European Journal of Pharmaceutics and Biopharmaceutics 85 (2013) 966–973

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Investigating the feasibility of temperature-controlled accelerated drug release testing for an intravaginal ring

Anna Externbrink [a], Meredith R. Clark [b], David R. Friend [b], Sandra Klein [a,*]

[a] Department of Pharmacy, University of Greifswald, Greifswald, Germany
[b] CONRAD, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Arlington, VA, USA

ARTICLE INFO

Article history:
Received 22 February 2013
Accepted in revised form 6 June 2013
Available online 18 June 2013

Keywords:
Diffusion-controlled drug release
Extended release delivery systems
Nuvaring®
USP apparatus 7
Reciprocating holder
Vaginal delivery
Quality control

ABSTRACT

The objective of the present study was to investigate if temperature can be utilized to accelerate drug release from Nuvaring®, a reservoir type intravaginal ring based on polyethylene vinyl acetate copolymer that releases a constant dose of contraceptive steroids over a duration of 3 weeks. The reciprocating holder apparatus (USP 7) was utilized to determine real-time and accelerated etonogestrel release from ring segments. It was demonstrated that drug release increased with increasing temperature which can be attributed to enhanced drug diffusion. An Arrhenius relationship of the zero-order release constants was established, indicating that temperature is a valid parameter to accelerate drug release from this dosage form and that the release mechanism is maintained under these accelerated test conditions. Accelerated release tests are particularly useful for routine quality control to assist during batch release of extended release formulations that typically release the active over several weeks, months or even years, since they can increase the product shelf life. The accelerated method should therefore be able to discriminate between formulations with different release characteristics that can result from normal manufacturing variance. In the case of Nuvaring®, it is well known that the process parameters during the extrusion process strongly influence the polymeric structure. These changes in the polymeric structure can affect the permeability which, in turn, is reflected in the release properties. Results from this study indicate that changes in the polymeric structure can lead to a different temperature dependence of the release rate, and as a consequence, the accelerated method can become less sensitive to detect changes in the release properties. When the accelerated method is utilized during batch release, it is therefore important to take this possible restriction into account and to evaluate the accelerated method with samples from non-conforming batches that are explicitly "out of specification" under real-time test conditions.

1. Introduction

Non-oral extended release dosage forms are often designed to deliver the incorporated drug over extended periods of time that can last from weeks to months or even years. Real-time dissolution testing of these dosage forms requires respective time spans which can be disadvantageous or even unacceptable, particularly with respect to quality control (QC) where the time to batch release and thus the product shelf life are directly affected [1]. In recent years, this problem has been addressed in the literature and some attention has been directed toward developing accelerated release tests for a variety of extended release parenteral dosage forms [2–6]. A general requirement for accelerated drug release testing is that the accelerated test can discriminate between formulations with different release characteristics, whereas real-time and accelerated release should at least show the same rank-order relationship between the release profiles [3]. Ideally, accelerated and real-time release should follow the same release mechanism with a linear correlation between the release profiles. *In vitro* release tests should be designed with biorelevance as the ultimate goal. Therefore, it is achievable that the accelerated test is predictive of *in vivo* performance, but even if a correlation between *in vivo* and *in vitro* release cannot be established, the accelerated test can still prove useful for QC during batch release [7]. Parameters that can be utilized to accelerate drug release can include temperature, solvent, ionic strength, pH, enzymes, surfactants, and agitation rate [1]. Temperature was found to accelerate drug release from biodegradable polymeric microparticles/microspheres, i.e., PLGA (poly(lactic-co-glycolic)acid) microspheres where drug release is controlled by diffusion, polymer erosion, and a combination thereof [3]. For such products, accelerated tests were able to predict the secondary,

* Corresponding author. Department of Pharmacy, Institute of Biopharmaceutics and Pharmaceutical Technology, Ernst Moritz Arndt University Greifswald, 3 Felix Hausdorff Street/Center of Drug Absorption and Transport, Greifswald 17489, Germany. Tel.: +49 3834 86 4897; fax: +49 3834 86 4886.
E-mail address: Sandra.Klein@uni-greifswald.de (S. Klein).

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http://dx.doi.org/10.1016/j.ejpb.2013.06.004

erosion-controlled, zero-order release phase at 37 °C with a linear correlation between real-time and accelerated release. The temperature dependence of the zero-order release constants was found to be well predicted by the Arrhenius equation. For the investigated PLGA microspheres, the increase in drug release upon exposure to elevated temperature was a result of an increase in polymer degradation. Temperature has also been reported to increase drug diffusion from biodegradable polymeric systems at temperatures above the glass transition temperature which can be explained by enhanced polymer mobility [5,8].

To date, hardly any information is available on temperature-controlled accelerated release testing from non-degradable polymers. Examples of non-degradable polymers in controlled release delivery systems are polysiloxanes, polyethylene vinyl acetate (pEVA), and polyurethanes. Controlled release devices based on these polymers include implants, intravaginal rings (IVR's), intrauterine devices, and ocular inserts [9]. One of the first controlled delivery devices was the contraceptive intravaginal ring [10,11]. In recent years, the use of IVR's has expanded from the controlled delivery of contraceptives and hormonal replacement therapy to the targeted delivery of microbicides and other drugs for prevention of sexually transmitted infections including HIV [11–13]. Depending on the intended use, the rings are usually designed to deliver the active drug for weeks up to an entire year and therefore the need for accelerated release testing should be addressed for this dosage form. To date commercially available IVR's are either matrix or reservoir type. An example for a marketed reservoir type IVR is Nuvaring®, a combined hormonal contraceptive IVR manufactured by Merck Sharp & Dohme (formerly Organon). The ring releases 120 μg etonogestrel (ENG) and 15 μg ethinylestradiol per day over a period of 21 days. Nuvaring® is made from two different types of pEVA that form a core and a membrane with the drug being incorporated in the core polymer. The permeability depends on the vinyl acetate content and is much higher in the core and thereby diffusion from the device is controlled by the rate controlling membrane. The drugs are present in the core in a supersaturated state, and the concentration remains spatially uniform to provide a driving force for diffusion that is nearly constant over time resulting in a near zero-order release. The ring is manufactured via a hot melt coextrusion process [9]. The physical–chemical characteristics of Nuvaring® have been thoroughly investigated by van Laarhoven et al. [9,14,15].

FDA-approved *in vitro* test conditions for Nuvaring® comprise of an automated "release-control system". The rings are stirred at 750 rpm in closed containers in 200 mL of deionized water that is maintained at 37 °C. The release medium is replaced daily for a duration of 21 days and analyzed for steroid content ([9,16], W. de Graaf, patent application PCT/EP05/51189). Further information on the test setup may be found in US Patent No. 7357046 assigned by Organon, wherein a dissolution test apparatus for ring shaped devices is described (R. Kraft, patent application PCT/EP03/50969). For these test conditions, an *IVIVC* with a level A correlation was successfully established and regarded to be predictive for *in vivo* performance and thus accepted as a basis for obtaining *in vivo* bioequivalence waivers based on the comparability of dissolution profiles [17].

The aim of this study was to investigate if temperature-controlled accelerated release testing is feasible to determine real-time etonogestrel release from Nuvaring®. Since the focus of the study was not to particularly develop an accelerated release test for Nuvaring® but rather a general verification of the principle, the analytical quantification was restricted to the release of one drug. To minimize material consumption and for comparative purpose, all experiments were performed with ring segments and the release was later standardized to release per ring. When the aim is to adapt a dissolution method for QC, it should be standardized and as possible fulfill the criteria set by international pharmacopoeia or regulatory agencies. Moreover, when temperature is used to accelerate drug release, a precise temperature control should be guaranteed. Due to the higher temperature applied and duration of the experiments, the risk for media evaporation is expected to be higher than in a standard experiment and therefore the equipment used for such experiments can be crucial for the outcome of the study. Based on these considerations, a small volume USP apparatus 7 (reciprocating holder) was used to determine etonogestrel release from ring segments under real-time and temperature-controlled accelerated test conditions with low evaporative loss of media. First, the real-time release profile was compared with a published etonogestrel release profile from Nuvaring® obtained under FDA-approved standard test conditions. Elevated temperature release profiles were then correlated with real-time release and the release profiles at different temperatures were investigated for an Arrhenius relationship. In a subsequent set of experiments, the applicability of the accelerated method to differentiate between rings with different release characteristics was evaluated.

2. Materials and methods

2.1. Materials

All chemicals applied to prepare the release media were of analytical grade and purchased either from Caelo (Hilden, Germany) or from Merck (Darmstadt, Germany). Etonogestrel reference standard (99.5%, lot # rc08102010) was purchased from Ratiochem (Untersteinach, Germany). HPLC grade methanol was purchased from VWR International (Radnor, PA, USA). Ultrapure water was obtained using a Milli-Q Ultrapure Water System (Millipore, Bedford, MA, USA). Nuvaring® (lot # 812419) was purchased from a local pharmacy in Germany.

2.2. Methods

2.2.1. Solubility experiments

In order to ensure sink conditions throughout the release experiments, the solubility of ENG in the release media was determined. Experiments were performed as follows: Approximately 3 mL of a vaginal fluid simulant (VFS) prepared as described by Owen and Katz [18] or purified water was given into a 15 mL Falcon® tube. A small amount of steroid was added to obtain a supersaturated solution (an excess of undissolved drug that could be detected visually was allowed to sink to the bottom of the container). The mixture was placed in an incubator shaker (Titramax 1000 with Incubator 1000, Heidolph Instruments, Schwabach, Germany) at 37 °C and 300 rpm for 24 h to reach equilibrium. Three samples were prepared for each medium. After 1 day, the supernatant was filtered through a preheated 0.45 μm pore PVDF filter (Whatman Inc., Florham Park, NJ, USA) and the steroid concentration was assessed via HPLC analysis.

2.2.2. Differential scanning calorimetry

To evaluate the influence of heat treatment on the polymeric structure of a commercial Nuvaring®, differential scanning calorimentry (DSC) was performed using a Shimadzu DSC-50 apparatus (Shimadzu Scientific Instruments, Columbia, MD, USA). A small piece of the core polymer was isolated from the membrane and transferred into an open aluminum pan. The heating rate was set at 10 °C/min and dry nitrogen was used as purge gas.

2.2.3. Determination of in vitro release

Prior to the release experiments, the rings were cut into segments that were approximately 1–1.5 cm long. The weight of the