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ORIGINAL ARTICLE

Permeation measurement of gestodene for some biodegradable materials using Franz diffusion cells

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Abstract Biodegradable poly(D,L-lactide) (PDLLA), Poly(trimethylene carbonate) (PTMC), polycaprolactone (PCL), poly(caprolactone-co-D,L-lactide) (PCDLLA) and poly(trimethylene carbonate-co-caprolactone) (PTCL) are recently used for clinical drug delivery system such as subcutaneous contraceptive implant capsule due to their biodegradable properties that they could possess long-term stable performance in vivo without removal, however their permeation rate is unknown. In the work, biodegradable material membranes were prepared by solvent evaporation using chloroform, and commercial silicone rubber membrane served as a control. Gestodene was used as a model drug. Gestodene has high biologic progestational activity which allows for high contraceptive reliability at very low-dose levels. The permeation rate of gestodene for several biodegradable materials was evaluated. In vitro diffusion studies were done using Franz diffusion cells with a diffusion area of 1.33 cm^2. Phosphate buffer solution (PBS, pH 7.4), 10% methanol solution and distilled water were taken in donor and receiver chambers at temperature of 37 °C respectively. The in vitro experiments were conducted over a period of 24 h during which samples were collected at regular intervals. The withdrawn samples were appropriately diluted and measured on UV–vis spectrophotometer at 247 nm. Conclusion data from our study showed that permeation rate of PCDLLA with CL ratio more than 70% could be more excellent than commercial silicone rubber membrane. They may be suitable as a candidate carrier for gestodene subcutaneous contraceptive implants in contraceptive fields.

1. Introduction

During the past decades, women had been looking forward to alternatives to the short-acting contraceptives and there were many studies with focus on long-acting contraceptives (Baldwin and Edelman, 2013; Neukom et al., 2011; Ferreira et al., 2014; Chen and Chen, 2007). Consistent use of short-acting methods such as injectables and pills is under constant

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threat from difficulty of the 'surprise' in case of a forgotten pill, inconvenience of daily intake, onset of side effects and other factors (Harel and Cromer, 1999; Lara-Torre and Schroeder, 2002; Likis, 2002; Brache and Faundes, 2010). Long-acting contraceptive methods such as intrauterine contraceptive device (Thonneau and Almont, 2008; Jacques et al., 1986), implants (Bhatia et al., 2011) and injections (Thurman et al., 2013; Rahimy et al., 1999) which could offer a long-period effect with good compliance (Urdl et al., 2005) and tolerance are more popular (Archer et al., 2004). Subcutaneous (SC) implantation (Zhang et al., 2011; Ma et al., 2006) is currently the most common route of self-administering biopharmaceuticals.

Gestodene (Stanczyk and Archer, 2014; Gao et al., 2009; Matějíček and Kubáň, 2007) – a progestin in the 19-nortestosterone series – today is widely used in recent years. Gestodene differs from levonorgestrel in chemical structure results in a shift in the conformational location of the 18-ethyl group and accounts for differences in the pharmacokinetics of the two steroids. Gestodene has high biologic progestational activity with respect to ovulation inhibition, endometrial morphology, and binding affinity to the progesterone receptor. This potent progestational activity allows for high contraceptive reliability at very low-dose levels (Shoupe, 1994). Gestodene is considered an effective, well-tolerated contraceptive option.

Controlled release drug delivery system (Bresolin et al., 2014; Campinez et al., 2013) is one of the most active fields of research and development, because of its advantages such as high-efficiency and low side effects. Coupled with this, methods for evaluation of drug carriers are in the center of attention. According to their degradation properties, carriers for implants can be further classified into biodegradable and non-biodegradable biopolymers such as silicone rubber. Degradable biomaterials do not need subsequent surgical removal after being implanted in bodies, a feature superior to non-degradable biomaterials. Long-term reversible contraceptives have been promoted as highly effective contraceptives that could lower rates of unintended pregnancy and are often viewed as particularly suitable methods for young women (Hoggart et al., 2013). Biodegradable polymers have been widely used and have greatly promoted the development of drug release system because of their biocompatibility and biodegradability. The development of biotechnology and medical technology has set higher requirements for biomedical materials.

Franz diffusion cell experiments (Kshirsagar et al., 2012; Rauma and Johanson, 2009) are emerging as a generally accepted method in the field of drug delivery. Although a new subcutaneous product is only of value if the clinical pharmacokinetic profile appears the appropriate pharmacodynamic response needed for the treatment of the patient, preclinical assessments strongly guide the product development. These include in vitro experiments for evaluating the penetration of a drug molecule through the biodegradable materials membranes. Moreover, measurement of the release profiles of the active pharmaceutical ingredient from the formulation is not only an important parameter for characterizing its release behavior, but it can also be considered as a significant quality attribute which is valuable in the development of a suitable formulation or in the evaluation of possible changes in formulation composition, production parameters and shelf-life stability (Vithlani et al., 2012; Boateng et al., 2012; Gao et al., 2014; Zare et al., 2008). Therefore, the regulatory health authorities are generally requesting these diffusion-release tests in the pharmaceutical dossier submitted to obtain the marketing authorization (Baert et al., 2011). In vitro permeation experiments are a valuable adjunct to in vivo absorption studies, and provide a convenient means for evaluating the permeation characteristics of drugs (Jung et al., 2012; Ng et al., 2012).

The purpose of this paper was to evaluate the permeation properties of gestodene on several biodegradable materials such as PTMC (Zhang et al., 2006; Kluin et al., 2009), PCL (Shen et al., 2013; Yen et al., 2009), PDLLA (Guo et al., 2007; Kumar et al., 2014), PCDLLA (Zhang et al., 2013b) and PTCL (Campos et al., 2013), which are proved to be used in human body by FDA (Tian et al., 2012; Ishaug-Riley et al., 1999; San Miguel et al., 2008; Kowalczuk et al., 2014). Although these biomaterials had been intensively studied, the permeation profiles of these materials can be different, especially when considering certain drug delivery system and were never reported. Gestodene was used as a model drug. The permeation studies, particularly for drug permeation, involved the use of Franz-type diffusion cells. These consisted of two compartments with a membrane clamped between the donor and receiver chambers. Such diffusion or permeation cells had a fixed volume of agitated donor and receptor solutions and can then be used to evaluate the time course for permeation of gestodene through these membranes. The concentration of gestodene was measured by UV–vis spectrophotometry. The method was previously validated and verified for accuracy, precision and linearity. A comprehensive profile of their properties comparing to commercial medical silicone rubber membrane was also provided. The results obtaining from UV–vis spectrophotometer clearly indicated that the diffusion cells provide a simple, precise and reliable system to monitor in vitro experiment.

2. Materials and methods

2.1. Materials

1,3-Trimethylene carbonate (TMC, Jinan Daigang Biomaterial Co., Ltd, China) and D,L-lactide (DLLA, Jinan Daigang Biomaterial Co., Ltd, China) were used without further purification. ε-caprolactone (CL, Alfa Aesar, USA) was purified by drying over CaH_2 (Sinopharm Chemical Reagent Co., Ltd, China) and distilled under reduced nitrogen pressure. Stannous octoate ($SnOct_2$, Sigma–Aldrich, USA) was used as received. Gestodene was obtained from Beijing (China) Zizhu Pharmaceutical Co., Ltd. Medical silicone rubber membrane was received from Jinan (China) Chensheng Medical Silicone Rubber Product CO., Ltd. Solvents used for the sample preparation and analytical procedures were of HPLC or analytical grade.

2.2. Polymer synthesis

PTMC, PCL, PDLLA, PCDLLA and PTCL were synthesized as previously described (Yang et al., 2010; Zhang et al., 2012; Zhang et al., 2013a). Briefly, the polymerizations were conducted by ring opening polymerization in evacuated and sealed glass ampules using $SnOct_2$ as catalyst (Feng et al., 2009).