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The Effect of Drug Content Reduction on the *In Vitro* and *In Vivo* Properties of Levonorgestrel-Releasing Intravaginal Rings

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ABSTRACT

Intravaginal rings (IVRs) are an option for continuous administration of drugs in women. However, a considerable amount of excess drug often remains in the ring upon removal. The current study focuses on comparing 2 IVRs releasing levonorgestrel (LNG). Both formulations were designed to release 40 μg of LNG daily, however, with a significant difference in the total amount of drug (10.6 vs. 176.9 mg). Numerical simulations and *in vitro* release rate testing were utilized in designing the IVRs and confirming the similarity of drug release. Moreover, a pharmacokinetic (PK) study was performed in 13 healthy Japanese women to investigate both formulations during the intended wearing period of 28 days. The primary PK metrics was the average concentration of LNG in plasma at defined time points under stable conditions. Statistical evaluation of the ratio of the main PK metrics indicated values almost in the bioequivalence range. Furthermore, drug content determinations for used and unused IVRs were analyzed for confirming the expected drug delivery *in vivo*. In summary, it was shown that with proper design, even major differences in the total drug content of IVR formulations might not result in significant effects in the *in vitro* and *in vivo* release properties.

Introduction

Intravaginal administration has been known to be a feasible route for local and systemic delivery for various pharmaceutically active agents, such as steroids.[1-3] One advantage of this administration over the oral route is the avoidance of hepatic first-pass metabolism[1]; others include the continuous drug delivery and reduced compliance risks. The first reports on steroid-releasing vaginal rings were already made in the early 1970s,[4] but it was not until the 1980s that the first contraceptive trials with vaginal rings were conducted.[5] Nowadays, commercial intravaginal rings (IVRs) are available for contraception (NuvaRing®, which releases etonogestrel and ethinylestradiol)[6-9] and for hormone replacement therapy.[10] Lately, efforts have been directed toward developing IVRs for preventing the transmission of HIV.[11-14]

Levonorgestrel (LNG) is a well-characterized drug substance approved for contraception as progestin-only pills (e.g., Norgeston, corresponding to Microlut in other countries), subcutaneous implants (e.g., Jadelle®), or intrauterine systems (e.g., Mirena®; Kyleena®). The first reports on clinical studies of contraceptive rings releasing LNG and estradiol were published in the early 1980s.[15] The rings were made from silicone elastomer, where an outer membrane was used for controlling the rate of drug release. IVRs releasing LNG are currently not commercially available, and there is room for improvement regarding the LNG formulation in experimental rings. For example, despite the layered structure, about 60% of LNG remained unused in the early contraceptive IVRs after 6 menstrual cycles.[15] A similar trend was also apparent in the IVRs developed for treating endometriosis and ensuring contraception with an intended wearing period of 28 days.[16,17] One study identified a target release rate of 40 μg/d LNG providing plasma concentrations that are similar to marketed contraceptive products. The rings used in this study had, however,

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a large excess of LNG compared to the amount released.[16] Among others for environmental reasons, it would be preferable to minimize the amount of excess drug in the IVR formulation. However, this should be done without affecting the release characteristics and clinical efficacy of the drug product. The most simple means to evaluate the effects of changes in the drug formulation is by evaluating the changes in the *in vitro* release characteristics. Nevertheless, in the absence of an *in vitro-in vivo* correlation, an *in vivo* comparison of the changed formulation is also a necessity. In the present study, the effects of reducing the LNG content in an IVR formulation have been explored. The aim of the study was to reduce the drug content in the formulation without affecting *in vitro* or *in vivo* release characteristics and pharmacokinetics (PK).

Materials and Methods

Materials

Micronized LNG from Bayer AG was used as the active pharmaceutical ingredient (API). Particle size according to laser diffraction was smaller than 20 μm for all particles. Two polydimethylsiloxane (PDMS) elastomer materials were used as material to manufacture the intravaginal drug delivery formulations, that is, a PDMS-containing silica for the membrane and drug-free parts, and a PDMS material with no silica for the drug-containing segment.

Intravaginal Ring

The intravaginal drug delivery system is a flexible elastomeric ring with an outer diameter of 55 mm and a cross-sectional width of 5 mm. The IVR holds a drug-free segment and drug-containing segment that releases the drug continuously for 28 days. The target nominal LNG release was 40 μg per day. The ring contains excess drug to enable a steady drug release. The outer surface is covered with 1 continuous transparent elastomeric membrane controlling the drug release.

Formulations A and B

Two distinct formulations were prepared for the clinical study. In formulation A, the drug was dispersed uniformly in a PDMS-elastomer matrix, which has been used for forming the drug-containing segment. In formulation B, the drug-elastomer matrix layer was sandwiched between the rate-controlling membrane and a drug-free elastomer core, thus, making the drug content smaller (Fig. 1). In addition, the drug concentration in the drug-containing elastomer material was higher in formulation A (50 weight (w)% vs. 5 w% in formulation B). For both formulations, the same release rate−controlling membrane was used as the outer surface.

Mathematical and Statistical Evaluation

Drug Release Model for Numerical Simulations. The release of LNG from the IVR was modeled numerically by applying Fick's diffusion equations to the cylindrical case. However, in order to describe the system in simple terms, some assumptions regarding system properties were made. First, it was assumed that the drug particles are dispersed homogenously inside the elastomer matrix. Second, the elastomer matrix was considered to be isotropic. Diffusion was only analyzed in radial direction, that is, diffusion to the sides of the drug segment was neglected. Moreover, solvation of drug molecules from the crystalline drug particles to the elastomer matrix was considered to be infinitely faster than diffusion. Therefore, the concentration of dissolved drug remains at saturation level, as long as crystalline drug particles are present in the drug-containing core. Depletion of the drug particles from the core was described by using the moving boundary approximation, that is Higuchi approximation, and is described schematically in Figure 2.[18]

The temporal evolution of concentration gradients in the system was calculated using Fick's second law, which in cylindrical form reads:

$$\frac{\partial C_i(r,\varphi,z)}{\partial t} = D_i \nabla^2 C_i(r,\varphi,z) = D_i \left[\frac{1}{r}\frac{\partial}{\partial r}\left(r \frac{\partial C_i(r,\varphi,z)}{\partial r} \right) + \frac{1}{r^2}\frac{\partial^2 C_i(r,\varphi,z)}{\partial \varphi^2} + \frac{\partial^2 C_i(r,\varphi,z)}{\partial z^2} \right], \quad (1)$$

where C_i is the individual concentration in a given zone (membrane or core), t is the time, D_i is the diffusion coefficient in a given zone (membrane or core), and r, φ, and z are the cylindrical coordinate variables. However, as we assume that diffusion is identical toward all angular directions, and also ignore diffusion in the z-axis direction, the equation can be simplified to the following form:

$$\frac{\partial C_i(r)}{\partial t} = D_i \left[\frac{1}{r}\frac{\partial}{\partial r}\left(r \frac{\partial C_i(r)}{\partial r} \right) \right] = D_i \left(\frac{\partial^2 C_i(r)}{\partial r^2} + \frac{1}{r}\frac{\partial C_i(r)}{\partial r} \right). \quad (2)$$

This equation was applied between the moving boundary and the membrane ($r_m < r < r_1$), and also inside the membrane ($r_1 < r < r_2$). Boundary conditions for solving the equations are obtained when concentration C is considered to be equal to the saturation concentration when drug particles are present ($r_0 < r < r_m$). The boundary condition at the interface of the membrane and core ($r = r_1$) is defined by the partition coefficient K, in the following manner:

$$C_2(t, r_1) = K_{2/1} C_1(t, r_1), \quad (3)$$

where C_2 (t, r_1) is the concentration of dissolved drug on the membrane side, and C_1 (t, r_1) is the same concentration on the side of the core. Calculations were performed in a way, which allowed for a saturated solution state inside the membrane to form before drug release through the membrane was possible (i.e., so-called membrane loading during storage was simulated by incorporating long enough storage time). Drug release through the membrane was calculated by assuming that the drug is transported from the membrane surface according to the following equation:

$$\Phi = k_c K_{f/2} C_2(r_2, t), \quad (4)$$

where Φ is the flux density, k_c is the mass transfer coefficient, $K_{f/2}$ is the partition coefficient between the reception medium and the membrane, and C_2 (r_2, t) is the concentration of dissolved drug at the outer edge of the membrane at a certain point in time. The position of the moving boundary is described simply by decreasing the outer radius of the drug-containing cylinder as drug particles are depleted. Total flux was obtained by multiplying the flux density Φ, with the outer surface area of the drug-containing cylinder. The model development and the numerical algorithms for solving the previously mentioned equations (which were solved using MATLAB®) were provided by Xemet Co.[19]

Formulation A used in the present study was prepared by mimicking the IVR formulation used in the earlier clinical study and resulted in a daily nominal release rate of 40 μg/d.[16] Numerical release rate simulations were utilized in designing formulation B with the aim of having a similar *in vitro* release rate profile as formulation A, but a significantly lower API content. First, the numerical release rate for formulation A was modeled. The dimensions of the API segment, drug solubility, and diffusion