PHYSICAL-CHEMICAL ASPECTS OF A COAXIAL SUSTAINED RELEASE DEVICE BASED ON POLY-EVA

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Fysisch-chemische aspecten van een coaxiaal
vertraagd afgifte systeem gebaseerd op poly-EVA

(met samenvatting in het Nederlands)

Proefschrift

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Cover: Cross section of a coaxial fiber; supersaturated steroid is crystallized in the core polymer under influence of polymeric shear just behind the spinning pump.

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Voor mijn ouders

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1. INTRODUCTION

1.1 GENERAL

One of the main objectives of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation. The therapeutic response of an active entity is normally dependent on an adequate maintenance of the drug concentration in biological fluids at the site of action of the drug. In the case of systematically acting drugs (i.e. drugs that reach the site of action via the systemic circulation), it is generally accepted for clinical purposes that a dynamic equilibrium exists between the concentration of drug at its site of action and the concentration of drug in blood plasma.

Ideally, the action of dosage forms should be independent of patient to patient variation. Factors that influence oral bioavailability are for example variations in pH of gastrointestinal fluids, gastric emptying rate, intestinal motility and influence of food. Oral absorption involves the drug release from the dosage form by dissolution and the subsequent passage of the drug across the cellular membranes of the gastrointestinal barrier. This absorption phase is followed by an elimination phase, in which the drug is removed out of the blood by hepatic and/or renal clearance. Repetitive per oral administration of equal doses at a fixed interval of time ensures the maintenance of an effective therapeutic effect when the concentration is kept between respectively the maximum safe plasma concentration and the minimum effective plasma concentration (Figure 1-1).

When the plasma half-life of a drug is short, tablets should be taken regularly, i.e. several times a day. In this situation, tablets with a sustained release may offer the possibility to reduce the dose frequency to once a day. It is, however, not possible to further reduce the frequency because of the limited residence time of a tablet in the gastrointestinal tract. In contrast, parenteral systems with sustained release characteristics can remain in position for a considerably longer time. These parenterally applied sustained release systems offer several further advantages over the daily oral administration of drugs. They can provide increased efficacy, safety, convenience and compliance.

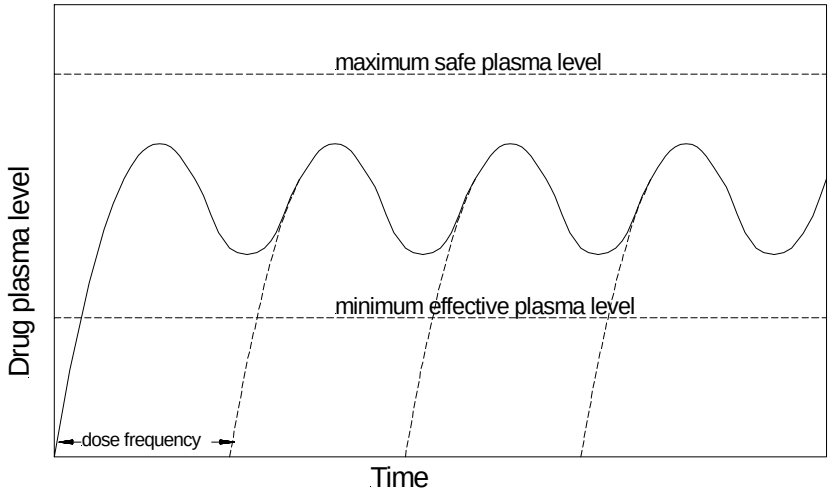


Figure 1-1, drug plasma levels during repetitive administration

A typical example of such a sustained release system is Nuvaring®, that offers a very good alternative for the daily intake of tablets (1,2). Nuvaring® is a contraceptive vaginal ring that was recently introduced on the US market by Organon. The ring has an outer diameter of approximately 5.4 cm and a thickness of 4 mm. It is designed to release both a progesterone and an estrogen for a period of 21 days.

Various types of similar drug delivery system have been developed to accurately control the release rate of a drug. Mostly the drug is incorporated inside a carrier material. Because of their suitable properties polymers are often used as a carrier. In literature various types of polymers are mentioned that can be used for drug delivery (3). These polymers can either be biodegradable or non-degradable.

Biodegradable materials distinguish themselves by the ability to be eliminated from the body. The first example of a synthetic polymer used in biomedical applications was poly (lactic acid) (4). Another example of a polymer specifically designed for biomedical application was poly (glycolic acid) (5). In an effort to achieve better control over polymer properties and erosion rates, copolymers of lactic and glycolic acid were developed. In parallel, efforts were made to develop other degradable polymers with adjustable properties. From this, two families emerged; poly-anhydrides and poly (ortho esters), which in turn were followed by other polymers designed to fulfill certain desirable properties. Biodegradable polymers have been

used to produce several dosage forms like implants, microcapsules and hydrogels. All have the advantage of lacking the need of removal after depletion. The drawback of this is, however, that an intermediate removal is difficult in case the therapy needs to be stopped prematurely.

In contrast, non-degradable polymers can be removed completely at any desired time. Examples of non-degradable polymers are polysiloxanes, polyethylene vinyl acetate and polyurethane.

Polysiloxanes are frequently used in medical and pharmaceutical applications. These polymers are characterized by backbones consisting of alternating atoms of silicon and oxygen. One of the most common polysiloxane polymers is poly-dimethylsiloxane. This polymer is used in a contraceptive vaginal ring, which releases both progesterone and estradiol (6). This ring consists of core matrix containing a steroid/silicone mixture and a cover of silicone tubing to modulate the release rate. The outer diameter and thickness of the ring is respectively 5.8 cm and 8.8 mm.

Pharmacia & Upjohn markets a vaginal ring, also containing a silicone polymer, called Estring®. This product is used to treat local symptoms of urogenital atrophy caused by estrogen deficiency. It is a slightly opaque ring, made of a silicone elastomer sheath surrounding a silicone elastomer core that contains estradiol, barium sulfate and a silicone fluid as a dispersing agent. When placed in the vagina, Estring® releases estradiol at a rate of approximately 7.5 µg/day in a consistent stable manner over 3 months. The dimensions of this ring are: outer diameter 55 mm; cross-sectional diameter 9 mm; core diameter 2 mm.

Another non-degradable polymer that is often applied for controlled drug delivery is polyethylene vinyl acetate (EVA). These polymers exhibit excellent permeability properties for various drugs and can be obtained in various grades. EVA polymers have already been used in number of commercial controlled release devices (7) (Figure 1-2).

Progestasert® is a T-shaped intrauterine device (IUD) marketed by the Alza Corporation. This IUD releases a hormone directly into the uterus to prevent pregnancy. The body of the IUD comprises a reservoir system where the drug is dispersed in a silicone fluid that is surrounded by a permeable membrane of an EVA copolymer. It is designed to release daily an amount of at least 65 µg progesterone for a period of 1 year.

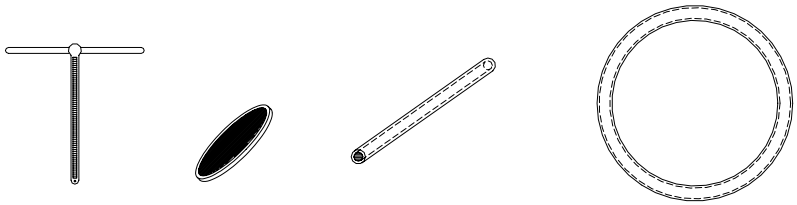


Figure 1-2, Various types of reservoir devices, a. Progestasert®, Ocusert®, Implanon®, Nuvaring®.

Also marketed by Alza is Ocusert®, which is designed to treat glaucoma. Ocusert® is an ocular insert reservoir system that is designed to release pilocarpine for 7 days at a rate of approximately 30 µg/hr. The reservoir system has an oval shape of about 13.4 x 5.7 mm and a thickness of 0.3 mm. In order to control the release of pilocarpine, the reservoir system is sandwiched between two EVA membranes.
EVA copolymers have also been used in a number of transdermal patches like Transderm-Nitro®, Estraderm® and Estalis® from Novartis.
Another sustained release system that is marketed by Organon is Implanon® (8). Implanon® is a contraceptive implant based on an EVA coaxial fiber with a length of 4 cm and a diameter of 2 mm that is designed to release a progestagen at a release rate of approximately 65 µg/day for a period of 3 years.
This thesis focuses on the application of EVA copolymers in reservoir systems. The release rate of a reservoir system is controlled by the permeability properties of the polymeric membrane. In literature it is well described that the polymeric structure of semi-crystalline polymers like polyethylene is significantly influenced by storage and manufacturing conditions. This influence is also reflected on the permeability properties of a drug in these polymers. In order to develop a drug delivery system based on a controlled diffusion process of a drug in a semi-crystalline polymeric matrix, knowledge of the factors that affect the permeability properties is essential.

1.2 POLYETHYLENE VINYL ACETATE COPOLYMER AND POLYMERIC STRUCTURE

The choice of EVA copolymers for use in controlled release systems offers several advantages:

- EVA polymers are biocompatible, non-toxic (9) and do not cause inflammatory reactions
- Rheological properties provide good processability (e.g. extrusion)
- Good material flexibility
- The permeability properties can be adapted by the content of vinyl acetate
- EVA polymers are non degradable and can therefore be removed completely at any desired time

Polyethylene vinyl acetate copolymers are high molecular weight semi-crystalline thermoplastic polymers that have a polyethylene backbone with pendant polar acetate groups. Mostly polyethylene vinyl acetate copolymers are prepared by bulk copolymerization of ethylene and vinyl acetate in continuous tubular reactors or stirred reactors under high pressure (2000-3000 bar) and temperatures (150-250 °C). The molecular weight can be adapted by varying the process conditions. Under these conditions a random copolymer is obtained that consists of ethylene sequences interrupted by vinyl acetate groups. Figure 1-3 depicts the structural formula of polyethylene vinyl acetate.

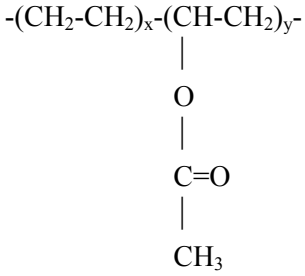


Figure 1-3, polyethylene vinyl acetate

Pure polyethylene crystallizes by chain folding which results in a polymeric matrix that consists of alternating crystalline lamellae and amorphous domains (Figure 1-4).

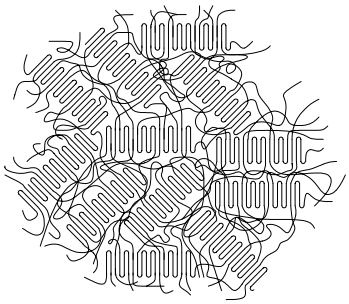
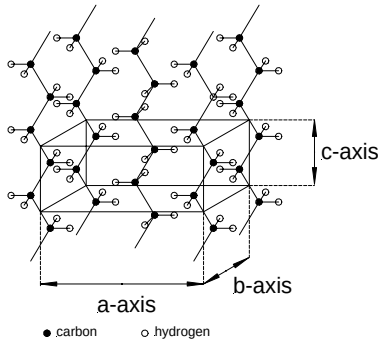


Figure 1-4, morphology of semi-crystalline polymer

The unit cell of a polyethylene crystal is orthorhombic (10). This means that the unit cell is specified by three mutually perpendicular axes of unequal length, normally called a, b and c axis. The c-axis is associated with the direction of the polyethylene chains in crystalline lamella. In the unit cell 5 ethylene sequences are present (Figure 1-5). The dimensions of the unit cell a, b and c were determined by X-ray diffraction and are respectively 7.41 Å, 4.94 Å and 2.55 Å (10).



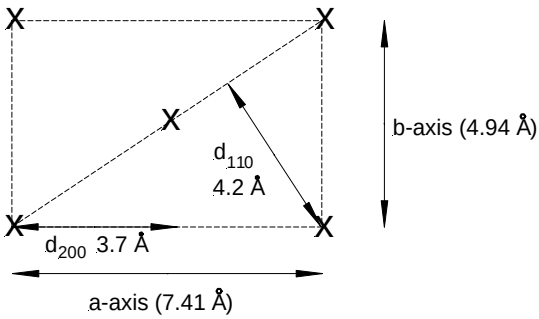


Figure 1-5a *Figure 1-5b*

Figure 1-5, dimensions of the polyethylene unit cell

In order to determine the orientation of the crystalline lamellae in polyethylene by means of X-ray diffraction, the 200 plane (perpendicular to the a-axis) and the 110 plane (parallel with the c-axis) are frequently used. In Figure 1-5b the distances between these crystalline planes are calculated.

Because the inter-spatial dimensions of the crystalline domains are normally smaller than the molecular size of the drug to be released, the diffusion process of the drug molecules takes place in the amorphous domains and is consequently hindered by the presence, size and orientation of the crystalline domains. As a result the permeability

properties of the drug in the polymer are influenced by the overall crystallinity, size and orientation of the crystalline domains.

The properties of polyethylene vinyl acetate copolymer are determined by the amount of vinyl acetate monomer units in the polyethylene backbone (11,12,13,14). By increasing the content vinyl acetate the crystallization of polyethylene is hindered and as a consequence a lower crystallinity is obtained. By increasing the vinyl acetate content from 0% to 60% the crystallinity decreases approximately from respectively 60% to 0%. Because the length of the polyethylene sequences is reduced at increasing vinyl acetate content (13), the height of the crystalline lamellae (crystal size) decreases and as a consequence the melting point of the polymer is reduced.

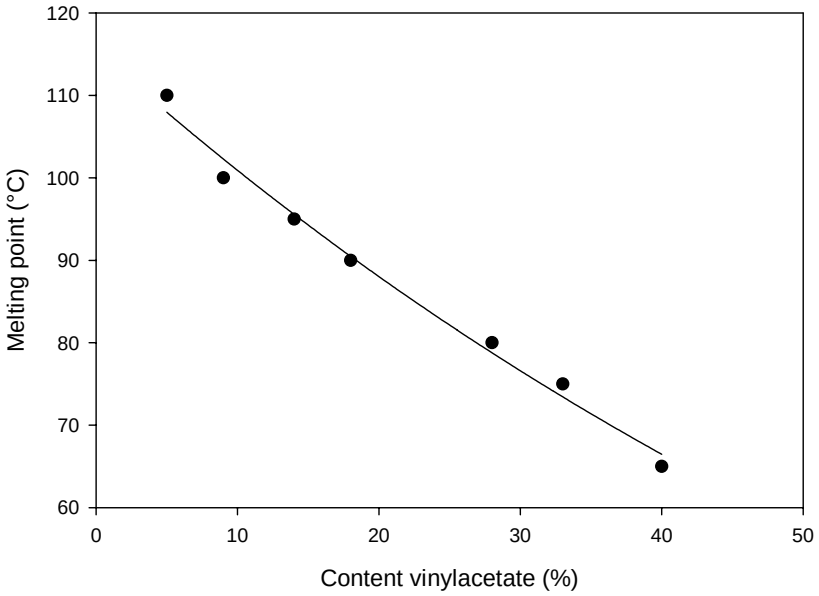


Figure 1-6, the melting point of polyethylene vinyl acetate copolymer

The decrease in crystallinity and increase in polar acetate groups also results in a higher solubility for most drugs (15,16). Furthermore, a higher flexibility is obtained at increasing vinyl acetate content.

A vinyl acetate content of more than 70% has an adverse effect on the flexibility and solubility. In literature it is reported that the stiffness of EVA copolymer has a minimum at approximately 70% vinyl acetate (14). Increasing the content of vinyl acetate above 70% results in a higher stiffness. In ref.15 the influence of the vinyl

acetate content on the permeability of camphor through EVA polymers was reported. Again a maximum permeability was demonstrated at a vinyl acetate content of 70%.
Besides the vinyl acetate content, the polymeric structure is also highly influenced by the manufacturing conditions of the final product. When polyethylene is crystallized under quiescent conditions and at a low cooling rate, a spherulitic macrostructure is obtained (12,17,18,19,20). Upon cooling crystallization nuclei are formed that subsequently grow in radial direction of the nuclei. By increasing the cooling rate more nuclei are formed which result in smaller but less perfect spherulites. Quenching results eventually in a structure where the crystalline and amorphous domains are randomly orientated (Figure 1-7).
If a high shear (21,22,23,24,25) is applied during crystallization the long polymeric chains are orientated in the direction of the flow field. Under these conditions the nucleation process occurs along a line or row rather than from a point. This phenomenon is also known as row nucleation. This row nucleation is followed by a secondary crystallization process where the polymeric chains crystallize by chain folding perpendicular to the row nuclei. The crystallization process under these conditions is called stress or flow induced crystallization and results in a macrostructure that is characterized by a lamellae stacked morphology at medium stresses and fibrilar at high stresses.

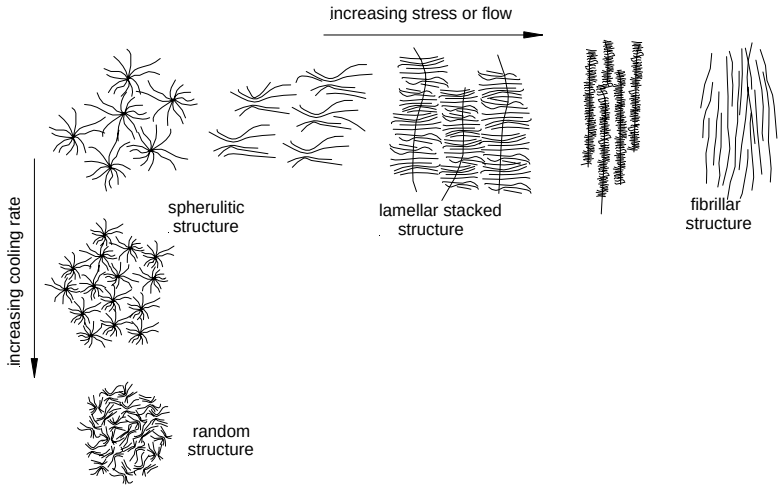


Figure 1-7, influence of the process conditions on the macrostructure of polyethylene (lines represent crystalline regions)

1.3 MELT EXTRUSION

Melt extrusion is one of the pharmaceutical operations to be applied as a manufacturing method for controlled drug delivery devices. Melt extrusion is considered to be an efficient technology which is already used for a variety of dosage forms like granules, pellets, tablets, implants, transdermal systems etc (26). The principle of the melt extrusion process is that a polymer is heated above its melting point where it can be shaped into any desired form.

Blend extrusion offers the possibility to disperse or dissolve a drug into a matrix or carrier (Figure 1-8). A homogeneous powder or granule mixture is fed to the blend extruder by means of a dosing system at an adjustable rate. The dosing system can either be volumetric, where the rate of the dosing screws is fixed, or gravimetric, where the delivery rate is controlled by weight. It is also possible to apply more than one dosing system at a time. The blend extruder consists of segmented barrel that can be heated to any desired temperature. Normally the first section is water cooled, whereas the temperature of the other sections gradually increases above the melting temperature of carrier mixture. Inside the barrel two blending screws provide for both transport and kneading of the mixture. Each screw consists of a combination of screw and kneading elements mounted on a shaft, which can be adapted to any desired combination. In literature (27) several elements are described with various purposes like conveyer elements, co- and counter rotating kneading elements etc. The shafts are rotated by a reducer gearbox in the same direction (co-rotating) or in opposite direction (counter-rotating). In general co-rotating provides better mixing capabilities because the surfaces of the screw elements move towards each other. Mostly the screws are fully intermeshing by which the elements are self-wiping, thus eliminating stagnation of melt and ensuring for a better and narrow residence time distribution.

In blend extrusion two types of mixing can be distinguished. While the residence time distribution provides for a proper distributive mixing, high shear between the kneading elements assures a good disperse mixing.

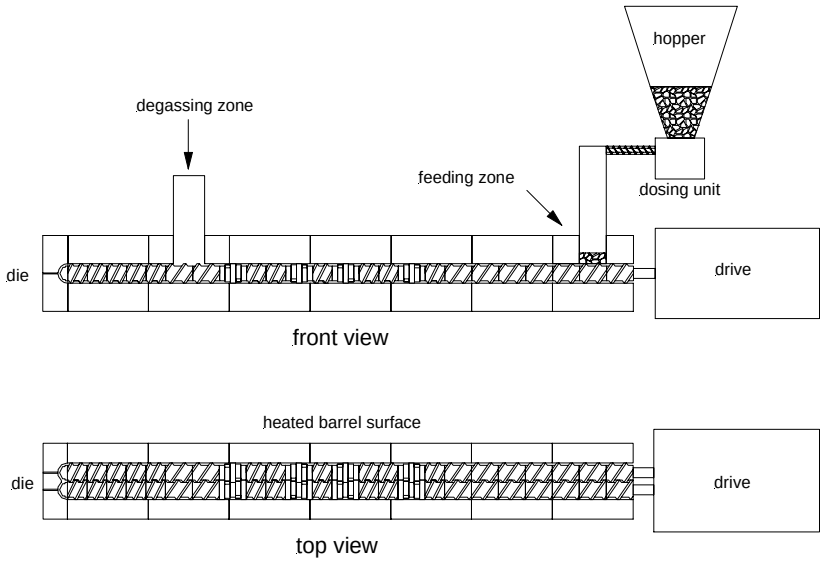


Figure 1-8, Schematic presentation of a twin screw blend extruder.

Sometimes a degassing zone is used. In this section volatile elements like water vapor or air are removed by vacuum. Subsequently one or more strands leave the extruder at the die and are cooled in a water bath. The strands can be granulated in water or after leaving the water bath using a strand granulator.
Normally the function of a single extruder is to re-melt the granulate at a specific temperature and deliver it to a system which forms the polymer to the required shape.

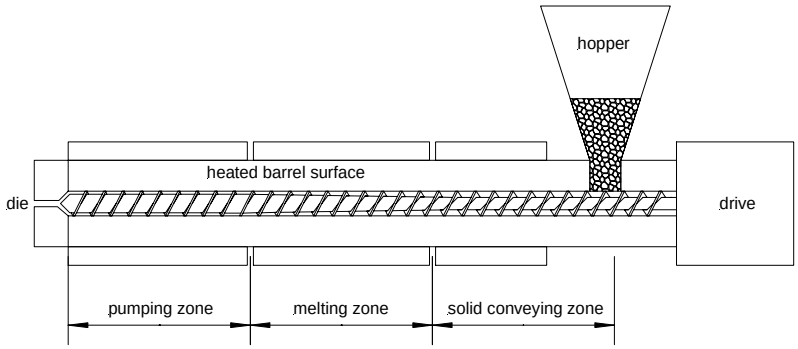


Figure 1-9, schematic presentation of a single screw extruder

In a single screw extruder a granulate, stored inside a hopper, is fed to the extruder by means of gravity. While the feeding section is normally cooled by water, the rest

of the barrel is heated by three or more heater bands above the melting point of the polymer.

Inside the barrel a screw transports the polymer subsequently to the die. Generally the extruder is divided into three sections. The solid conveying zone is characterized by deeper flights, which allow a better transport for the granules. The pitch and helix angle determine the throughput rate at a constant rotation speed of the screw. The polymer is transported as a solid plug to the melting zone, where the granules are melted and subsequently compressed into a homogeneous melt. In this zone the depth of the flight is gradually reduced. The purpose of the pumping zone is to deliver the melt to the die at a homogenous temperature, flow and pressure. The length of the screw and each zone is commonly expressed as a factor of the screw diameter (D). Typical values for the length of the feeding, compression and pumping zone are respectively 7D, 8D and 8D.

Because of different transport mechanisms in the feeding, compression and pumping zone, the design of the screw may be adapted to obtain an optimum extrusion process for different polymers.

Commonly a dedicated device is mounted behind the extruder in order to form the polymer into a desired shape. This can either be a device to manufacture films, fibers or other shapes.

Another frequently applied configuration is a coextrusion installation, which is used to manufacture coaxial fibers (Figure 1-10). This equipment consists of two single screw extruders each responsible for melting respectively a core and membrane polymer. Both molten polymers are subsequently delivered to two spinning pumps that are mounted on a spinning block. These pumps deliver an accurate flow of both polymers to a spinneret, where the coaxial fiber is formed. The rotation speed of the pumps determines the spinning velocity, whereas the ratio between the spinning pumps determines the thickness of the membrane. Finally the fiber is cooled down in a water bath which is positioned below the spinneret.

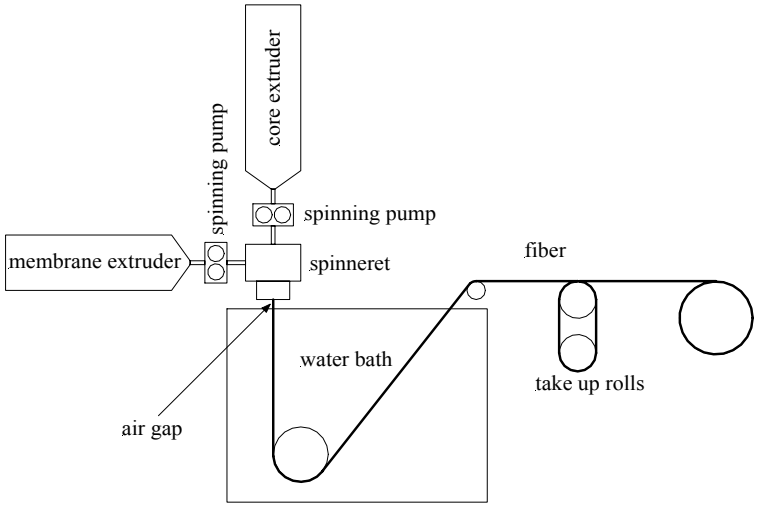


Figure 1-10, schematic presentation of a co-extrusion installation

1.4 RESERVOIR DEVICE

In a reservoir device the drug is incorporated in a core that is surrounded by a rate limiting membrane. In a monolithic device this membrane is absent. Although controlled delivery from a monolithic device is very well possible, the presence of a membrane normally provides a better release profile. In principle, a zero order release (constant release in time) can be approached with reservoir systems when the drug concentration in the core is far above the saturation solubility.

The diffusion process of a drug through the membrane can be described by Fick's Law of diffusion (7):

$$J = -D\frac{dC}{dx} \qquad \textit{Equation 1-1}$$

In this equation J is the flux of the drug through the membrane in kg/m^2 s, D is the diffusion coefficient of the drug in the membrane polymer (m^2/s) and dC is the concentration difference in kg/m^3 over a distance dx in m.

In order to predict the release rate from a planar reservoir system the following equation can be deduced from Fick's law:

$$\frac{dM}{dt} = \frac{ADKC_c}{l}$$ *Equation 1-2*

Where A is the area of the membrane (m^2) and l is the membrane thickness (m).
K is the interfacial partitioning of the drug between the core and the membrane and is related to the solubility's in the core (C_c) and in the membrane polymer (C_m) as defined by:

$$K = \frac{C_m}{C_c}$$ *Equation 1-3*

It should be noted that Equation 1-2 is only valid if the concentration of the drug in the surrounding medium approaches zero (sink conditions).
In Figure 1-11 the diffusion process through the membrane is schematically shown.

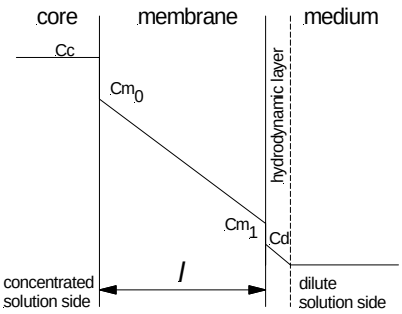


Figure 1-11, diffusion over a membrane

As a result of the concentration difference over the membrane the drug that is dissolved in the core polymer diffuses through the membrane to the surrounding medium at a controllable rate and time. In a reservoir system the permeability of the core should be preferably much higher than the permeability of the membrane polymer. Furthermore, the thickness and permeability of the hydrodynamic layer surrounding the membrane should be much smaller than those of the membrane. In that case the membrane is rate limiting. Here the permeability is defined as the product of the diffusion coefficient and saturation solubility of the drug ($P=D*C_s$).
In order to predict the release rate for cylindrical and spherical geometry's the following equations are reported in literature (28):

$$\frac{dM}{dt} = \frac{2\pi hDKC_c}{\ln\left(\frac{r_0}{r_1}\right)}$$

a) cylindrical geometry

$$\frac{dM}{dt} = \frac{4\pi DKC_c(r_0 r_i)}{r_0 - r_i}$$

b) spherical geometry

Where:

h = length of the cylinder

r_o = outer radius membrane

r_i = inner radius membrane

In this thesis a drug delivery reservoir system is described that is manufactured by a means of a coextrusion process. It consists of a flexible polyethylene vinyl acetate coaxial fiber where the drug is incorporated in the core polymer. The core polymer is surrounded by a rate limiting membrane polymer (Figure 1-12).

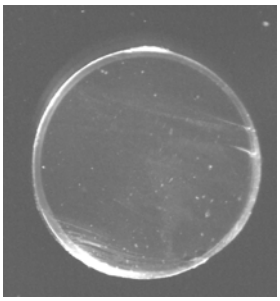


Figure 1-12, cross section of the coaxial fiber

The drug inside the core can either be present in a dissolved state or in a dispersed state. If the drug is present in a dissolved state, the concentration in the core will gradually decrease in time and as a consequence the release rate will also decrease. Because the total amount of drug in the core is limited by the saturation solubility, the release time is normally not very long. The release rate from this system can be adapted by varying the initial concentration of the drug dissolved. In principle, the release rate of more than one drug can be controlled by varying the concentration of each drug.

If on the other hand the drug is present in a dispersed state, the amount of dissolved drug is fixed by its saturation solubility. In this case the release rate can only be controlled by the thickness of the membrane. As a consequence this method can only be used to control the release rate of a single drug. Because the content of dispersed

drug can be much higher than the saturation concentration, the release time is normally much longer.

Figure 1-13 depicts the influence of the storage time on the release of a drug from a coaxial fiber. Immediately after manufacturing the drug content in the membrane is still zero. If the release rate is determined immediately after manufacturing, as shown in Figure 1-13a (black symbols), the release rate is zero on t=0 and gradually increases in time until steady state is obtained. If, however, the coaxial fiber is first stored at 25 °C, the drug content in the membrane increases upon storage until equilibrium is achieved with the amount of drug dissolved in the core polymer. The distribution of drug between both core and membrane is determined by the partition coefficient and the volume of each compartment. If the release rate is determined subsequently, the release curve shows a burst release. This burst release is attributed to the amount of drug that is dissolved in the membrane. In this case approximately half the amount of drug dissolved in the membrane is released quickly until again steady state release is obtained. If the total amount of released drug is plotted versus time, the so-called time lag and burst effect curves are obtained (28). The diffusion coefficient of the membrane can be deduced from the intercept of the steady state part of each curve with the time axis.

For a planar reservoir system the intercept of the steady state part of the time lag and burst effect curve with the time axis is respectively $l^2/3D$ and $-l^2/6D$. Where l is the membrane thickness and D is the diffusion coefficient.

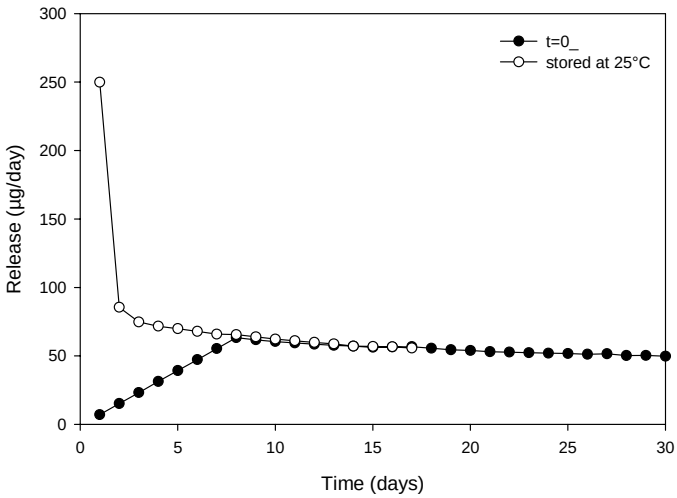


Figure 1-13a, time lag and burst effect curves

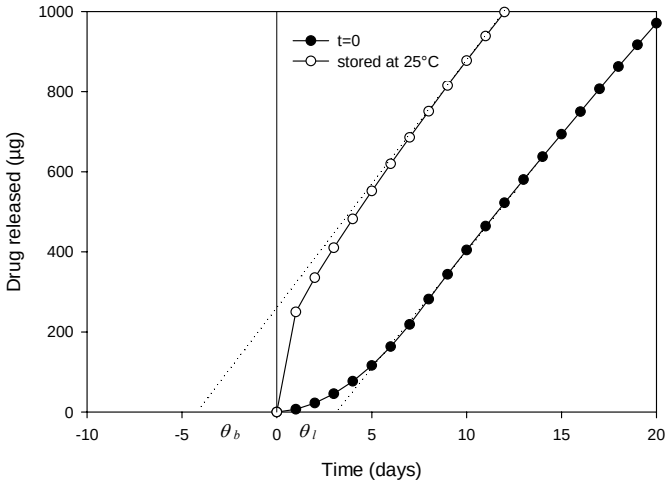


Figure 1-13b, time lag and burst effect curves

1.5 OUTLINE OF THIS THESIS

The aim of the study reported in this thesis was to obtain a better understanding of the mechanisms and factors that influence the release properties of a drug from a coaxial controlled release device based on polyethylene vinyl acetate copolymers.

In *chapter 2* the release properties of two steroids, etonogestrel and ethinyl estradiol from a contraceptive vaginal ring is described. The solubility and diffusion coefficients of the steroids in polymeric carrier (polyethylene vinyl acetate) were determined by pre(formulation) studies. Furthermore, an interaction between the two steroids is described that is also reflected on the release properties.

Chapter 3 deals with the influence of supersaturation on the release rate. The release rate from a coaxial reservoir system is determined by the amount of dissolved steroid. The amount of dissolved steroid is not only dependent on the saturation solubility but also on manufacturing and subsequent storage conditions.

The manufacturing and storage conditions have a significant influence on the polymeric structure and as a result on the release rate of a steroid from the coaxial fiber.

Chapter 4 discusses the effect of storage temperature on both polymeric structure and release rate of the coaxial reservoir system. Polymeric films and fibers were stored at various temperatures. Subsequently, the solubility and release properties were determined. Differential scanning calorimetric measurements were performed to

investigate the change in the polymeric structure. Furthermore, the influence of the cooling rate during the manufacturing process of the fibers is discussed.

Chapter 5 shows that the process parameters of the extrusion process have a significant effect on both release rate and mechanical properties of the coaxial reservoir system. A relation is shown between the release rate and mechanical properties. This relation is explained by a change in polymeric structure of the fiber.

The influence of the process parameters during the extrusion process on the final release rate is discussed in *chapter 6*. Upon leaving the spinneret a drawing force is needed to elongate the fiber to its desired diameter. The force needed is depended on the applied process conditions. A relation is demonstrated between the release rate and the drawing force. Wide Angle X-ray Scattering (WAXS) measurements were performed to investigate this relation and confirm a change in the polymeric structure of the fibers with increasing drawing force.

Chapter 7 describes the influence of the process parameters on the morphology of the membrane and on the mechanical properties of the coaxial fibers.

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2. IN-VITRO RELEASE PROPERTIES OF ETONOGESTREL AND ETHINYL ESTRADIOL FROM A CONTRACEPTIVE VAGINAL RING

Abstract

The release properties of steroids from a combined contraceptive vaginal ring were investigated. The product design is based on a coaxial fiber consisting of two types of polyethylene vinyl acetate copolymers. Inside the core of the fiber, two steroids are present in a molecularly dissolved state. In order to design a controlled release system with specified release characteristics, diffusion coefficient and solubility properties are required. These data can either be determined during pre-formulation studies on e.g. polymeric flat films or from in-vitro release measurements of the actual coaxial fibers.

It can be concluded from this study that polyethylene vinyl acetate copolymers exhibit suitable properties to develop a controlled release system with the two steroids etonogestrel and ethinyl estradiol. It was found that the permeability data obtained in the pre-formulation studies are useful in semi-quantitative terms, but deviate from the permeability data found from the in-vitro release of coaxial fibers. This is most likely due to differences in the polymeric structure of films and coaxial fibers. As a consequence, further studies should be initiated to evaluate the relationship between the manufacturing process and the resulting polymeric structure.

It was also found that the solubility and release of etonogestrel are influenced by the concentration of ethinyl estradiol. This phenomenon was investigated by thermoanalysis and it appeared that the steroids form an eutectic. The lower melting point results in an increase in solubility and hence in altered permeability properties.

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International Journal of Pharmaceutics 232 (2002) 163–173

2.1 INTRODUCTION

Sustained release of drugs is often preferred above the daily administration of drugs. Controlled release systems can provide optimized efficacy, safety and convenience because they can be designed to deliver a drug at a specified rate, for a specific period of time and even at a desired location. In literature several types of parenteral release systems have been described like polymeric systems, hydrogels, diffusion pumps, microcapsules etc.

An example of a sustained release system is a contraceptive vaginal ring that is designed to release steroid hormones. This product can serve as an alternative for the daily administration of tablets.

This report describes the (pre)formulation studies on such a contraceptive vaginal ring, which consists of a coaxial fiber, prepared of polyethylene vinyl acetate (EVA) copolymers. The choice of this type of polymer for use in controlled release systems is based on the following characteristics:

- Polymers are biocompatible, non-toxic and do not cause inflammatory reactions.
- Processability (e.g. extrusion) is technically feasible.
- Favorable release properties for many active substances.
- Solubility and diffusion coefficient of the drug can be varied by the content of vinyl acetate.

The coaxial fiber consists of a core polymer, with one or more steroids incorporated, that is enveloped with a thin polymeric membrane. This is most often referred to as a reservoir system. The steroids may be present inside the core polymer in a solid crystalline state ("dispersion"), or in a molecularly dissolved state ("solution"). When crystals are present inside the core, the concentration of the dissolved drug is fixed by its saturation solubility. In this case the release rate can be controlled by the thickness and the permeability of the membrane. As a consequence this concept can only be used to control the release of one single drug. When it is anticipated to control the release of two drugs it is necessary to dissolve the drugs completely. In this way the release can be controlled independently by the concentration of each drug and by the membrane characteristics. In this report coaxial fibers are described in which two steroids (etonogestrel and ethinyl estradiol) are completely dissolved in the core polymer.

As indicated, the release of steroids from the coaxial fiber is influenced by the solubility and diffusion coefficient of the drug in the polymer. In order to design an

adequately performing system, it is of importance to determine these parameters. Therefore, several physical methods to determine these are applied.
In pharmaceutical literature several reports were found that describe the physical and chemical interaction between pharmaceutical compounds. Some of them describe the interaction between steroids and its consequences on the solubility and release in several formulations (Yanez et al., 1988; Diaz-Sanchez et al., 1991; Kaplun-Frischoff and Touitou, 1997).
The interaction between the applied steroids in this chapter has also been assessed and its consequences subsequently determined. In particularly the influence of ethinyl estradiol on the solubility and release properties of etonogestrel was investigated.

2.2 THEORY

In a reservoir system the drug is incorporated in a bulk polymer that is surrounded by a permeable membrane polymer. The permeability of both polymers is given by:

$$P = D * S \qquad \textit{Equation 2-1}$$

Where:
P = permeability (kg/m·s)
D = diffusion coefficient (m^2/s)
S = solubility (kg/m^3)

In order to achieve a constant release, the permeability of the bulk polymer should be much higher than that of the membrane polymer. In this way the release from the system is mainly controlled by the membrane.
The steady state release from the system can be described by Fick's law of diffusion, which describes the diffusion of a drug through the rate controlling membrane as a result of a concentration gradient:

$$J = -D\frac{dC}{dx} \qquad \textit{Equation 2-2}$$

Where:
J = Mass flux (kg/m^2 s)
D = Diffusion coefficient (m^2/s)
dC = Concentration gradient over the membrane (kg/m^3)
dx = Distance of diffusion (m)

This basic equation can only be used for flat systems. In literature (Baker and Lonsdale, 1974) the following model is derived from Fick's law to predict the release rate of a cylindrical reservoir system:

$$\frac{dM_t}{dt} = \frac{2\pi LDK\Delta C}{\ln (r_0/r_i)} \qquad \textit{Equation 2-3}$$

Where:
$\frac{dM_t}{dt}$ = Release rate (kg/s)
L = Length of the cylinder (m)
D = Diffusion coefficient (m^2/s)
K = Partition coefficient between membrane and core
ΔC = Concentration gradient over the membrane (kg/m^3)
r_o = Outer radius (m)
r_i = Inner radius (=outer radius - membrane thickness) (m)

The partition coefficient can be calculated from the solubility of drug in both polymers:

$$K = \frac{Cs_{skin}}{Cs_{core}} \qquad \textit{Equation 2-4}$$

Where:
Cs_{skin} = solubility of the drug in the membrane polymer (kg/m^3)
Cs_{core} = solubility of the drug in the core polymer (kg/m^3)

In literature (Martin et. al., 1983) the relation between the mole fraction solubility and temperature of a solid drug in non-ideal solutions is described as a logarithmic

function (Equation 2-5). Although this equation was originally derived for liquids it can also be used to predict the solubility of chemically similar compounds such as the diverse steroids in polymers (Chien et. al., 1976).

$$\log X_2 = -\frac{\Delta H_f}{2.303R} * \frac{T_0 - T}{T_0 T} + \log \gamma_2 \qquad \textit{Equation 2-5}$$

Where:

T_0 = Melting point solute (K)

T = System temperature (K)

ΔH_f = Heat of fusion solute (J/mole)

X_2 = Molar fraction solute

R = Gas law constant (8.314 J/mole K)

γ_2 = Activity coefficient of the solute

The activity coefficient γ is a measure for the balance between the intermolecular forces of both solute and solvent. In Equation 2-6 the relation between the activity coefficient and solubility parameters (which express the cohesion forces between similar molecules) of both solute and solvent is given:

$$\log \gamma_2 = (\delta_1 - \delta_2)^2 \frac{V_2 \Phi_1^2}{2.303RT} \qquad \textit{Equation 2-6}$$

Where:

δ_1 = solubility parameter solvent

δ_2 = solubility parameter solute

Φ_1^2 = volume fraction of the solvent

V_2 = molar volume of the solute

Consequently, the molar fraction solubility can be expressed as the sum of two terms: the solubility in an ideal system and the logarithm of the activity coefficient of the solute. For ideal solutions the solubility parameters of solute and solvent are equal and so the last term of Equation 2-5 will be zero.

2.3 MATERIALS AND METHODS

2.3.1 Materials

The steroids used in this study, etonogestrel and ethinyl estradiol, were received from Diosynth B.V. and complied with the internal standards.
Some of the most important thermodynamical parameters are given in Table 2-1.

Table 2-1, Thermodynamical parameters of etonogestrel and ethinyl estradiol

Steroid	Melting point (°C)	Heat of fusion (J/g)	Molar weight (g/mole)	Solubility parameter (Rowe, 1988) $(MPa)^{½}$
Etonogestrel	199	96	324	20.0
Ethinyl estradiol	182-184	93	296	23.7

Different types of polyethylene vinyl acetate copolymers were used. “EVA 28” contains 28% of vinyl acetate and is used as core material in the coaxial fibers because of a high solubility and permeability of mentioned steroids. “EVA 9” contains 9 % of vinyl acetate and is applied in the membrane because of lower solubility and permeability properties.

2.3.2 Methods

2.3.2.1 Solubility in polymer films (at low temperatures)

In order to determine the solubility of steroids at low temperatures in polyethylene vinyl acetate copolymers, films of about 200 μm were prepared by film extrusion. The films were cut in pieces of 5x5 cm and subsequently immersed in saturated aqueous steroid solutions at 25 °C and 37 °C. In order to study steroid interaction the aqueous solution was saturated with both a single steroid as well as mixtures of steroids. After 6 weeks of incubation, equilibrium was reached and the films were analyzed on the content of steroid. The samples were extracted with methanol for 20 hours at a temperature of 70 °C and subsequently the concentration of steroid was assessed by HPLC.

HPLC conditions:

Column	: Novapak C18 3.9 x 150 mm
Column temperature	: 30° C
Mobile phase	: Acetonitril: water solution (30/70 v/v %)
Flow rate	: 1.5 ml/min
Injection volume	: 10 µL
Detection	: UV detection 205 nm
Apparatus	: HP 1090
Runtime	: 13 min.

2.3.2.2 Solubility in melted polymer (at elevated temperatures)

The solubility of steroids in polyethylene vinyl acetate copolymers was also determined at elevated temperatures. The micronized steroids were mixed thoroughly with ground EVA 28 in varying ratios and were stored in a furnace at different temperatures (90 to 180 °C) for several hours. The solubility of the steroids in EVA 28 was determined visually; where a clear state (absence of crystals) was interpreted as a fully dissolved situation.

2.3.2.3 Time lag method

Diffusion experiments with polymeric films were carried out in order to determine the permeability properties of the membrane polymer from the so-called "time-lag" (Baker and Lonsdale, 1974). Flat films (EVA 9) with a thickness of about 200 µm were clamped between two diffusion cells (i.e. one donor cell and one acceptor cell). The volumes of both cells were respectively 50 ml and 100 ml. While the donor cell was filled with a saturated aqueous solution of etonogestrel, the acceptor cell was filled with only water. The effective membrane surface through which the drug could diffuse was 7.067 cm^2. Both cells were maintained at a temperature of 37 °C. As a consequence of the concentration difference between the two cells, steroid molecules migrate through the membrane to the acceptor cell. After varying periods of time, samples of 0.5 ml were taken from the acceptor cell. In order to keep the cells filled, fresh water was added. Finally, the samples were analyzed by HPLC on steroid content. The diffusion of steroids through the polymeric film is dependent on the permeability of the polymer. The permeability can be calculated from the following equation:

$$P = \frac{dM_t}{dt} * \frac{d}{A}$$ *Equation 2-7*

Where:

P = permeability (kg/m·s)

$\frac{dM_t}{dt}$ = increase of steroid by the time in the acceptor cell (kg/s)

d = thickness of membrane (m)

A = area of membrane (m^2)

If the amount of steroid measured in acceptor cell is plotted against the time (time-lag curve), the ratio dM_t/dt can be calculated from the slope of the obtained regression line. In this curve the intercept with the time-axis is called the lag-time L. For L the following equation is adopted:

$$L = \frac{d^2}{6D}$$ *Equation 2-8*

Where:

L = Lag-time (s)

d = thickness of membrane (m)

D = Diffusion coefficient (m^2/s)

From the time lag curve the permeability and diffusion coefficient can be calculated using equations 2-7 and 2-8. The maximal saturation of the membrane (C_s) can be calculated from the permeability and the diffusion coefficient (Equation 2-1).

2.3.2.4 Differential Scanning Calorimetry

A Perkin Elmer differential scanning calorimetry (DSC7) apparatus was used to study the compatibility between the steroids. Open aluminum pans (50 µl) were used in order to allow removal of any residual water. The heating and cooling rates were 10 °C/min. Dry nitrogen was used as a purge gas and a cooler was used to cool below room temperature.

The mixtures were prepared in small containers (about 5 ml) and were mixed thoroughly with a small spatula.

2.3.2.5 Manufacturing of coaxial fibers

In order to study the release of steroids from the polymeric reservoir system, coaxial fibers with a diameter of 4 mm were produced with varying steroid concentrations in the core polymer. EVA 28 and EVA 9 were used respectively as core and membrane polymer. The thickness of the membrane was adjusted to 110 μm. Before manufacturing the coaxial fiber, a steroid loaded core granulate was produced by mixing micronized steroid and ground EVA 28 in the desired ratios. Subsequently, the powder mixtures were blended in a twin screw blend extruder at a temperature of 125 °C. As a consequence of the high temperatures the polymer melted and the steroids completely dissolved in the polymer. After leaving the blend extruder the strands were cooled to room temperature and granulated using a strand granulator, thereby forming steroid loaded pellets with diameter of about 2.5 mm and a length of 3 mm.

For the preparation of the coaxial fibers, a co-extrusion installation was used. The installation consists of two single screw extruders that are connected to a spinning block. The two extruders are used to melt the core and membrane polymer at temperatures above 110 °C. The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers. The thickness of the membrane polymer is determined by the ratio between rotation speeds of both pumps. Subsequently, the membrane and core polymers are combined in the spinneret, thereby forming the coaxial fiber. In order to cool the fiber to room temperature a water bath was positioned below the spinneret. The outer diameter of the fiber was measured on-line using a laser scan micrometer.

2.3.2.6 Determination of the in-vitro release rate from the coaxial fibers

An automated release control system was used to measure the in-vitro release rate of the coaxial fibers. Samples were immersed in water in 200 ml stirred containers. The temperature of the water was maintained at 37 °C. Water samples were taken every day and were analyzed on steroid content.

2.4 RESULTS AND DISCUSSION

2.4.1 Preformulation studies

2.4.1.1 Solubility in flat films

Table 2-2 depicts the solubility data for etonogestrel, ethinyl estradiol and their mixture in both EVA 28 and EVA 9 determined on polymer films at a temperature of 25 °C and 37 °C. Furthermore, the partition coefficients are calculated in order to enable prediction of the release from the coaxial fibers (Equation 2-4).

Table 2-2, The solubility and polymer/polymer partition coefficient of etonogestrel and ethinyl estradiol at 25 °C and 37 °C

	25 °C			37 °C		
	Solubility (wt.%)			Solubility (wt.%)		
Steroid	EVA 28	EVA 9	Partition Coefficient	EVA 28	EVA 9	Partition Coefficient
Etonogestrel	0.35	0.046	0.131	0.43	0.058	0.135
Ethinyl estradiol	1.23	0.093	0.076	1.67	0.124	0.075
Etonogestrel (+ Ethinyl estradiol)	0.40	0.055	0.138	0.51	0.077	0.151
Ethinyl estradiol (+ Etonogestrel)	1.46	0.095	0.065	1.71	0.128	0.075

As can be seen, the solubility of etonogestrel at 37 °C in EVA 28 and EVA 9 is respectively 0.43 wt.% and 0.058 wt.%. However, when the aqueous solution was saturated with a mixture of both etonogestrel and ethinyl estradiol, the solubility of both steroids increases. This interaction may influence the release of both steroids when the partition coefficient is also changed (Equation 2-3). Unfortunately, the effect is not very consistent. For etonogestrel, K seems to increase, while ethinyl estradiol shows a reverse tendency.

2.4.1.2 Solubility in molten polymer

Figure 2-1 plots the solubility of etonogestrel and ethinyl estradiol in EVA 28 at elevated temperatures. In this figure the solubility of etonogestrel was also determined in the presence of ethinyl estradiol in an equal molar fraction. It should be noted that for the mixture, the least soluble compound is of course the visible one, thereby determining the outcome of the measurement. In fact, this figure is a reflection of Equation 2-5. Because ethinyl estradiol has a lower heat of fusion and melting temperature, it exhibits a higher solubility in EVA 28 than etonogestrel.

Furthermore, solubility is higher when the temperature is closer to the compounds melting point. However, a less expected phenomenon is the increase in etonogestrel solubility when ethinyl estradiol is added in an equal quantity. This can be understood from thermoanalytical data, which indicate an eutectic behavior of the steroid mixture.

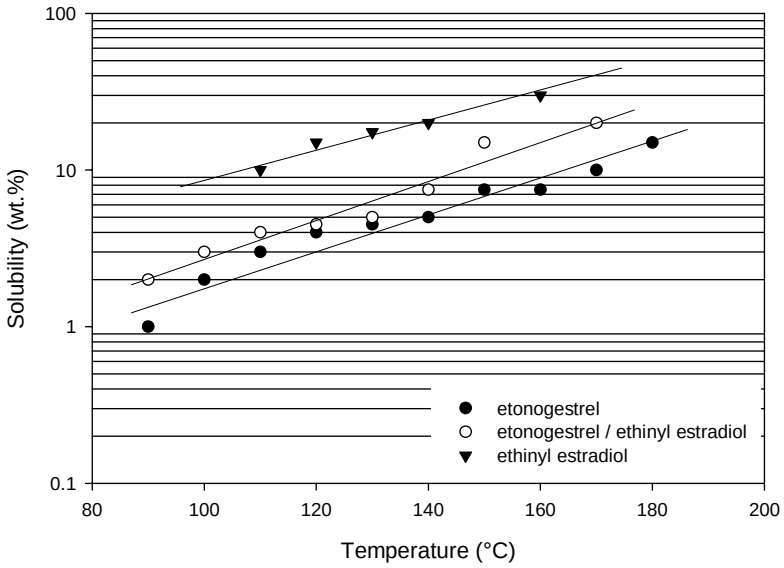

Figure 2-1, The solubility of steroids in EVA 28

Figure 2-2 shows the melting point of the steroid mixture as a function of the mixing ratio. As can be seen, the eutectic temperature, found at a ratio of 1:1, is about 50 °C lower than the individual melting points. It was also observed that the eutectic is physically stable and did not crystallize upon cooling to lower temperatures. Even upon storage at low temperatures the steroids in the eutectic did not crystallize and remained in an amorphous state. Similar behavior was observed for other mixtures of steroids used in other investigations.

Eutectic behavior of steroids in a physical mixture is a consequence of a so-called dynamic equilibrium that exists at the melting point of each steroid. When foreign molecules (another steroid) are added to this equilibrium, the crystallization of the steroid will be hindered and so the equilibrium will be disturbed. By lowering the temperature, the melting process will be diminished (i.e. shifted towards the solid phase) and so the equilibrium of the system will be reestablished.

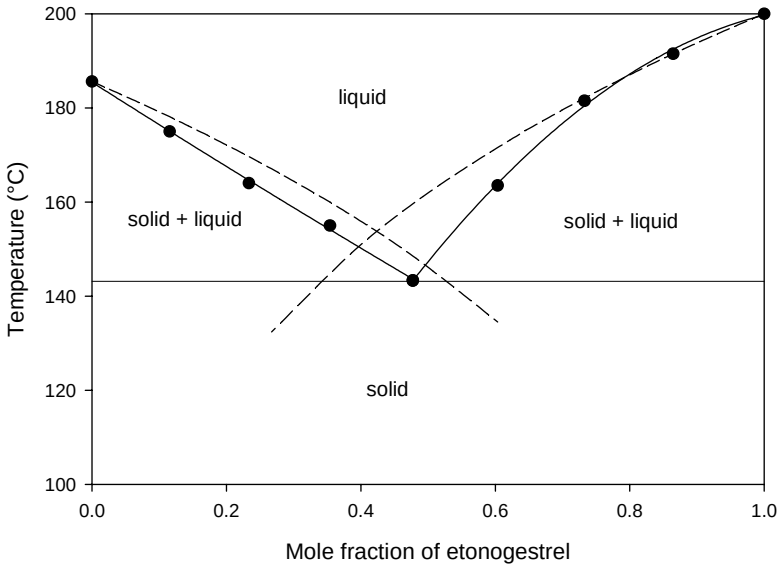

Figure 2-2, Phase diagram of etonogestrel and ethinyl estradiol; dashed lines were calculated using equation 2-9

Equation 2-5 can also be used to describe the eutectic behavior of steroid mixtures (Dorset, 1988, 1992). In order to calculate the eutectic behavior of the steroids investigated in this report, Equation 2-9 was deduced from Equation 2-5. Because the solubility parameters of the steroids investigated are almost equal (Table 2-1), the second term in Equation 2-5 will be zero.

$$T_{(A)} = -\frac{\Delta H_{f(A)} * T_{0(A)}}{2.303 * R * \log(1 - X_{(B)}) * T_{0(A)} - \Delta H_{f(A)}} \qquad \textit{Equation 2-9}$$

Where:

$T_{(A)}$ = Decreased melting point of steroid A (K)
$\Delta H_{f(A)}$ = Heat of fusion steroid A (J/mole)
$T_{0(A)}$ = Melting point of steroid A (K)
R = Gas law constant (8.314 J/mole K)
$X_{(B)}$ = Molar fraction steroid B

In Figure 2-2, Equation 2-9 is used to calculate the melting point depression between etonogestrel and ethinyl estradiol. Because the equation is meant for ideal solutions

the calculated melting point depression does not fit perfectly. Most important, however, is to realize that the lower melting point $T_{(A)}$ will result in a higher solubility in the polymer (Equation 2-5). Hence, the solubility of etonogestrel is raised in the presence of ethinyl estradiol because of the eutectic melting point depression.

2.4.1.3 Time lag method

The amount of steroid measured in the acceptor cell was plotted against time. The permeability and diffusion coefficients were calculated from the slope and intercept of the curve, using Equations 2-7 and 2-8. The maximal saturation of the membrane (C_s) was calculated from the permeability and the diffusion coefficient.
It was found that the solubility and diffusion coefficient of etonogestrel in EVA 9 was respectively 0.055 wt.% and $1.84*10^{-9}$ cm^2/s. The solubility found with the time lag method is almost equal to the value found with the saturation experiments in flat films (0.058 wt.%).

2.4.2 Formulation studies

2.4.2.1 The influence of the steroid concentration on the release

In Figure 2-3 the release of coaxial fibers with varying concentrations of etonogestrel in the core is plotted. In the first few days a higher release rate is observed. This so-called burst release is caused by release of steroid from the membrane polymer. The membrane is not loaded with steroid during production, but takes up a quantity of the compounds during storage until equilibrium according to Equation 2-4 is reached. Logically, the higher the solubility of the membrane polymer, the higher the burst. In this phase the release rate is inversely proportional to the square root of time (Narasimhan and Peppas, 1997). After some days a steady state release is achieved that can be described by Equation 2-3.
The steady state release on zero time was calculated by extrapolating the steady state release curve to t=0 and was plotted versus the concentration of etonogestrel in the core (Figure 2-3b). It can be seen that the release rate is proportional to the concentration of etonogestrel in the core. With the knowledge of the dimensions of the fiber, the product K*D can be derived from the slope of the regression line (Equation 2-3). In order to calculate the diffusion coefficient (D) the partition coefficient (K) has to be determined.

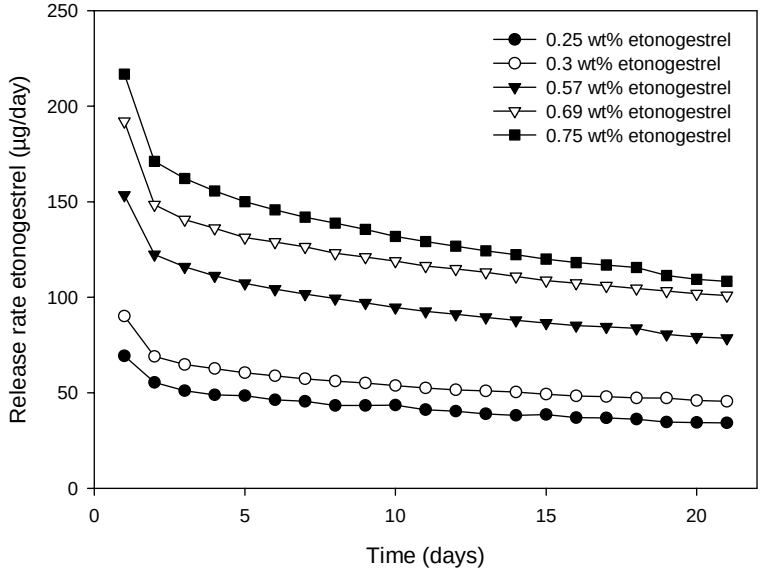

Figure 2-3a, The in-vitro release of etonogestrel at several concentrations etonogestrel

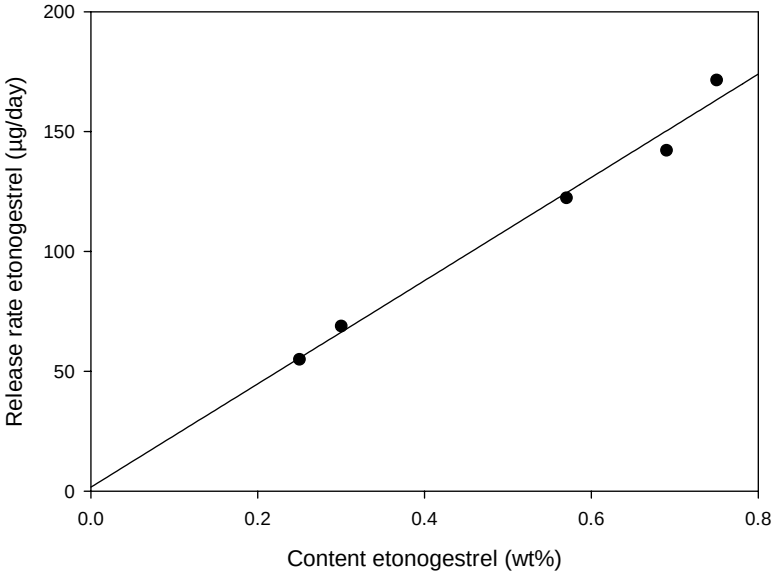

Figure 2-3b, The influence of the concentration etonogestrel in the core on the steady state release (t=0)

Since the relation between release and concentration is a straight line, it can be concluded that the diffusion coefficient in this case is independent of the concentration and that in this case indeed Fick's first law applies. This is not always true for this type of polymeric systems (Narasimhan and Peppas, 1997) and should therefore be checked.

The amount of steroid dissolved in the membrane polymer during storage can be calculated from the burst release. Because the diffusion coefficient is not influenced by the concentration, the concentration gradient in the membrane polymer will be a straight line. Under perfect sink conditions the concentration of etonogestrel at the surface of the membrane will be practically zero. By subtracting the steady state release from the burst release (integrating area on the curve) and subsequently multiplying it by two, the amount of etonogestrel that is dissolved in the membrane polymer before release can be calculated. In Figure 2-4 this amount is plotted versus the concentration of etonogestrel in the core.

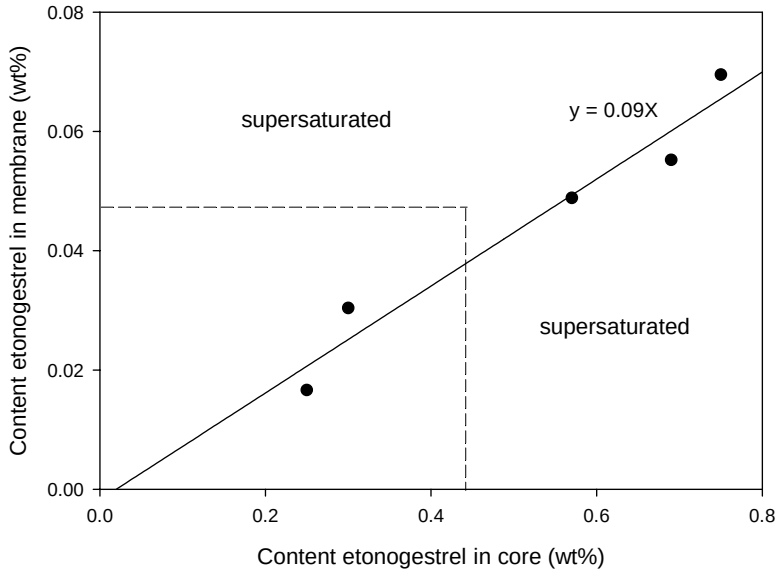

Figure 2-4, Relation between the concentration of etonogestrel in core and membrane

The partition coefficient between the membrane and core polymer can be calculated from the slope of the regression line. According to this method the partition coefficient is 0.09. This value is not exactly equal to the partition coefficient found from the solubility in flat films (i.e. 0.13). Now the diffusion coefficient can be

calculated. The value of the diffusion coefficient of etonogestrel in EVA 9 is in this case $1.54*10^{-9}$ cm^2/s, which is lower than the value found with the time lag method (i.e. $1.84*10^{-9}$ cm^2/s). It is known from literature (Johnsen and Nachtrab, 1969; Salyer and Kenyon, 1971; Brinker, 1977;) that the physical structure of EVA copolymers in terms of crystallinity, size of crystal regions etc. is influenced by the conditions of treatment (e.g. temperature) and storage (i.e. aging). It is therefore quite well possible that the polymeric structure in films is different from the structure in coaxial fibers. This needs to be investigated in subsequent studies. In 2.3.2.1. it was determined that the solubility of etonogestrel in EVA 28 and EVA 9 at a temperature of 37 °C is respectively 0.43 wt.% and 0.058 wt.%. This means that etonogestrel in both membrane and core is present in a supersaturated state for three of the five coaxial fibers.

2.4.2.2 Diffusion coefficients

The values for D and K obtained with the methods described can be used to calculate the anticipated release for a fiber with 0.69% etonogestrel and a membrane of 110 µm. Figure 2-5 shows that a reasonable estimate can be made. The curve, calculated from the data given in Figure 2-3 coincides with the actually found curve, which is in fact logical, since this figure is based on real coaxial fiber data.

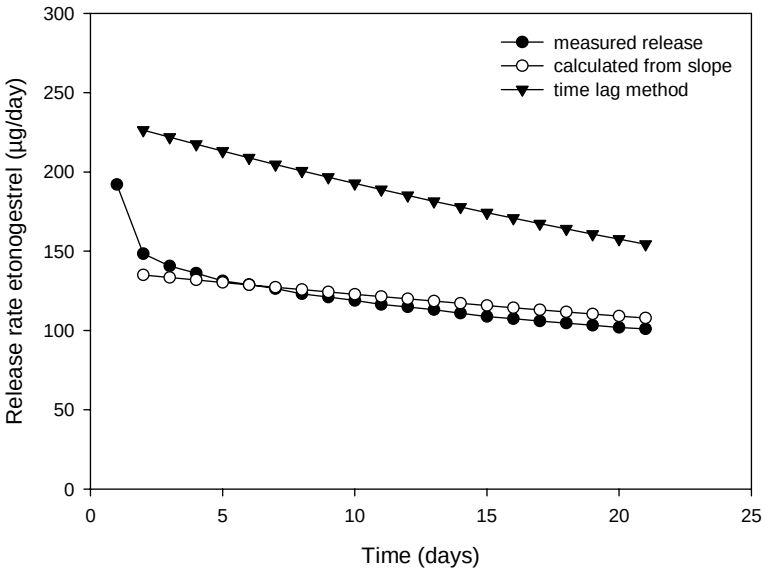

Figure 2-5, The release calculated from the diffusion coefficient obtained by the time lag method and obtained from the slope of Figure 2-3b.

When data from the pre-formulation studies are used to calculate the release, a less perfect fit is obtained. Obviously, the values of D and K are less representative for the coaxial fiber. This again points to differences in polymeric structure that may exist between the coaxial fibers and the films. Realizing that this affects solubility and permeability, it is understandable that the measurements performed with the films yield not more than estimates.

2.4.2.3 Influence of steroid interaction on the release

It was earlier shown (2.4.1.1) that the solubility of etonogestrel in polyethylene vinyl acetate polymeric films increased as a consequence of a physical interaction between etonogestrel and ethinyl estradiol. In order to study the consequences of steroid interaction on the release from a coaxial fiber, fibers were prepared with a fixed concentration of etonogestrel (0.69 wt.%) and with varying concentrations of ethinyl estradiol (0, 0.16, 0.5, 1 wt.%) in the core. As is demonstrated in Figure 2-6a, the release of etonogestrel decreases by about 13% by increasing the ethinyl estradiol content from 0% to 1%. Because the release is dependent on both diffusion and partition coefficient (Equation 2-3) it is essential to investigate the nature of the decrease.

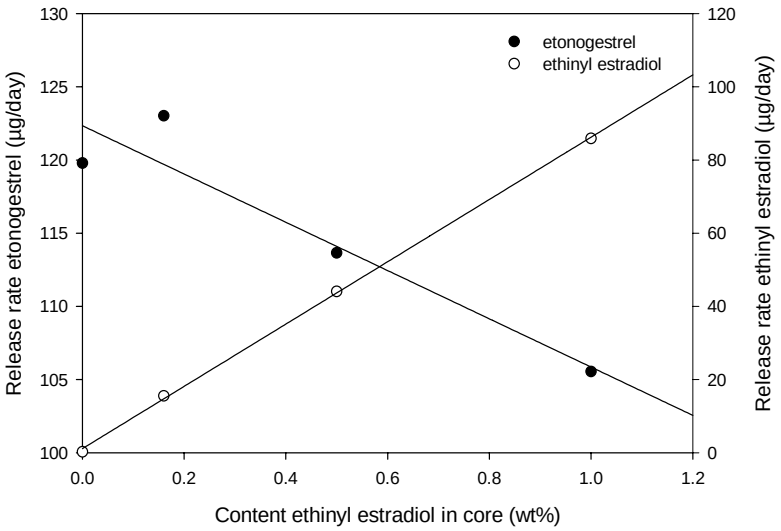

Figure 2-6a, The influence of the content ethinyl estradiol on the average release of etonogestrel and ethinyl estradiol

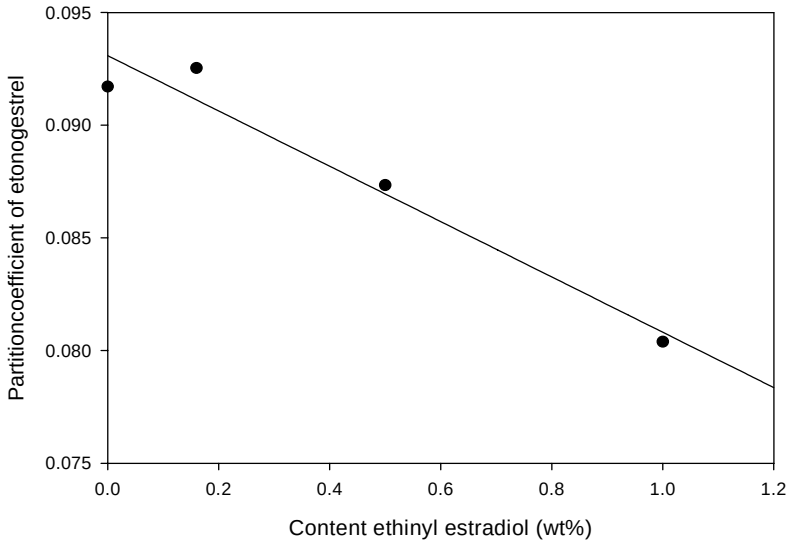

Figure 2-6b, The influence of the content ethinyl estradiol in the core on the partition coefficient of etonogestrel

Therefore, the partition coefficient of etonogestrel as a function of the ethinyl estradiol content was calculated from the burst release of the saturated membrane (same method as used in 2.4.2.1, Figure 2-4). In Figure 2-6b it can be seen that by increasing the content of ethinyl estradiol in the core, the partition coefficient of etonogestrel decreased also about 12%. This result is not in agreement with the data of the partition coefficients found during the preformulation studies with the flat film solubility's, where K showed a tendency to increase. This again seems to confirm that the polymeric structure in flat films is different from that in coaxial fibers. Therefore, it should be concluded that the solubility and diffusion coefficient data found during preformulation studies (time-lag method and solubility in flat films) should be interpreted with care.

2.5 CONCLUSION

It can be concluded from this study that polyethylene vinyl acetate copolymers exhibit suitable properties to develop a controlled release system with the two steroids etonogestrel and ethinyl estradiol. In order to design a controlled release system with specified release characteristics, values of diffusion coefficient and solubility are required. These data can either be determined during pre-formulation studies on e.g. polymeric flat films or from in-vitro release measurements of the

actual coaxial fibers. It was found that the permeability data found during the pre-formulation studies are useful in semi-quantitative terms, but deviate from the permeability data found from the in-vitro release of coaxial fibers. This is most likely due to differences in the polymeric structure between films and coaxial fibers. As a consequence, further studies should be initiated to evaluate the relationship between the manufacturing process and the resulting polymeric structure.

In literature it has been described for polymeric systems that the diffusion coefficient is mostly influenced by the concentration of the steroids. However, it was found in this study that within the investigated design this is not the case. This fact makes it possible to deduct the amount of steroid that is present in the membrane polymer by integrating the burst release. By doing so, it was found that the steroid can be present in the membrane polymer at a supersaturated level.

It was also found that the solubility and release of etonogestrel are influenced by the concentration of ethinyl estradiol. By investigating this phenomenon by thermoanalysis, it was shown that the steroids form an eutectic. The lower melting point of the steroids results in an increase in solubility and hence in altered permeability properties.

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3. EFFECT OF SUPERSATURATION AND CRYSTALLIZATION PHENOMENA ON THE RELEASE PROPERTIES OF A CONTROLLED RELEASE DEVICE BASED ON EVA COPOLYMER

Abstract

This study describes the influence of steroid concentration, manufacturing and storage on the release properties of etonogestrel from polyethylene vinyl acetate (EVA) based coaxial fibers. Coaxial fibers were manufactured by extrusion technology. As a consequence of the high extrusion temperatures large amounts of etonogestrel dissolve in the polymeric melt. Since the release from the coaxial fibers is directly proportional to the concentration gradient over the membrane, the amount of dissolved drug that recrystallizes upon cooling is of crucial importance. Therefore crystallization kinetics was studied using thermal analysis and hot stage microscopy. It was found that below a critical nucleation concentration at room temperature, etonogestrel remains in a supersaturated state. On the other hand if the amount of dissolved steroid is just above the critical nucleation concentration, the supersaturated steroid recrystallizes very slowly. It is concluded that the release of etonogestrel from an extruded coaxial fiber is a result of a complicated set of parameters, where respectively process conditions, concentration of etonogestrel and both time and temperature of storage are of importance.

J.A.H. van Laarhoven, M.A.B. Kruft and H. Vromans
Journal of Controlled Release 82 (2002) 309–317

3.1 INTRODUCTION

Extrusion technology has proven to be an elegant method for the production of controlled release reservoir systems. Based on this technology, Organon has developed two controlled release systems i.e. Implanon® and NuvaRing® (1,2). Both products are made of polyethylene vinyl acetate (EVA) copolymers. Implanon® is an implant and is designed to release a progestagen for a period of three years. NuvaRing® is a contraceptive vaginal ring, designed to release both a progestagen and an estrogen for a period of 21 days.

The concept of these systems comprises a coaxial fiber, wherein a drug is dispersed or dissolved in a core polymer. The release from these coaxial fibers depends directly on the concentration gradient over the rate limiting membrane. If the drug is present in a concentration that exceeds the saturation solubility, the gradient is determined by the saturated core. It is therefore essential to know the amount of dissolved drug and to investigate factors that may influence the solubility of a drug in the polymeric matrix.

In this paper it is demonstrated that the solubility of drug in the polymer is influenced by the temperature of the extrusion process. Typical extrusion temperatures are far below the melting point of the drug but significantly above room temperature (usually between 110-150 °C). Upon cooling of the extruded fibers, dissolved steroid may either recrystallize or remain soluble, resulting in a supersaturated state. Since the amount of dissolved steroid is directly correlated to the release properties, it is important to understand the crystallization behavior after the extrusion process. In this paper both the crystallization behavior of etonogestrel in EVA and the consequences on the release properties were investigated

3.2 MATERIALS AND METHODS

3.2.1 Materials

The steroid used in this study, etonogestrel, was obtained from Diosynth B.V. The melting temperature of etonogestrel is 199 °C. Two types of polyethylene vinyl acetate polymers were used in this study. “EVA 28” contains 28% of vinyl acetate and has a melting temperature of 80 °C. “EVA 9” contains 9 % of vinyl acetate and has a melting temperature of 100 °C. The crystallinity of both polymers is approximately 20 and 38 % respectively (3,4,5).

The molecular weights are given in Table 3-1.

Table 3-1, Molecular weights of EVA 28 and EVA 9

	M_w	M_n	M_w/ M_n
EVA 28	50000	14700	3.4
EVA 9	83500	15500	5.4

M_w = weight-average molar mass
M_n = number-average molar mass

3.2.2 Methods

3.2.2.1 Solubility in polymeric films (at low temperatures)

The interfacial partitioning of a drug molecule between a solution and a polymer is related to the solubility's in the solution (C_s) and in the polymer (C_p) as defined by the partition coefficient $K = C_s / C_p$ (6,7). By keeping the solution saturated, the polymer will also become saturated.

In order to determine the solubility of etonogestrel at low temperatures, films of EVA 28 (200 µm) were cut in pieces of 5x5 cm and subsequently immersed in saturated aqueous steroid solutions at 25 and 37 °C. In order to keep the solution saturated, an excess of crystalline steroid was added. After 6 weeks of storage, equilibrium was reached and the films were analyzed for the content of steroid. The samples were extracted with methanol for 20 hours at a temperature of 70 °C and the concentration of steroid was determined by HPLC.

HPLC conditions:

Column	: Novapak C18, 3.9 x 150 mm
Column temperature	: 30° C
Mobile phase	: Acetonitril: water solution (30/70 v/v %)
Flow rate	: 1.5 ml/min
Injection volume	: 10 µL
Detection	: UV detection, 205 nm
Apparatus	: HP 1090
Runtime	: 13 min.

3.2.2.2 Solubility in molten polymer (at elevated temperatures)

Micronized etonogestrel was mixed thoroughly with ground EVA 28 in small transparent containers in varying concentrations and were subsequently stored in an oven at distinct temperatures (90 to 180 °C). The molten mass was stirred regularly

with a spatula. In order to determine the solubility, the samples were visually inspected in time until no further change was observed. A clear state (absence of crystals) was interpreted as a fully dissolved state.
By increasing the temperature in distinct steps, the steroid in all containers finally dissolved. Subsequently all samples were cooled down to room temperature and were stored for two months at 20 °C. During storage the samples were frequently visually examined in order to study the recrystallization behavior of etonogestrel and to determine the lowest concentration at room temperature at which the steroid still seems to crystallize.

3.2.2.3 Blend extrusion

5 wt.% etonogestrel was mixed with 95 wt.% EVA 28 in a Berstorff ZE25 twin screw blend extruder. The extrudate was prepared under various process conditions. In order to prevent the dissolved steroid from recrystallization in the polymeric matrix, the extrudate was temporarily stored at –50 °C.

3.2.2.4 Hot Stage Microscopy

Hot stage microscopy was used to study the crystallization behavior of etonogestrel in EVA 28. The equipment consisted of a Jenaval light microscope and a Linkam hot plate heating/cooling system. Small coupes were cut from the extrudate described in paragraph 3.2.2.3 and examined with transmission light microscopy at various temperatures.

3.2.2.5 Scanning Electron Microscopy

In order to study the crystallization process of the supersaturated steroid in the solid structure of EVA 28, the extrudate that was produced at 105 °C and 160 °C was also examined with scanning electron microscopy. After storage at 20 °C during 1 month, coupes were cut at a temperature of –20 °C. In order to locate the position of the crystals on the surface of the coupe, the steroid crystals were removed by etching the surface of the coupes with methanol for 30 seconds. Subsequently the surface of the coupe was examined by scanning electron microscopy.

3.2.2.6 Differential Scanning Calorimetry

A Perkin Elmer differential scanning calorimetry (DSC7) apparatus was used for thermal analysis of the extrudate described paragraph in 3.2.2.3. Open aluminum pans (30 µl) were applied. The heating rate was set at 5 °C/min. Dry nitrogen was used as a purge gas and a cryogenic cooler was used to cool below room temperature.

3.2.2.7 Manufacturing of coaxial fibers

Coaxial fibers with a diameter of 4 mm were produced with steroid concentrations of 2, 3.5, 5, 10 and 20 wt.%. EVA 28 is used in core of the fiber because of the higher solubility and permeability. EVA 9 is applied in the membrane because of the lower solubility and permeability. The thickness of the membrane was adjusted to 110 µm. In order to prepare a coaxial fiber, a steroid loaded core granulate was manufactured by mixing micronized steroid and ground EVA 28 in the desired ratios. Subsequently, the powder mixtures were blended in a twin screw blend extruder (Berstorff ZE25) at a temperature of 150 °C. After leaving the blend extruder, the strands were cooled to room temperature and subsequently granulated using a Scheer strand granulator. The thereby formed pellets had a diameter of about 2.5 mm and a length of about 3 mm.

The co-extrusion installation (Plastik Maschinenbau) consists of two single screw extruders that are connected to a spinning block. The maximum extrusion temperature of the extruders was set to 145 °C. The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. The thickness of the membrane is determined by the ratio between rotation speed of both pumps. Subsequently, the membrane and core polymers are combined in a spinneret, where eventually the coaxial fiber is formed. The temperature of the spinneret was set to 110 °C.

A water bath was positioned below the spinneret in order to cool the fiber to room temperature. The outer diameter of the fiber was measured on-line using a Mitutoyo laser scan micrometer. Immediately after extrusion the fibers were stored at –50 °C, in order to maintain the physical state of the fibers. In order to investigate the influence of storage conditions on the degree of supersaturation, part of the fibers were also stored at 20, 30 and 40 °C.

3.2.2.8 Determination of the in-vitro release rate

An automated release control system was used to measure the in-vitro release rate of the coaxial fibers. The coaxial fibers were cut into pieces of 157 mm and the ends were sealed with Loctite®acrylate glue, which is impermeable for steroids. The samples were immersed in 200 ml water of 37 °C under continuous stirring (750 rpm). The steroid concentration of the release medium was determined daily by UV spectroscopy. In order to maintain sink conditions the water in the containers was refreshed daily by an auto-sampler.

In literature (8) the following model is derived to predict the release rate from a cylindrical reservoir system:

$$\frac{dM_t}{dt} = \frac{2\pi LDK\Delta C}{\ln (r_0/r_i)} \qquad \textit{Equation 3-1}$$

Where:

$\frac{dM_t}{dt}$ = Release rate (kg/s)

L = Length of the cylinder (m)

D = Diffusion coefficient membrane (m^2/s)

K = Partition coefficient between membrane and core

ΔC = Concentration gradient over the membrane (kg/m^3)

r_o = Outer radius (m)

r_i = Inner radius (=outer radius - membrane thickness) (m)

3.3 RESULTS AND DISCUSSION

3.3.1 Solubility in EVA 28

Figure 3-1 depicts the solubility of etonogestrel as a function of temperature. In this graph, data obtained from the film saturation method at low temperatures are combined with data obtained at higher temperatures in molten polymer. Remarkably, the results appear to be reasonable in line with each other, despite the fact that different approaches were applied and a phase transition (solid-melt) is present between the two data sets.

As can be seen, the solubility of etonogestrel at typical extrusion temperatures (110-150 °C) is about 10 times higher than at room temperature. This means that a considerable amount of steroid will dissolve during the extrusion process. When rapid cooling prevents the recrystallization of the excess, a supersaturated solution will result. The stability of the supersaturated solutions was investigated by assessing the transparency of samples containing various amounts of dissolved steroid after two months of storage at 20 °C. Below a concentration of about 2 wt.% etonogestrel, no crystallization was observed and the samples remained transparent. In Figure 3-1 it is shown that the saturation solubility at room temperature is only 0.35 wt.%. This

suggests that the 2% dissolved etonogestrel represents a supersaturated state at room temperature.

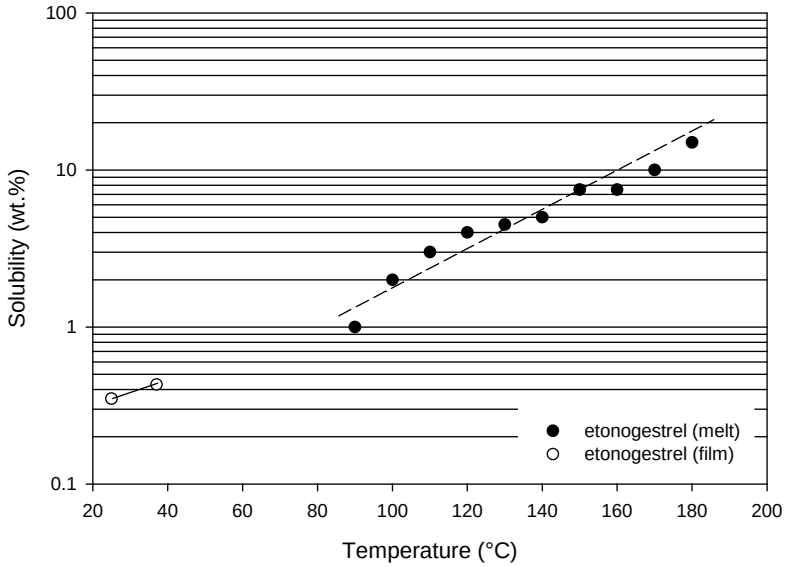

Figure 3-1, The solubility of etonogestrel in EVA 28 at both extrusion and ambient temperatures.

3.3.2 Solubility and recrystallization as a function of process parameters

Extrudate containing 5 wt.% etonogestrel and 95 wt.% EVA 28 was prepared by blend extrusion at various process conditions. As a result of the process conditions the amount of dissolved etonogestrel varied from partly dissolved at 90 °C to completely dissolved at 160 °C. At room temperature crystallization phenomena were observed within one day for the extrudate that was prepared at 160 °C. After another two days no significant changes could be observed.

It was found that the formation of crystals progressed considerably faster when the extrudate was stored at higher temperatures, most probably because of the increased mobility of the polymeric chains and steroid. While the recrystallization time at 20 °C was approximately three days, the recrystallization time at 70 °C was only 1.5 minutes.

This rapid process enables the measurement of the heat of crystallization by differential scanning calorimetry. Therefore, thin coupes were cut from the extrudate and examined by DSC from 30 to 90 °C with a rate of 5 °C/min. Hot stage

microscopy was carried out using the same temperature program in order to visualize the thermodynamic effects observed with DSC.

Because the polymer itself also has a complex melting curve, it appeared not possible to measure the small crystallization heat of steroid in the polymer directly. Therefore it was tried to determine the crystallization heat of steroid in the polymeric matrix by subtracting the melting curve of placebo EVA 28 (no crystallization of etonogestrel). In order to be used as a reference curve for all measurements, the sample was pretreated above its melting point during 2 minutes and cooled down quickly. This reference curve was normalized and subtracted from the curves of the steroid loaded samples. The resulting curve showed an exothermic peak at approximately 55 °C to 72 °C (Figure 3-2). Hot stage microscopy revealed that this peak is a result of crystallization of the steroid (see inserted photographs).

It appeared that the area of this peak varied with the amount of etonogestrel dissolved. Except for this peak the shape of the DSC curve was found to be similar for all samples. The crystallization heat of etonogestrel in the extrudate (produced at 160 °C) in which all steroid (5 wt.%) was dissolved, was approximately 2 J/g extrudate. This was determined from the area under the curve in Figure 3-2. Since the solubility of etonogestrel in EVA 28 at 70 °C can be estimated as approximately 0.7 wt.% (Figure 3-1), it is possible to deduce the solubility of etonogestrel in supersaturated extrudate produced at other process conditions.

Figure 3-3 depicts the amount of dissolved etonogestrel at zero time in EVA 28 extrudate prepared with the blend extruder at various extrusion conditions. It shows that the amount of dissolved steroid is influenced by the process conditions. By increasing the rotation speed of the screws, the amount of shear will increase and as a consequence more etonogestrel will dissolve.

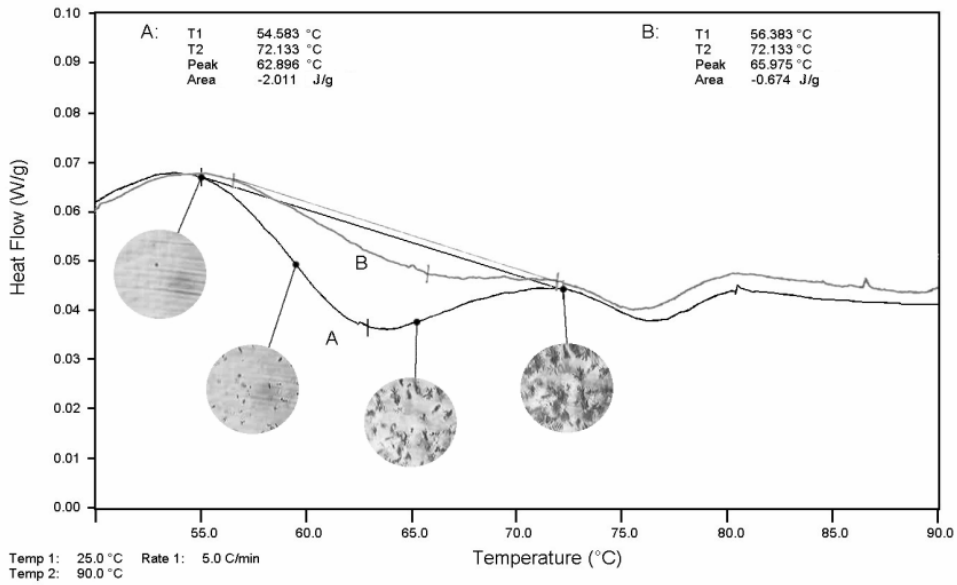

Figure 3-2; Crystallization of etonogestrel in extrudate containing 5% etonogestrel and 95% EVA 28. Samples were prepared at different extrusion temperatures (A: 160 °C and B: 105 °C). In this figure observations done with hot stage microscopy are combined with DSC measurements.

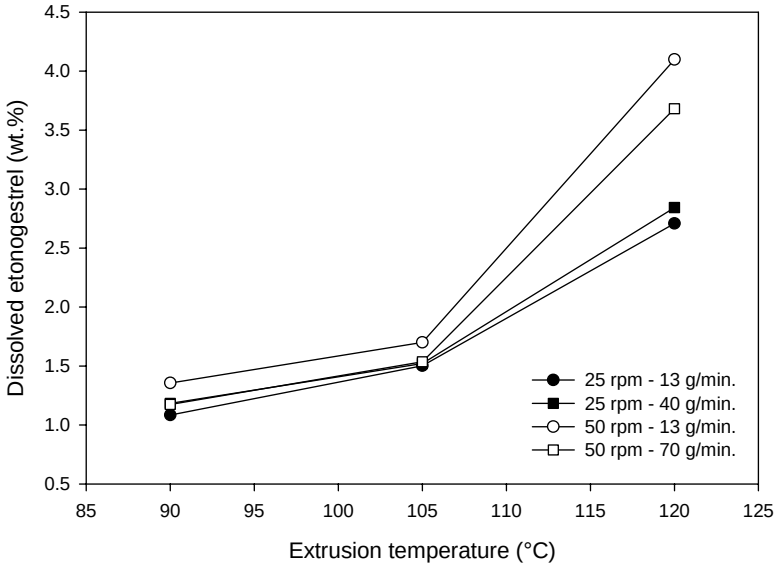

Figure 3-3, The influence of the process conditions on the amount of dissolved etonogestrel in EVA 28 during blend extrusion at various screw speed and throughput rates.

The extrudates depicted in Figure 3-3 were stored at room temperature. The amount of dissolved etonogestrel was determined after different storage times by means of DSC. Figure 3-4 shows results of the thermoanalytical measurements, where the amount of etonogestrel in solution is plotted as a function of storage time. As already was indicated, most of the supersaturated steroid recrystallizes in the first few days. However, a remaining amount of dissolved etonogestrel of approximately 1 wt.% was found for all extrudates.

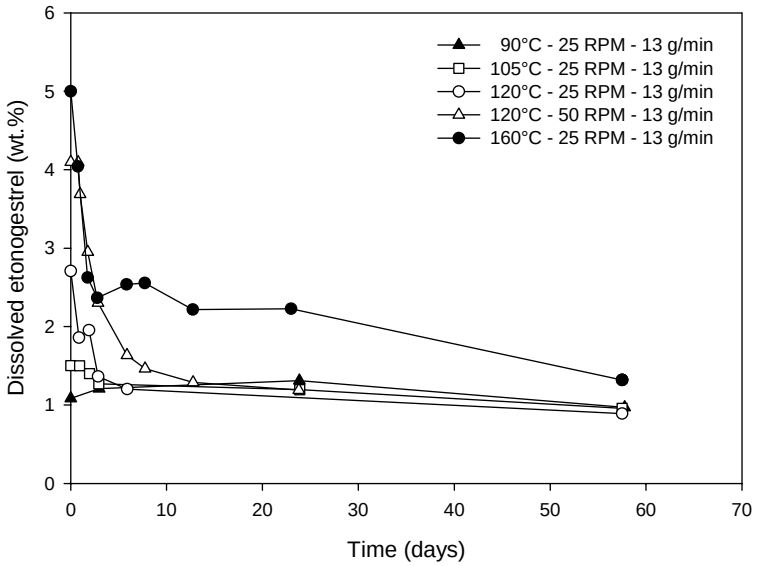

Figure 3-4, The amount of dissolved etonogestrel in extrudates containing 5% etonogestrel and 95% EVA 28 upon storage at 20 °C. The extrudates were prepared under various extrusion conditions.

This suggests that the amount of dissolved etonogestrel remains above the saturation solubility of 0.35% at 20 °C that was found in saturated flat films. If the degree of supersaturation at room temperature is defined as:

$$degree\ of\ supersaturation = \frac{concentration\ of\ dissolved\ steroid}{saturation\ solubility} \qquad \textit{Equation 3-2}$$

then the degree of supersaturation is approximately 3 (1 wt.% divided by 0.35 wt.%).

3.3.3 The influence of supersaturation and recrystallization on the release properties

According to Equation 3-1 the release rate from the coaxial fiber is directly proportional to the concentration, i.e. the amount of dissolved steroid. As a consequence the degree of supersaturation is directly reflected in the release rate.

Figure 3-5 depicts the release rate for a coaxial fiber containing 2 wt.% etonogestrel (completely dissolved during extrusion) upon storage during 7 weeks at respectively 20, 30 and 40 °C. It can be seen that the corresponding release rate from the coaxial fibers is dependent on both storage time and temperature. This is a logical result of the proceeded crystallization of the steroid. It is also obvious from the figure that all fibers exhibit a higher release rate than the one containing 0.35 wt.% etonogestrel. Since this represents the saturation solubility at 25 °C, it seems to be likely that the fibers remain to a certain degree supersaturated.

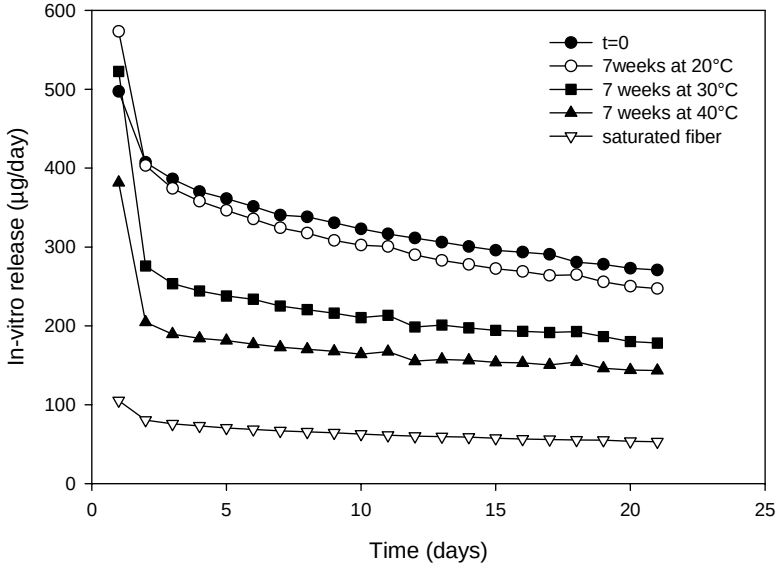

Figure 3-5, The in-vitro release of etonogestrel at 37 °C from coaxial fibers containing 2 wt.% steroid upon storage at various temperatures. The in-vitro release of a fiber containing 0.35 wt.% etonogestrel (based on the saturation solubility at 25 °C) is also plotted.

Similar experiments were performed with fibers containing different concentrations of etonogestrel. Microscopic examination on freshly prepared fibers confirmed that the steroid was dissolved in the fibers with concentrations up to 5 wt.%. The fibers

containing 10 and 20 wt.% were opalescent, indicating that only a part of the etonogestrel was dissolved.

The degree of supersaturation of several fibers was calculated by dividing the average (day 2-21) release rate by that of a saturated fiber. Figure 3-6 shows both the average steady state release rate and the degree of supersaturation upon storage at respectively 20, 30 and 40 °C versus the steroid concentration in the core. The release data of the fibers with a steroid content lower than 2 wt.% were obtained from ref. 9. The average release rate from a saturated fiber is approximately 63 µg/day.

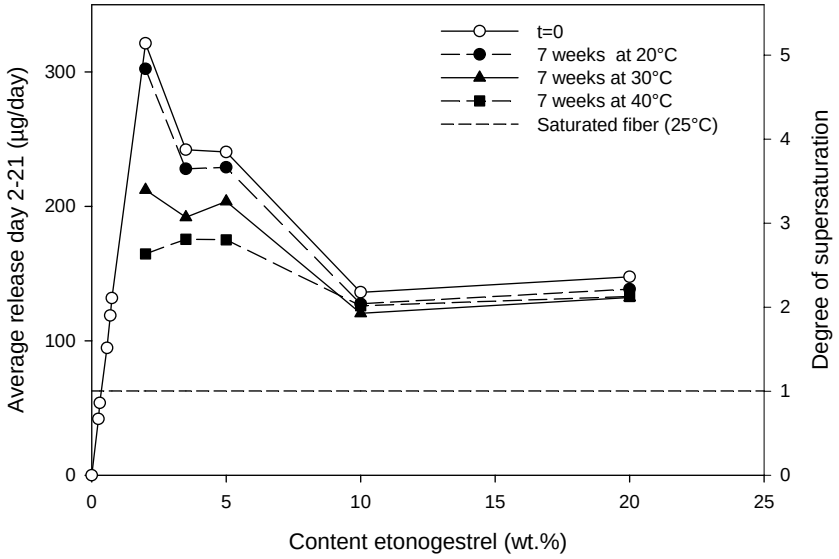

Figure 3-6, The influence of the core concentration on the average release at 37 °C upon storage at various conditions.

As can be seen, the release rate from the coaxial fiber increases with increasing steroid content in the core. However, when the amount of dissolved steroid is higher than a certain threshold, further increase in steroid concentration results in a decrease in release rate. This is attributed to crystallization. Apparently, there exists a critical nucleation concentration, where the dissolved steroid recrystallizes in the polymeric matrix. By increasing the steroid content in the core even more, the average release rate levels off to about 140 µg/day. Obviously, crystallization is facilitated in the presence of a large amount of steroid crystals. However, it can be seen that the release rate is still not equal to the release from a saturated fiber. This suggests that

the amount of dissolved etonogestrel is still in a supersaturated state (degree of supersaturation = 2). In the fibers containing 5 wt.% of steroid almost all etonogestrel dissolves during extrusion at 145 °C. For these fibers a theoretical release of about 880 µg/day is expected directly after extrusion. As can be seen the release on "t=0" is only 240 µg/day. Obviously, recrystallization already occurs during the release measurement at 37 °C.

After seven weeks storage at 20 °C the fiber had become opalescent indicating recrystallization of etonogestrel. However it can be seen that the average release rate has not changed significantly and therefore etonogestrel is still in a supersaturated state (degree of supersaturation = 3.5). This value is well in agreement with the result found earlier with the DSC measurement on the extrudate containing 5 wt.% etonogestrel.

3.3.4 Crystallization in polymer

In order to study how the supersaturated steroid has crystallized in the solid structure of the polymer, the extrudate containing 5 wt.% etonogestrel and prepared at 105 °C and 160 °C was also examined with scanning electron microscopy. In order to allow the steroid to crystallize, the extrudate was first stored at 20 °C during 1 month. Subsequently coupes were cut from the extrudate.

The coupes that were examined with scanning electron microscopy were first pretreated. The steroid on the surface of the coupe was removed by etching the surface with methanol for about 30 seconds. In this way the steroid on the surface was dissolved and as a consequence the position of the steroid crystals can be seen more easily.

In Figure 3-7 the presence of steroid crystals can be seen in the extrudate that was produced at 105 °C. At this temperature only a small fraction of the steroid was initially dissolved upon extrusion. Scanning electron microscopy (Figure 3-7b) reveals the original position of the steroid crystals that were not dissolved during the extrusion process.

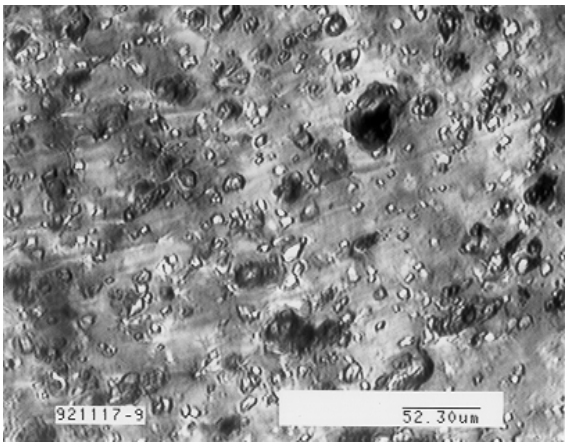

Figure 3-7a

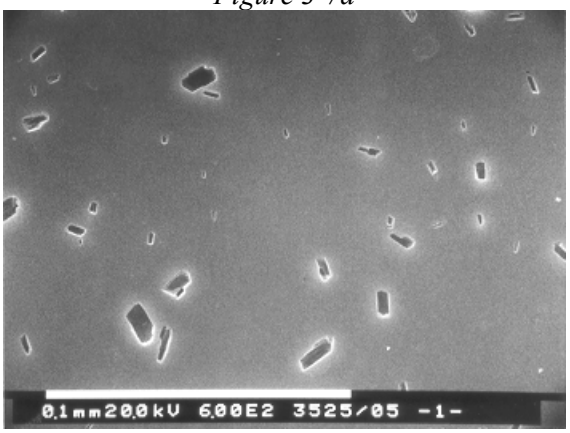

Figure 3-7b

Figure 3-7, The presence of etonogestrel crystals in the polymeric matrix after 1 month storage at 20 °C in a 5 wt.% steroid / EVA 28 mixture, prepared at extrusion temperature of 105 °C (Figure 3-7a transmission light microscopy; Figure 3-7b scanning electron microscopy).

Figure 3-8 shows the presence of steroid crystals in the extrudate that was produced at an extrusion temperature of 160 °C. Initially all steroid was dissolved due to of the higher extrusion temperature. Therefore all crystals that can be seen with transmission microscopy (Figure 3-8a) are associated with recrystallized steroid.
While a large amount of recrystallized steroid crystals can be seen with transmission light microscopy, scanning electron microscopy only reveals a few small indentations (Figure 3-8b). Therefore it can be concluded from this picture that the steroid can only recrystallize in the amorphous domains of the polymer or by pressing the polymeric matrix aside. Most probably the recrystallization of steroid in

this case is severely hindered by the polymeric matrix. As a consequence it is expected that not all supersaturated steroid will recrystallize.

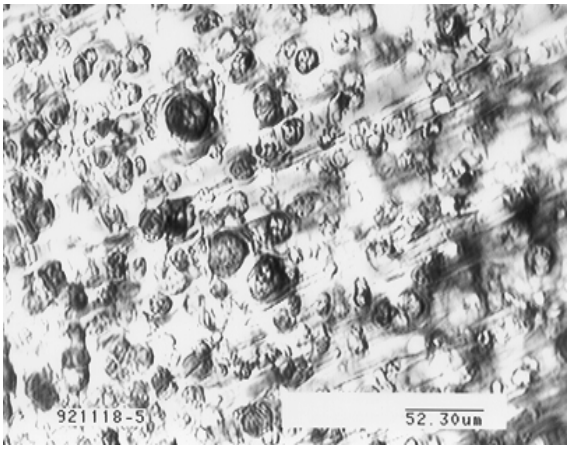

Figure 3-8 a

Figure 3-8b

Figure 3-8, The presence of recrystallized etonogestrel crystals in the polymeric matrix after storage at 20 °C for 1 month in a 5 wt.% steroid / EVA 28 mixture, prepared at extrusion temperature of 160 °C (Figure 3-8a transmission light microscopy; Figure 3-8b scanning electron microscopy).

CONCLUSION

The solubility of etonogestrel in polyethylene vinyl acetate copolymers is much higher at elevated temperature than at room temperature. Therefore considerable amounts of steroid dissolve in the polymeric melt during the manufacturing of the coaxial fibers.

If the amount of steroid in the core is completely dissolved during the extrusion process and at the same time is lower than the critical nucleation concentration, the steroid will remain in a dissolved (supersaturated) state. The release rate will be proportional to the amount of dissolved steroid. On the other hand if the amount of dissolved steroid is larger that the nucleation solubility, the major part of the dissolved steroid will crystallize gradually. The rate and the amount of steroid that will crystallize are influenced by the steroid concentration and the storage temperature. This means that the corresponding release rate from the coaxial fibers is dependent on the storage time and temperature.

The results indicate that the concentration of dissolved steroid remains higher than the saturation solubility measured at room temperature.

In conclusion, the release of etonogestrel from an extruded coaxial fiber is a result of a complicated set of parameters, where process conditions, concentration of etonogestrel and finally time and temperature of storage are of importance.

3.4 ACKNOWLEDGEMENTS

The authors would like to thank P. van Blokland of Akzo Nobel Chemicals for his contribution to the scanning electron microscopy studies.

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4. TEMPERATURE EFFECTS ON THE RELEASE PROPERTIES OF A COAXIAL CONTROLLED RELEASE DEVICE BASED ON EVA POLYMERS

Abstract

Coaxial controlled release systems were prepared by means of a co-extrusion process using various grades of polyethylene vinyl acetate (EVA) copolymers. EVA polymers are semicrystalline. The polymeric structure and permeability properties of these polymers can be adapted by varying the vinyl acetate content. Besides the vinyl acetate content, the polymeric structure is also influenced by the manufacturing method and the storage conditions.

This study investigates the influence of temperature on the release properties of EVA. It is demonstrated that the release rate of etonogestrel increases when the coaxial fibers are stored at elevated temperatures or are cooled down slowly during manufacturing. Changes in release rate are shown to be related to the size of the crystalline and amorphous domains of the polymer. The cooling rate of a membrane diminishes in radial direction. As a consequence, permeability of a membrane is not constant but increases in the radial direction. It was found that the influence of temperature on permeability of EVA decreases at lower vinyl acetate content. This is due to the lower crystallinity of these polymers.

J.A.H. van Laarhoven and H. Vromans

4.1 INTRODUCTION

Because of their suitable properties EVA copolymers have frequently been investigated for application in controlled release systems. EVA copolymers are biocompatible and do not cause inflammatory reactions. The permeability properties can be varied by adapting the vinyl acetate content (1,2). Furthermore, these polymers are flexible and offer excellent processability properties to produce various types of controlled release systems (Progestasert®, Ocusert®, Estraderm®). Based on EVA copolymers Organon developed two controlled delivery systems. Implanon® is an implant that is designed to release a progestagen for a period of three years. NuvaRing® is a contraceptive vaginal ring (3), designed to release both a progestagen and an estrogen for a period of 21 days. Both systems comprise a fiber in which a steroid is dissolved or dispersed in a core polymer that is surrounded by a release controlling membrane. In this paper the release properties of such coaxial systems are described. Various EVA copolymers were applied for the membrane.

EVA copolymers are semicrystalline and the crystallinity is determined by the vinyl acetate content (4,5,6,7,8). By increasing the vinyl acetate content the crystallization process of the polyethylene segments is hindered. As a consequence the polymeric structure of EVA polymers consists of a mixture of crystalline and amorphous regions. As the diffusion process of drugs like steroids takes place in the amorphous domains the vinyl acetate content influences the permeability properties of the polymeric matrix.

However the permeability of the polymeric matrix is not only determined by the vinyl acetate content but is also influenced by the manufacturing method and storage conditions of the final product. Depending on the process parameters, structural characteristics like size, orientation and the ratio of the crystalline and amorphous regions may vary. In ref. 9 it has been demonstrated that the release rate of etonogestrel from a coaxial controlled release device is influenced by the process conditions of the co-extrusion process. Upon leaving the spinneret the polymeric fiber expands as a consequence of the viscoelastic properties of the applied polymers. In order to obtain the desired diameter it is necessary to elongate the fiber. It was found that the polymeric structure of the membrane is orientated in axial direction as a consequence of spinline stress.

It is well known that the polymeric structure of semicrystalline polymers is also influenced by temperature effects (10,11,12,13,14). The size of both crystalline and amorphous domains increases by applying lower cooling rates upon crystallization of

the melt or by subsequent heat treatments (annealing). This paper discusses the influence of cooling rate and heat treatment on the release properties of coaxial fibers with various EVA membranes.

4.2 MATERIALS AND METHODS

4.2.1 Materials

The steroid used in this study, etonogestrel, was obtained from Diosynth B.V. The melting temperature of etonogestrel is 199 °C. Several grades of EVA polymers were used. EVA 28 contains 28% of vinyl acetate and is applied in the core of the coaxial fibers. EVA 18, EVA 14, EVA 9 and EVA 5 contain respectively 18, 14, 9 and 5% vinyl acetate and were applied in the membrane.

4.2.2 Methods

4.2.2.1 Solubility of etonogestrel in EVA at room temperature

The solubility of etonogestrel in EVA polymers at 37 °C was determined by sorption measurements; In order to study the effect of heat treatment on the solubility of etonogestrel, EVA films with a thickness of approximately 200 µm were stored in climatic rooms at various temperatures. Subsequently the films were cut in pieces of 5x5 cm and immersed in saturated aqueous steroid solutions at 37 °C. An excess of crystalline steroid was added to keep the solution saturated. After 6 weeks equilibrium was obtained and the films were removed from the solution. The surface of the films was rinsed with methanol in order to remove crystalline steroid. Subsequently the films were analyzed for the content of steroid. The samples were extracted with methanol for 20 hours at a temperature of 70 °C and subsequently the concentration of steroid was assessed by HPLC.

4.2.2.2 Differential Scanning Calorimetry

A Mettler DSC 822e differential scanning calorimetry apparatus was used to determine the melting behavior and crystallinity of the EVA polymers applied. In order to study the effect of heat treatment on the polymeric structure the EVA polymers were stored in climatic rooms at various temperatures. The DSC measurements were performed with open aluminum pans (40 µl). The thermodynamic behavior was studied from –50 to 130 °C. The heating rate applied was 10 °C/min. Dry nitrogen was used as a purge gas and a cryogenic cooler was used to cool below room temperature.

4.2.2.3 Manufacturing of coaxial fibers

Coaxial fibers were manufactured using a Plastik Maschinenbau co-extrusion installation. This equipment consists of two single screw extruders, two spinning pumps and one spinneret (Figure 4-1). A steroid loaded core polymer prepared by blend extrusion and a membrane polymer are fed to hoppers positioned on top of two extruders.

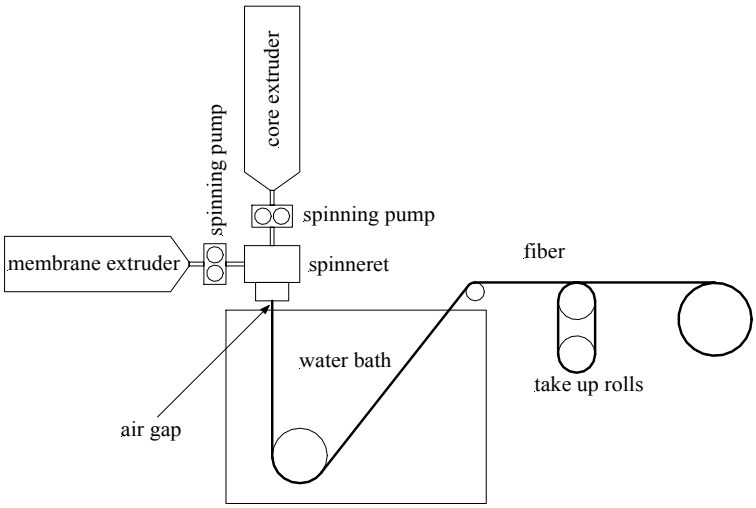


Figure 4-1, Manufacturing process of the coaxial fibers

Subsequently both polymers are melted in the two extruders and transported to the spinning pumps. The spinning pumps deliver an accurate flow of core and membrane polymer to a spinneret, where the coaxial fiber is formed. The rotation speed of the spinning pumps determines the spinning velocity, whereas the ratio between the spinning pumps determines the thickness of the membrane. Upon leaving the spinneret the fiber is elongated by means of take up rolls until the anticipated diameter is achieved. The diameter of the fiber is monitored online with a Mitutoyo laser scanner.

Finally the fiber is cooled down in a water bath which is positioned below the spinneret. All fibers described in this paper (except fibers depicted in Figure 4-9) exhibited equal dimensions. Therefore the release properties can be directly compared. The diameter and the membrane thickness of the produced fibers were respectively 4 mm and 110 µm. Etonogestrel was present in the core in a dissolved state with a concentration of 0.69 wt%. Depending on the membrane polymer applied, the extrusion temperature varied from 105 °C to120 °C.

The coaxial fibers depicted in Figure 4-9 were prepared with various membrane thicknesses (21 μm – 110 μm). Depending on the membrane thickness the fiber diameter varied from respectively 3.8 mm to 4 mm. In order to prevent depletion, crystalline etonogestrel was present in the core polymer at a concentration of 5 wt%.

4.2.2.4 Determination of the in-vitro release rate

The influence of heat treatment on the release properties of etonogestrel from the various fibers was determined. Samples were stored in climatic rooms at various temperatures. The in-vitro release rate of the coaxial fibers was then determined using an automated release control system. For this purpose the fibers were cut into pieces of 157 mm. To prevent release of etonogestrel from the open ends, the ends were sealed with Loctite®acrylate glue, which is impermeable for steroids. Subsequently the samples were immersed in 200 ml water of 37 °C under continuous stirring (750 rpm). The steroid concentration of the release medium was determined daily by UV spectroscopy. In order to maintain sink conditions the water in the containers was refreshed daily by an auto-sampler. The release from each fiber was determined in threefold. Subsequently the average release was determined.

4.3 RESULTS AND DISCUSSION

4.3.1 The influence of the vinyl acetate content on the release properties

The influence of the vinyl acetate content on the crystallinity was determined by measuring the melting enthalpy of various EVA copolymers. The crystallinity was then calculated using the following equation:

$$C = \frac{\Delta H}{\Delta H_{100\%}} * 100\% \qquad \textit{Equation 4-1}$$

Where:

C = crystallinity (%)

ΔH = heat of fusion semi-crystalline polymer (J/g)

$\Delta H_{100\%}$ = heat of fusion of the 100% crystalline polyethylene (J/g)

The heat of fusion of 100% crystalline polyethylene is 293.6 J/g (15).

Figure 4-2 depicts the crystallinity as function of vinyl acetate content. These results are well in agreement with data found in literature. In ref. 9 the crystallinity of

EVA 9 was determined by Wide Angle X-ray Scattering (WAXS) to be approximately 35%. Furthermore, it can be seen that at higher vinyl acetate content the crystallinity decreases rapidly. At a content of approximately 50% the polymer is almost fully amorphous.

Figure 4-3 depicts the difference in permeability between an EVA 5 and EVA 14 membrane. It is shown that by using a polymer with higher vinyl acetate content in the membrane the release rate of etonogestrel from the fiber is increased significantly.

According to Figure 4-2 the crystallinity of EVA 5 and EVA 14 are respectively 42% and 30%. It can be seen that this leads to a three-fold increase in the release rate of etonogestrel.

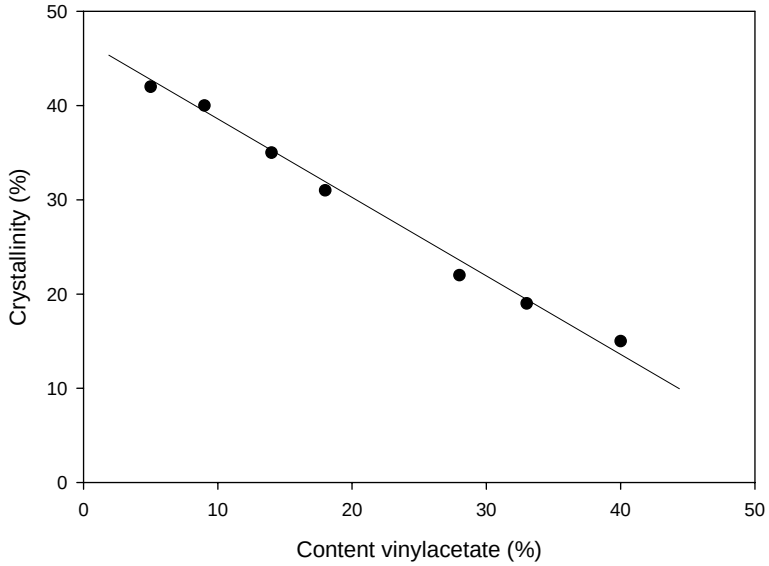


Figure 4-2, The influence of the VA content on crystallinity of EVA copolymers

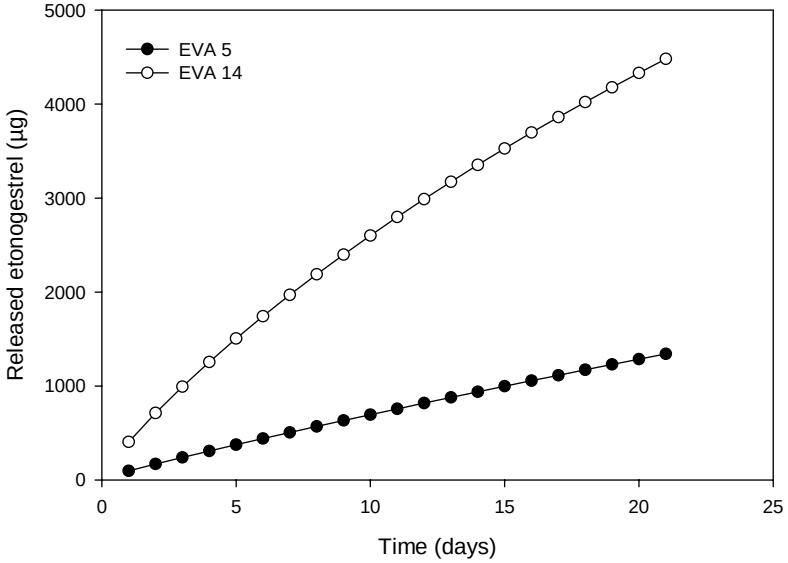


Figure 4-3, The influence of the VA content in the membrane on the release of etonogestrel from coaxial fibers

4.3.2 The influence of heat treatments on the release rate

It is well known that the polymeric structure is influenced by the cooling rate during crystallization and by heat treatment (11,12,13,14). The crystalline perfection and the size of the crystalline lamellae increase by applying slower cooling rates or by subsequent heat treatments. In Figure 4-4 thermograms are depicted of EVA 28 polymeric films that were stored during 1 day at various temperatures. In order to obtain the t=0 curve the polymer was melted and cooled down to –50 °C at a rate of 10 °C/min. Subsequently the thermodynamic behavior of the polymer was measured from –50 °C to 130 °C. It can be seen that EVA copolymers exhibit a complex melting behavior which also dependents on the storage conditions. In order to interpret these curves the Thomas-Gibbs equation can be applied (16,17,18). This equation relates the lamellae thickness (L) of a polymeric crystal to its melting point T_m.

$$T_m = T_{m\infty}(1 - \frac{2\sigma_e}{\Delta HL}) \qquad \textit{Equation 4-2}$$

Where:

$T_{m\infty}$ = Melting temperature of an ideal crystal

σ_e = Surface energy of the crystal

ΔH = Heat of fusion of the crystal

According to this equation the melting point of a polymeric crystal increases with increasing lamellae thickness or crystal size.

From the DSC measurements it can be deduced that EVA copolymers exhibit a large distribution of crystal sizes. Heat treatments result in a significant change of the polymeric structure, resulting in more perfection, characterized by larger crystals. The dashed lines represent the annealing temperature at 60 °C and 70 °C. Polymeric crystals that exhibit melting points below these temperatures are melted and/or recrystallized to larger crystals. After two days storage at elevated temperatures no changes were observed anymore. Although the melting behavior of the polymer indicates that larger and more perfect crystals are created, it is remarkable that no significant influence on the crystallinity is observed. Similar results were also obtained with other EVA grades.

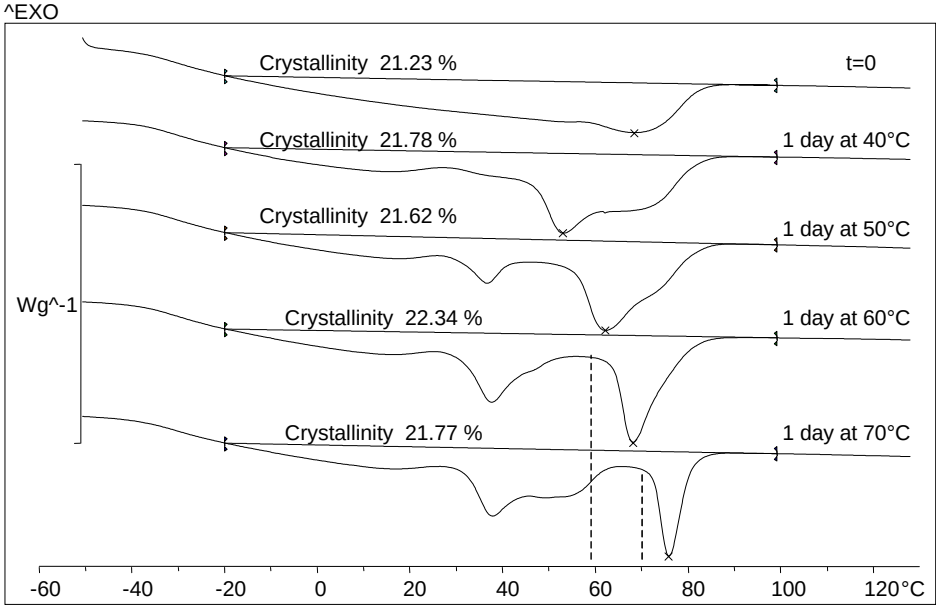


Figure 4-4, Differential scanning calorimetry measurements on EVA 28 stored at various temperatures during 1 day

It is likely that these changes in polymeric structure will also be reflected in the permeability properties of the polymer. Figure 4-5 shows that the release rate of etonogestrel from a coaxial fiber, where EVA was applied in the membrane, increases significantly with increasing annealing temperature. An increase in release rate of 40% was observed when the fibers were stored at 70 °C during 1 day.

The change in release rate was also calculated for other EVA membranes. Figure 4-6 illustrates that for all EVA membranes investigated the release rate of etonogestrel increases with elevated annealing temperature. The figure also shows that the influence of heat treatment on the permeability properties seems to be smaller with higher vinyl acetate content. Because the amount of crystalline polymer diminishes with increasing vinyl acetate content, the contribution of the crystallinity on the release properties also reduces. Therefore a larger size of the crystalline domains has less effect on the release rate.

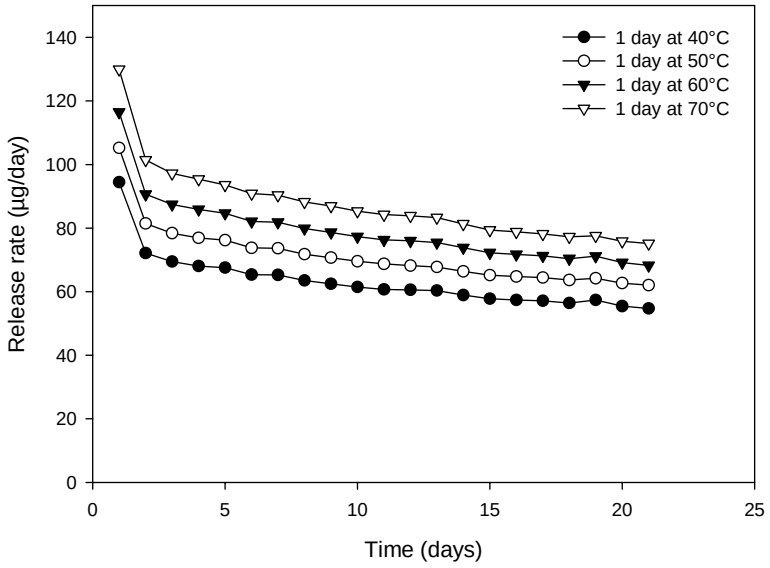


Figure 4-5, The influence of the annealing temperature on the release rate of etonogestrel from coaxial fibers (at 37 °C) with EVA 5 applied in the membrane (n=3)

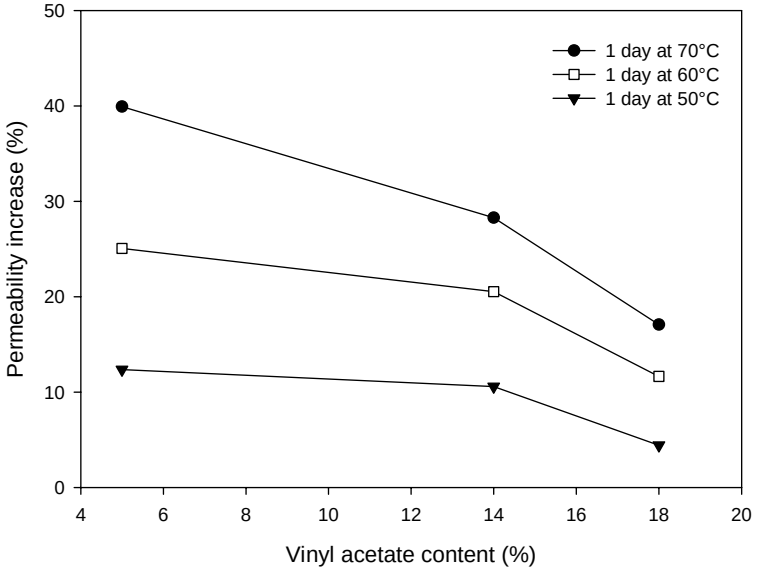


Figure 4-6, The influence of heat treatments on the permeability as a function of the VA content

The amount of steroid that can be dissolved (C_s) dependents on the crystallinity of the polymeric matrix. As already mentioned the steroid can only dissolve in the amorphous phase of the polymer. A higher crystallinity results in a smaller amount of amorphous polymer and as a consequence the polymer exhibits a lower solubility.
Films of EVA 9 and EVA 28 were stored at various temperatures during 1 day. Differential scanning calorimetry was performed to determine the crystallinity. Furthermore, the solubility of etonogestrel as a function of heat treatment was determined by sorption measurements.
It can be seen in Table 4-1 that neither crystallinity nor solubility change significantly at various annealing temperatures. The permeability of a drug through the polymer is described by $P = D * C_s$ (19). As the solubility remains constant it can be concluded that the diffusion coefficient of etonogestrel in the EVA polymer increases as a consequence of the heat treatment. In ref. 20 and 21 it is described that the diffusion coefficient D_d of a drug through a semicrystalline polymer does not only depend on the crystallinity (or volume fraction amorphous polymer) but also on the tortuosity τ, which is a measure for the variation in path length of diffusion.

$$D_d = D_a(\frac{1-V_c}{\tau}) \qquad \textit{Equation 4-3}$$

Where:

D_a = diffusion coefficient 100% amorphous polymer (m^2/s)

V_c = crystallinity or volume crystalline polymer (%)

From this equation and the data in the table it can be concluded that it must be the tortuosity that is responsible for the changes in diffusivity. Apparently the increased size of the crystalline and amorphous regions is responsible for the change in tortuosity.

Table 4-1, The influence of annealing temperature on the crystallinity and solubility of EVA 9 and EVA 28

Temperature (°C)	EVA 9		EVA 28	
	Crystallinity (%)	Solubility (%)	Crystallinity (%)	Solubility (%)
20	38.3	0.053	21.2	0.44
40	37.8	n.d.*	21.8	0.45
50	37.6	0.052	21.6	0.44
60	40.2	0.055	22.3	0.44
70	39.7	0.055	21.8	n.d.*

* not determined

4.3.3 The effect of cooling rate

Both the perfection and the size of crystals depend on the way the crystals grow. In the case of the EVA polymers it can be expected that the speed in which the molten polymer is cooled is of influence on its structure. Because the coaxial fibers are cooled down in a water bath, it is essential to study the influence of the water temperature on the release properties.

Figure 4-7 shows the effect of the water bath temperature on the release properties of the coaxial fiber. Fibers were prepared under similar process conditions but were cooled down in the bath at various water temperatures. As the coaxial fiber enters the water bath the temperature of the surface of the fiber is immediately cooled down to a new boundary temperature. This interface temperature is determined by the

physical properties of both water and polymer. This is described by the following equation:

$$\frac{T_p - T_0}{T_0 - T_w} = \sqrt{\frac{\lambda_w c_{p,w} \rho_w}{\lambda_p c_{p,p} \rho_p}} \qquad \textit{Equation 4-4}$$

Where:

T_0 = new boundary temperature (K)
T_p = initial surface temperature of the polymer (K)
T_w = temperature of the water bath (K)
λ_w , λ_p = heat transfer coefficient of water and polymer (W/m·K)
$c_{p,w}$, $c_{p,p}$ = heat capacity of water and polymer (J/kg·K)
ρ_w , ρ_p = density of water and polymer (kg/m3)

The surface temperature of the fiber before entering the water bath is approximately 110 °C. At a water bath temperature of respectively 8 °C and 55 °C the boundary temperature is respectively 28 °C and 66 °C. Logically the cooling rate of the fiber (especially at the fiber surface) increases with decreasing water bath temperature.

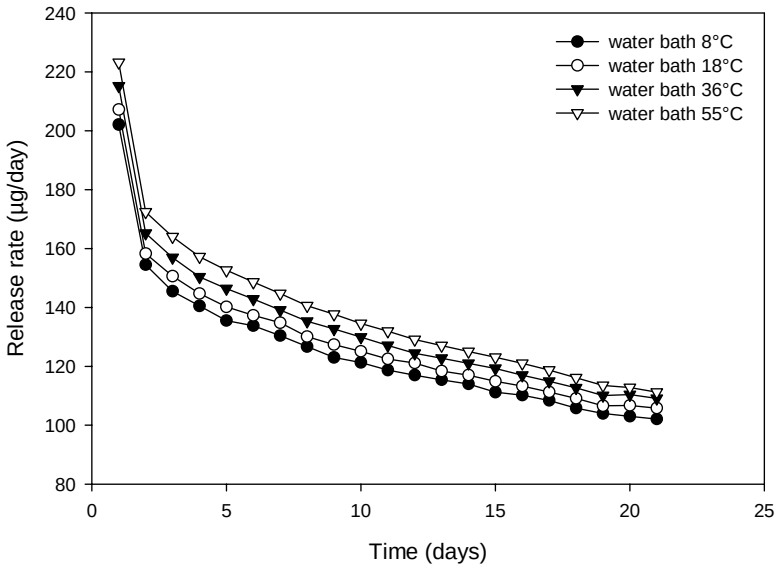
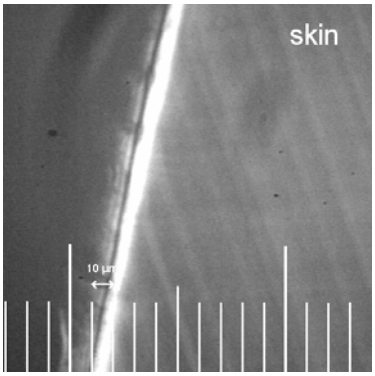
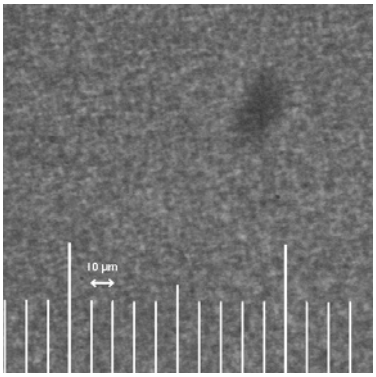


Figure 4-7, Influence of the water bath temperature on the release rate of etonogestrel from coaxial fibers (fiber diameter 4 mm, core EVA 28, membrane EVA 9 (110 µm))

It can be seen that the release rate of etonogestrel increases with rising water temperature (lower cooling rate). Again, this has to be attributed to the changes in polymeric structure. The change in structure can be measured by different methods. In previous papers we used X-ray methods as well as microscopic techniques (9). In order to visualize the effect of the cooling rate on polymeric structure of EVA 9, two extreme examples are given in Figure 4-8. On the left side, it shows the structure of EVA 9 that is cooled down rapidly (surface of the coaxial fiber). On the right side, it illustrates the structure of EVA 9 that is cooled down more slowly. In this case, large spherulitic structures can be seen, in contrast to the rapidly cooled polymeric structure at the surface of the fiber, which shows no visible polymeric structures.



EVA 9 rapidly cooled down (surface fiber)



EVA 9 slowly cooled down

Figure 4-8, The influence of cooling rate on the microstructure of EVA 9

When the fiber enters the water bath the surface of the fiber is cooled down more rapidly than the inner part of the fiber. As a consequence it is expected that the polymeric structure and permeability of the membrane varies in radial direction.
In ref. 22 the permeability of ethinyl estradiol through EVA membranes was discussed. A linear relation was demonstrated between the release rate of ethinyl estradiol (up to 15 µg/cm^2/hr) and the reciprocal of the membrane thickness.
The release rate from a cylindrical device can be described by (23):

$$\frac{dM_t}{dt} = \frac{2\pi LDK\Delta C}{\ln (r_0/r_i)}$$ *Equation 4-5*

Where:

$\frac{dM_t}{dt}$ = Release rate (kg/s)

L = Length of the cylinder (m)

D = Diffusion coefficient membrane (m^2/s)

K = Partition coefficient between membrane and core

ΔC = Concentration gradient over the membrane (kg/m^3)

r_o = Outer radius (m)

r_i = Inner radius (=outer radius - membrane thickness) (m)

If $r_i >> (r_o - r_i)$ then:

$$\frac{dM_t}{dt} \approx \frac{2\pi r_i LDK\Delta C}{(r_o - r_i)} \qquad \textit{Equation 4-6}$$

The coaxial fibers described in this report apply to these conditions. Therefore the release rate is inversely proportional to the membrane thickness.

Coaxial fibers were prepared with various thicknesses and the release rate of etonogestrel at 37°C was determined. In Figure 4-9 the measured release rate of the coaxial fibers is plotted versus the reciprocal of the membrane thickness. In the same figure the theoretical release rate (calculated with Equation 4-5) is plotted.

The figure shows that in this case the release rate is not proportional to the reciprocal of the membrane thickness and that it levels off at decreasing membrane thickness.

This suggests that the average permeability of a thin membrane (21μm) is lower than then average permeability of a thick membrane (110 μm). This can be explained by the fact that the surface of the fiber is cooled down more quickly and, in line with the previous results, exhibits a lower permeability. Polymer mass located more inside the fiber cools down more slowly and can form larger crystals.

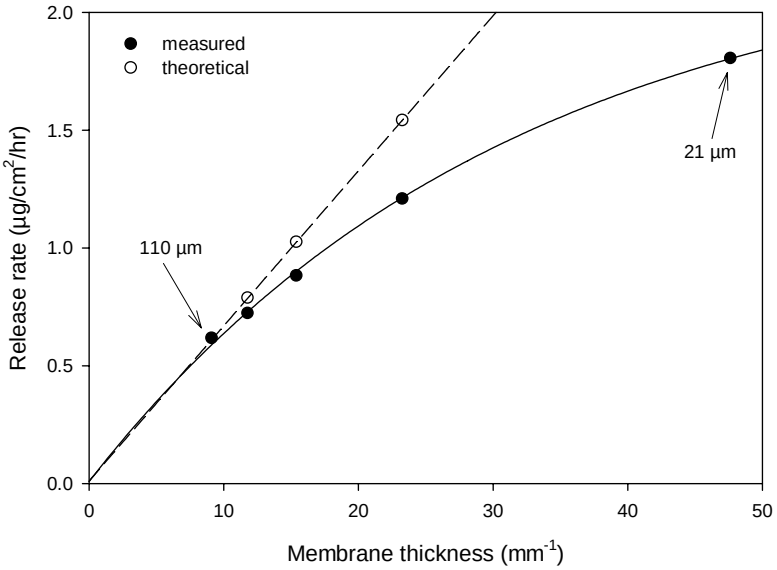


Figure 4-9, The influence of membrane thickness on the release rate (average day 2-21) of a coaxial fiber (n=3, membrane EVA 9)

4.4 CONCLUSIONS

The release rate from the coaxial fibers is determined by a complex set of variables. The crystallinity of the polymer can be adapted by varying the vinyl acetate content, resulting in a change of the permeability. The permeability properties are also influenced by the process parameters of the co-extrusion process. In ref. 9 it was demonstrated that as a consequence of spinline stress the polymeric structure was altered and as a result the permeability properties changed. It is shown in this paper that the temperature of the water bath or the storage temperature also have a significant influence on the release properties of the coaxial fiber. It was found that the release rate of etonogestrel from the coaxial fiber increases with increasing temperature of the water bath, in which the fibers are cooled down. This can be explained by the differences in cooling rate of the molten polymeric fiber. Differences in cooling rate will also result in differences in the polymeric structure of the membrane. At a lower cooling rate, the size of the crystalline and amorphous domains increases and as a result the release rate increases. Larger crystalline and amorphous domains can also be obtained by heat treatments. It is demonstrated that the release rate of etonogestrel increases, if the fibers are temporarily stored at elevated temperatures. Furthermore, it was found that the influence of temperature

decreases if an EVA membrane is applied with higher vinyl acetate content, as a result of the lower overall crystallinity.

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5. THE INFLUENCE OF THE EXTRUSION PARAMETERS ON RELEASE AND MECHANICAL PROPERTIES OF A COAXIAL CONTROLLED RELEASE DEVICE BASED ON EVA COPOLYMER

Abstract

This paper describes the influence of the process parameters on the permeability and mechanical properties of a coaxial controlled release device based on polyethylene vinyl acetate (EVA) copolymers. This device is prepared by means of a co-extrusion process where two EVA copolymers are melted and finally elongated into a coaxial fiber. The force needed to elongate the fiber is dependent on the process conditions applied. It was found that these process conditions have a significant influence on the final permeability properties of the coaxial fiber. The release rate of a drug from the coaxial fiber increases, if the fibers are manufactured at lower extrusion temperatures and smaller air gaps (the distance between die and water surface). Furthermore, a relation is demonstrated between the release properties of the fiber and mechanical properties (the elongation at break).

J.A.H. van Laarhoven and H. Vromans

5.1 INTRODUCTION

Polyethylene vinyl acetate (EVA) copolymers are often used in controlled release systems. Progestasert®, a progesterone releasing IUD marketed by the Alza Corporation, consists partly of an polyethylene vinyl acetate copolymer. Other products based on ethylene vinyl acetate copolymers are Ocusert®, an ocular delivery system (Alza Corporation), transdermal delivery systems (e.g. Estraderm® of Novartis) and Implanon®, an etonogestrel releasing implant (Organon, 1). EVA polymers are biocompatible, non-toxic and do not cause inflammatory reactions in humans. The polymers are available in a wide variety of vinyl acetate contents, making it possible to produce a tailor made dosage form based on the permeability of the EVA copolymers.

The permeability properties can be adapted by varying the amount of vinyl acetate (2,3). By increasing the amount of vinyl acetate, the crystallization process of the polyethylene segments is disturbed. As a consequence the copolymer will be less crystalline and therefore more permeable. The influence of vinyl acetate on the crystallinity of the polymer has been reported by several authors (4,5,6,7). In addition, the rheological and thermal properties of the polymers make it possible to produce concentric coaxial fibers by extrusion technology. In this paper a controlled release system is described that is manufactured from EVA polymers by means of a coaxial melt spinning process.

During the extrusion process several process parameters play an important role. It is well known from literature that the process parameters during melt spinning influence the microstructure of the polymer (8,9,10,11). As a consequence both release and mechanical properties vary. In ref. 12 it has been reported that films and coaxial fibers (both based on EVA polymers) display different permeability properties. It was suggested that this was probably due to differences in the polymeric structure. Therefore a study was initiated to investigate the influence of the process parameters on the release and mechanical properties of the coaxial fiber.

5.2 MATERIALS AND METHODS

5.2.1 Materials

The steroid used in this study, etonogestrel, was obtained from Diosynth B.V. The melting temperature of etonogestrel is 199 °C. Several types of polyethylene vinyl acetate polymers were used in this study. The permeability of polyethylene vinyl acetate polymers is dependent on the amount of vinyl acetate (2,3). EVA 28 contains 28% of vinyl acetate and is used as core material in the coaxial fibers because of the higher solubility and permeability for steroids. EVA 18, EVA 9 and EVA 5 contain respectively 18, 9 and 5% vinyl acetate and were applied in the membrane because of the lower solubility and permeability properties.

5.2.2 Methods

5.2.2.1 Manufacturing of coaxial fibers

Coaxial fibers with a diameter of 4 mm were produced with a fixed concentration of etonogestrel in the core (0.69 wt.%). For all fibers the thickness of the membrane was adjusted to 110 μm. In order to prepare a coaxial fiber, a steroid loaded core granulate was manufactured by mixing micronized steroid and ground EVA 28 in the desired ratio. Subsequently, the powder mixture was blended in a Berstorff blend extruder above the melting temperature of EVA 28. After leaving the blend extruder the strands were cooled to room temperature and granulated using a Scheer strand granulator, thereby forming steroid loaded pellets. The coaxial fibers were manufactured with a Plastik Maschinenbau coextrusion installation (Figure 5-1). The installation consists of two single screw extruders that are connected to a spinning block.

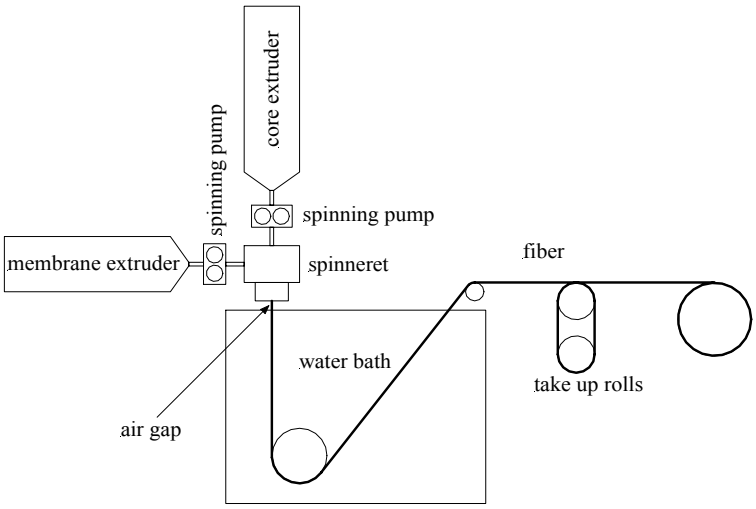


Figure 5-1, principle of the extrusion process

The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. The thickness of the membrane polymer is determined by the ratio between rotation speeds of both pumps. Subsequently, the membrane and core polymers are combined in a spinneret, thereby forming a coaxial fiber.

After leaving the spinneret, the molten polymer exhibits a die swell as a consequence of its visco-elastic properties. To obtain the anticipated diameter, the fiber is elongated in an air gap (distance between spinneret and water surface) by means of take up rolls until the desired diameter is achieved. In order to cool the fiber to room temperature a water bath was positioned below the spinneret. The outer diameter of the fiber was measured on-line using a laser scan micrometer.

In the co-extrusion process of the coaxial fiber several process parameters are of importance. These parameters are: the temperature of the spinneret, length of the air gap and the spinning velocity of the fiber. In order to investigate the influence of these parameters on the release rate of etonogestrel, coaxial fibers were prepared under various process conditions.

5.2.2.2 Determination of the in-vitro release rate

An automated release control system was used to measure the in-vitro release rate of the coaxial fibers. The coaxial fibers were cut into pieces and the ends were sealed with Loctite®acrylate glue, which is impermeable for steroids. The samples were

immersed in 200 ml water of 37 °C under continuous stirring (750 rpm). The steroid concentration in the release medium was determined daily by UV spectroscopy. In order to maintain sink conditions the water in the containers was refreshed daily by an auto-sampler.

The release from each fiber is determined in six or threefold. Subsequently the average release is calculated.

In order to predict the release rate from cylindrical reservoir system (or coaxial fiber) the following equation was used (13):

$$\frac{dM_t}{dt} = \frac{2\pi LDK\Delta C}{\ln(r_0/r_i)} \qquad \textit{Equation 5-1}$$

Where:

$\frac{dM_t}{dt}$ = Release rate (kg/s)

L = Length of the cylinder (m)

D = Diffusion coefficient (m^2/s)

K = Partition coefficient between membrane and core

ΔC = Concentration gradient over the membrane (kg/m^3)

r_o = Outer radius (m)

r_i = Inner radius (=outer radius - membrane thickness) (m)

5.2.2.3 Differential Scanning Calorimetry

The crystallinity of the EVA membranes was measured using a Mettler DSC 822e differential scanning calorimetry apparatus. The DSC measurements were performed with open aluminum pans (40 µl). The thermodynamic behavior was studied from –50 to 130 °C. The heating rate applied was 10 °C/min. Dry nitrogen was used as a purge gas and a cryogenic cooler was used to cool below room temperature.

The crystallinity was then calculated using the following equation:

$$C = \frac{\Delta H}{\Delta H_{100\%}} * 100\% \qquad \textit{Equation 5-2}$$

Where:

C = crystallinity (%)

ΔH = heat of fusion semi-crystalline polymer (J/g)

$\Delta H_{100\%}$ = heat of fusion of the 100% crystalline polyethylene (J/g)

The heat of fusion of 100% crystalline polyethylene is 293.6 J/g (14).

5.2.2.4 Mechanical properties

In order to study the mechanical properties of the fibers produced stress-strain curves were determined on the coaxial fibers using a Lloyd tensile tester. The initial fiber length was 50 mm. The fibers were deformed with a strain rate of 500 %/min (lower rates were also used, however gave similar results).

From the stress-strain curve, the elongation at beak was deduced, which is defined as:

$$\%\mathrm{EL} = \left(\frac{l_f - l_0}{l_0} \right) \times 100 \qquad \textit{Equation 5-3 (15)}$$

Where:

%EL = percentage of elongation (%)

l_f = fracture length (m)

l_0 = initial length (m)

5.3 RESULTS AND DISCUSSION

5.3.1 The influence of process parameters on release properties

Figures 5-2 and 5-3 depict the in-vitro release rate of etonogestrel from coaxial fibers that were prepared at various extrusion temperatures and air gaps. The polymer applied in the membrane is EVA 9. It is shown that the release increases with decreasing temperature and decreasing air gap. Since the dimensions of the fibers are comparable, it is obvious that the permeability and polymeric structure of the polymers used are influenced by the process parameters.

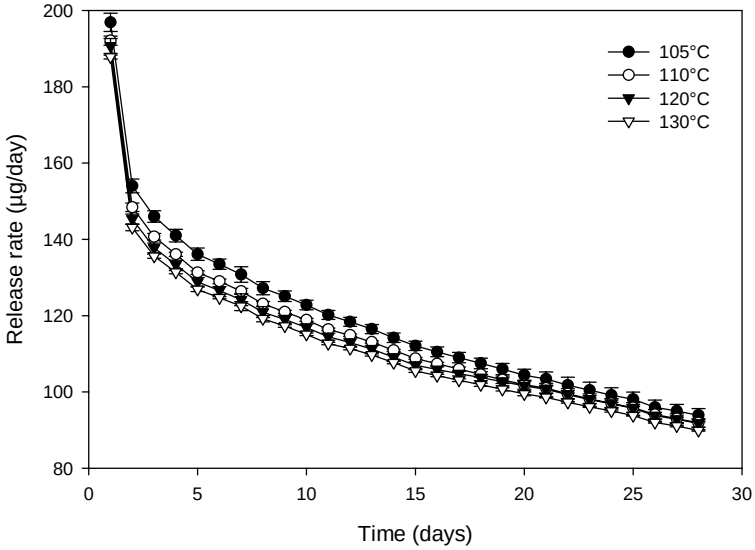


Figure 5-2, The influence of the extrusion temperature on the in-vitro release of etonogestrel from a coaxial fiber (n=6, core EVA 28, membrane EVA 9, spinning velocity 3 m/min, air gap 30 mm)

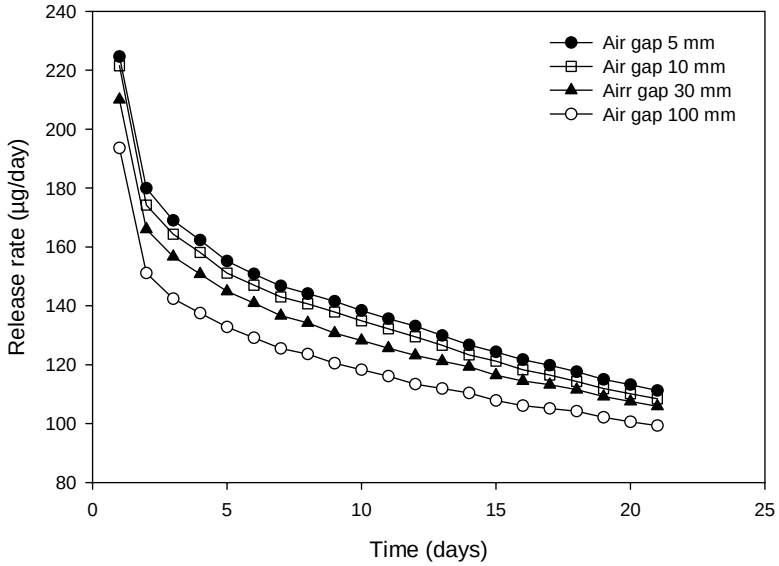


Figure 5-3, The influence of the distance between spinneret and water bath (air gap) on the in-vitro release of etonogestrel from a coaxial fiber (n=3, core EVA 28, membrane EVA 9, temperature 105 °C, spinning velocity 3 m/min)

As the coaxial fiber leaves the spinneret it expands (die swell) to a diameter larger than the anticipated diameter of the final product. Therefore it is necessary to apply a force to elongate the fiber to the desired diameter. It was observed that the force needed to elongate the coaxial fiber is dependent on the process parameters of the co-extrusion process (extrusion temperature, take up velocity, length air gap). By decreasing the temperature, the viscosity of the polymeric fiber decreases. As a consequence a larger drawing force is needed. A larger force is also needed at decreasing air gap and increasing spinning velocity.
It is often described in literature (8,9,10,11) that spinline stress during crystallization of the polymer has a pronounced influence on the microstructure of the polymer. If a high drawing force or shear is applied to the polymeric melt, the polymeric chains which are randomly distributed in the melt, are drawn and subsequently aligned in the fiber direction. Subsequently these elongated chains serve as the nuclei of a secondary crystallization where polymeric chains crystallize by chain folding perpendicular to the fiber axis. As the fiber is cooled down a polymeric structure is achieved that is characterized by a lamellae stacked structure. This phenomenon is called orientation of the polymer. In principle, the higher the spinline stress the higher the degree of orientation. This behavior is well described by Dees and Spruiell (8,9). They report the influence of stress on the structure development during melt spinning of polyethylene fibers. Under quiescent conditions (or almost no spinline stress) a spherulitic or random macro structure is obtained (Figure 1-7). By increasing the spinline stress this structure changes into a lamellae stacked structure and, at even higher spinline stress into a fibrillar structure.

5.3.2 The relation between mechanical and release properties

Because variations in the polymeric structure should also be reflected in the mechanical properties of the fiber, stress-strain curves were determined using a Lloyd tensile tester. In Figure 5-4 several curves are depicted of fibers that were prepared with various air gaps (equal fibers as presented in Figure 5-3). It is shown that the elongation at break decreases significantly with decreasing air gap.

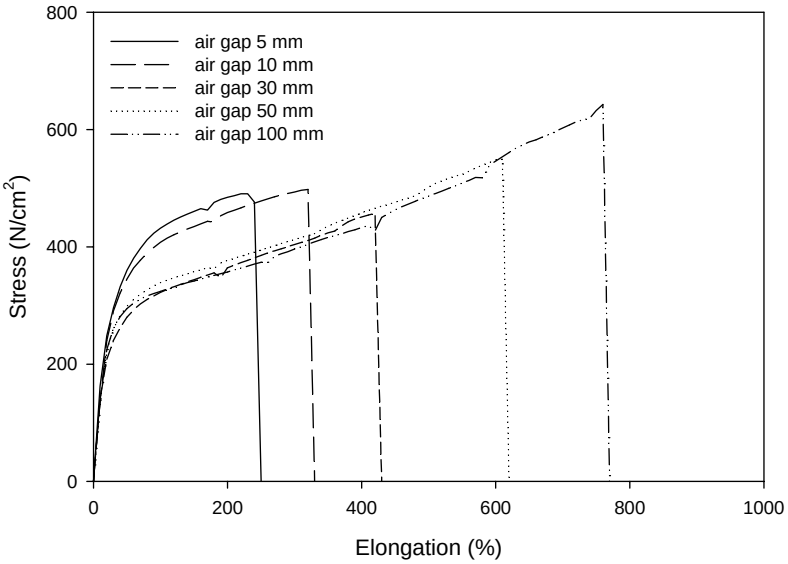
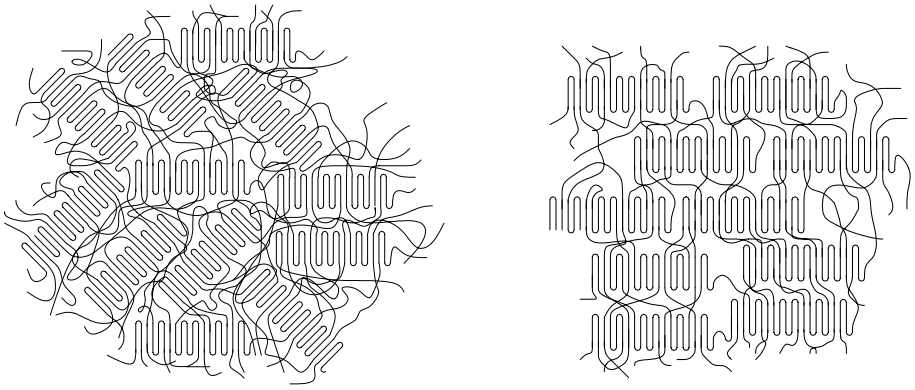


Figure 5-4, The mechanical behavior of coaxial fibers prepared with various air gaps (fiber diameter 4 mm, membrane 110 µm, core EVA 28, membrane EVA 9, temperature 105 °C, spinning velocity 3 m/min)

When the crystalline and amorphous domains of the polymer are already orientated in axial direction of the fiber this will logically also be reflected in the elongation at break. This is schematically shown in Figure 5-5. In Figure 5-5b the crystalline and amorphous domains of the polymer are orientated during the spinning process and the tie molecules between the crystalline lamellae hinder the polymeric structure from being stretched. The mechanisms involved upon stretching of EVA copolymers are well described in literature (16,17,18).

Furthermore, it can be seen that the break strength of the fibers decreases with decreasing air gap. Most probably the orientation of the polymeric structure varies in radial direction of the fiber and the outer surface of the fiber is more orientated. As a consequence the distribution of stress during the tensile measurement also varies in radial direction. This results eventually in a lower tensile strength.



a) Random non-orientated structure *b) Orientated lamellar stacked structure*

Figure 5-5, Schematic presentation of the crystalline and amorphous regions in orientated and non-orientated polymeric fibers

The influence of the process parameters during melt spinning of polyethylene fibers on the mechanical properties has also been reported by Abbott and White (11). They determined the degree of orientation by X-ray measurements and compared it to the mechanical properties. They found a direct relation between the elongation at break and the orientation factor (f_c).

In Figure 5-6 the average release rate (day 2-21) is plotted versus the elongation at break for fibers that were produced at various process conditions. Although the fibers were produced at various process conditions the figure suggests a linear relation between the release properties and the elongation at break. It is clearly demonstrated in Figure 5-2, Figure 5-3 and Figure 5-4 that that the process conditions influence the permeability and mechanical properties. Therefore a relation between release rate and mechanical properties is obvious.

It seems logical that an orientated lamellae stacked structure also exhibits anisotropic permeability properties. Probably the diffusion of etonogestrel in radial direction of the coaxial fiber increases with increasing degree of orientation and as a consequence results in a higher release rate. However further studies should be initiated to investigate the influence of spinline tension on the permeability properties of the coaxial fiber.

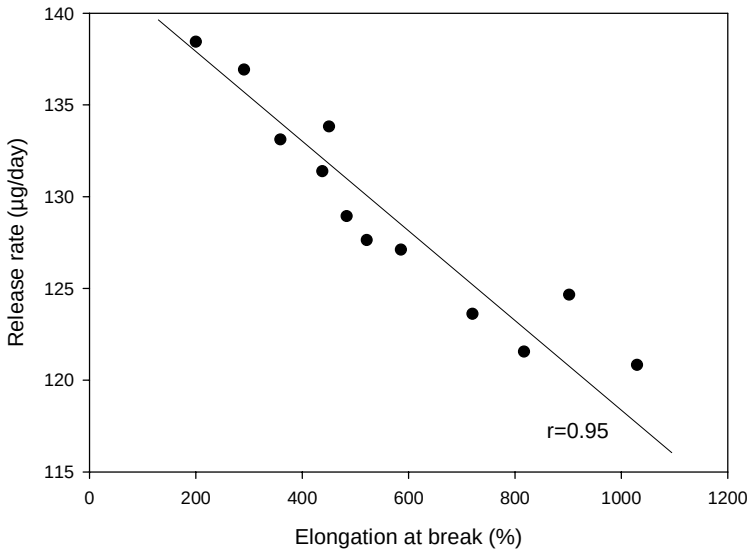


Figure 5-6, The relation between average release (day 2-21) of etonogestrel and the elongation at break of coaxial fibers produced at various process conditions (temperature, velocity, air gap); core EVA 28, membrane EVA 9.

5.3.3 Influence of the vinyl acetate content in the membrane polymer

It was demonstrated above that the process parameters have a significant influence on the release and mechanical properties of a coaxial fiber when EVA 9 was used as membrane polymer.

In order to investigate the influence of other grades of polyethylene vinyl acetate, coaxial fibers were also produced with EVA 18 and EVA 5 as membrane polymer. These fibers were prepared with comparable dimensions and were also produced at various air gaps. Figure 5-7 and Figure 5-8 depict the influence of EVA 5 and EVA 18 on the release and mechanical properties of the coaxial fibers.

Table 5-1, The crystallinity of the EVA polymers applied

Polymer	Crystallinity (%)
EVA 28	22
EVA 18	31
EVA 9	38
EVA 5	42

Because of the higher crystallinity (Table 5-1), the permeability of EVA 5 is lower than the permeability of EVA 9. As a consequence the in-vitro release of etonogestrel is also lower (Figure 5-7). The influence of the process parameters on the release and mechanical properties is comparable to EVA 9. It is shown that by decreasing the air gap (increasing spinline stress) the release of etonogestrel increases and the elongation at break decreases.

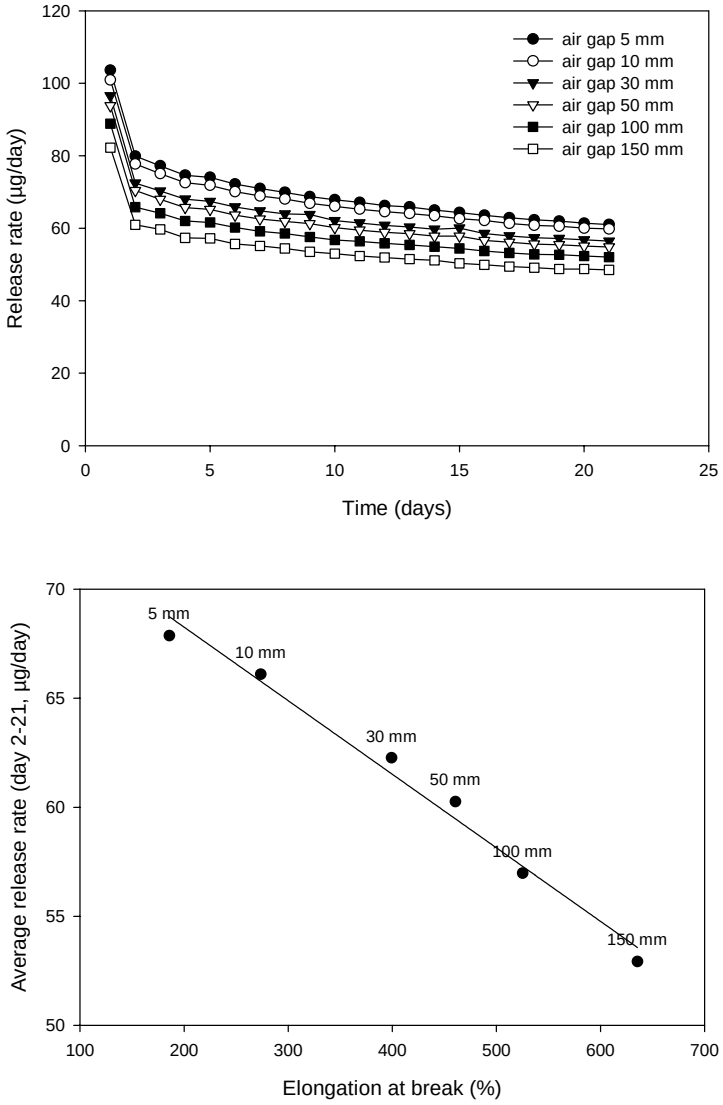


Figure 5-7, The influence of the air gap on the in-vitro release of etonogestrel and the mechanical properties of a coaxial fiber (n=3, core EVA 28, membrane EVA 5, temperature 120 °C, spinning velocity 3 m/min)

Because of a lower crystallinity, the permeability of EVA 18 is higher than the permeability of EVA 9. The corresponding release of etonogestrel is therefore also higher (Figure 5-8). Similar to EVA 5 and EVA 9 a relationship was also found between the air gap and the elongation at break. By decreasing the air gap from 150 mm to 5 mm the elongation at break decreases from approximately 1000% to 600%. This means that the polymeric structure of EVA 18 is also orientated as a consequence of the process conditions. Although an influence of the air gap can be seen on the elongation at break, no significant influence was found on the release properties. An explanation for this phenomenon is that there are less crystalline domains in EVA 18. As the diffusion of a drug takes place in the amorphous domains, orientation of the fewer crystalline domains obviously have less influence on the release properties. If on the other hand the amorphous domains are orientated (polymeric chains are elongated) a lower elongation at break is obtained. This result indicates that the influence of the process parameters on the release properties decreases with increasing vinyl acetate content in the membrane.

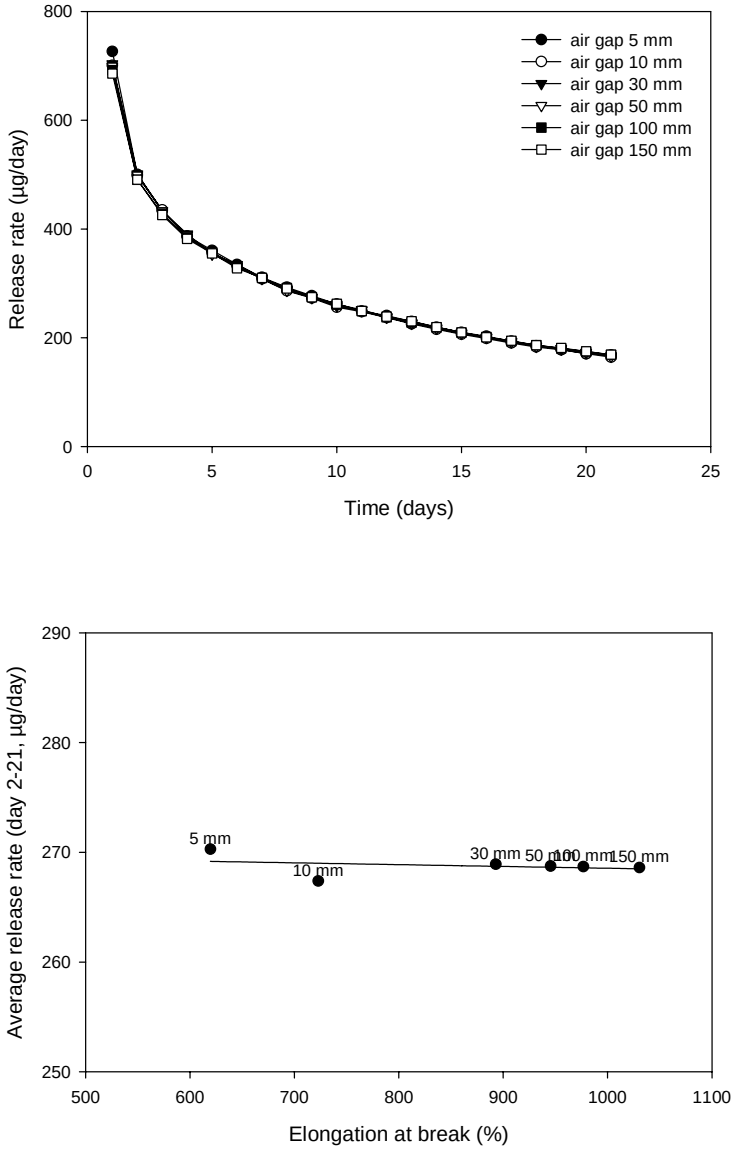


Figure 5-8, The influence of the air gap on the in-vitro release of etonogestrel and the mechanical properties of a coaxial fiber (n=3, core EVA 28, membrane EVA 18, temperature 105 °C, spinning velocity 3 m/min)

5.4 CONCLUSION

It has been extensively reported in literature, that spinline stress during melt spinning of polymeric fibers has a significant influence on the microstructure of the polymer. The degree of spinline stress during melt spinning of coaxial fiber is dependent on the process parameters (extrusion temperature, spinning velocity, length air gap etc). If a high drawing force is being applied to the polymeric melt, the polymeric structure becomes orientated in axial direction. As a consequence the mechanical properties of the fiber change.

Although the influence of spinline stress during melt spinning on the polymeric structure has been described extensively, less has been reported on the influence of spinline stress on the permeability properties of drugs in semi-crystalline polymers.

In this paper it is shown that the process parameters have an important influence on the permeability properties of a coaxial controlled release system prepared by extrusion technology. It is demonstrated that the process parameters have a significant influence on the release rate of a drug from a coaxial fiber based on EVA polymers. This influence increases with decreasing content of vinyl acetate in the membrane. It is shown that the release rate of etonogestrel from the coaxial fibers increases if the fibers are manufactured at lower extrusion temperatures and smaller air gaps. By decreasing the temperature and air gap the drawing force needed to elongate the fiber to its desired dimensions increases. As a consequence the polymeric structure is orientated in axial direction. This is also reflected in the mechanical properties of the fiber.

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6. INFLUENCE OF SPINLINE STRESS ON RELEASE PROPERTIES OF A COAXIAL CONTROLLED RELEASE DEVICE BASED ON EVA POLYMERS

Abstract

The purpose of this study was to investigate the influence of the extrusion parameters on the polymeric structure and release properties of polyethylene vinyl acetate (EVA) coaxial fibers, used for controlled release of steroids.

Coaxial fibers were prepared under various extrusion conditions. Both spinline stress and release properties were determined. The polymeric structure of the membrane was investigated with Wide Angle X-ray Scattering (WAXS).

Upon leaving the spinneret the polymeric fiber exhibits a large die swell. As a consequence, it is necessary to apply a force to draw the fiber to its desired diameter. A larger drawing force is needed at lower extrusion temperature, at a smaller air gap or at a higher spinning velocity. It was found that the release rate of a steroid from the coaxial fiber increases, when the fibers are prepared at a higher spinline stress. X-ray measurements reveal that at higher spinline stress the crystalline volume fraction of the membrane decreases. As a result of a decreasing crystallinity the permeability of the polymer increases.

It is demonstrated that the extrusion parameters and spinline stress have a significant influence on the polymeric structure of the membrane and hence the release properties. Higher spinline stress results in a higher release rate.

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Pharmaceutical Research, 21 (2004) 1811-1817

6.1 INTRODUCTION

Polyethylene vinyl acetate (EVA) copolymers are very suitable for the production of controlled release systems. In this report a controlled release system is described that is manufactured from two types of polyethylene vinyl acetate copolymers by means of a coaxial melt spinning process. With this process, coaxial fibers are obtained that can be used for controlled release of steroids. Because the release from this type of systems is influenced by the polymeric structure, it is essential to investigate the parameters that affect the polymeric structure.

The properties of the polymer can be adapted by varying the amount of vinyl acetate (1,2,3). By increasing the amount of vinyl acetate, the crystallization process of the polyethylene segments is disturbed. As a consequence the copolymer becomes less crystalline and therefore more permeable (4,5).

The polymeric structure of the fiber is also influenced by the process parameters of the melt spinning process. During the melt spinning process the polymer emerges from the die into an extensional flow field (or shear free flow). The velocity profile changes from a parabolic profile in the die to a flat profile in the extensional flow field. Several authors have described the mechanics of steady spinning of both Newtonian and non-Newtonian melts (6,7). As a consequence of the viscoelastic properties of the polymer, the polymeric fiber expands to a diameter larger than the diameter of the die. In order to achieve a fiber diameter that is smaller than the die swell it is necessary to apply a drawing force. Crystallization kinetics of a polymer under these circumstances can be quite different than under quiescent conditions. Ziabicki and Kedzierska (8,9,10,11,12) studied the influence of spinline stress on the polymeric orientation of polyethylene. Other authors (13,14,15) used wide-angle and small-angle X-ray diffraction and other measurements to study the influence of the process parameters on the structure development during melt spinning of polypropylene and polyethylene fibers.

Although the influence of process parameters on the polymeric structure during the melt spinning process has been investigated extensively, the influence on the release properties of a controlled release system prepared by this process has received less attention. In ref. 16 it has been reported that films and coaxial fibers based on EVA polymers displayed different permeability properties. It was suggested that this was probably due to differences in the polymeric structure.

The aim of this paper is to discuss the influence of the process parameters and spinline stress during the melt spinning process on the release properties of a steroid from a coaxial fiber.

6.2 THEORETICAL BACKGROUND

The principle of a reservoir system is that the drug is incorporated in a bulk polymer that is surrounded by a permeable membrane polymer. As a consequence of the concentration difference over the membrane, the drug that is dissolved in the core will diffuse through the membrane. The diffusion rate is dependent on the concentration in the core, the partition coefficient between core and membrane, the thickness and surface area of the membrane and the diffusion coefficient of the drug in the membrane. In order to achieve a constant release profile the permeability of the core polymer should be much higher than the permeability of the membrane polymer.

In order to predict the release rate from a cylindrical reservoir system (or coaxial fiber) the following model was derived from literature (17):

$$\frac{dM_t}{dt} = \frac{2\pi LDK\Delta C}{\ln (r_0/r_i)} \qquad \textit{Equation 6-1}$$

Where:

$\frac{dM_t}{dt}$ = Release rate (kg/s)

L = Length of the cylinder (m)

D = Diffusion coefficient of the drug in the membrane (m^2/s)

K = Partition coefficient between membrane and core ($K = C_{membrane}/C_{core}$)

ΔC = Concentration gradient over the membrane (kg/m^3)

r_o = Outer radius (m)

r_i = Inner radius (=outer radius - membrane thickness) (m)

The fibers described in this report are prepared by a melt spinning process. Both membrane and core polymer are melted and pumped to a spinneret. Upon leaving the die, the fiber expands to certain diameter (die swell) as a consequence of the viscoelastic behavior (18) of both polymers (Figure 6-1).

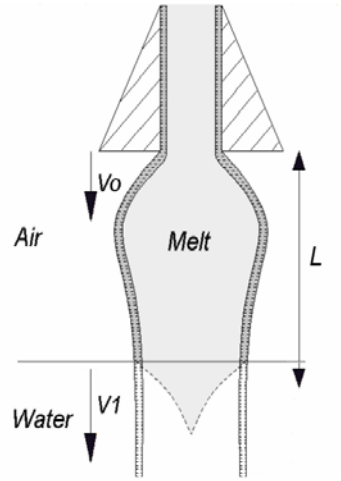


Figure 6-1, The rheological behavior of the coaxial fiber in the air gap and water bath.

If the die swell results in a fiber diameter larger than the anticipated diameter, it is necessary to apply a force in order to draw the fiber to the desired diameter. Immediately after leaving the die, the coaxial fiber is cooled in an air gap and subsequently in a water bath. Because the air gap applied in this study is relatively small (5 to 150 mm) the fiber will finally solidify at a short distance below the water surface.

During the melt spinning process several forces are involved. The most significant forces are the rheological force and the force needed to draw the fiber through the water bath (resistance transport wheels, bending force fiber etc.). In this report only the rheological force (or drawing force) is considered because of its influence on the polymeric structure of the fiber.

At a certain distance z from the spinneret, the stress (σ_z) on a cross sectional area (A_z) of the fiber is:

$$\sigma_z = \frac{F_{rheo}}{A_z} \qquad \textit{Equation 6-2}$$

The relation between stress and the deformation of the fiber at a certain point z from the spinneret is described by:

$$\sigma_z = \eta_{e*}\dot{\varepsilon} = \eta_e * \frac{dv_z}{dz}$$ *Equation 6-3*

Where:

η_e = elongational viscosity (Pa·s)

$\dot{\varepsilon}$ = elongational rate (1/s)

v_z = fiber velocity at distance z (m/s)

By adding the volume flow ($Q = v_z * A_z$) and considering the boundary conditions the following relation can be deduced from Equation 6-2 and 6-3 (12):

$$F_{rheo} = \frac{Q\eta_e \ln\left(\frac{v_1}{v_0}\right)}{L}$$ *Equation 6-4*

Where:

F_{rheo} = rheological force (N)

Q = volume flow (m^3/s)

v_1 = fiber velocity fiber at distance $z = L$ (take up velocity) (m/s)

v_0 = fiber velocity fiber at distance $z = 0$ (velocity fiber at maximum die swell) (m/s)

L = drawing distance (m)

6.3 MATERIALS AND METHODS

6.3.1 Materials

Etonogestrel, as obtained from Diosynth B.V, was used as a model steroid. The melting temperature of etonogestrel is 199 °C. Two types of polyethylene vinyl acetate polymers were used in this study. Both EVA 28 and EVA 9 are random copolymers and have a melting temperature of respectively 80 and 100 °C. EVA 28 contains 28 wt% vinyl acetate and is used as core material in the coaxial fiber because of the higher permeability. EVA 9 contains 9 wt% vinyl acetate and is applied in the membrane because of the lower permeability properties. The crystallinity of both polymers is about 20 and 38%, respectively (1,2,3). The molecular weights are given in Table 6-1.

Table 6-1, Molecular weights of EVA 28 and EVA 9

	M_w	M_n	M_w/ M_n
EVA 28	50000	14700	3.4
EVA 9	83500	15500	5.4

M_w = weight-average molar mass
M_n = number-average molar mass

6.3.2 Methods

6.3.2.1 Manufacturing of coaxial fibers

Coaxial fibers with a diameter of 4 mm were produced with a fixed concentration of etonogestrel in the core (0.69 wt.%). The thickness of the membrane was adjusted to 110 µm. In order to prepare a coaxial fiber, a steroid loaded core granulate was manufactured by mixing micronized steroid and ground EVA 28 in the desired ratio. Subsequently, the powder mixture was blended in a Berstorff ZE25 blend extruder at a temperature of 120 °C. After leaving the blend extruder the strands were cooled to room temperature and granulated using a Scheer strand granulator, thereby forming steroid loaded pellets.

The coaxial fibers were prepared with a Plastik Maschinenbau extrusion installation that consists of two single screw extruders that are connected to a spinning block. The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. The thickness of the membrane polymer is determined by the ratio between rotation speeds of both pumps. Subsequently, the membrane and core polymers are combined in a spinneret, thereby forming a coaxial fiber. The diameter of the die was 3.6 mm. In order to cool the fiber to room temperature a water bath was positioned below the spinneret. The outer diameter of the fiber after the water bath was measured on-line using a Mitutoyo laser scan micrometer. The fibers were prepared under various process conditions i.e. extrusion temperature, air gap and spinning velocity.

6.3.2.2 Determination of the fiber diameter in the air gap and below the water surface

The diameter of the coaxial fiber in the air gap and below the water surface was determined using a digital camera. By moving the camera in a vertical direction, digital pictures were made of the fiber at various distances from the spinneret. The

exact diameter was determined by enlarging these pictures and measuring the dimensions of the fiber. A reference was used with a diameter of 4.0 mm. In order to examine the diameter of the fiber below the water surface a small window was mounted in the wall of the water bath.

6.3.2.3 Determination of the drawing force

The drawing force needed to draw the fiber to its desired diameter, was determined using a Schmidt tension meter.

6.3.2.4 Polarized light microscopy

A Jenaval light microscope was used to examine differences in the polymeric structure of the coaxial fibers. Small coupes were cut from the fibers and were examined by polarized light microscopy.

6.3.2.5 Determination of the in-vitro release rate

An automated release control system was used to measure the in-vitro release rate of the coaxial fibers. Samples were cut from the fibers (157 mm) and the ends were sealed with Loctite®acrylate glue, which is impermeable for steroids. The samples were immersed in 200 ml water of 37 °C under continuous stirring (750 rpm). The steroid concentration of the release medium was determined daily by HPLC, using a Novapak C18 column of 3.9 x 150 mm at column temperature of 30°C, a mobile phase of acetonitril:water (30/70 v/v%), a flow rate of 1.5 ml/min and an injection volume of 10 µl. Detection was carried out by UV detection at 205 nm.
In order to maintain sink conditions, the water in the containers was refreshed daily. Typical release curves from these fibers have been reported in a previous study (16). On the first day a burst release is observed that is followed by a gradual decrease in release rate. In order to study the effect of spinline stress on the release properties of the coaxial fiber average release rates were calculated (day 2-21).

6.3.2.6 Wide Angle X-ray Scattering (WAXS)

The polymeric structure of both core and membrane polymer as a function of process parameters was investigated with Wide Angle X-ray Scattering (WAXS). The measurements were performed using a Philips X'pert-diffractometer. Because no differences were observed in the polymeric structure of the core polymer, the investigation was focused on the membrane polymer. Slices of membrane polymer of about 100 µm were cut from the fiber in axial direction. Two separate parallel layers of membrane slices were placed on both sides of an X-ray sample holder.

Subsequently the polymeric structure of the membrane was investigated with both mapping (a compilation of radial scans with varying azimuthal angle) and azimuthal scans.

For the azimuthal scans the detector angle 2θ was set at 21.3°, being the maximum intensity of the [110] reflection of the unit cell of the polyethylene crystals. The sample was set at θ = 10.65°. Subsequently the sample was rotated between φ = -90° and φ = 90°. The angle φ = 0° corresponded to the direction parallel to the fiber axis. For each sample four azimuthal scans were made each with a different position of the sample holder. From these four scans an average azimuthal scan was calculated.

For the mapping scans, the azimuthal angle was initially set at φ = -90° while the detector angle 2θ was programmed from 8° to 32°. Hereafter the azimuthal angle was increased 5° and another radial scan was performed. This was repeated for 36 times so that radial scans at 37 different azimuthal angles (from -90° till 90°) with 5° intervals were performed.

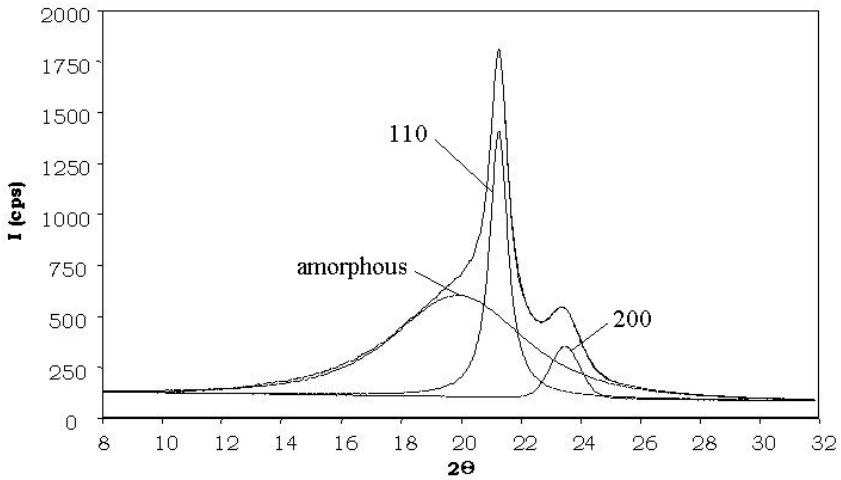


Figure 6-2, Typical radial scan of the EVA 9 membrane

The diffractograms were fitted using Pearson VII functions (Figure 6-2). The diffraction pattern is composed of reflections of the crystalline [110] and [200] planes and of an amorphous contribution. By determining the surface area of the [110], [200] and amorphous contribution the crystalline volume fractions (V_c) were calculated using following equation.

$$V_c = \frac{\sum A_{110} + A_{200}}{\sum A_a + A_{110} + A_{200}}$$ *Equation 6-5*

Where:

A_{110} = Area [110] peak

A_{200} = Area [200] peak

A_a = Area amorphous peak

6.4 RESULTS AND DISCUSSION

6.4.1 The influence of process parameters on the drawing force

In order to determine the die swell, the fiber was allowed to flow freely out of the spinneret into the water bath. The fiber diameter was measured afterwards. The diameter of the die was 3.6 mm. In Table 6-2 typical die swell values of the coaxial fiber are given for an extrusion temperature of 105 °C. In the presence of the membrane polymer, which is about three times more viscous than the core polymer, the die swell of the coaxial fiber is enhanced significantly.

Table 6-2, The die swell upon freely leaving the die (∅ 3.6 mm) at 105 °C (n=3).

Spinning velocity (m/min.)	core + skin (mm)	core only (mm)
1	6.7	5.6
3	6.8	5.3

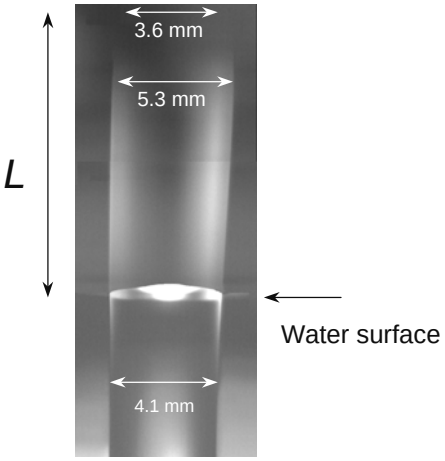


Figure 6-3, Compilated picture of the fiber diameter in the air gap

In order to achieve a desired fiber diameter of 4 mm it is necessary to apply a drawing force. In Figure 6-3 an overall picture (compilation of three pictures) of the coaxial fiber between spinneret and water surface is shown. Similar pictures were prepared under various process conditions. By determining the fiber diameter from these pictures Figure 6-4 was obtained. Here the fiber diameter between spinneret and water surface is plotted as a function of distance from the spinneret. The extrusion temperature and

spinning velocity were respectively 105 °C and 3 m/min. Each curve is associated with a different air gap. The last point of each curve indicates the diameter of the fiber upon entering the water surface.

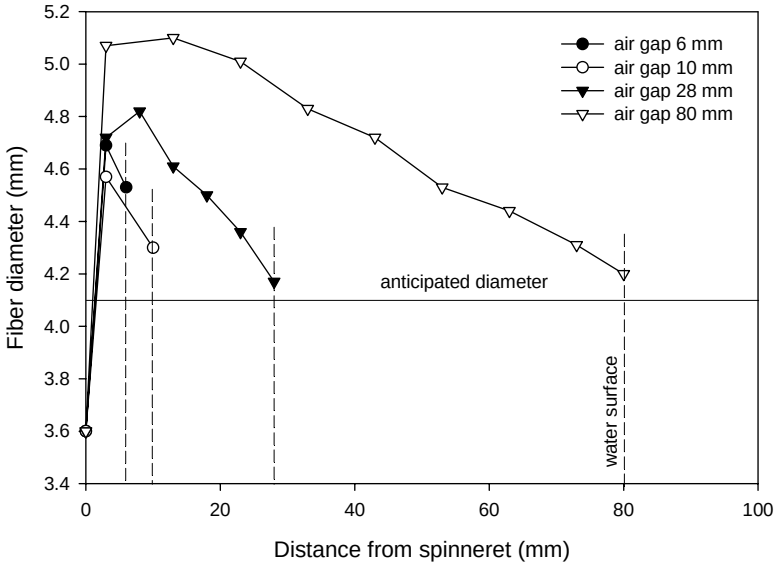
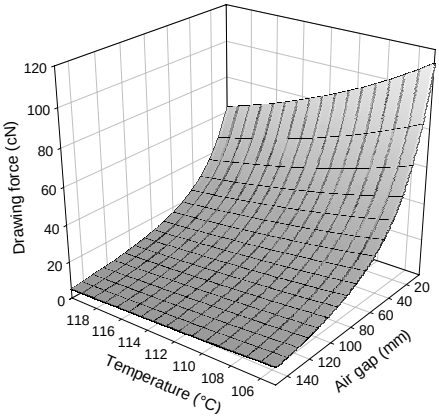


Figure 6-4, The diameter of the fiber in the air gap (extrusion temperature 105 °C, spinning velocity 3 m/min)

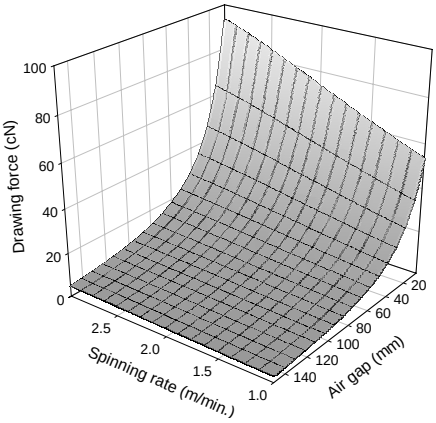
Before solidification of the polymer, the anticipated fiber diameter should be approximately 4.1 mm. During solidification the fiber finally shrinks to the desired diameter of 4.0 mm. At an air gap of 80 mm the fiber enters the water bath at a diameter of approximately 4.2 mm, which is almost equal to 4.1 mm. However, at an air gap of 6 mm the fiber enters the water bath at a much larger diameter of 4.5 mm. This means that for a small air gap, the fiber is also stretched in the water bath. Measurements below the water surface revealed that the fiber is stretched in the water bath over a distance of approximately 5 -10 mm. Therefore the drawing distance (L) in Equation 6-4 is the total of the air gap and the drawing distance below the water surface.

It can be deduced from equation 4, that the force needed to draw the fiber to the anticipated diameter increases with decreasing air gap. In order to examine the relationship between the process parameters of the extrusion process and the drawing force, coaxial fibers were manufactured with various process parameters and the drawing force was measured (extrusion temperature 105, 110 and 130 °C; air gap 5,

10, 20, 30, 50, 100 and 150 mm; spinning velocity 1 and 3 m/min). In Figure 6-5 the measured drawing force is depicted as a function of temperature, air gap and spinning velocity. Figure 6-5a and b consist of respectively 21 and 14 data points that were fitted with a Lorentzian 3D function. It can be seen that the drawing force increases significantly with decreasing air gap. Also temperature of the spinneret and the spinning velocity have a significant influence on the drawing force. By decreasing the temperature and increasing the spinning velocity respectively, both viscosity and volume flow increase. As a consequence the drawing force increases.



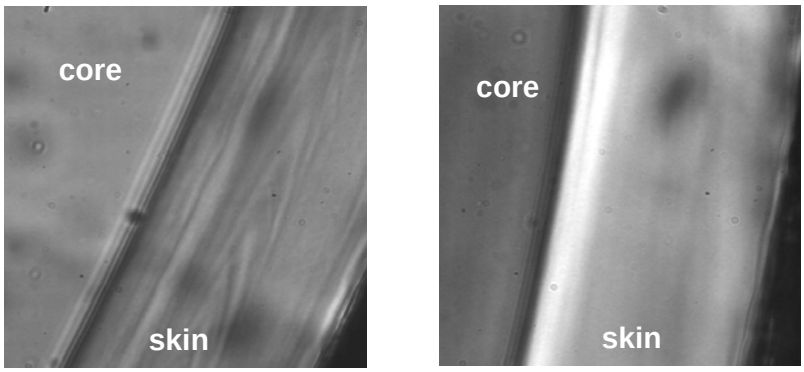
a) spinning velocity 3 m/min



b) extrusion temperature 110 °C

Figure 6-5, The influence of temperature of the spinneret, air gap and spinning velocity on the drawing force during melt spinning of the coaxial fiber

It is well known that polymeric crystallization under stress may influence the microstructure of the membrane. This could already be observed from the appearance of the fiber. An opalescent appearance was observed for the fibers prepared at a higher spinline stress. At low spinline stress the fibers were more transparent. In order to visualize differences in the polymeric structure of the coaxial fibers, thin cross-sectional coupes of the fibers were examined with polarization microscopy. The microscope is focused inside the bulk of the polymer. In Figure 6-6a large structures are visible in the membrane of the fibers produced at a high spinline stress. These structures were not present in samples produced at low spinline stress (Figure 6-6b).



a) High spinline stress *b) Low spinline stress*

Figure 6-6, Cross-sectional pictures of the membrane of coaxial fibers produced at high and low spinline stress (pictures were made with polarization microscopy)

6.4.2 Wide Angle X-ray Scattering (WAXS)

Polymeric orientation

In Figure 6-7 average azimuthal scans are plotted of the fiber membranes that were obtained at different extrusion temperatures (105 °C-130 °C). The drawing force varied from respectively 65 to 25 cN.

The detector angle was set at the maximum intensity of the [110] reflection. It can be seen that by rotating the sample in the X-ray beam the intensity of reflection is not constant in all directions. Apparently all fibers are more or less orientated in the direction parallel to the fiber axis. Most likely the opalescent appearance observed at higher spinline stress is related to an increasing orientation of the polymeric structure of the membrane. Furthermore, two additional peaks are formed at ± 25° from the symmetry axis at decreasing temperature (increasing drawing force). The appearance of these peaks has also been observed by others for polyethylene (14,19,20) and are attributed to the radial symmetry of the b-axis axis of the unit cell of a polyethylene crystal. Depending on the spinline stress the a- and c-axis are orientated around the b-axis.

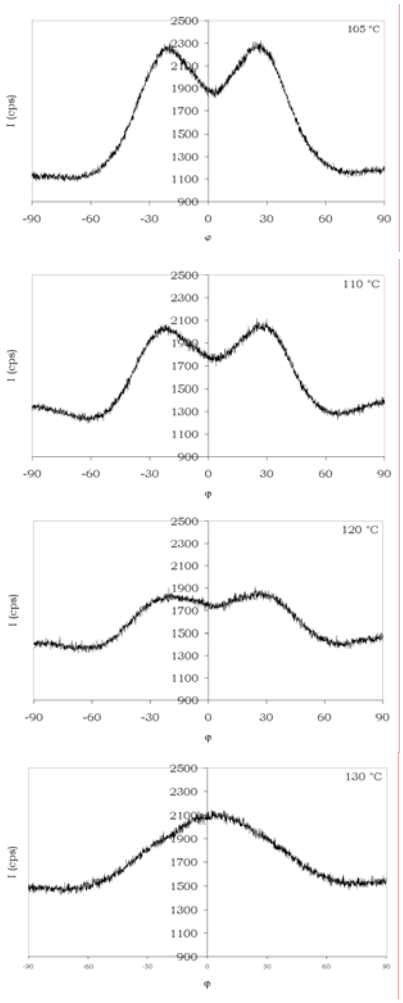


Figure 6-7, The influence of the extrusion temperature on the orientation of the membrane. The intensity of the [110] reflection is plotted versus the azimuthal angle.

Keller and Machin (21,22) proposed a model for the way crystallization proceeds under stress. They described a two-stage nature of crystallization. First crystals are formed of which the c-axis is orientated parallel to the stress field. Subsequently these crystals serve as nuclei of a secondary crystallization process.

This phenomenon during melt spinning of

polymeric fibers has been investigated extensively by other authors. Dees and Spruiell (14) describe the influence of stress on the structure development during melt spinning of polyethylene fibers. By increasing the spinline stress the polymeric morphology of the polyethylene segments changes from a spherulitic structure to a row nucleated lamellae structure. Wide-angle X-ray measurements were performed to measure the orientation of the a, b and c-axis of the unit cell of polyethylene as a function spinline stress.

Crystallinity

From the azimuthal scans it appeared that the polymeric structure of the fibers is orientated in axial direction. This means that the radial scans presented in Figure 6-2 vary as a function of the azimuthal angle. This also implies that the volume crystalline polymer (V_c) is not constant in all directions. In order to determine the crystallinity of the membrane, 37 radial scans, with varying azimuthal angle, were performed for each sample. From these mapping scans the average crystalline volume fraction polymer was calculated using Equation 6-5. In Figure 6-8 the crystalline volume fraction is shown versus the average release rate of the fibers that were manufactured under various process conditions and spinline stresses.

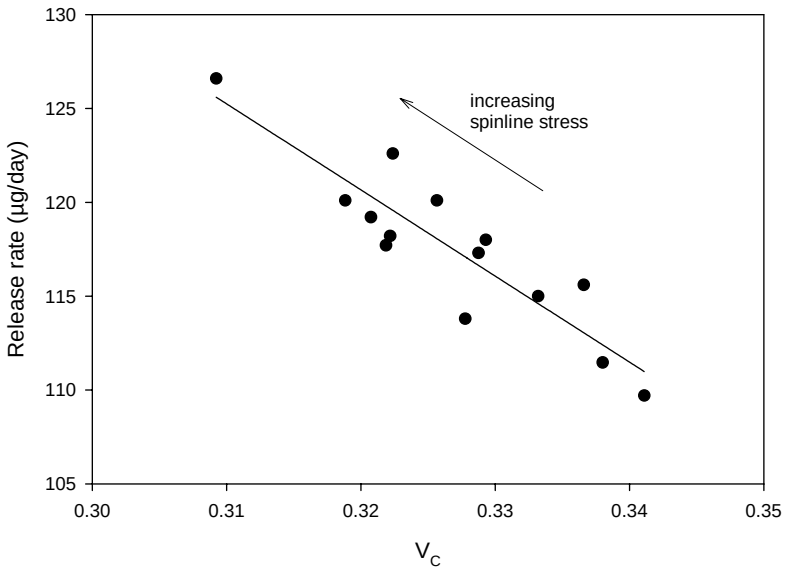


Figure 6-8, The average crystalline volume fraction (V_c) as a function of the average release rate (day 2-21, n=6) of fibers prepared at various process conditions (temperature, air gap, spinning velocity)

It can be seen that the crystalline volume fraction decreases with increasing spinline stress. Most probably the crystallization process of the polyethylene vinyl acetate membrane is hindered with increasing spinline stress. At the same time the permeability (expressed as release rate) increases. When the crystalline volume fraction decreases, the amorphous volume fraction increases. Because the steroid can only dissolve in the amorphous regions, an increasing amorphous fraction results in a higher solubility and therefore higher release rate.

6.4.3 The relationship of spinline stress and release properties

In order to study the effect of spinline stress on the in-vitro release properties of a coaxial fiber, the in-vitro release rate at 37 °C was determined for fibers that were prepared under various process conditions (temperature, air gap, spinning velocity). As a consequence hereof the drawing force varied from approximately 35 to 110 cN. In Figure 6-9 the average release rate is plotted as a function of the drawing force.

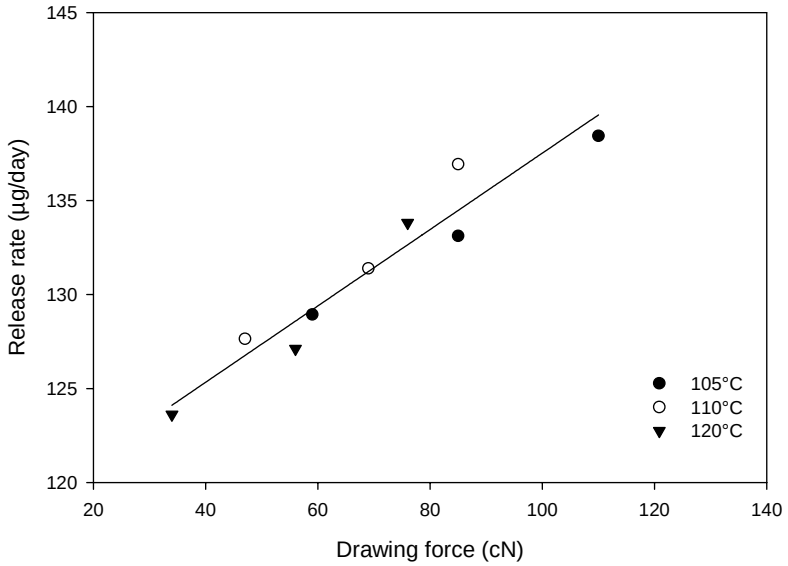


Figure 6-9, The influence of the drawing force on the average release rate (day 2-21, n=3) of etonogestrel

The figure suggests a linear relation between the drawing force and the in-vitro release rate. It is shown that the average release rate increases with increasing drawing force. In paragraph 6.4.2 it was demonstrated that an increasing spinline

stress results in orientated polymeric structure. Furthermore, it was found that the crystallinity also decreases with increasing spinline stress. It is expected that the combination of these findings results in the higher release rate.

6.5 CONCLUSION

It was demonstrated in this paper that the extrusion parameters and spinline stress have a significant influence on the release properties of a coaxial controlled release system based on EVA polymers. As a consequence of the viscoelastic behavior of the EVA polymers used, the polymeric melt exhibits a die swell upon leaving the die. Because the die swell is larger than the desired diameter it is necessary to apply a force to draw the fiber to its desired diameter. By decreasing the spinning temperature and air gap or by increasing the spinning velocity a larger drawing force (or spinline stress) is needed. It was found that the in-vitro release rate of etonogestrel from the coaxial fiber increases with increasing drawing force.

It was demonstrated with polarized light microscopy and WAXS measurements that the membrane polymer is orientated as a consequence of higher spinline stress.

WAXS measurements also reveal that the crystalline volume fraction in the membrane polymer decreases with increasing spinline stress. The combination of these findings results in the observed differences in the release properties of the coaxial fibers that are produced under various process conditions.

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7. EFFECT OF PROCESS INDUCED CHANGES IN MEMBRANE MORPHOLOGY OF A COAXIAL CONTROLLED RELEASE DEVICE

Abstract

This study discusses a coaxial controlled release system based on EVA polymers which is manufactured by means of a melt spinning process. In a previous study it was shown that the process conditions of the melt spinning process exhibit a pronounced effect on the release properties of the coaxial fibers, which is attributed to variations in the polymeric morphology of the membrane. In the present study it is demonstrated that these changes in the polymeric structure of the membrane also have a significant influence on the mechanical properties of the coaxial fiber. After leaving the spinneret it is necessary to apply a drawing force to elongate the fiber to its desired dimensions. The elongation of the fiber not only takes place in the air gap but also to some extend in a cooling bath. The major part of the exerted stress during elongation is due to the membrane. Transmission electron microscopy (TEM) confirms differences in the polymeric morphology of the membrane. A high spinline stress results in a polymeric morphology of the membrane that characterized by a lamellar stacked structure where the lamellae are orientated perpendicular to the fiber axis.

J.A.H. van Laarhoven, M. Ypma and H. Vromans

7.1 INTRODUCTION

Previous papers (1,2) discussed an EVA polymer based device that can be used for controlled release of steroids. This device comprises a coaxial fiber that is prepared by a melt extrusion process. Here two polymers are melted in two separate extruders. In a spinneret the core polymer is subsequently enveloped by a membrane polymer. After leaving the spinneret the molten fiber exhibits a die swell as a consequence of the viscoelastic behavior of both polymers. The resulting fiber is subsequently elongated to the desired diameter and finally cooled down in a water bath where it solidifies. The drawing force needed to draw the fiber to its desired diameter is dependent on the applied process parameters. It is well described in literature that the spinline stress has a pronounced influence on the properties of the semi-crystalline polymeric fiber. Several authors have investigated the change in microstructure upon melt spinning of polymeric materials. Ziabicki and Kedzierska (3,4,5,6,7) studied the influence of spinline tension on the polymeric orientation of polyethylene. Other authors (8,9,10,11,12,13,14) used wide-angle and small-angle X-ray diffraction together with other measurements to study the influence of the process parameters on the structure development during melt spinning of polypropylene and polyethylene fibers. This change in microstructure however does not only affect the mechanical properties of the fiber but also the permeability properties of a drug in a controlled release device prepared by a melt spinning process (§5 and ref.15).

Frequently melt-spinning processes of thin fibers are considered to be isothermally in radial direction. However fibers described in this report have a diameter of 4 mm and are rapidly cooled in a water bath. Therefore temperature and stress gradients can be expected to occur in radial direction of the fiber axis. This will most likely be reflected in the resulting microstructure of the membrane and will likewise have a significant influence on both mechanical and permeability properties of the fiber. This study focuses primarily on the mechanical properties of the extrudates.

7.2 THEORETICAL BACKGROUND

After leaving the spinneret (Figure 7-1) the molten fiber exhibits a die-swell as a consequence of the viscoelastic behavior of both polymers. If the die-swell is larger than the anticipated diameter of the fiber, it is necessary to apply a force to draw the fiber to its desired dimension.

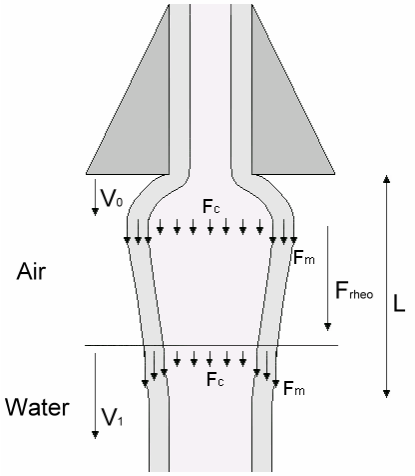

Figure 7-1, The rheological behavior of the coaxial melt in the air gap and water bath. (for symbols see text)

In literature several forces are described that play a role during the melt spinning process (4). The most significant forces are the rheological force (the force required to elongate the fiber) and the force needed to draw the fiber through the water bath (resistance transport wheels, bending force fiber etc.). In this investigation only the rheological force is considered because of its influence on the polymeric structure of the fiber. The relation between the rheological force and the process parameters can be described by the following equation (7):

$$F_{rheo} = \frac{Q\eta_e \ln\left(\frac{v_1}{v_0}\right)}{L} \qquad \textit{Equation 7-1}$$

Where:

F_{rheo} = rheological force
Q = volume flow
η_e = elongational viscosity polymer
v_1 = fiber velocity fiber at distance x = L (= take up velocity)
v_0 = fiber velocity fiber at distance x = 0 (velocity fiber at maximum die swell)
L = drawing distance (L = 0, fiber at outlet die; L = L, fiber at final thickness)

The drawing distance (L) over which the fiber is being stretched is also known as the extensional flow field. Immediately after leaving the spinneret the temperature can still be regarded as isothermal. Because the core and membrane polymer exhibit a different viscosity, the rheological force on the fiber can be divided into parts that are respectively associated with the core (F_c) and membrane (F_m) (see Figure 7-1).
Therefore Equation 7-1 can also be written as:

$$F_{rheo,tot} = F_c + F_m = \frac{\left(Q_c \eta_{e,c} + Q_m \eta_{e,m}\right) \ln\left(\frac{v_1}{v_0}\right)}{L} \qquad \textit{Equation 7-2}$$

Where:
F_c = rheological force core
F_m = rheological force membrane
Q_c = volume flow core
Q_m = volume flow membrane
$\eta_{e,c}$ = elongational viscosity core
$\eta_{e,m}$ = elongational viscosity membrane

With knowledge of the surface area of both membrane and core, the spinline stress on the individual components of the coaxial fiber can be derived.
After leaving the spinneret the fiber begins to cool down in the air gap and solidifies eventually in the water bath. Logically the surface of the fiber solidifies first, while the inner part of the fiber remains molten. Crystallization kinetics of polymer under high rheological force or spinline stress is quite different than under quiescent conditions. Depending on the amount of stress the microstructure of the polymer is subsequently orientated in a direction parallel to the fiber axis. At a certain distance from the spinneret (L) the fiber will not be stretched anymore and achieves its final dimension. As a consequence of the cooling process the microstructure of the membrane polymer may vary in radial direction of the fiber.

7.3 MATERIALS AND METHODS

7.3.1 Materials

The drug used in this study, etonogestrel, was obtained from Diosynth B.V.
Etonogestrel has a melting temperature of 199 °C. In this study several types of polyethylene vinyl acetate polymers were used. These polymers are semicrystalline materials. Both the crystallinity and the permeability properties of the polymers can be adjusted by varying the amount of vinyl acetate (16,17). The lower the vinyl acetate content, the higher the crystallinity and the lower the permeability. EVA 28 contains 28% of vinyl acetate and was used as core material because of the higher solubility and permeability. EVA 18, EVA 9 and EVA 5 contain respectively 18, 9 and 5% vinyl acetate and were applied in the membrane because of the lower solubility and permeability properties.

7.3.2 Methods

7.3.2.1 Manufacturing of coaxial fibers

Coaxial fibers with a diameter of 4 mm were produced with a fixed concentration of etonogestrel in the core (0.69 wt.%). For all fibers the thickness of the membrane was adjusted to 110 μm. In order to prepare a coaxial fiber, a steroid loaded core granulate was manufactured by mixing micronized steroid and ground EVA 28 in the desired ratio. Subsequently, the powder mixture was blended in a Berstorff blend extruder above the melting temperature of EVA 28. After leaving the blend extruder the strands were cooled to room temperature and granulated using a Scheer strand granulator, thereby forming steroid loaded pellets.
The coaxial fibers were prepared using a Plastik Maschinenbau co-extrusion installation. The installation consists of two single screw extruders that are connected to a spinning block.
The molten polymers are delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. The thickness of the membrane polymer is determined by the ratio between rotation speeds of both pumps. Subsequently, the membrane and core polymers are combined in a spinneret, thereby forming a coaxial fiber. In order to cool the fiber to room temperature a water bath was positioned below the spinneret. The outer diameter of the fiber was measured on-line using a Mitutoyo laser scan micrometer, which was positioned behind the water bath. After

leaving the spinneret, the fiber is elongated by means of take up rolls until the desired diameter is achieved.

7.3.2.2 Determination of the fiber diameter below the water surface

The fiber diameter below the water surface was determined with a digital camera. A window was mounted in the water bath below the water surface. By moving the camera in a vertical direction, digital pictures were made of the fiber at various distances below the water surface. The exact diameter was determined by enlarging these pictures and measuring the dimensions of the fiber.

7.3.2.3 Determination of the rheological force

The rheological force needed to draw the fiber to its desired diameter was determined using a Schmidt tension meter.

7.3.2.4 Temperature measurement

The surface temperature of the coaxial fiber in the air gap was measured using a Cyclops TI35 (LAND) IR camera. The camera was positioned at a short distance from the spinneret and focused on the coaxial fiber in the air gap. The air gap was adjusted to 100 mm, the temperature of the spinneret was varied at 105 °C and 130 °C, the spinning velocity was varied from 1 to 3 m/min.

7.3.2.5 Mechanical properties

Stress-strain curves were determined on the coaxial fibers using a Lloyd tensile tester. The fibers were deformed starting with an initial length of 50 mm with a strain rate of 500 %/min. From the stress-strain curve, the elongation at break was deduced, which is defined as:

$$\%EL = \left(\frac{l_f - l_0}{l_0} \right) \times 100 \qquad \textit{Equation 7-3 (18)}$$

Where:

%EL = percentage of elongation (%)

l_f = fracture length (m)

l_0 = initial length (m)

7.3.2.6 Differential Scanning Calorimetry

A Mettler DSC 822e differential scanning calorimetry apparatus was used to determine the crystallization temperatures of the EVA polymers applied. The DSC measurements were performed with open aluminum pans (40 µl). The thermodynamic behavior during respectively heating and cooling was studied from –50 to 130 °C. The applied heating and cooling rate was 10 °C/min. Dry nitrogen was used as a purge gas and a cryogenic cooler was used to cool below room temperature.

7.3.2.7 Transmission Electron Microscopy

The influence of spinline tension on the polymeric structure of the membrane was investigated by Transmission Electron Microscopy. The coaxial fiber was examined in radial direction. This is schematically shown in Figure 7-2. In this way it was possible to study the polymeric structure at the surface of the fiber as well as at the interface between core and membrane polymer.

Thin sections were prepared using a cryo ultra-microtome (model Reichert-Jung Ultracut E). The sections were approximately 200 µm * 300 µm. The thickness of each section was approximately 90 nm.

In order to improve the contrast in the TEM the sections were plasma etched for 2 minutes at 10 W (model Polaron PT7150). Plasma etching was chosen in preference to staining techniques. Subsequently the samples were examined using a JEOL 2010 TEM operating at 200 KV.

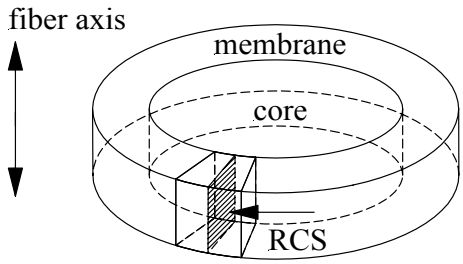

Figure 7-2, Schematic position of the radial cross section of the membrane (RCS)

7.4 RESULTS AND DISCUSSION

7.4.1 Length of the extensional flow field

After leaving the spinneret the polymeric fiber is stretched until the point where the polymer at the surface of the fiber begins to solidify. IR temperature measurements in the air gap revealed (Table 7-1) that the temperature decrease of the fiber surface in the air gap is only a few degrees.

Table 7-1, The temperature decrease of the coaxial fiber (4 mm) in an air gap of 10 mm at an extrusion temperature of respectively 105 °C and 130 °C and a spinning velocity of respectively 1 and 3 m/min.

Temperature spinneret	1 m/min	3 m/min
105 °C	ΔT=10 °C	ΔT=4 °C
130 °C	ΔT=10 °C	ΔT=6 °C

DSC measurements were performed to determine the crystallization temperature under quiescent conditions. It was found that the crystallization temperature of EVA 9, EVA 18 and EVA 28 under these conditions is respectively 87, 77 and 56 °C (cooling speed 10 °C/min). This means that the fiber remains molten in the air gap and that it finally solidifies in the water bath when the crystallization temperature is reached. Logically when EVA 9 is applied in the membrane, the surface will solidify earlier than in case EVA 18 is applied. As a consequence the distance below the water surface over which the fiber is stretched is smaller in case of EVA 9.

As already mentioned the rheological force during melt spinning has a pronounced influence on the microstructure of the polymer. Because the rheological force (Equation 7-1) is inversely proportional to the length of the extensional flow field, it is important to investigate the length of the flow field as a function of the membrane polymer applied. This was done by measuring the fiber diameter below the water surface. Before solidification of the membrane polymer, the anticipated fiber diameter should be approximately 4.1 mm. Upon solidification of the core polymer the diameter of the fiber finally shrinks to the desired diameter of 4.0 mm.

In Figure 7-3 the fiber diameter profile below the water surface is depicted of coaxial fibers with various EVA membranes. All fibers were produced at an extrusion temperature of 105 °C, an air gap of 5 mm and a spinning velocity of 3 m/min.
In case EVA 9 is applied as membrane the fiber is stretched below the water surface for approximately 5-10 mm. When EVA 28 is applied the distance is significantly larger. Since the length of the extensional flow field is proportional to the reciprocal of the rheological force, this will also be reflected in the rheological force. Based only on the length of the flow field a much lower rheological force is expected in case EVA 28 would be used in the membrane.

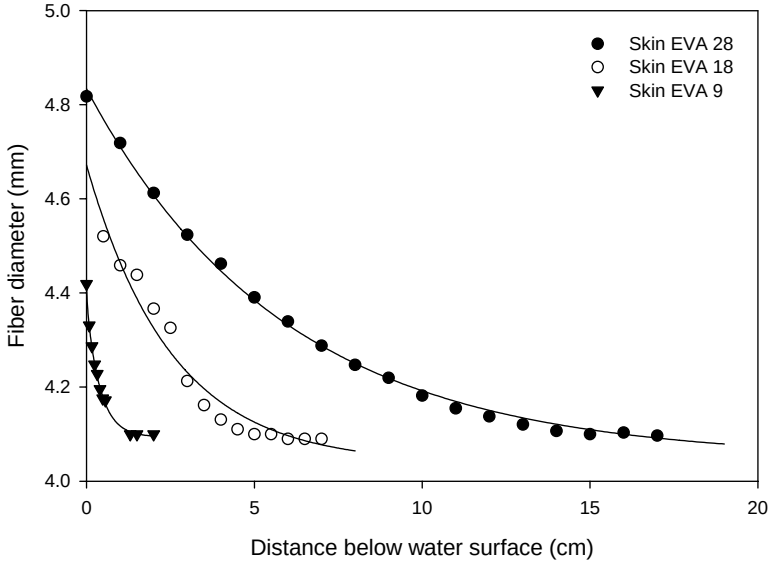

Figure 7-3, The relation between membrane polymer and the length of the flow field below the water surface (core EVA 28, extrusion temperature 105 °C, air gap 5 mm, spinning velocity 3 m/min)

7.4.2 The amount of spinline stress on the membrane.

In ref. 15 we evaluated the influence of the rheological force on the release properties of coaxial fibers. A relationship appeared to exist between the release rate of etonogestrel and the average rheological force during melt spinning. In this case, the force over the whole fiber was considered. Because the release properties of the coaxial fiber are predominantly determined by the polymeric structure of the membrane it is however important to distinct between the amount of spinline stress on the membrane and core polymer. For this purpose coaxial fibers were prepared at

an extrusion temperature of 105 °C and a spinning velocity of 3 m/min. The air gap was varied from 5 mm to 150 mm.

The spinline stress of the individual components of the coaxial fiber in the air gap was calculated from the total rheological force using Equation 7-2.

In ref. 19 the viscosity of EVA 9 and steroid loaded (0.69%) EVA 28 was determined. It was found that at the applied process conditions the shear viscosity of EVA 9 and EVA 25 is respectively 9100 Pa·s and 3200 Pa·s.

With this knowledge and the dimensions of the fiber the spinline stress of the individual components of the coaxial in the air gap was calculated. Figure 7-4 plots the stress of both membrane and core. Because of the highest viscosity the membrane exhibits the highest spinline stress. At an air gap of 5 mm the average spinline stress on the membrane is approximately 20 N/cm^2.

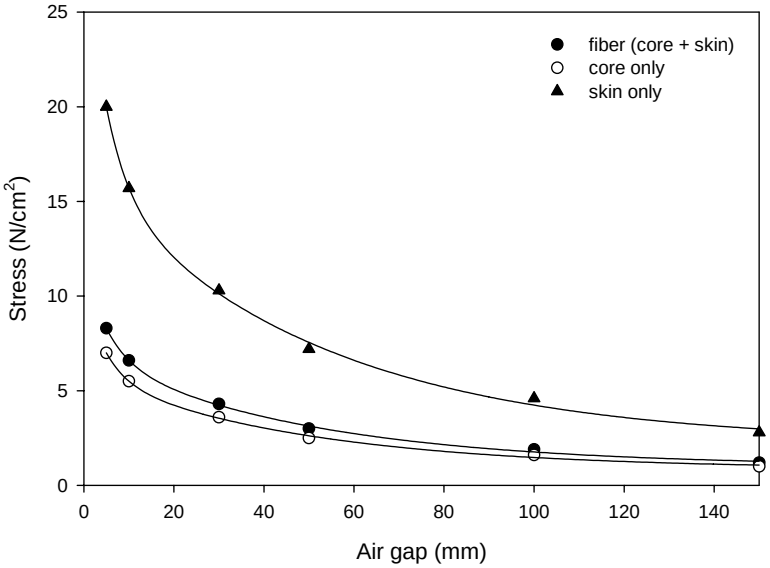

Figure 7-4, The stress on the individual components of the coaxial fiber (temperature 105 °C, spinning velocity 3 m/min, calculations based a fiber diameter of 4 mm)

It should be noted that some simplifications were made in the aforementioned approach. For instance a homogenous temperature is assumed in the coaxial fiber. Therefore Figure 7-4 only gives an approximation of the average stress. When the membrane is solidified in the water bath (EVA 9 crystallizes at 87 °C) and the core polymer is still molten (EVA 28 crystallizes at 56 °C), most of the force on the fiber

is carried by the membrane. The stress on the membrane is therefore higher than indicated. Therefore data for the membrane illustrated in Figure 7-4 can be considered as underestimated.

According to Equation 7-1 the length of the extensional flow field (L) should be inversely proportional to the rheological force or spinline stress. In Figure 7-5 the spinline stress of the individual components is plotted versus the reciprocal of L. (L was calculated by adding the length of the air gap to the drawing distance below the water surface (section 5.1)). It can be seen that the rheological force or spinline stress is indeed proportional to the reciprocal of L. From the angle of the curve the elongational viscosity can be deduced (Equation 7-2).

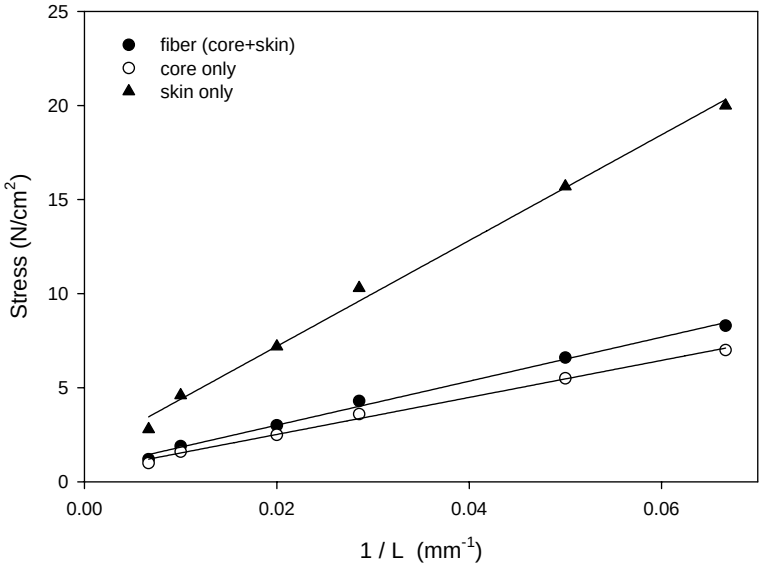

Figure 7-5, The relation between spinline stress and length of the flow field (temperature 105 °C, spinning velocity 3 m/min)

7.4.3 The relation between spinline stress and elongation at break

The amount of spinline stress during melt spinning has a significant influence on the microstructure of the polymer. This is also reflected on the mechanical properties of the coaxial fibers. In §5 a relation is demonstrated between the release rate of a steroid from the coaxial fiber and the elongation at break. It was found that the release rate of etonogestrel from the fiber increased with decreasing elongation at break. In order to investigate this phenomenon Wide Angle X-ray scattering (15)

measurements were performed on fibers that were prepared at various process conditions. It was demonstrated that as a consequence of spinline tension the polymeric structure is orientated in a direction parallel to the fiber axis. The orientation of the membrane was assessed by azimuthal scans, where the sample was rotated in X-ray beam and the reflection of the [110] crystalline plane was measured as a function of the rotation angle (φ). In ref. 20 the degree of orientation (f_c) of polyethylene fibers was related to the elongation at break. It was demonstrated that the degree of orientation has a direct influence on the elongation at break.

In order to investigate the relation between rheological force during melt spinning and the mechanical properties stress-strain curves were measured of fibers that were produced under various process conditions (temperature 105-130 °C, air gap 5-150 mm, spinning velocity 1-3 m/min.). As a consequence of the process parameters the rheological force varied from 0 to approximately 120 cN. In Figure 7-6 the elongation at break is plotted as a function of the rheological force during melt spinning. The figure suggests a linear relation between the two parameters. At a rheological force of 0 cN a coaxial fiber is obtained that exhibits a non orientated membrane which can be stretched to approximately 1000% before breaking. Upon increasing rheological force the membrane becomes more orientated as indicated by the small inserts (azimuthal scans obtained from 15). Similar azimuthal scans where also reported by other authors (21,22). At a rheological force of approximately 130 cN the elongation at break is extrapolated to be 0%. However this point is never reached because the fiber already breaks during the melt extrusion process. It is expected that just before this point the polymeric chains are highly orientated. It has frequently been reported in literature that at very high spinline stress the polymeric chains are fully extended and upon crystallization a fibrillar polymeric structure is obtained. However it is not certain whether this is also the case in the coaxial fibers described in this paper.

Orientation phenomena during melt spinning of polyethylene fibers have been described extensively by other authors. In ref. 11, 12, and 13, the development of the microstructure during melt spinning of polyethylene ant polyethylene terephtalate fibers was studied. By increasing spinline stress the crystalline morphology changes from a spherulitic structure (low stress) to a row nucleated, lamellae stacked structure (medium stress) and finally a fibrillar structure where the polymeric chains are fully extended.

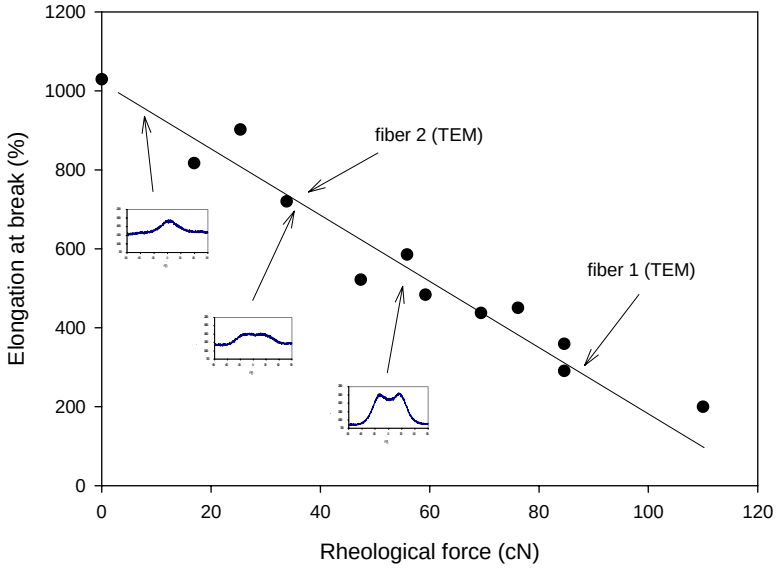

Figure 7-6, The elongation at break of coaxial fibers prepared under various conditions and EVA 9 as membrane (fiber diameter 4 mm, membrane 110 µm, position of WAXS and TEM measurements are indicated by arrows). (azimuthal scans were obtained from 15)

In order to investigate the influence of EVA polymer on the elongation at break, coaxial fibers were also produced with EVA 18, EVA 14 and EVA 5 as membrane polymer. These fibers were prepared with comparable dimensions and were produced at various air gaps (5-150 mm). It is shown in Figure 7-7 that a similar relation exists between the elongation at break and the rheological force.

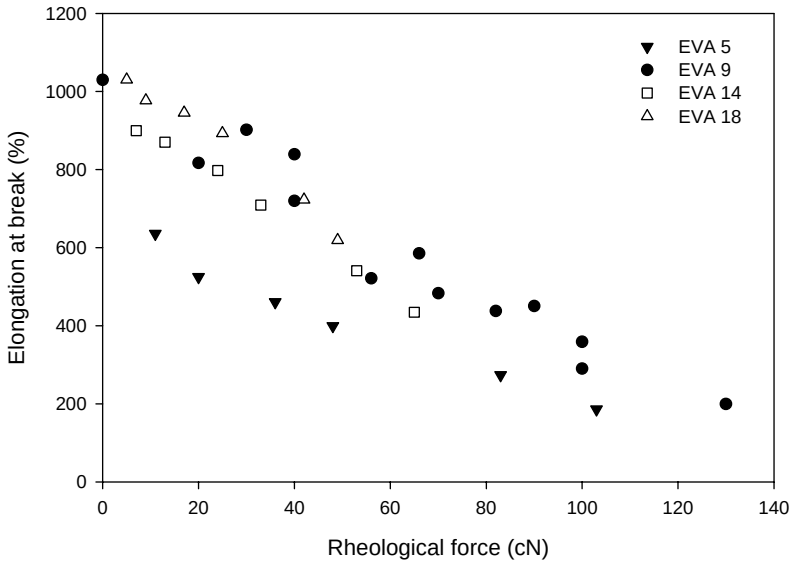

Figure 7-7, The elongation at break of coaxial fibers prepared under various conditions and with various membrane polymer (fiber diameter 4 mm, membrane 110 μm).

7.4.4 Transmission Electron Microscopy (TEM)

Differences between fibers produced at high and low spinline stress are also reflected in the visual appearance of the fibers. At higher spinline stress the fibers were more opalescent while the fibers produced at low spinline stress were completely transparent. Transmission Electron Microscopy was used to examine the effect of spinline stress on the polymeric structure. For this study two fibers were selected. Both fibers had a diameter of 4 mm and a membrane of EVA 9 with a thickness of 110 μm. Fiber 1 was produced at higher spinline stress (extrusion temperature 105 °C, air gap 10 mm, velocity 3 m/min). Fiber 2 was produced at moderate spinline stress (extrusion temperature 130 °C, air gap 10 mm, velocity 3 m/min). Figure 7-6 depicts the position of these fibers. In this figure the result can be directly compared to WAXS measurements obtained from 15. Radial cross sections were made of the coaxial fibers at the interface between membrane and core polymer. In Figure 7-8 a typical TEM image can be seen of the fiber that was produced at moderate spinline stress (fiber 2).

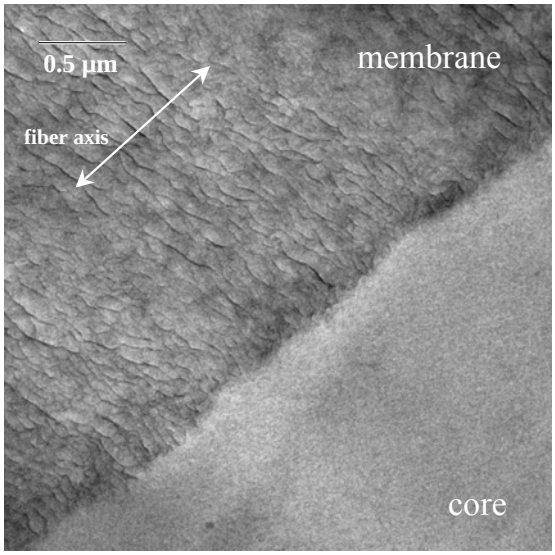

Figure 7-8, Morphology of the membrane polymer of a coaxial fiber produced at moderate spinline stress (fiber 2: 130 °C, air gap 10 mm, velocity 3 m/min)

Examination of this image shows that the morphology of the membrane consists of network of dark bands in a light background. The dark banding seen in the TEM images has also been reported in other TEM studies of PE/PEVA (23,24,25,26,27) and are associated to alternating crystalline and amorphous regions. The thickness of the dark bands was measured and was found to be approximately 200 Å. This value is also found in literature and is a typical value for the thickness of the crystalline lamellae. The direction of the bands in the membrane are orientated in a direction perpendicular to the fiber axis. This suggests a lamellar stacked structure where the crystalline regions are orientated perpendicular to the fiber axis as is described in literature.

Furthermore, a significant difference can be seen between the morphology of the membrane and the core polymer. This is expected because during melt spinning of coaxial fibers most spinline stress is carried by the membrane only. When the membrane crystallizes the core polymer is still molten and eventually crystallizes under quiescent conditions.

In Figure 7-9 a similar TEM image is shown of the coaxial fiber that was produced at higher spinline stress. It can be seen that the morphology of the membrane is different from that of the fiber produced at moderate spinline stress. The perpendicularly orientated structures are hardly present any more, which is in fact a

direct consequence of the higher spinline stress by which the polymeric chains are further elongated and more orientated in the longitudinal direction.

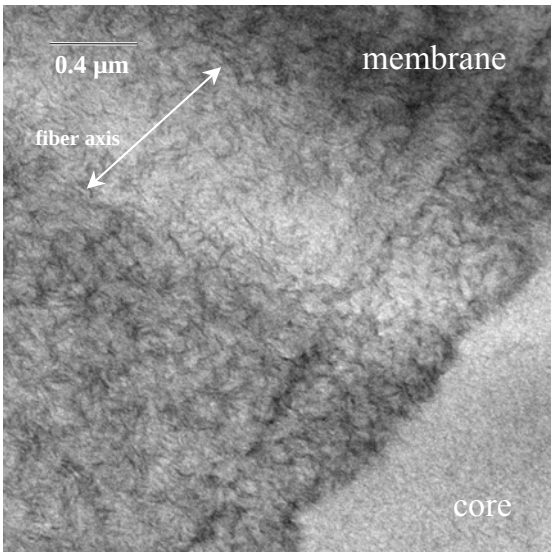

Figure 7-9, Morphology of the membrane polymer of a coaxial fiber produced at high spinline tension (fiber 1: 105 °C, air gap 10 mm, velocity 3 m/min)

7.5 CONCLUSION

In former studies (§5 and 15). it was demonstrated that spinline tension has a pronounced influence on properties of a controlled release device prepared by a melt spinning process. It was demonstrated that the release rate from such a fiber was inversely proportional to the rheological force. WAXS measurement revealed that at higher spinline stress the coaxial fiber becomes orientated in a direction parallel to the fiber axis.

In this study the effect on spinline tension on the properties of the fiber was further investigated. Depending on the polymer applied in the membrane the fiber is not only stretched in the air gap but also to a varying extent in the water bath. If EVA 9 is applied as membrane material the fiber is stretched for approximately 10 mm below the water surface. Under similar process conditions this distance is increased to approximately 150 mm if EVA 28 is applied in the membrane. Because the surface of the fiber is cooled down more rapidly than in the core, stress and temperature gradients are expected in the membrane. As a result this will also be reflected in the microstructure and properties of the membrane.

It is demonstrated that the mechanical properties of the fiber are influenced by the degree of spinline stress during melt spinning. The elongation at break is decreased with increasing spinline stress. This phenomenon can be explained by the morphology of the membrane and the degree in orientation.

Transmission electron microscopy reveals that at moderate spinline stress the morphology of the membrane is characterized by a lamellar stacked structure perpendicular to the fiber axis, which is in agreement with literature. As a consequence of spinline stress the polymeric chains are elongated and subsequently crystallize in axial direction. These elongated chains serve as nuclei of a secondary crystallization process were polymeric chains crystallize by chain folding perpendicular to the fiber axis. Higher spinline stress yield fibers with deviating appearance, which can be explained by the mentioned decreased elongation.

7.6 ACKNOWLEDGEMENT

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8. SUMMARY

Sustained release of dugs offers several advantages like increased efficacy, safety, compliance and convenience. As a consequence sustained drug delivery is often preferred above daily administration of drugs. Furthermore, drug delivery systems can be designed to deliver one or more drugs at a specified rate, for a specific period of time and even at a desired location. Because of their suitable properties, which can also be easily adapted, polymers are often applied in controlled release systems. Polymers can either be degradable or non-degradable. The choice between a degradable or non-degradable polymer depends on the specific needs and demands of the sustained release device to be developed.

A degradable polymer is eliminated from the body by means of biochemical or physical mechanisms. Of course elimination from the body should only occur after or during depletion of the drug. This implies that the degradation time of the applied polymer should be adapted to the intended life time of the drug delivery system.

Examples of frequently applied degradable polymers are poly (lactic acid), poly (glycolic acid), copolymers of lactic and glycolic acid, poly-anhydrides and poly (ortho esters). Removal from the body before its life time is difficult and is normally not intended.

A non-degradable polymer is preferred above a biodegradable polymer if there is a specific need to remove the drug delivery device from the body at any desired time. Examples of removable systems are contraceptive devices like vaginal rings or implants.

A non-degradable polymer that is often applied in medical and pharmaceutical applications because of its desired properties is polydimethylsiloxane. Based on this polymer several commercial controlled release devices (Estring®, Norplant®) have reached the market.

In this thesis a sustained release device is described that is manufactured from another non-degradable polymer, namely polyethylene vinyl acetate (EVA). These EVA polymers have also been used in several products (Progestasert®, Ocusert®,

Nuvaring®, Implanon®). EVA polymers exhibit excellent permeability properties for various drugs and can be obtained in various grades.

The sustained release device described in this thesis consists of a coaxial fiber that is based on two types of EVA polymers and is used for sustained release of steroids. These coaxial fibers are manufactured by means of a coextrusion process. The production equipment consists of two single screw extruders, two spinning pumps and a spinneret. A steroid loaded core granulate, which is prepared by a blend extrusion process, and a membrane polymer are fed to hoppers positioned on top of the extruders. Subsequently both polymers are melted in the extruders and transported to the spinning pumps. The spinning pumps deliver an accurate flow of core and membrane polymer to a spinneret, where the coaxial fiber is formed. The rotation speeds of the spinning pumps determine the spinning velocity, whereas the ratio between the rotation speeds determines the thickness of the membrane. Upon leaving the spinneret the fiber is elongated by means of take up rolls until the anticipated diameter is achieved. A laser scanner is applied for online monitoring of the fiber diameter. Finally the fiber is cooled down in a water bath which is positioned below the spinneret.

Polyethylene vinyl acetate polymers are semi-crystalline. This means that the polymeric structure consists of alternating crystalline and amorphous regions. Because the molecular distances within the polymer crystals are normally smaller than the molecular size of the drug to be released the diffusion process of the drug molecules takes place in the amorphous domains. The presence, size and orientation of the crystalline and amorphous regions are influenced by the manufacturing and storage conditions of the coaxial fibers. As a consequence the release rate of a drug is influenced by the manufacturing and storage conditions of the coaxial fiber.

The aim of the study reported in this thesis is to obtain more insight into the mechanisms and factors that influence the release properties of a drug from a coaxial controlled release device based on polyethylene vinyl acetate.

In chapter 2 *the in-vitro release properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring* are described.

The core polymer of the coaxial fiber used to manufacture the vaginal ring contains two steroids, etonogestrel and ethinyl estradiol, which are present in a molecularly dissolved state. In order to predict the in-vitro release rate of etonogestrel and ethinyl estradiol from the coaxial fiber and to design a sustained release system with specified release characteristics, values of diffusion coefficient and solubility are

required. These data were obtained during pre-formulation studies. The solubility and diffusion coefficient of the steroids in the applied polymers were obtained by saturation of polymeric films in saturated steroid solutions and by time lag measurements.

The permeability data were also derived from in-vitro release measurements of the coaxial fibers. It is demonstrated that the permeability data obtained in the pre-formulation studies are useful in semi-quantitative terms, but deviate from the permeability data found at the in-vitro release of the coaxial fibers. It is suggested that this is most likely due to differences in the polymeric structure of films and coaxial fibers.

Furthermore, it is shown that the solubility and release of etonogestrel is influenced by the presence of ethinyl estradiol. The solubility of etonogestrel in EVA polymer increases with increasing concentration of ethinyl estradiol. Because the release rate is influenced by the solubility this will also be reflected on the release rate. An increasing concentration of ethinyl estradiol in the core decreases the release rate of etonogestrel.

By investigating this phenomenon with differential scanning calorimetry, it was shown that the steroids form an eutectic. The lower melting point results in an increased solubility and hence in altered release properties of the coaxial fibers.

In chapter 3 the *effect of supersaturation and crystallization phenomena on the release properties of a coaxial controlled release device based on EVA copolymer* is described.

This chapter discusses the influence of the steroid concentration, the process parameters during extrusion and storage conditions on the release properties of etonogestrel from the coaxial fibers. Because of the high extrusion temperatures a large amount of etonogestrel dissolves in the polymeric melt. Since the release from the coaxial fibers is proportional to the concentration gradient over the membrane, the amount of dissolved drug that recrystallizes during cooling to room temperature and subsequent storage is of crucial importance. The solubility of etonogestrel was determined at both room and at elevated temperatures. The amount of etonogestrel that dissolves at typical extrusion temperatures was found to be approximately 10 times higher than at room temperature.

Both mono filament (blend extrusion) and coaxial fibers with various steroid concentrations were prepared under different process conditions. The crystallization kinetics of steroid in the core polymer (mono filament fibers) was studied using

thermal analysis and hot stage microscopy. It was demonstrated with differential scanning calorimetry that besides temperature also throughput rate of the polymer during blend extrusion and the screw speed (increasing shear) have an influence on the amount of steroid that dissolves during extrusion.

Coaxial fibers were subsequently stored at various storage conditions and the influence of the steroid content and storage condition on the release properties of the fiber was studied. It was found that if the amount of etonogestrel in the core polymer is below a critical nucleation concentration at room temperature, the dissolved steroid remains in a supersaturated state. If on the other hand the amount of dissolved steroid is just above the critical nucleation concentration, the recrystallization process of supersaturated steroid in the polymers progresses very slowly. Because the recrystallization process is temperature dependent, the in-vitro release is influenced by the storage conditions and varies in time.

Scanning electron microscopy and transmission light microscopy studies were performed to examine the crystallization process of the supersaturated steroid in the solid polymeric matrix. It is expected that the recrystallization of steroid in the core polymer is severely hindered by the polymeric matrix and that not all supersaturated steroid will recrystallize. As a consequence a low amount of steroid remains in a supersaturated state. This was confirmed by comparing the release profile of a saturated fiber with fibers where an excess of crystalline etonogestrel was present. It appeared that the release rate from the saturated fiber was approximately two times lower than the release rate of the fibers containing crystalline steroid.

Chapter 4 describes the influence of *temperature effects on the release properties of a coaxial controlled release device based on EVA polymers*.

The crystallinity of various EVA polymers was determined by measuring the melting enthalpy with differential scanning calorimetry. The melting enthalpy of 100% crystalline polyethylene (293 J/g) was obtained from literature and was used to calculate the crystallinity of the EVA polymers. It is shown that the crystallinity decreases from 43 to 15% upon a vinyl acetate content increase from 5 to 40%. By increasing the vinyl acetate content from 5 to 14% a threefold increase in permeability is observed.

It is known from literature that heat treatment (annealing) has an influence on the structure of polymers. By increasing the temperature, the size of the crystalline and amorphous domains increases. In order to study the effect of heat treatments on the crystallinity, EVA polymers with various vinyl acetate content were stored at various

temperatures (40, 50, 60 and 70 °C). Again the crystallinity was determined with differential scanning calorimetry. It was found that although the shape of the melting curve was completely altered by the temperature treatments, the crystallinity of the polymers did not change significantly. Steroid loaded coaxial fibers were prepared with various grades of polyethylene vinyl acetate applied in the membrane. The coaxial fibers were subsequently stored for one day at 40, 50, 60 and 70 °C. It was found that the release rate of the steroid increased significantly with increasing storage temperature. The influence of heat treatment on the permeability properties of the coaxial fiber seems to be smaller if an EVA polymer with higher vinyl acetate content is applied in the membrane. Because the amount of crystalline domains decreases with increasing vinyl acetate content, the influence of the crystalline domains on the release properties also diminishes. Therefore a change in size of the crystalline domains has less impact. As the permeability is the product of solubility and diffusion coefficient, the solubility of etonogestrel was determined in EVA polymers that were annealed at elevated temperatures. It was found that the solubility was not significantly influenced by the annealing process. Therefore it can be concluded that the increase in permeability must be attributed to an increasing diffusion coefficient.

The polymeric structure is not only influenced by storage temperature but is also affected by the speed of cooling during crystallization of the polymer. It was found that the release rate decreases with increasing cooling rate. It is argued that the size of the crystalline and amorphous domains decreases with increasing cooling speed leading to lower permeability properties.

Chapter 5 discusses *the influence of the extrusion parameters on release and mechanical properties of a coaxial controlled release device based on EVA copolymer*.

It is known from literature that the process parameters during melt spinning have a significant influence on the polymeric structure of the fibers. Because the permeability properties of a polymer are determined by the polymeric structure, the influence of the process conditions should also be reflected on the release properties of the coaxial fibers. In order to investigate this, fibers were prepared at different extrusion temperature, air gap (distance between die and water surface) and extrusion speed. It was found that these process parameters have a significant influence on the final permeability properties of the coaxial fiber. The release rate of etonogestrel

from the coaxial fiber increases, as the fibers are manufactured at lower extrusion temperatures and smaller air gap.

The influence of the polymeric structure is not only reflected on the release properties but also on the mechanical properties of the fiber. In order to study this, the mechanical properties of the coaxial fibers were determined using a tensile tester. It was demonstrated that the elongation at break of the fibers decreases with decreasing extrusion temperature and air gap and increasing extrusion speed. Furthermore, a linear relation is demonstrated between the release properties and the elongation at break. This phenomenon can be explained by a polymeric structure that is orientated as a consequence of the applied process parameters. In literature it is described that the polymeric structure in orientated fibers is characterized by lamellar stacked structure of crystalline and amorphous domains where the direction of the lamella is perpendicular to the fiber axis. It seems logical that an orientated lamellae stacked structure also exhibits different permeability properties.

Chapter 6 describes *the influence of spinline stress on release properties of a coaxial controlled release device based on EVA polymers*.

During melt spinning of polymeric fibers, the molten polymer is forced to flow through a small capillary. As a consequence the polymeric melt becomes stressed from the shear and extensional forces at the die entrance and within the die. Upon leaving the die the melt is no longer constrained and relaxes by swelling. This results in a diameter that is larger than the die. The amount of die swell is influenced by the process parameters and the visco-elastic properties of the polymers applied. If the die swell is larger than the anticipated diameter of the coaxial fiber it is necessary to apply a force to elongate the fiber to its desired diameter.

The amount of force needed is again dependent on the process conditions and the type of polymers. It is demonstrated that a larger drawing force is needed at lower extrusion temperature, a smaller air gap or at a higher spinning velocity. In order to investigate the nature of this phenomenon steroid loaded coaxial fibers (with a diameter of 4 mm) were prepared at various process conditions and the drawing force was measured. After manufacturing of the coaxial fibers the in-vitro release of etonogestrel was measured at 37 °C. A linear relationship was found between the release rate and the applied drawing force. Because the release from the coaxial fiber is predominantly influenced by the membrane, the polymeric structure of the membrane was investigated with Wide Angle X-ray Scattering (WAXS). These measurements revealed that at increasing drawing force the polymeric structure of

the membrane becomes orientated in axial direction. Furthermore, at higher spinline stress the crystalline volume fraction of the membrane decreases and as a result permeability of the polymer increases.

In chapter 7 the e*ffect of process induced changes in membrane morphology of a coaxial controlled release device* is described.

Coaxial fibers were prepared under various process conditions and with various EVA polymers applied in the membrane. It was demonstrated that the major part of the spinline stress during elongation of the fiber is due to the membrane. The fiber is not only elongated in the air gap but also to some extent below the water surface. The total length of the flow field is depended on the EVA polymer applied and increases with increasing vinyl acetate content. It is shown that the length of the flow field is inversely proportional to the spinline stress. Therefore coaxial fibers that are manufactured from EVA polymers with lower vinyl acetate content exhibit a shorter flow field and as a consequence a higher spinline stress is observed. The higher the spinline stress the more the fiber becomes orientated. Again this is reflected in the mechanical properties of the fiber. It is demonstrated that for all EVA polymers applied that the elongation at break is inversely proportional to the spinline stress. Transmission electron microscopy (TEM) confirms differences in the polymeric morphology of the membrane. A high spinline stress results in a polymeric morphology of the membrane that characterized by a lamellar stacked structure where the lamellae are orientated perpendicular to the fiber axis.

9. SAMENVATTING

Gereguleerde afgifte van actieve stoffen biedt verscheidene voordelen zoals verhoogde effectiviteit, veiligheid, toedieningsgemak en naleving. Om deze reden wordt vertraagde afgifte dikwijls geprefereerd boven dagelijks toediening van actieve stoffen. Gereguleerde afgifte systemen kunnen zodanig ontworpen worden dat één of meerdere actieve stoffen zijn toe te dienen met een bepaalde afgiftesnelheid, gedurende een bepaalde tijdsduur en zelfs op een gewenste plaats. Wegens hun geschikte eigenschappen, worden polymeren vaak toegepast in gereguleerde afgifte systemen. Polymeren kunnen zowel biodegradeerbaar als niet biodegradeerbaar zijn. De keuze tussen een biodegradeerbaar of niet biodegradeerbaar polymeer hangt af van de specifieke behoeften en eisen die aan het gereguleerde afgifte systeem zijn gesteld.

Een biodegradeerbaar polymeer bezit de eigenschap dat het in het lichaam door middel van biochemische of fysische mechanismen wordt geëlimineerd. Natuurlijk moet de eliminatie van het polymeer uit het lichaam slechts na of gedurende de afname van de actieve stof geschieden. Dit impliceert dat de degradatietijd van het polymeer aan de gewenste levensduur van het gereguleerde afgifte systeem moet worden aangepast.

Enkele voorbeelden van de meest toegepaste biodegradeerbare polymeren zijn poly(melkzuur), poly(glycolzuur), copolymeren van melkzuur en glycolzuur, poly-anhydriden en poly(ortho esters). Een eventuele voortijdige verwijdering van het biodegradeerbare afgifte systeem uit het lichaam is vaak lastig of zelfs onmogelijk.

De keuze voor een niet biodegradeerbaar polymeer heeft de voorkeur boven een biodegradeerbaar polymeer als er een specifieke behoefte bestaat om het afgifte systeem op elk gewenst tijdstip uit het lichaam te kunnen verwijderen. Enkele voorbeelden van verwijderbare systemen zijn contraceptieve preparaten zoals vaginale ringen en implants.

Een niet biodegradeerbaar polymeer dat vaak in medische en farmaceutische preparaten wordt toegepast wegens zijn geschikte eigenschappen is

polydimethylsiloxane. Dit polymeer is al toegepast in diverse commerciële gereguleerde afgifte systemen (Estring®, Norplant®).
In dit proefschrift wordt een gereguleerd afgifte systeem beschreven dat is gebaseerd op een ander niet biodegradeerbaar polymeer, namelijk polyethyleen vinyl acetaat (EVA). Ook dit polymeer is al toegepast in enkele commerciële producten zoals Progestasert®, Ocusert®, Nuvaring® en Implanon®. EVA polymeren hebben een uitstekende permeabiliteit voor diverse actieve stoffen en zijn beschikbaar in diverse soorten met verschillende eigenschappen.
Het gereguleerd afgifte systeem bestaat uit een coaxiale vezel welke vervaardigd is uit twee typen EVA polymeren en is bestemd voor gereguleerde afgifte van steroïden. Deze coaxiale vezel wordt gemaakt door middel van een coëxtrusieproces. De coëxtrusie apparatuur bestaat uit twee enkelschroef extruders, twee spinpompen en een spingarnituur. Een steroïd beladen kern polymeer, bereid door middel van een mengextrusie proces, en een membraan polymeer worden door middel van trechters toegevoerd aan de extruders. In de extruders worden beide polymeren gesmolten en door middel van de schroef getransporteerd naar de spinpompen. Deze pompen het gesmolten kern- en membraan polymeer met een nauwkeurig debiet naar het spingarnituur, waar de coaxiale vezel wordt gevormd. De omwentelingssnelheid van beide spinpompen bepaalt de vezelsnelheid terwijl de verhouding in omwentelingssnelheid de dikte van het membraan bepaalt. Als de nog gesmolten vezel het spingarnituur verlaat, wordt hij door middel van een afname apparaat verstrekt naar de gewenste vezel diameter. De vezeldiameter wordt on-line gecontroleerd door middel van een laserscanner. Uiteindelijk wordt de vezel afgekoeld in een waterbad dat zich onder het spingarnituur bevindt.
Polyethyleen vinyl acetaat is een semi-kristallijn polymeer. Dit betekent dat de structuur van het polymeer uit afwisselende kristallijne en amorfe gebieden bestaat. Omdat de moleculaire afstanden binnen de kristallijne domeinen over het algemeen kleiner zijn dan de molecuul grootte van de actieve stof vindt het diffusie proces in de amorfe domeinen plaats. De aanwezigheid, grootte en oriëntatie van de kristallijne en amorfe domeinen worden beïnvloed door productie- en opslag condities van de coaxiale vezels. Hierdoor is de afgiftesnelheid van de actieve stof afhankelijk van de productie- en opslag condities van de coaxiale vezel.
Het doel van dit proefschrift is een beter inzicht te krijgen in het mechanisme en de factoren die een rol spelen bij gereguleerde afgifte van een actieve stof uit een coaxiale vezel die vervaardigd is van polyethyleen vinyl acetaat polymeer.

In hoofdstuk 2 worden de *in-vitro afgifte eigenschappen van etonogestrel en ethinyl estradiol uit een contraceptieve vaginale ring* beschreven.
In de kern van de coaxiale vezel die gebruikt is voor de vervaardiging van de vaginale ring, zijn twee steroïden etonogestrel en ethinyl estradiol aanwezig in een opgeloste toestand. Om het in-vitro afgifte profiel van etonogestrel en ethinyl estradiol van de coaxiale vezel te kunnen voorspellen en een gereguleerd afgifte preparaat te kunnen ontwerpen met een gewenst afgifte profiel, zijn gegevens over de oplosbaarheid en diffusiecoëfficiënt van de actieve stof in het polymeer vereist. Deze gegevens werden verkregen door middel van pre-formulering studies.
De oplosbaarheid en diffusiecoëfficiënt van de steroïden in de gebruikte polymeren werden verkregen door verzadiging van polymeer films in verzadigde steroïd oplossingen en door middel van "time lag" metingen.
Deze permeabiliteit gegevens werden ook afgeleid uit de release metingen van coaxiale vezels. Hieruit bleek dat de diffusiecoëfficiënt en oplosbaarheid, verkregen uit de pre-formulering studies, afwijken van de uit de in-vitro afgifte metingen verkregen waarden. Aangenomen werd dat dit verschil waarschijnlijk veroorzaakt wordt door verschillen in de structuur van het polymeer in films en coaxiale vezels.
Tevens wordt in hoofdstuk 2 beschreven dat de oplosbaarheid en afgiftesnelheid van etonogestrel door de aanwezigheid van ethinyl estradiol worden beïnvloed. De oplosbaarheid van etonogestrel in EVA polymeer neemt toe als de concentratie van ethinyl estradiol toeneemt. Omdat de afgiftesnelheid afhankelijk is van de oplosbaarheid zal ook de afgiftesnelheid veranderen. Bij een toenemende concentratie van ethinyl estradiol in de kern zal de afgiftesnelheid van etonogestrel uit de coaxiale vezel afnemen. Differential scanning calorimetry metingen laten zien dat beide steroïden een eutectic vormen. Het lagere smeltpunt van het eutectic resulteert uiteindelijk in een hogere oplosbaarheid en een toename van de permeabiliteit.
In hoofdstuk 3 wordt *het effect van oververzadiging en kristallisatie op de eigenschappen van een gecontroleerd afgifte preparaat gebaseerd op EVA polymeer* beschreven. Dit hoofdstuk beschrijft de invloed van de steroïd concentratie, de procesparameters tijdens bereiding en de opslag condities van de coaxiale vezel op de afgiftesnelheid van etonogestrel uit de vezel. Door de hoge temperaturen tijdens bereiding van de coaxiale vezel lost een grote hoeveelheid etonogestrel in het gesmolten polymeer op. Aangezien de afgiftesnelheid uit de coaxiale vezels recht evenredig is met de concentratiegradiënt over het membraan, is de hoeveelheid

opgeloste actieve stof die tijdens het afkoelen naar kamertemperatuur en opslag van de vezels weer uitkristalliseert van essentieel belang. De oplosbaarheid van etonogestrel werd bepaald bij zowel kamer- als extrusietemperatuur. De hoeveelheid etonogestrel die bij normale extrusietemperatuur oplost, is ongeveer 10 keer hoger dan bij kamertemperatuur. Om de invloed van oververzadiging en kristallisatie te onderzoeken werden coaxiale vezels bereid met verschillende steroïd concentraties. Het kristallisatie gedrag van het steroïd in het kernpolymeer werd bestudeerd door middel van thermische analyse en "hot stage" microscopie. Met differential scanning calorimetry werd aangetoond dat het polymeer debiet tijdens mengextrusie en de schroefsnelheid (toename van afschuifkrachten) ook invloed hebben op de hoeveelheid steroïd die tijdens bereiding van de vezel oplost.

De invloed van opslag condities op de afgiftesnelheid werd onderzocht door de vezels op te slaan bij diverse temperaturen. Gevonden werd dat als de hoeveelheid etonogestrel in het kernpolymeer kleiner is dan de kritische nucleatie concentratie bij kamertemperatuur, het opgeloste steroïd niet uitkristalliseert en in oververzadigde toestand blijft. Als anderzijds de hoeveelheid opgelost steroïd iets groter is dan de kritische nucleatie concentratie, zal het oververzadigde steroïd slechts zeer langzaam uitkristalliseren. Hierdoor is afgiftesnelheid uit de coaxiale vezels afhankelijk van de opslagcondities en zal in tijd veranderen. Elektronenmicroscopie en transmissie licht microscopie werden toegepast om kristallisatie gedrag van het oververzadigde steroïd in het polymeer te onderzoeken.

Vermoed wordt dat rekristallisatie van het oververzadigde steroïd ernstig wordt belemmerd door de polymeer matrix en dat het oververzadigde steroïd niet volledig kan uitkristalliseren. Als gevolg hiervan zal een kleine hoeveelheid steroïd in oververzadigde toestand blijven. Dit werd bevestigd door het release profiel van een verzadigde vezel te vergelijken met het release profiel van vezels waarin een overmaat kristallijn etonogestrel aanwezig was. Hierbij bleek dat de afgiftesnelheid van een verzadigde vezel ongeveer twee keer lager is dan de afgiftesnelheid van een vezel waarin kristallijn steroïd aanwezig is.

Hoofdstuk 4 beschrijft *de invloed van temperatuur effecten op de afgifte eigenschappen van een coaxiaal gereguleerd afgifte preparaat gebaseerd op EVA polymeren*. Differential scanning calorimetry werd toegepast om de invloed van de hoeveelheid vinyl acetaat op de kristalliniteit te bepalen. De kristalliniteit van diverse EVA polymeren werd bepaald door de smelt enthalpie te meten. De smelt enthalpie van 100% kristallijn polyethyleen (293 J/g) werd verkregen uit de literatuur en werd

gebruikt om de kristalliniteit van de EVA polymeren te berekenen. De kristalliniteit van de toegepaste EVA polymeren neemt af van ca. 43% naar 15% als het gehalte vinyl acetaat stijgt van 5% tot 40%. Als het gehalte vinyl acetaat toeneemt van 5% tot 14% stijgt de permeabiliteit ongeveer met een factor 3.

In de literatuur is beschreven dat thermische behandelingen (annealing) invloed hebben op de structuur van het polymeer. Door de temperatuur te verhogen neemt de grootte van de kristallijne en amorfe domeinen toe. Het is duidelijk dat een verandering in structuur van het polymeer invloed heeft op de afgifte eigenschappen van de coaxiale vezels. Om dit effect te onderzoeken, werden EVA polymeren met diverse gehaltes vinyl acetaat opgeslagen bij verschillende temperaturen (40, 50, 60 en 70 °C). Daarna werd de kristalliniteit bepaald door middel van differential scanning calorimetry. Hoewel de vorm van het thermogram beduidend veranderde onder invloed van de temperatuur behandelingen, was er geen significant effect op de kristalliniteit waarneembaar.

Steroïd beladen coaxiale vezels werden bereid met diverse typen polyethyleen vinyl acetaat in het membraan. Vervolgens werden vezels opgeslagen gedurende één dag bij 40, 50, 60 en 70 °C. Gevonden werd dat de afgiftesnelheid van het steroïd significant toeneemt met stijgende opslag temperatuur. Dit effect neemt af als een EVA polymeer in het membraan wordt toegepast met hoger gehalte vinyl acetaat. Omdat de hoeveelheid kristallijne domeinen met een stijgend gehalte vinyl acetaat afneemt, neemt ook de bijdrage van de kristallijne domeinen op de afgifte eigenschappen af. Daarom heeft een toename in de grootte van de kristallijne domeinen een kleinere invloed op de release. Aangezien de permeabiliteit het product is van zowel oplosbaarheid als diffusiecoëfficiënt werd de oplosbaarheid van etonogestrel bepaald in EVA polymeren als functie van warmte behandeling. Gevonden werd dat de oplosbaarheid niet significant toeneemt, met hogere opslag temperatuur. Daarom kan geconcludeerd worden dat de toenemende permeabiliteit veroorzaakt wordt door een toenemende diffusiecoëfficiënt.

De structuur van het polymeer wordt niet alleen beïnvloed door de opslag temperatuur maar wordt ook beïnvloed door de afkoelsnelheid tijdens kristallisatie van het polymeer. Gevonden werd dat de afgiftesnelheid afneemt bij een toenemende afkoelsnelheid. Deze afname wordt verklaard doordat de grootte van de kristallijne en amorfe domeinen afneemt bij een grotere afkoelsnelheid. Dit resulteert uiteindelijk in een in een lagere permeabiliteit.

In hoofdstuk 5 wordt *de invloed van de extrusie parameters op de afgifte en mechanische eigenschappen van een coaxiaal gereguleerd afgifte preparaat gebaseerd op EVA co-polymeer* beschreven. In de literatuur wordt beschreven dat de procesparameters tijdens het smeltspinnen van polymeer vezels een significante invloed op de structuur van het polymeer kunnen hebben. Omdat de permeabiliteit van een polymeer beïnvloed wordt door de structuur van het polymeer, zullen de procesparameters ook invloed hebben op de afgifte eigenschappen van de coaxiale vezels. Om dit te onderzoeken, werden vezels bereid met verschillende extrusie temperatuur, lucht spleet (afstand tussen spingarnituur en wateroppervlak) en extrusie snelheid. Gevonden werd dat deze procesparameters een significante invloed op de afgifte eigenschappen van de coaxiale vezel hebben. De afgiftesnelheid van etonogestrel uit de coaxiale vezel neemt toe, indien de vezels bij lagere extrusie temperatuur en kleinere luchtspleet worden vervaardigd. De structuur van het polymeer heeft niet alleen invloed op de afgifte eigenschappen maar ook de mechanische eigenschappen van de vezel. Om dit te onderzoeken werden de mechanische eigenschappen van vezels bepaald door middel van een trekbank. Gevonden werd dat de verstrekking tot breuk van de vezel afneemt als de vezel wordt bereid bij een lagere extrusie temperatuur, kleinere luchtspleet en hogere extrusie snelheid. Een lineaire relatie werd aangetoond tussen de afgiftesnelheid en verstrekking tot breuk. Dit fenomeen wordt verklaard doordat de structuur van het polymeer georiënteerd raakt als gevolg van de procescondities. In de literatuur wordt beschreven dat de structuur van het polymeer in georiënteerde vezels gekenmerkt wordt door een gestapelde structuur van kristallijne lamellen en amorfe domeinen waarbij de lamellen loodrecht staan op de vezel-as. Het is aannemelijk dat een georiënteerde structuur van gestapelde lamellen die loodrecht op de vezelas staan ook een significante invloed heeft op de afgifte eigenschappen van de coaxiale vezels.

Hoofdstuk 6 beschrijft *de invloed van spinlijn spanning op de afgifte eigenschappen van een gereguleerd afgifte preparaat gebaseerd op EVA polymeren*. Tijdens het smelt spinnen van polymeer vezels, wordt het gesmolten polymeer gedwongen door een smal capillair te stromen. Daardoor wordt het gesmolten polymeer voor en in het capillair blootgesteld aan afschuifkrachten en externe krachten. Bij het verlaten van het capillair is het gesmolten polymeer niet meer omsloten en zal zich ontspannen door te zwellen. Dit resulteert in een diameter die groter is dan het capillair. De mate van zwelling wordt beïnvloed door de procesparameters en de visco-elastische

eigenschappen van het polymeer. Als de mate van zwelling groter dan de gewenste diameter van de coaxiale vezel, is het noodzakelijk is om de vezel met een bepaalde kracht naar de gewenste diameter te verstrekken.

De benodigde spinkracht is afhankelijk van de procesparameters en het gebruikte polymeer. Gebleken is dat de benodigde kracht toeneemt bij lagere extrusie temperatuur, een kleiner luchtspleet of bij een hogere spinsnelheid. Om de aard van dit fenomeen te onderzoeken werden steroïd beladen coaxiale vezels (met een diameter van 4 mm) bereid bij verschillende procescondities en werd de spinkracht gemeten. Na productie van de coaxiale vezels werd de afgiftesnelheid van etonogestrel bepaald bij 37 °C. Een lineair verband werd gevonden tussen de afgiftesnelheid en de spinkracht. Omdat de afgiftesnelheid uit de coaxiale vezel voornamelijk door het membraan wordt bepaald, werd de structuur van het polymeer in het membraan onderzocht met "Wide Angle X-ray Scatering" (WAXS). Hieruit bleek dat bij toenemende spinkracht de structuur van het polymeer in de lengte richting van de vezel georiënteerd raakt. Tevens bleek dat bij toenemende spinkracht de het kristalliniteit afneemt en dientengevolge de permeabiliteit van het polymeer toeneemt.

In hoofdstuk 7 wordt het *effect van proces afhankelijke veranderingen in de morfologie van het membraan van een coaxiaal gereguleerd afgifte preparaat* beschreven. Coaxiale vezels werden bereid bij verschillende procescondities en met verschillende EVA polymeren in het membraan. Gevonden werd dat de spinkracht tijdens het verstekken van de gesmolten vezels voornamelijk bepaald wordt door het membraan polymeer. De vezel wordt niet alleen verstrekt in de luchtspleet maar ook voor een gedeelte onder het wateroppervlak. De totale lengte waarover verstrekt wordt, is afhankelijk van het EVA polymeer en neemt toe voor EVA polymeren met een groter gehalte vinyl acetaat. Gevonden werd dat de lengte waarover verstrekt wordt omgekeerd evenredig is met de spinkracht. Coaxiale vezels bestaande uit EVA polymeren met een lager gehalte vinyl acetaat worden verstrekt over een kleinere lengte met een hogere spinkracht. Hoe hoger de spinkracht des te meer de vezel georiënteerd raakt. Dit komt wederom tot uitdrukking in de mechanische eigenschappen van de vezel. Gevonden werd dat voor de onderzochte EVA polymeren de verstrekking tot breuk omgekeerd evenredig is met de spinkracht. Transmissie Elektronen Microscopie (TEM) bevestigt verschillen in de polymeer morfologie van het membraan. Een toenemende spinkracht resulteert in een polymeer morfologie van het membraan dat gekenmerkt wordt door een gestapelde

structuur van kristallijne lamellen en amorfe domeinen waarbij de lamellen loodrecht staan op de vezel-as.

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Curriculum Vitae

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Research scientist; Development of a unary color toner to be used in existing copiers; development of alternative color printer technologies.

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Validation Officer; validation of pharmaceutical equipment and processes.

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Development scientist; development of new pharmaceutical technologies: development of alternative freeze dried products and technology (lyospheres); extrusion technology of polymers and development of coaxial sustained release devices based on polyethylene vinyl acetate polymer.

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