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Original Article

Preparation of a Reservoir Type Levonorgestrel Delivery System using High Molecular Weight Poly L-Lactide

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Abstract

Implantable contraceptive is likely to be a promising new option for fertility control, as we have entered the twenty-first century and the world's population grows by one billion people in a single decade. The main objective of this study was to develop a subdermal implant for levonorgestrol (a synthetic progestin from 19-norandrostanes) using a high molecular weight biodegradable polymer , i.e. poly L-lactide (PLA), to combine the advantages of both biodegradable systems (i.e. no need to surgery for the removal of the system after the drug delivery period) and non-biodegradable reservoirs (zero order release kinetics). The implants were fabricated using a simple dip casting method. Results demonstrated that the drug release profile could be completely controlled by factors such as implant body weight, presence or absence of polyethylene glycol (PEG) in the formulation, the molecular weight of the added PEGs and their amounts, presence of osmotically active agents inside the implant , and finally the amount of loaded levonorgestrel. A constant release of levonorgestrel for at least 9 months was achieved.

Keywords: Implant; Poly lactide; Reservoir; Contraceptive; Levonorgestrel; Polyethylene glycol.

Introduction

With worldwide unintended pregnancy rates approaching 50% of all pregnancies, there is an increased need for the development of new methods of effective, safe, and acceptable hormonal contraception (1). The recent interest in contraceptive development follows turbulent times in the pharmaceutical industry in which a litigious climate in the United States adversely affected sales of contraceptives. In 1980s and 1990s litigation forced the market withdrawal of many intrauterine devices (IUDs) and attacks on Norplant™ (Wyeth Pharmaceutical, Collegeville, Pa) were associated with a dramatic decline in sales in the United States. Although oral contraceptives (OCs) escaped controversy, the devastating effects on the IUD and Norplant™ resulted in strict limitation in the development of new contraceptives.

In the late 1990s as worldwide use of birth control methods rose and fertility rate declined, industry renewed its interest in contraceptive development. This rise in use is continuing so that by 2025 it is estimated that 2.5 billion women may use contraception. As a result, and to meet the individual needs of this growing

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group of users, it is essential that pharmaceutical companies continue to develop a variety of long-term, reversible, highly effective, and user-friendly contraceptive methods to meet the future needs of the female population (2).

Subdermal contraceptives offer women an effective method of birth control that is easy to use. The insertion and removal of subdermal implants can be expensive, but single-rod implants such as Implanon™ make it more tolerable. Women in Europe and Asia have access to Implanon™, but it is still pending FDA approval in the United States. A 2-rod levonorgestrel system (Jadelle™) has been approved for use in the United States by FDA but has not yet been made available for contraceptive use (3). Implants are inserted subcutaneously by minor surgery or by using special types of pellet injector. In the case of non-biodegradable polymers, the implant has to be removed at the end of the release period, while the use of biodegradable polymers such as poly L-lactide, avoids the removal of the implant from the site of administration. However, the surgery needed for implantation of the delivery system cannot be avoided (4).

Progestins have been used for contraception for more than 30 years. The main goal was to develop a contraceptive method devoid of the metabolic or clinical-side effects associated with the use of estrogens. Progestin-only contraceptives may be preferable in situations that have absolute or relative contraindications to estrogen (5). Contraceptive systems that provide sustained release of low doses of synthetic progestogens are of special interest because they have important clinical advantages over conventional oral contraceptive pills. Firstly, they contain no estrogen, a hormone that accounts for some of the minor and major side effects of combined oral contraceptives. Secondly, contraceptive effects are achieved with a very low dose of progestin. When administered in relatively high doses, progestins may alter lipoprotein patterns and may have accounted for some of the cardiovascular effects of high-dose oral contraceptives. Thirdly, sustained release systems provide progestogen at a rate that is constant, thus avoiding unnecessary high levels. Further more, these systems need little effort and compliance by the user and therefore may achieve clinical use-effectiveness rates close to those measured during research (6).

The main objective of this study was to develop a subdermal implant for levonorgestrel (LNG) (a synthetic progestin from 19-norandrostanes) using biodegradable polymers to achieve a constant, therapeutically sufficient drug release rate over a long period of time.

Experimental

Materials

Poly L-lactide (Resomer® L210) (PLA) molecular weight (GPC) 680000, inherent viscosity (0.1% in chloroform) 3.3-4.3 dl/g was purchased from Boehringer Ingelheim. Poly ethylene glycol 1000 and 4000 (PEG 1000 and PEG 4000), methylene chloride and sodium chloride were obtained from Merck. Levonorgestrel was acquired from Schering.

Methods

Preparation of the polymeric reservoir

Dip casting method was used to prepare cylindrical polymeric devices (7). A stainless steel rod (4 mm in diameter) was dipped into a solution of PLA in dichloromethane for 2 sec. Then the rod was air dried for 10 sec. The dipping and drying procedure was repeated several times to obtain the desired body weight. In order to find the optimum casting solution, different concentrations of PLA in dichloromethane (1.5, 2, 2.5% w/v) were examined. In some formulations, different amounts of PEG 1000 or 4000 as hydrophilic agents were added to the polymeric solution. The device was then kept at room temperature for 24 h to dry completely. Then the reservoir devices were filled with 25 mg levonorgestrel powder. In some formulations, the drug was mixed with amount ratio of NaCl to investigate the effect of osmotically active filler on drug release profile.

The cylinders were sealed with a cap made by the same procedure used to make the body. The body and the cap were joined together with small amounts of dichloromethane**.**

LNG in vitro release profile determination

Each implant was placed in a vial containing

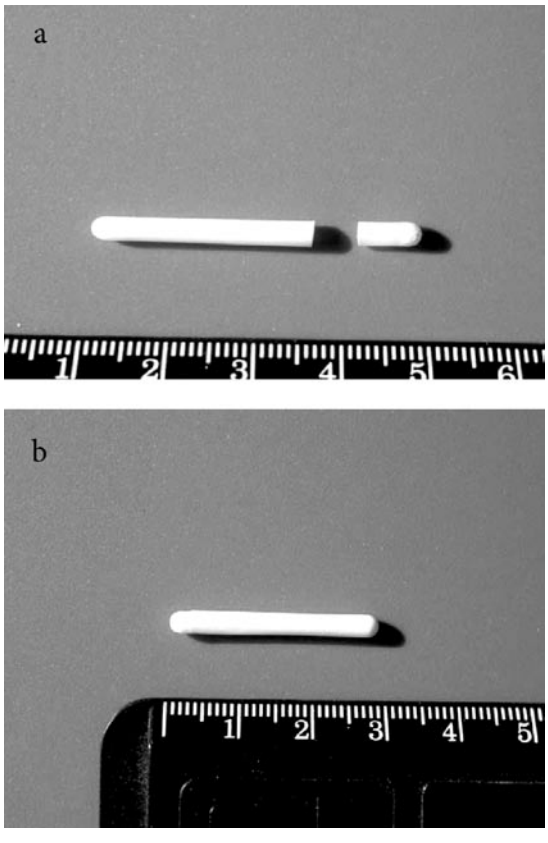

Figure 1. Appearance of PLA implants. Body and cap before (a) and after (b) being joint together.

15 ml of a hydro-alcoholic solution (double distilled water:ethanol in a ratio of 70:30). It is important to mention that saturated solubility of LNG in distilled water at 37°C is 5 µg/ml.Therefore, ethanol was added to the release medium as a co-solvent to keep sink condition during the experiment period. The vial was kept in water bath at 37±0.5°C (static method) and samples were taken at predetermined time intervals ranging from one day (during the first 14 days) to one month. The amount of released drug was determined spectrophotometrically at 248.5 nm.

Results and Discussion

PLA implants containing LNG were prepared using a dip casting technique. The first step was determining the optimum concentration of the polymeric solution in order to obtain an implant with a smooth surface without any crack or hole. After examining different concentrations of

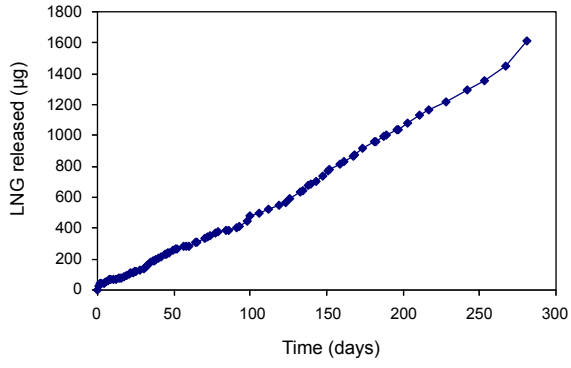

Figure 2. First order LNG release kinetics (r^2=0.993) from PLA implant during a 280 days period (implant body weight 13 mg).

PLA in methylene chloride (1.5, 2, 2.5% w/v), 2% w/v solution was selected as the optimum concentration. In higher concentrations, the reservoir was stuck to the mold and impossible to be removed from the mold. Concentrations less than 2% were too diluted to be able to form a homogenous layer around the mold.

Figure 1 shows the appearance of an implant. Implants had a body length of 25 mm and cap length of 7 mm with an internal diameter of 4 mm.

Figure 2 depicts LNG release from PLA implants with 13 mg implant body weight and 0.16 mm wall thickness during a 240 days period. It showed a constant release rate fitting zero order kinetics (r^2=0.993).

Reservoir devices have the advantage of providing constant release rate over a substantial portion of their lifetime since the driving force (i.e., the concentration gradient) can be made to be constant. For these devices, the release rate is critically dependent on membrane thickness, permeability and the available area for diffusion (8). These kinds of devices are generally made of non-biodegradable polymers to keep the integrity of implants during the drug delivery period and to provide a constant release rate through diffusion. The disadvantage of these implants is the necessity of surgery at the end of the drug delivery period to remove the implant. The high molecular weight PLA which was selected for this study has a very slow degradation rate (24 months) (8). Thus, it could behave like a non-biodegradable polymer

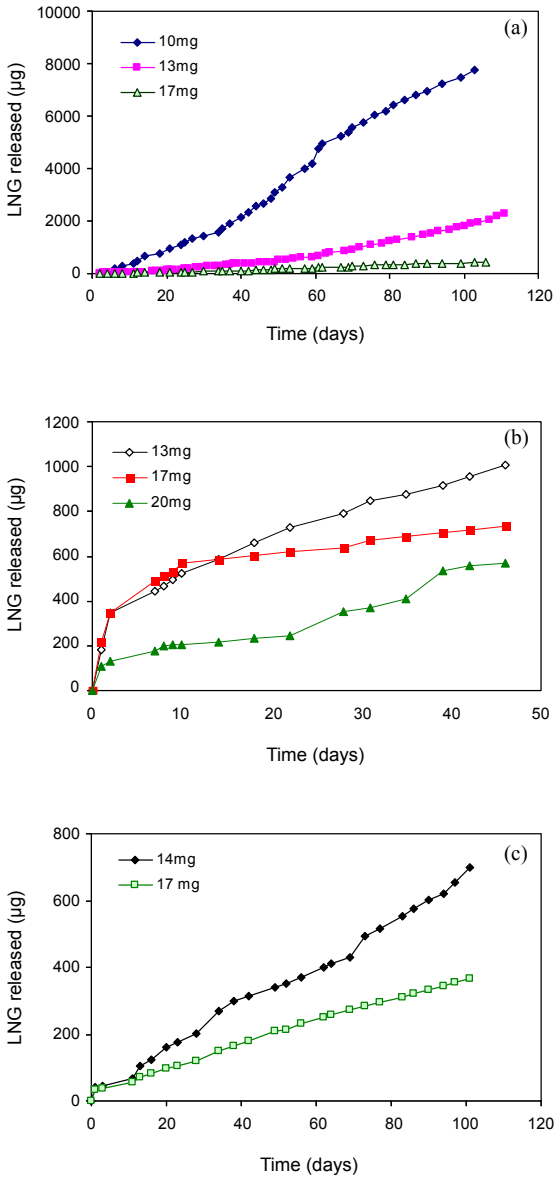

Figure 3. Effect of reservoir body weight on LNG release from PLA implants. a) PLA implants, b) PLA: PEG4000, and c) PLA: PEG1000 implants.

during LNG delivery time and provide a constant release rate as can be seen in Figure 2. On the other hand, the degradation of the polymer after this time eliminates the necessity of a surgery to remove the implants. these implants kept their integrity even after one year incubation in the release medium and successfully provided a constant LNG release.

As all fabricated implants had the same length, the empty polymeric device weight was considered as a representative of membrane thickness. Figure 3a shows LNG release from implants with different body weights (10, 13 and 17 mg). The implant with 10 mg body weight released about 40% of its LNG content during a 3 months period. The released amounts were 10% and 5% for 13 and 17 mg implants, respectively. Results indicated that an increase in membrane thickness decreased its permeability. This parameter interferes with the diffusion of levonorgestrel through the membrane due to the increased diffusion path and possible reduction in porosity of the membrane (9). Figures 3b and 3c depicts the effect of implant body weight on drug release from implants made of PLA:PEG 1000 and PLA:PEG 4000, respectively. It was concluded that by changing the implant body weight, it is possible to control the LNG release rate. The problem associated with this method was the poor mechanical strength of implants with a body weight less than 11 mg. This resulted in making attempts to control LNG release rate by adding a hydrophilic polymer to the implant wall instead of decreasing the implant thickness. Poly ethylene glycol was selected for this purpose due to its safety.

PEGs are hydrophilic and biocompatible polymers that are available in a wide range of molecular weights (200-20,000 g/mol) and have been used extensively as plasticizers for nonbiodegradable polymers such as ethyl cellulose. Further more, similar to PLA, PEGs are also freely soluble in methylene chloride and insoluble in *n*-hexane, a property that may enable homogenous monolithic PLA:PEG films to be manufactured. Studies have also demonstrated that the similar solubility of PLA and PEG in nonpolar solvents used exploited to fabricate reservoir drug delivery systems consisting of porous, biodegradable PLA:PEG membranes for controlling the release rate control. As PEG exhibits high aqueous solubility, the controlled incorporation of PEG enhances the permeability of otherwise impermeable PLA membranes. Studies also indicate that incorporation of PEG improves the physical properties of PLA films to enable fabrication of controlled release drug delivery systems and increases fractional crystallinity, as well. PEG also lowers residual

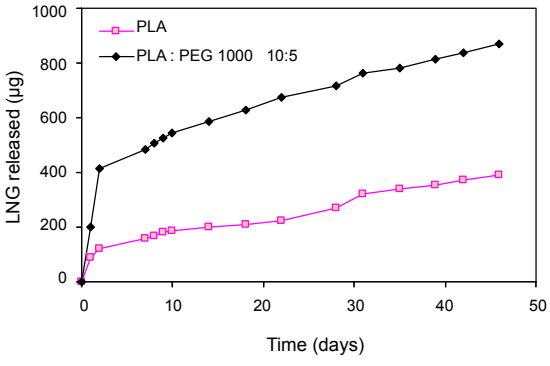

Figure 4. Effect of addition of PEG to the body of PLA implants. a) PLA: PEG 1000 10:5 and b) PLA: PEG 4000 10:5

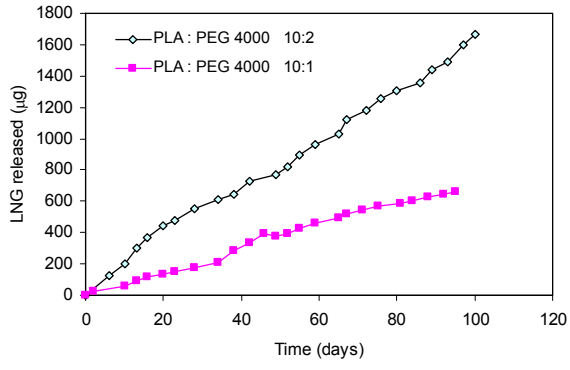

Figure 5. Effect of different amount of PEG 4000 on LNG release rate from PLA implants.

solvent level, which is an important advantage when using organic solvents for preparation of such systems. PEG incorporation improves the thermodynamic stability of PLA and therefore, these membranes are less likely to undergo polymorphic transformation during storage (10-13).

Incorporation of PEG 1000 in the formulation, increased LNG release rate (Figure 4). During about 45 days of incubation, 850 µg LNG was released from the implants made of PLA:PEG 1000. By comparing this to the 350 mcg released from the PLA implants, it can be concluded that adding PEG 1000 increased the release rate more than 2 times. This increase in the rate of drug release from devices containing PEG 1000 could be attributed to the increase in the hydrophilicity of the reservoir membrane and thus enhancement of water penetration and formation of aqueous channels within the membrane, which led to the faster diffusion of drug molecules (14).

A modification of the release characteristics was made by varying the amount and molecular weight of PEG was made. The influence of PEG amount on the release profile is indicated in Figure 5. When the ratio of PEG:PLA used in implant was increased from 1:10 to 2:10, the release rate increased for about 3 times. Microscopic study of the implant structure after dissolution revealed more porous structure in the implants with higher PEG:PLA ratio. Also mixing of PEG with PLA caused a decrease in the Tg of PLA that was proportional to the PEG content, which could be responsible for faster LNG release.

Figure 6 represents the effect of PEG molecular weight on LNG release rate. PLA implants prepared using PEG 1000 showed faster release rate compared with implants prepared with PEG 4000. The difference in release rate of LNG from implants made with PEG of different MWs could be explained on the basis of different dissolution rates of PEGs after hydration in the release medium. Comparing polymers of the same chemical compositions with different molecular weights, the release is slower from the polymers of higher molecular weights. This is due to the physical properties (permeability, hydrophobicity and crystallinity) related to molecular weight. The reason for higher drug release from PLA implants containing PEG is attributed to the aqueous solubility of PEG. When implants are put in the release media, the PEG content of the implant membrane is dissolved, hence increasing the porosity of the membrane which causes a burst release effect.

Figure 7 shows the LNG release profile from two systems: one with NaCl and the other without it. Presence of NaCl increased the LNG release rate. This effect could be attributed to the hydrostatic pressure generated inside the implant, which pumps the drug from the device. The effect of NaCl on drug release from implants is seen as a burst effect. The drug release rate after this burst release is however similar to the implants without NaCl confirming that NaCl is dissolved and released at early

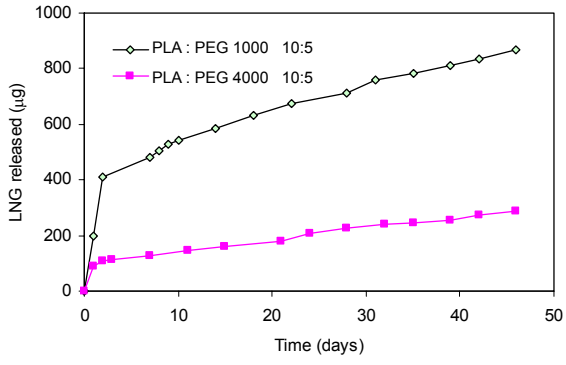

Figure 6. Effect of PEG molecular weight on LNG release from PLA implants.

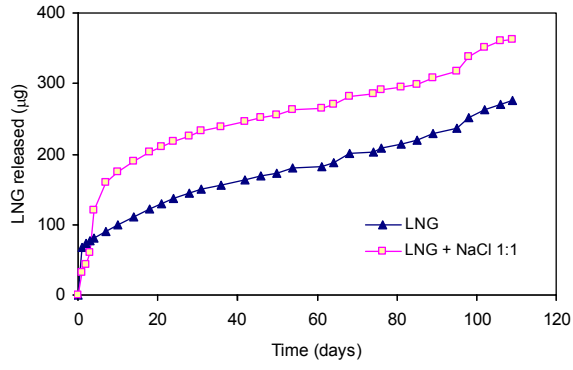

Figure 7. Effect of addition of NaCl as osmotic agent inside the PLA reservoir on LNG release.

stages of drug release. This result is in contrary to some previous reports which have mentioned that the release profile was not influenced by the presence of osmotic agents in formulations whose reservoir were made of high molecular weight polymers (13).

Comparing the developed systems with available ones in the market

Contraceptive systems that provide sustained release of low doses of synthetic progestogens have been studied for nearly 20 years. Such contraceptive systems are of special interest because they have important clinical advantages over conventional oral contraceptive pills. These sustained release systems provide progestogen at a constant rate thus avoiding unnecessary high levels. These systems require little effort by the user and therefore may achieve clinical use-effectiveness rates close to those measured during research (6).

One of these subdermal implants is Norplant™ which releases about 20 mcg levonorgestrel per day. Clinical trials have shown that Norplant™ is one of the most effective reversible contraceptives ever developed. Unfortunately, the inconvenience of its removal is a principal reason that U.S. clinicians do not recommend Norplant™ to their patients. This fact is sufficient to motivate the researchers to develop implant systems that are simpler to use. Furthermore, new types of implants could also be less apparent under the skin, degradeable so not requiring removal could use simple, disposable devices to speed up the insertion process and reduce the risk of blood-borne disease transmission.

Figure 8 shows daily LNG release from two developed implants. Both formulations were made of PLA:PEG 4000 and contained 40 mg LNG. As shown in the diagram, the daily release is more constant (especially after a while) and more similar to Norplant in systems made of PLA:PEG 4000 in a 10:2 ratio than those made in a ratio of 10:1. Daily release of LNG from the former system is comparable to that of Norplant™ (around 20 µg/day).

In conclusion, using high molecular weight poly L-lactide for preparation of reservoir type implants by a simple dip casting technique resulted in devices with zero order release kinetics of levonorgestrel over a long period of time. Results demonstrated that the drug release profile could be completely controlled by factors such as implant body weight, incorporation

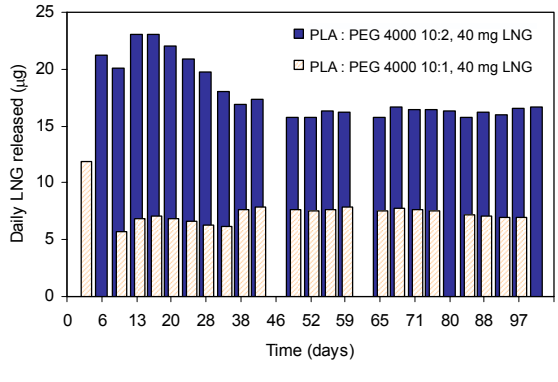

Figure 8. Daily released amount of LNG from implants made of PLA:PEG4000 10:1 and 10:2 which contain 40 mg drug.

of PEG in the formulation, the amount and molecular weight of added PEGs, presence of osmotically active agent inside the implant, and finally the amount of loaded levonorgestrel.

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