.34 kg/hour for core. • Downstream line speed was controlled by water bath wheel puller.	• Accuracy of diameter

Characterization of the implant:

- Samples at steady-state were collected for analysis.
- **Drug content:** 2 mm x 2 mm pellet was cut and mixed in 50 mL of 80:20 acetonitrile:water solution. Drug concentration was measured by HPLC.
- **Degree of supersaturation:** in-vitro drug release in water through skin was conducted by sealing both ends using etonogestrel-impermeable Loctite® 4011 glue. The degree of drug supersaturation in core was calculated based on mass balance and compared with that of Nexplanon® [1].

RESULTS

Figure 1(A). Schematic illustration of coextrusion line for etonogestrel implant preparation.

Figure 1(B). Schematic illustration of screw profile of twin-screw extruder.

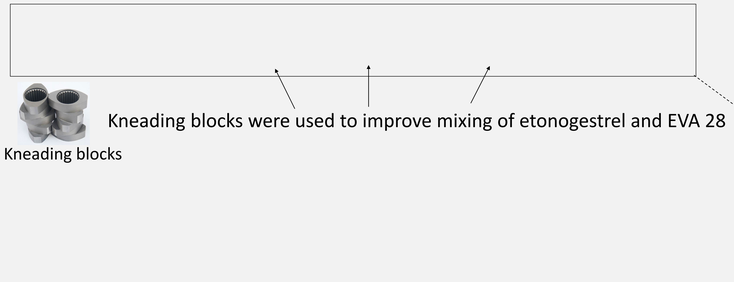

Figure 2. processing control parameters

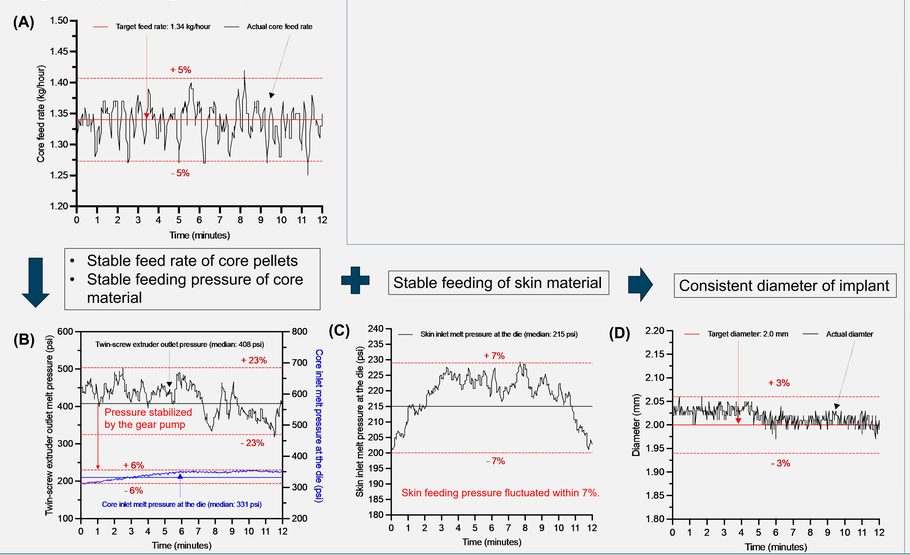

Table 1. Composition of prepared implant

Figure 3. Light microscope image of cross section of the etonogestrel implant, 46 mg.

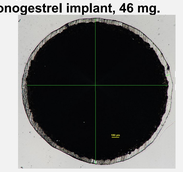

Figure 4. Excessive energy input led to drug supersaturation in implant.

Prepared implant shown higher burst release rate compared to Nexplanon®.

Table 2. Selected quality attributes of etonogestrel implant at steady state.

CONCLUSION(S)

A coextrusion process to prepare etonogestrel implant modelled after Nexplanon® was developed (**Figure 1**). Processing control strategies (**Figure 2A-2C**) were applied to produce implant with target quality attributes. The prepared implant shown precise and accurate diameter (**Figure 2D**), same thickness of rate-controlling membrane to Nexplanon® (**Figure 3**) and uniform content uniformity, and consistent density (**Table 2**). These quality attributes were achieved by:

(1) Implementation of a double extrusion process.
(2) Proper usage of kneading blocks in twin-screw corotating extruder (TSE).
(3) Stable feed rates and inlet die pressures of core and skin materials.

Higher burst release rate through skin was observed compared to Nexplanon® due to higher degree of drug supersaturation (**Figure 4**). The degree of supersaturation of prepared implant tested after 6 months of storage (1.9) was higher than that of Nexplanon® (1.2).

To minimize supersaturation, the number of kneading blocks can be reduced, or the specific feed rate (feed rate/screw speed) can be increased to reduce energy input. The usage of kneading blocks should be balanced between sufficient mixing efficiency and excessive energy input.

REFERENCE

[1] Zhong, Ren, et al., "Reverse engineering of Nexplanon® contraceptive implant: physicochemical properties and in vitro drug release", AAPS 2024
[2] Veenstra, H. and W. De Graaff, X-ray visible drug delivery device. 2014, US 8,722,037 B2.

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