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Correlation between material properties, extrusion processing conditions and permeability of etonogestrel in polyethylene vinyl acetate films implants

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PURPOSE

Polyethylene vinyl acetate (EVA) is a biocompatible, non-biodegradable and semicrystalline copolymer that has been widely used for long-acting implants. [1] The objective of this study was to investigate the effect of material properties and extrusion processing conditions on the permeability of etonogestrel in EVA using free film as a model. The results from this study can be used to guide the investigation of the effect of manufacturing process conditions on drug release properties of implant.

METHODS

Permeability

The flux of etonogestrel diffusing through EVA films at 37℃ and lag time were measured using a PermeGear side-by-side diffusion cell apparatus. Drug concentration in receptor side was measured by HPLC. The permeability was calculated based on the flux, thickness, and effective area of the film. Drug solubility and diffusivity in EVA films were calculated using time lag method. [2]

Effect of material properties

Permeability of EVA films with different vinyl acetate (VA) contents and melt indexes were compared. Lower melt index corresponds to higher molecular weight and vice versa.

Effect of processing conditions

Permeability of EVA films prepared at different draw down ratios (DDR) and cooling rates and were measured and compared. The DDR is calculated by:

$$DDR = K * \frac{output\ (\frac{g}{min})}{\text{film thickness } (cm) * \text{film width } (cm)}$$

Measurement of crystallinity

The melt enthalpy EVA films were measured by a Discovery DSC 2500. The crystallinity of EVA film is calculated by: $C = \Delta H_{EVA}/\Delta H_{100\%} * 100\%$, where C is wt. % crystallinity, ΔH_{EVA} is heat of melting of EVA film (J/g) and $\Delta H_{100\%}$ is melt enthalpy of the 100% crystalline polyethylene (293.6 J/g).

Data acquiring and processing

Measurements were repeated three times (N = 3, SD errors bar). Data were processed and modeled using GraphPad Prism 9. Simple linear regression was used to model the effect of VA content and DDR. The R square value, p-value and 95% confident intervals were shown. Unpaired t-test was used to compared two sets of data. Ordinary one-way ANOVA test was used to compared more than two sets of data.

RESULTS

Effect of material properties

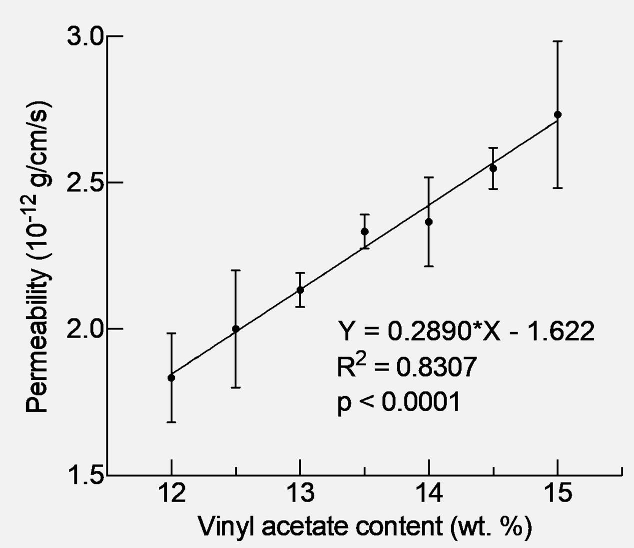

Figure 1. Effect of VA content on permeability of etonogestrel in EVA films at 37℃

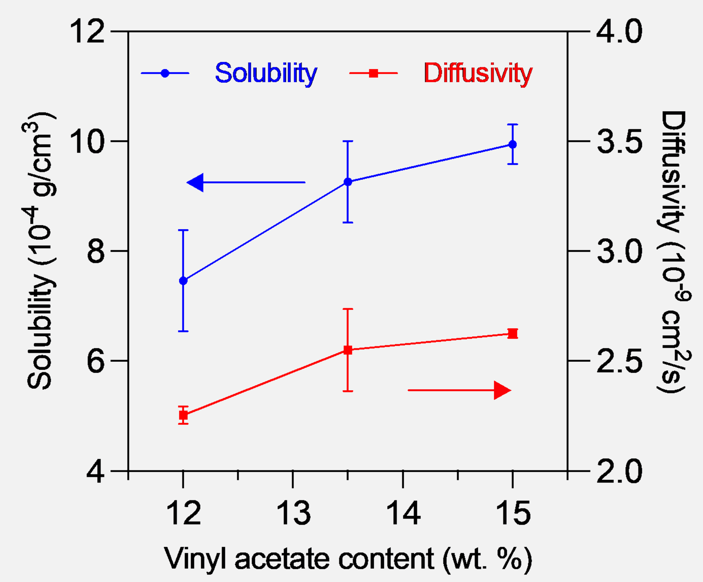

Figure 2. Effect of VA content on solubility and diffusivity of etonogestrel in EVA films at 37℃

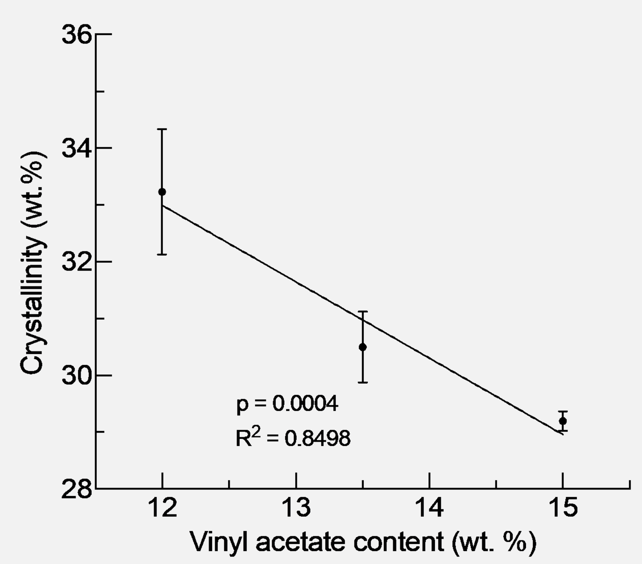

Figure 3. Effect of VA content on crystallinity of EVA films

- Every 0.5 wt.% increase of VA contents leads to about 8% increase in permeability (**Figure 1**).
- The increase in permeability was attributed to lower crystallinity (**Figure 3**), which resulted in increased solubility and diffusivity (**Figure 2**).
- When VA content increased from 12.0 wt.% to 15.0 wt.%, solubility increased by 30% and diffusivity increased by 18% (**Figure 2**).

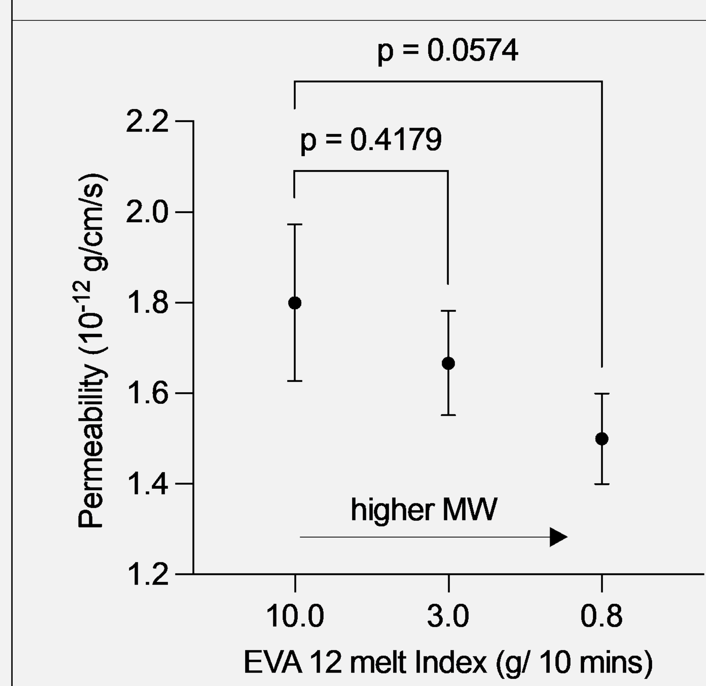

Figure 4. Effect of molecular weight on permeability of etonogestrel in EVA 12.0 film at 37℃

- The effect of molecular weight on etonogestrel permeability in EVA 12.0 (12.0 wt.% VA content) was not statically significant (p > 0.005) **(Figure 4).**

Effect of processing conditions

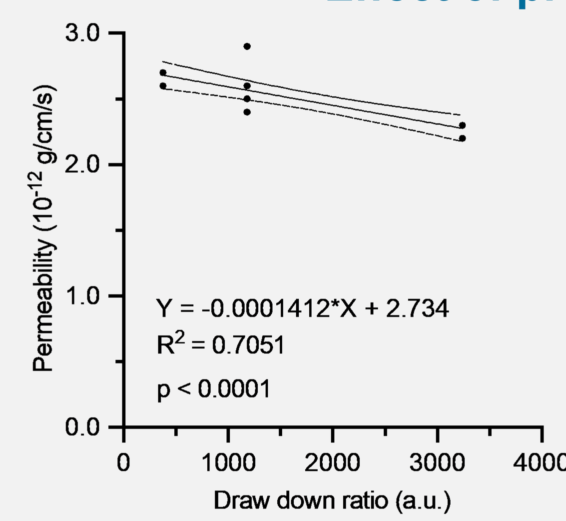

Figure 5. Effect of draw down ratio on permeability of etonogestrel in **EVA 15** film at 37℃

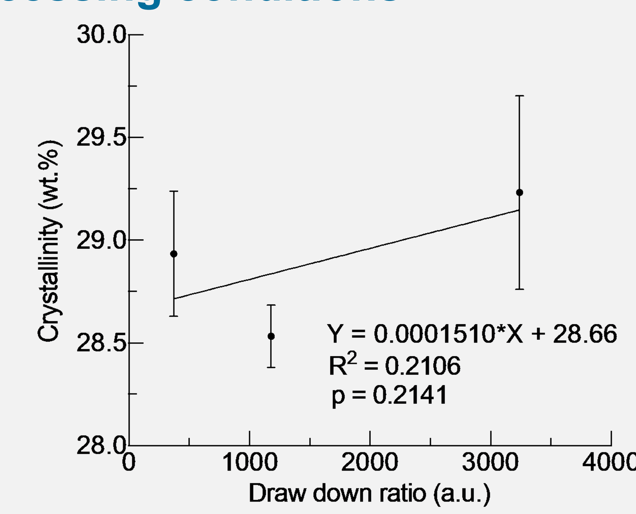

Figure 6. Effect of draw down ratio on crystallinity of **EVA 15** film

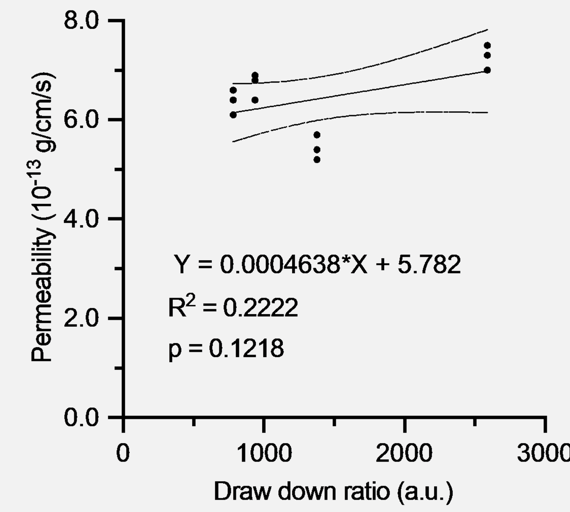

Figure 7. Effect of draw down ratio on permeability of etonogestrel in **EVA 9** film at 37℃

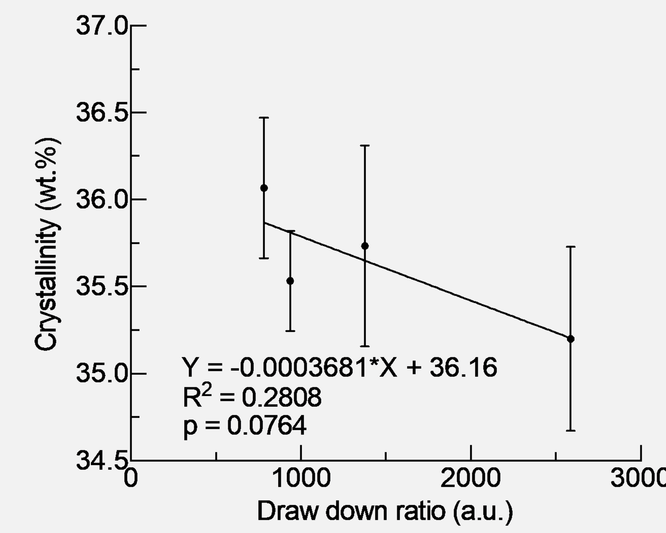

Figure 8. Effect of draw down ratio on crystallinity of **EVA 9** film

- The absolute value of the slope of linear regression line of EVA 15 dataset of effect of DDR on etonogestrel permeability was less than 0.0002 across the tested drawing range (**Figure 5**).
- The slope of EVA 9 data regression line (0.00046) was steeper than that of EVA 15 (-0.00014). The dataset of EVA 9 is more variable than that of EVA 15 (**Figure 5, Figure 7**).
- The slope of linear regression line of effect of DDR on crystallinity of EVA 9 (-0.00037) film is greater than that of EVA 15 (0.00015) while the p-value of EVA 9 regression line is smaller than that of EVA 15 **(Figure 6, Figure 8).**

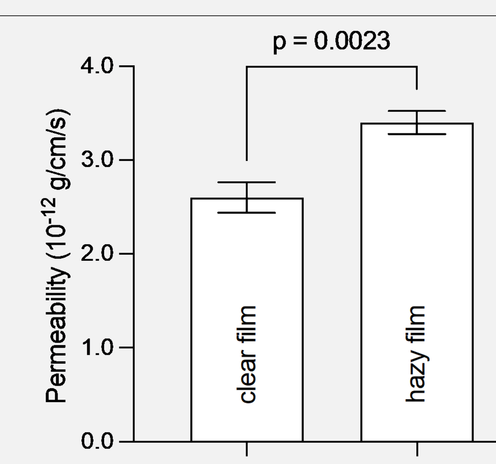

Figure 9. Effect of cooling rate on permeability of etonogestrel in EVA 15 film at 37℃

- EVA 15 film prepared using chill roll cooled method (higher cooling rate) is clear while using air cooling method (lower cooling rate) is hazy.
- The permeability of EVA 15 film cooled by air was 30% higher than film cooled by chill roll (p = 0.0023) **(Figure 9).**

CONCLUSIONS

1. A 0.5 wt. % increase in VA content leads to an 8% of increase in permeability over the tested VA contents ranging from 12.0 wt.% to 15.0 wt.% (Figure 1).
2. The increase in permeability was attributed to lower crystallinity (Figure 3), which resulted in increased solubility and diffusivity (Figure 2). Solubility is more subjected to effect of VA content than diffusivity (Figure 2).
3. The impact of molecular weight of EVA on permeability of etonogestrel in EVA is not statistically significant (Figure 4).
4. The impact of draw down ratio during extrusion on permeability of etonogestrel in EVA 15 and crystallinity of EVA 15 is not statistically significant (Figure 5, Figure 6).
5. Lower VA content EVA is more subjected to drawing effect than higher VA content EVA (Figure 5, Figure 7). The drawing effect on permeability is due to change of EVA crystallinity (Figure 6, Figure 8).
6. EVA film prepared under lower cooling rate was hazy with higher permeability (Figure 9).
7. **The permeability of EVA films is predominantly controlled by VA content while the impact of processing condition including draw down ratio and cooling rate is not as significant.**

REFERENCE

[1] Schneider C, Langer R, Loveday D, Hair D. Applications of ethylene vinyl acetate copolymers (EVA) in drug delivery systems. Journal of Controlled Release. 2017;262:284-95.
[2] Lee EK, Lonsdale H, Baker R, Drioli E, Bresnahan P. Transport of steroids in poly (etherurethane) and poly (ethylene vinyl acetate) membranes. Journal of membrane science. 1985;24(2):125-43.

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