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In vitro release properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring

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Abstract

The release properties of steroids from a combined contraceptive vaginal ring have been investigated. The product design is based on a coaxial fiber consisting of two types of polyethylene vinylacetate 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, 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 can be concluded from this study that polyethylene vinylacetate copolymers exhibit suitable properties to develop a controlled release system with the two steroids etonogestrel and ethinyl estradiol. It has been 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 has also been 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.

Keywords: Drug delivery; Vaginal ring; Controlled release; Steroid interaction

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.

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An example of a sustained release system is a contraceptive vaginal ring that is designed to release steroid hormones, which 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 vinylacetate (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 vinylacetate.

The coaxial fiber consists of a core polymer, with one or more steroids incorporated, that is enveloped with a thin polymer 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 however, 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).

For this reason the interaction between the applied steroids has also been assessed and its consequences subsequently determined. In particularly the influence of ethinyl estradiol on the solubility and release properties of etonogestrel has been investigated.

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:

$$P = D\,S, \tag{1}$$

where P is permeability (kg/ms); D is diffusion coefficient (m^2/s); S is solubility (kg/m^2).

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:

$$J = -D\frac{\mathrm{d}C}{\mathrm{d}x}, \tag{2}$$

where J is mass flux (kg/m^2 s); D, diffusion coefficient (m^2/s); $\mathrm{d}C$, concentration gradient over the membrane (kg/m^3); $\mathrm{d}x$, 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:

$$\frac{dM_t}{dt} = \frac{2\pi LDK\,\Delta C}{\ln(r_o/r_i)}, \quad (3)$$

where 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:

$$K = \frac{Cs_{skin}}{Cs_{core}}, \quad (4)$$

where Cs_{skin} is solubility of the drug in the membrane polymer (kg/m^3); Cs_{core}, solubility of the drug in the core polymer (kg/m^3).

Literature (Martin et al., 1983) describes the relation between the mole fraction solubility and temperature of a solid drug in non-ideal solutions as a logarithmic function (Eq. (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).

$$\log X_2 = -\frac{\Delta H_f}{2.303\,R}\frac{T_0 - T}{T_0\,T} + \log \gamma_2, \quad (5)$$

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 Eq. (6), the relation between the activity coefficient and solubility parameters (which express the cohesion forces between like molecules) of both solute and solvent is given:

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

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 Eq. (5) will be zero.

3. Materials and methods

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 1.

Different types of polyethylene vinylacetate copolymers were used. 'EVA 28' contains 28% of vinylacetate 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 vinylacetate and is applied in the membrane because of lower solubility and permeability properties.

3.2. Methods

3.2.1. Solubility in polymer films (at low temperatures)

In order to determine the solubility of steroids at low temperatures in polyethylene vinylacetate

Table 1
Thermodynamical parameters of etonogestrel and ethinyl estradiol

Steroid	Melting point (°C)	Heat of fusion (J/g)	Molar weight (g/mole)	Solubility parameter$_{\frac{1}{2}}$ (Rowe, 1988) $(MPa)^{\frac{1}{2}}$
Etonogestrel	199	96	324	20.0
Ethinyl estradiol	182–184	93	296	23.7

copolymers, films of about 200 μm were prepared by film extrusion. The films were cut in pieces of 5 × 5 cm and subsequently immersed in saturated aqueous steroid solutions at 25 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 h at a temperature of 70 °C and subsequently the concentration of steroid was assessed by HPLC.

HPLC conditions:

Column	Novapak C18 3.9 × 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. Solubility in melted polymer (at elevated temperatures)

The solubility of steroids in polyethylene vinylacetate copolymers has also been 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 (90–180 °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.

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 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:

$$P = \frac{\mathrm{d}M_t}{\mathrm{d}t}\frac{d}{A}, \tag{7}$$

where P is permeability (kg/ms); $\mathrm{d}M_t/\mathrm{d}t$, 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 $\mathrm{d}M_t/\mathrm{d}t$ 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:

$$L = \frac{d^2}{6D}, \tag{8}$$

where L is 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 Eqs. (7) and (8). The maximal saturation of the membrane (Cs) can be calculated from the permeability and the diffusion coefficient (Eq. (1)).

3.2.4. Differential scanning calorimetry

A Perkin–Elmer differential scanning calorimetry (DSC7) apparatus was used to study the com-

Table 2
The solubility of etonogestrel and ethinyl estradiol at 25 and 37 °C

Steroid	25 °C			37 °C		
	Solubility (wt.%)		Partition coefficient	Solubility (wt.%)		Partition Coefficient
	EVA 28	EVA 9		EVA 28	EVA 9	
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

patibility 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.

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 have been produced with varying steroid concentrations in the core polymer. EVA 28 and 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 has been 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 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 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.

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.

4. Results and discussion

4.1. Pre-formulation studies

4.1.1. Solubility in flat films

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

As can be seen, the solubility of etonogestrel at 37 °C in EVA 28 and 9 is respectively 0.43 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 (Eq. (3)). Unfortunately, the effect is not very consistent. For etonogestrel, K seems to increase, while ethinyl estradiol shows a reverse tendency.

4.1.2. Solubility in molten polymer

Fig. 1 plots the solubility of etonogestrel and ethinyl estradiol in EVA 28 at elevated temperatures. In this figure the solubility of etonogestrel has also been determined when ethinyl estradiol was added 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 Eq. (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.

Fig. 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 has also been 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 has been 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 dimin-

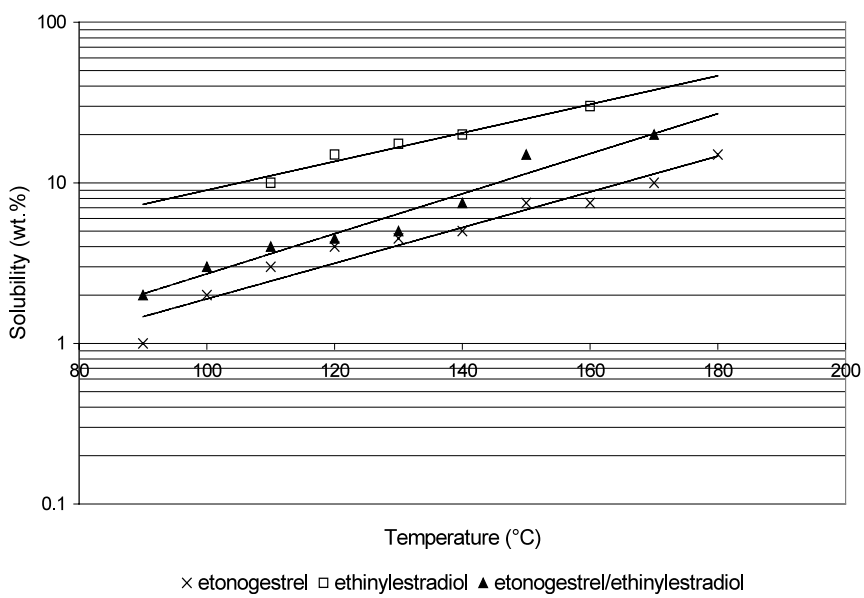

Fig. 1. The solubility of steroids in EVA 28.

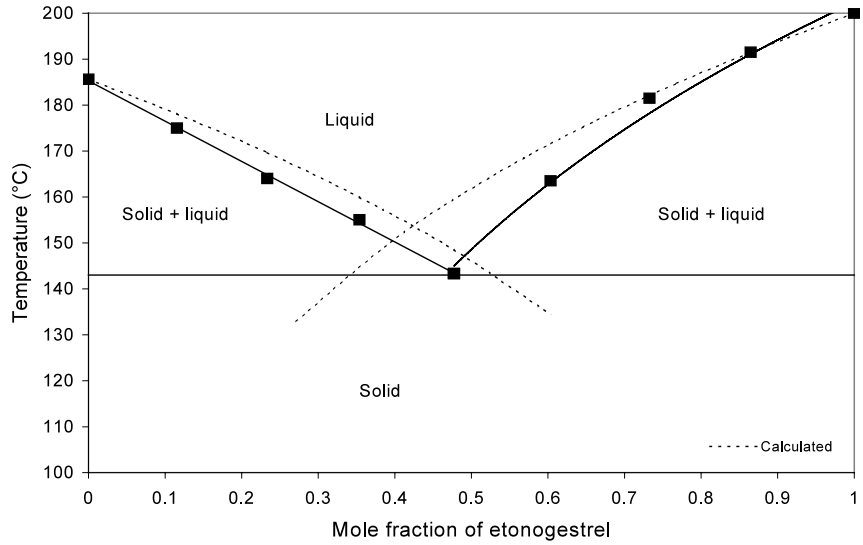

Fig. 2. Phase diagram of etonogestrel and ethinyl estradiol.

ished (i.e. shifted towards the solid phase) and so the equilibrium of the system will be reestablished. Eq. (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, Eq. (9) was deducted from Eq. (5). Because the solubility parameters of the steroids investigated are almost equal (Table 1), the second term in Eq. (5) will be zero.

$$T_{(A)} = -\left[\frac{1}{(\log(1 - X_{(B)})\,(2.303R/\Delta H_{f(A)})) - 1/T_{0(A)}}\right], \quad (9)$$

where $T_{(A)}$ is 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 Fig. 2, Eq. (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 (Eq. (5)). Hence, the solubility of etonogestrel is raised in the presence of ethinyl estradiol because of the eutectic melting point depression.

4.1.3. Time–lag method

The amount of steroid measured in the acceptor cell has been plotted against time. The permeability and diffusion coefficients were calculated from the slope and intercept of the curve, using Eqs. (7) and (8). The maximal saturation of the membrane (Cs) 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.%).

4.2. Formulation studies

4.2.1. The influence of the steroid concentration on the release

In Fig. 3 the release of coaxial fibers with varying concentrations of etonogestrel in the core has been plotted. In the first few days a higher release rate can be observed. This so-called burst release is caused by release of the 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 Eq. (4) exists. 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 Eq. (3).

The zero time release was calculated by extrapolating the steady state release to $t = 0$ and was plotted versus the concentration of etonogestrel in the core (Fig. 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 KD can be derived from the slope of the regression line (Eq. (3)). In order to calculate the diffusion coefficient (D) the partition coefficient (K) has to be determined.

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 zero time release from the burst release and subsequently multiplying it by two, the amount of etonogestrel that is dissolved in the membrane polymer before release can be calculated. In Fig. 4 this amount is plotted versus the concentration of etonogestrel in the core.

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

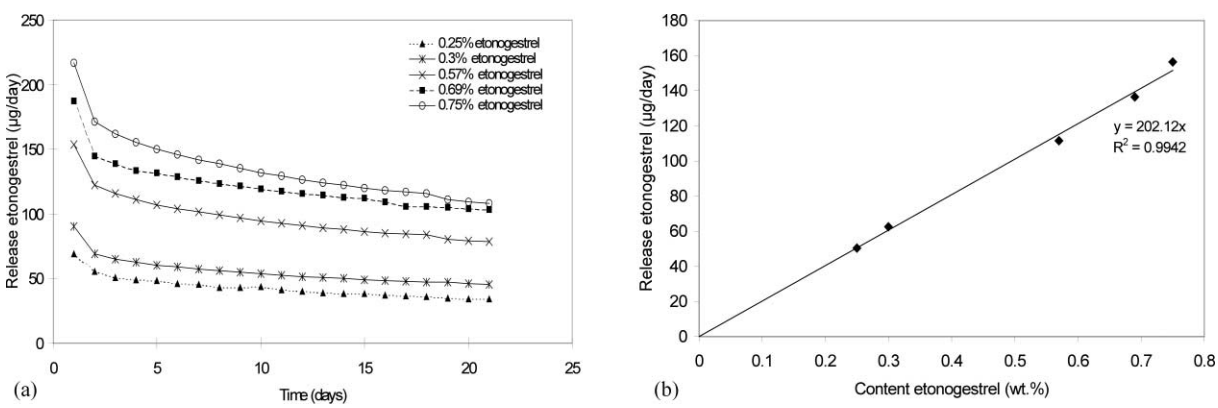

Fig. 3. (a) The in vitro release of etonogestrel at several concentrations etonogestrel; (b) the influence of the concentration etonogestrel in the core on the steady state release ($t = 0$).

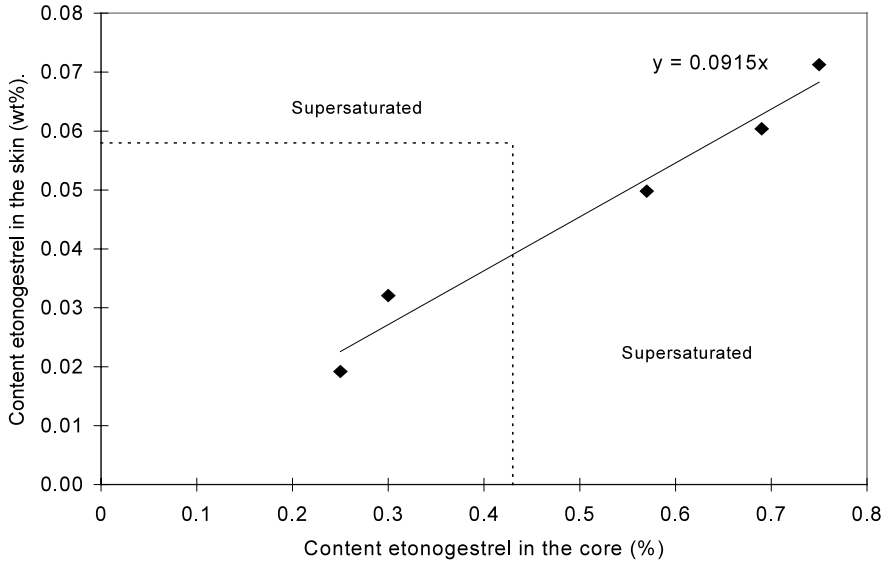

Fig. 4. Relation between the concentration of etonogestrel in core and membrane.

Section 3.2.1 it has been determined that the solubility of etonogestrel in EVA 28 and 9 at a temperature of 37 °C is, respectively 0.43 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.

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. Fig. 5 shows that a reasonable estimate can be made. The curve, calculated from the data given in Fig. 3 coincides with the actually found curve, which is in fact logical, since this figure is based on real coaxial fiber data.

When data from the pre-formulation studies are used to calculate the release, a less perfect fit is obtained. Obviously, the value 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.

4.2.3. Influence of steroid interaction on the release

It was earlier shown Section 4.1.1 that the solubility of etonogestrel in polyethylene vinylacetate 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 Fig. 6a, the release of etonogestrel decreases by about 12% by increasing the ethinyl estradiol content from 0 to 1%. Because the release is dependent on both diffusion and partition coefficient (Eq. (3)) it is essential to investigate the nature of the decrease.

Therefore, the partition coefficient of etonogestrel as a function of the ethinyl estradiol content has been calculated from the burst release of the saturated membrane (same method as used in Section 4.2.1, Fig. 4). In Fig. 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 pre-formulation studies with the flat film solubilities, 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 pre-formulation studies (time–lag method and solubility in flat films) should be interpreted with care.

5. Conclusion

It can be concluded from this study that polyethylene vinylacetate 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 has been 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 has been 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 has been found that the steroid can be present in the membrane polymer at a supersaturated level.

It has also been 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.

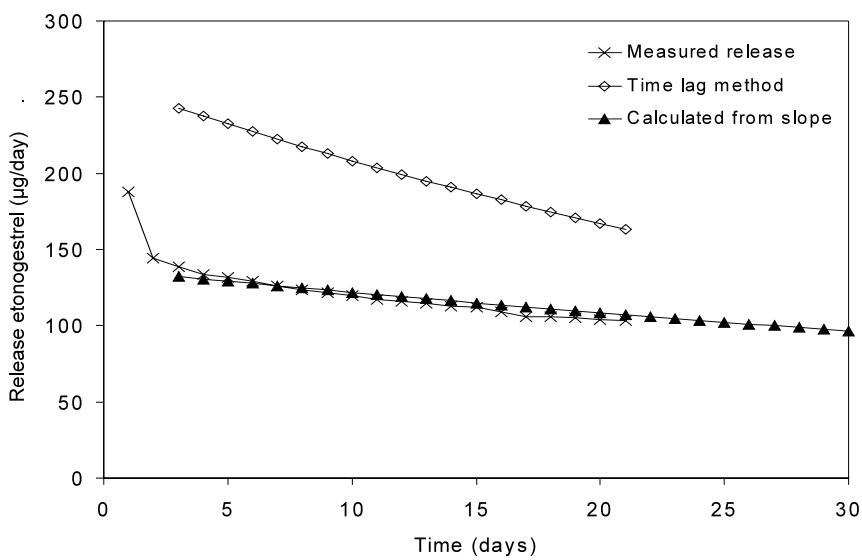

Fig. 5. The release calculated from the diffusion coefficient obtained by the time–lag method and obtained from the slope of Fig. 3b.

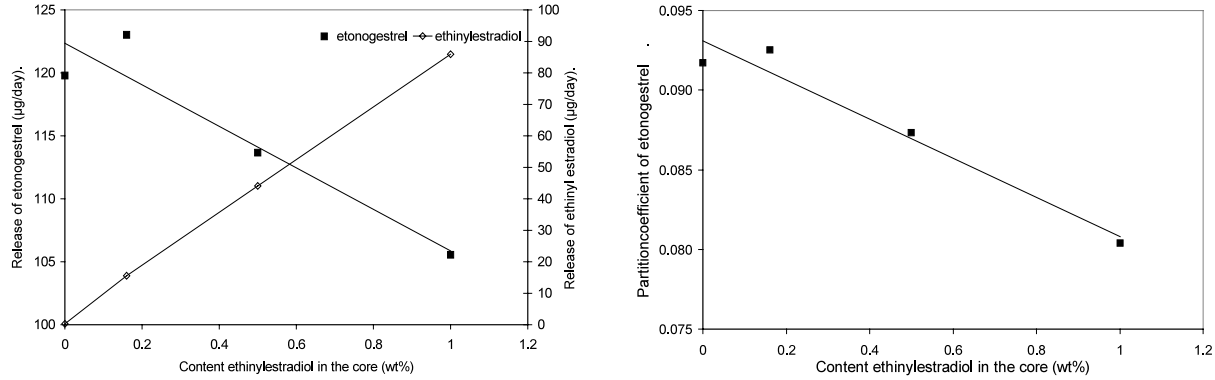

Fig. 6. (a) The influence of the content ethinyl estradiol on the average release of etonogestrel and ethinyl estradiol; (b) the influence of the content ethinyl estradiol in the core on the partition coefficient of etonogestrel.

References

Baker, R.W., Lonsdale, H.K., 1974. In: Tanquarry, A.C., Lacey, R.E. (Eds.), Controlled Release of Biologically Active Agents. Plenum, New York, pp. 15–71.

Brinker, K.C., 1977. EVA Copolymers: Raw Materials for Hot Melt Pressure-Sensitive Adhesives, Adhesives Age, August, pp. 38–40.

Chien, W., Paul, D., Harris, F., 1976. Thermodynamics of Controlled Drug Release from Polymeric Delivery Devices, Controlled Release Polymeric Formulations ACS Symposium Series, No. 33, chap. 5.

Diaz-Sanchez, V., Antunez, O., Vargas, L., Boeck, L., Noguera, M., 1991. Absorption of oral ethinyl estradiol is delayed by its eutectic mixture with cholesterol. Contraception 43, 45–53.

Dorset, D.L., 1988. Co-solubility of saturated cholesterol esters: a comparison of calculated and experimental binary phase diagrams. Biochim. Biophys. Acta 963, 88–97.

Dorset, D.L., 1992. Binary phase behavior of angiotoxic oxidized cholesterols with cholesterol. Biochim. Biophys. Acta 1127, 293–297.

Johnsen, U., Nachtrab, G., 1969. Die Kristallinität von Äthylen-Vinylacetat-Copolymeren. Die Ang. Makromol. Chem. 7, 134–146.

Kaplun-Frischoff, Y., Touitou, E., 1997. Testosterone skin permeation enhancement by menthol through formation of eutectic with drug and interaction with skin lipids. J. Pharma. Sci. 86, 1349–1399.

Martin, A., Swarbrick, J., Cammarata, A., 1983. Physical Pharmacy, third ed. pp. 281–287.

Narasimhan, B., Peppas, A., 1997, The Role of Modeling Studies in the Development of Future Controlled-Release Devices, Controlled Drug Delivery ACS, chap. 26, pp. 529–557.

Rowe, R.C., 1988. Binder-substrate interactions in tablets: a theoretical approach based on solubility parameters. Acta Pharm. Technol. 34, 144–146.

Salyer, I.O., Kenyon, A.S., 1971. Structure and property relationships in ethylene–vinyl acetate copolymers. J. Poly. Sci.: Part A1 9, 3083–3103.

Yanez, L., Jung, H., Garza-Flores, J., Pérez-Palacios, G., Diaz-Sanchez, V., 1988. Norethisterone–cholesterol eutectic mixture as an oral sustained-release hormonal preparation: bioequivalence study in humans. Contraception 37, 349–357.