Journal of Controlled Release 240 (2016) 235–241

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Development of controlled release systems over the past 50 years in the area of contraception

David R. Friend

Evofem, Inc., 12400 High Bluff Drive, Suite 600, San Diego, CA 92130, United States

ARTICLE INFO

Article history:
Received 2 September 2015
Received in revised form 22 December 2015
Accepted 23 December 2015
Available online 28 December 2015

Keywords:
Prevention of unintended pregnancy
Contraception
Injectable
Implants
Intrauterine systems
Intravaginal rings
Transdermal patches

ABSTRACT

The field of controlled release has contributed significantly to female reproductive health and in particular the prevention of unintended pregnancy. For at least 50 years, there have been significant advances in controlled release dosage forms used for contraception. These advances have been driven by the need to provide women a wide array of products that address adherence problems noted with oral contraceptives. The first long-acting injectable product (Depo-Provera®) was approved in the US in 1959. Since then, there has been an emphasis on development of long-acting reversible contraceptives. These products include implants, intrauterine systems, and vaginal rings. A shorter acting contraceptive option is the transdermal patch. Despite these advances there are still a large number of unplanned pregnancies around the world. New controlled release technologies will be needed to continue providing women safe and easy to use contraceptive products.

1. Introduction

The field of controlled drug release has experienced significant advances since the field was founded (which can be considered when the first Annual Meeting of the Controlled Release Society was held in 1973). The focus of novel controlled release systems over this time moved from simply controlling the rate of release from a dosage form to the present day focus on nanomedicine. The level of sophistication used presently to improve the therapeutic benefit of drugs through novel targeting techniques is a remarkable advance in science.

Looking back at the formative years of controlled drug release, there was (and continues to this day) a focus on female reproductive health, particularly prevention of unintended pregnancy. This focus was driven largely by the fact that the first contraceptive drugs required once-daily oral administration. For many women, this dosing regimen, created adherence challenges. Effectiveness of oral contraceptives is compromised if doses are missed. In addition, the needs of women for contraception changes over her reproductive life span. This led to the development of what would later be called method choice. The development of novel contraceptive delivery systems has been followed more recently by similar approaches to protect women from transmission of various sexually transmitted infections (STIs) including HIV-1. There is considerable overlap in these approaches and while yet to be realized, the goal of combining prevention of unintended pregnancy and transmission of STIs is currently an area of considerable interest. These types of products are called multipurpose prevention technologies (MPTs) [1].

This review covers two general types of delivery systems used in the area of women's reproductive health: 1) injectable/implantable and 2) topically applied. The general motivation behind these delivery systems is to provide a wide-range of products that promote adherence. Thus, these systems act from a week up to many years.

A major goal in the field of contraception has been development of long-acting contraceptives. Examples of long-acting injectable products are Depo-Provera® and Depo-subQ Provera 104® (Pfizer, Inc.). The need for reversibility led to the development of long-acting reversible contraceptives (LARCs). Examples of LARCs are Nexplanon® and Jadelle®. There remains considerable interest in long-acting injectable contraceptives as well [2]. Other examples of longer acting contraceptive products are based on intrauterine systems and intravaginal rings (IVRs). The most prominent example of a vaginal ring product is NuvaRing® (Merck, Inc.) which lasts a single cycle (28 days). Longer acting contraceptive IVRs are in development. Finally transdermal patches have been developed for a number of indications including prevention of unintended pregnancy. The currently marketed contraceptive patch is Ortho Evra® (Janssen Pharmaceuticals, Inc.).

E-mail address: Dfriend@evofem.com.

http://dx.doi.org/10.1016/j.jconrel.2015.12.043
0168-3659/

2. Long-acting contraceptives

2.1. Injectables

The need for long-acting contraceptives helped drive innovation in early days of the field of controlled release. In 1984, an edited book was published covering a wide range of topics on long-acting contraceptive delivery systems under development [3]. The need for effective, safe, and long-acting products was viewed as critical compared with contraceptives available at the time (the only long-acting products available in 1984 was Depo-Provera). This product was finding use in a number of developing world-settings. While widely used, the product (which is a rather simple aqueous-based suspension of depomedroxyprogesterone acetate, DMPA), was prone to slow and unpredictable return to fertility. Also the product was (and remains) irreversible. Perhaps due to the activities in reversible long-acting contraceptives (see below), there has been little advancement in long-acting injectables since Depo-Provera was approved by the FDA in 1959. However, Pfizer recently received approval for a new form of Depo-Provera called Depo-SubQ Provera 104® [4,5]. This product differs from Depo-Provera in that the dose is lower (104 mg vs. 150 mg) and is administered subcutaneously rather than intramuscularly. Both products provide protection against unintended pregnancy for 3 months. Other injectable contraceptives include norethisterone enanthate (NET) [6] (200 mg/1.0 mL) which has a 2 month duration and Cyclofem®, which contains 25 mg DMPA and 5 mg estradiol cypionate (one month duration of action). The addition of the estrogen creates more acceptable bleeding patterns [7,8]. Neither NET nor Cyclofem are marketed in the US.

All the products (with the exception of Depo-SubQ 104) discussed above were developed many years ago. In addition, these products are all similar in that they are microcrystalline drug suspensions. Newer approaches to preparing long-acting injectable contraceptives include microencapsulation and in situ forming depot systems [2]. A comparison of these approaches is shown in Fig. 1. The use of microspheres for controlled release of drugs has been studied for many years; an example of commercial product based on this approach includes Lupron Depot®. Over the years, a number of papers have been published describing the use of biodegradable polymers to controlled (i.e., extend) the release of progestins such as LNG (see [2] for a summary of these papers) and a paper by Beck et al. [9]). Newer approaches to create degradable contraceptive dosage forms include dripping using electronic force, ultrasonic excitation, and vibration [10–12]. Other methods used to prepare microcapsules/microparticles include extrusion through needles and microfabricated microchannel devices [13–15]. These newer technical approaches may improve delivery rates and help reduce side effects.

2.2. Implants

The need for better control of drug release and termination when needed drove the development of implants. These included pellets,

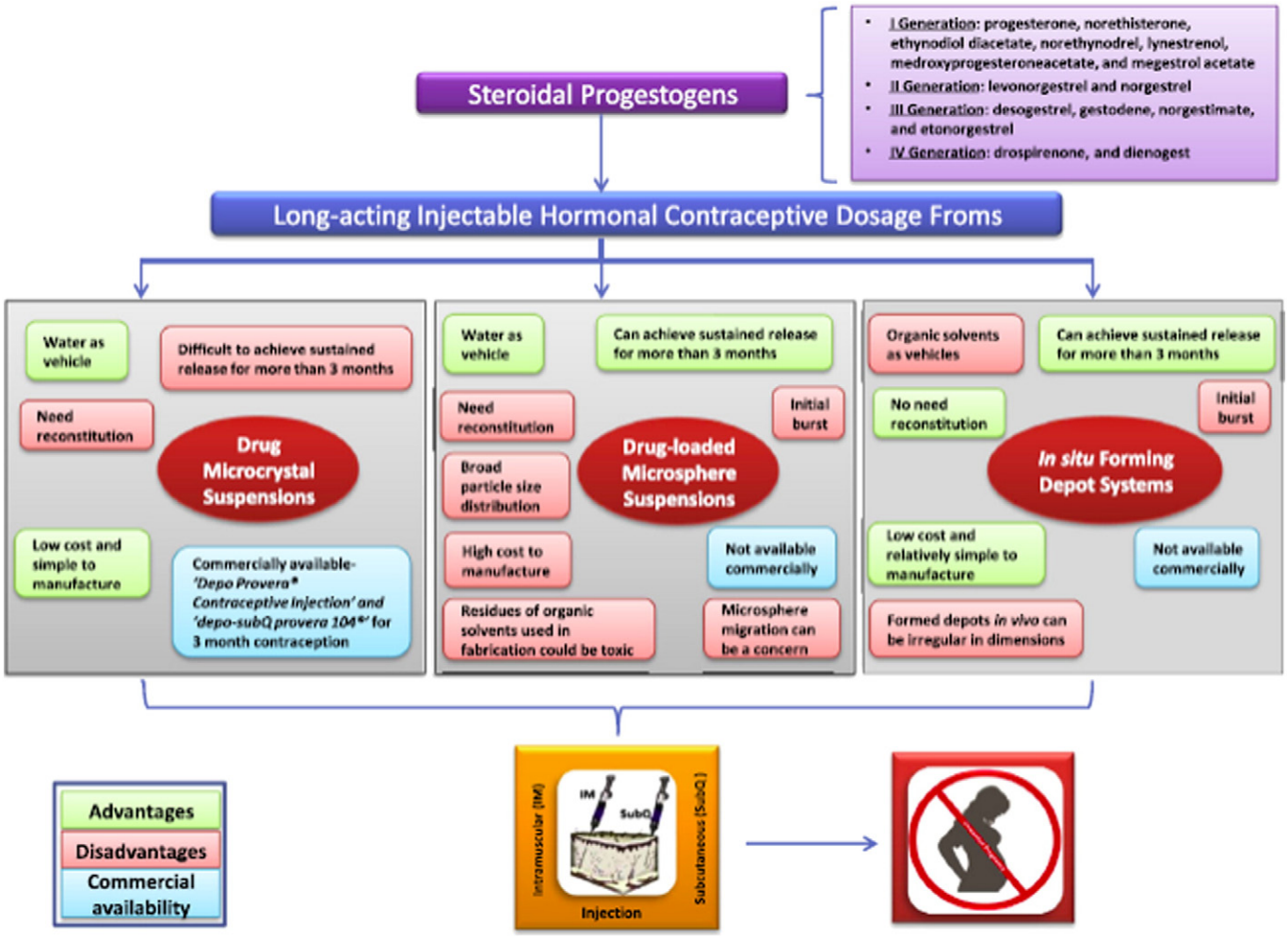

Fig. 1. Flow chart of the advantages, disadvantages, and commercial availability of long-acting injectable hormonal contraceptive dosage forms including drug microcrystal suspensions, drug-loaded microsphere suspensions and in situ forming depot systems. From [2] with permission.