International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 10, Issue 6, 2018

Review Article

EVOLUTION OF CONTRACEPTIVE IMPLANTS: A REVIEW

NASRUL WATHONI*, TAZYINUL QORIAH ALFAUZIAH, NOPI RANTIKA

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor 45363, Indonesia
Email: nasrul@unpad.ac.id

Received: 10 Jul 2018, Revised and Accepted: 04 Sep 2018

ABSTRACT

Oral contraceptives are widely used hormonal contraceptives compared to other dosage forms. There are modifications of hormonal contraceptives dosage forms to reduce side effects and improve effectivity and compliance during contraceptive usage. The implantable drug delivery system is a suitable contraception technique for women who are difficult to recall the time of use, such as pills. The contraceptive implant is a small size of rod, and it is placed in the upper arm subcutaneously. Many advantages by using contraceptive implants, such as high effectivity, easy to use, free from estrogen influences, fast recovery of the normal ovulatory cycle, safe for breastfeeding women, and safer for women that have the certain medical condition. However, implant removal procedures are becoming the problem because it requires trained personnel. The unscheduled period is also one of the disadvantages of implants. Although for most women, the implant could reduce blood loss when the period, for some cases it could prolong the period of time. In this article, we reviewed implant contraceptives development due to its application increased rapidly in the last decade. The history of implants, advantages, and disadvantages, and marketed products of the implant were also described in this article. The challenges and opportunities of the contraceptive implant development were summarized based on literature. Designing in situ forming implant and polymeric implant for contraception could be the great future in contraceptive implant development. Finally, contraceptive implants are promising hormonal contraception dosage forms to develop in unintended pregnancies prevention over the world.

Keywords: Implant, Contraception, Polymer, Biodegradable

DOI: http://dx.doi.org/10.22159/ijap.2018v10i6.28391

INTRODUCTION

Over the last 35 y, the use of contraceptive implants has been used by millions of women all over the world and permitted in more than sixty countries. Its high efficacy and easy applicability led implants becoming a prior choice as hormonal contraceptives for women. Contraceptive implants have a high progression rate compared with other dosage forms and also have a very high efficacy which prevalence of unintended pregnancies are less than 1 per 100 women in a year. Over 5 y, there were 2 million unintended pregnancies avoided with the contraceptive implant usage. Nowadays, the use of short-acting contraceptive dosage forms, such as oral or injection contraceptive, is switched into contraceptive implants [1, 2].

Implants usage were registered in more than 100 countries around the world, Indonesia has many users of it, where its use for the last decade has increased rapidly. Over 5 y, the use of the contraceptive implant increased and more than 15-fold in Ethiopia and Rwanda, 4-fold in Tanzania, and 2-fold in Malawi [3, 4].

Contraceptive implants in most countries were available in two types: the single-rod implant of etonogestrel and two-rod implant of levonorgestrel. Pharmacological profile and physical effects of those contraceptive implants were same. The product of two-rods contraceptive implant was Sino-implant (II)® and Jadelle®, while the single-rod contraceptive implant was Implanon®. Contraceptive implants are very effective and safe to use as well as a contraception method with a long duration of action [5, 6].

However, implant removal procedures were becoming the problem because it requires trained personnel. To overcome this problem, contraceptive implants were developed degradable polymer as a carrier. The use of degradable polymer could make the matrix degrade into monomers and by-products that can be cleared by the body without removal procedures after the duration of therapy was completed [7]. The literature used in this review was obtained from PubMed, Google Scholar, and Science Direct search engine without year based restriction but we prefer to select the latest article.

Brief history of implants

In the 1930s, there was a pellet containing hydrophobic compounds with continuous drug release. This pellet system including estradiol pellets for prostate cancer treatment and testosterone pellets for testosterone deficiency treatment. In addition, the formulation of drugs or esters with very poor aqueous solubility can also offer an extended drug delivery system [8].

The history of implantable drug delivery systems began by Deansby and Parkes research in 1983. They were investigated how compressed pellets of estrone affected castrated male chicken that inserted subcutaneously. In the 1960s, Folkman and Long pioneered the formulation of the implant. They were designed as a polymeric membrane from silicone rubber to control the release rate of the drug. The silicone rubber was made into capsules and filled with various drugs, then inserted into the cardiac muscle of dogs. The result showed that the formulation was succeeded to deliver various drugs into the target and the capsules were biocompatible. In addition, the formulation became the basic formula for implantable drug delivery systems [9–11]. Since these first few years, the implantable drug delivery system research has increased. The formulation was developed by using various drugs, implantation technique, carriers (more bioerodible and biostable), and implantation sites [12].

In the early 1960s, T. Higuchi proposed the "Higuchi equation" [1]. Initially, this equation is applied to ointment drug release but then applied to drug release of various matrix systems. This equation showed that extended drug release could be perceived from dispersed solid in the matrix, but the half-life would be varied.

$$M_t/M_\infty = 2\,[DC_s(2C_0 - C_s)t]^{1/2}/C_0 l \quad [1]$$

In this equation, C0 is the total concentration, D is the diffusivity and Cs is the drug solubility in the matrix. The surface area is A and depot thickness is l. This equation explained the rectangular piece release, so ∞ = AlC0. The model mentioned above represented the dosage forms which the rate limiting step was drug diffusion rate through the matrix system. It was assumed that the drug was transported rapidly through the surface diffusion boundary layer of the system [13].

Implantable drug delivery systems are designed to diminish or avoid the problems linked with oral (powder, gel, tablet, or liquid) dosage form administration. Various design methodologies have been pursued based on drug development at that time [12]. Improving

safety and efficacy is the main goal of any design methodology. It was made by adjusting dose rate and dose at the chosen site.

There was the problem linked with oral dosage forms [9]:

- Drug bioavailability — drug solubility is low, so the amount of drug absorbed is also low
- Drug stability — most of the drugs are not stable when delivered orally because of GITs condition
- Drug toxicity — because of poor physicochemical properties of drugs, the dose must be increased. Therefore the unacceptable side effects arise.
- Duration of release — it is hard to formulate the oral dosage form in order to release slowly for more than 24 h.
- Drug half-life is too short — drug potency loses quickly so it becomes less effective.

Contraceptive implant

The contraceptive implant is a small size of rod, and it is placed in the upper arm subcutaneously.

It could release hormones such as progesterone slowly into the bloodstream in a long time period, months or even until 5 y. Its effectivity decreased in women who have a disease or bleeding disorders [14].

Contraceptive implants as a long-acting reversible dosage forms

It was predicted that about half of pregnancies in England and other high-income countries are expected as a result of unintended pregnancy [15]. These problems came because of the use of less effective contraceptive dosage forms, such as condoms and pills. Contraceptive implants were long-acting reversible dosage forms, so it was expected to prevent or delay pregnancies [16].

Long-acting reversible contraception was predetermined by National Institute for Health and Care Excellence as a hormonal contraception method which the administration required was once per cycle or even less. It was including intrauterine copper (given every 5-10 y), subdermal implants of progestin (given every 3-5 y), the combination of the vaginal ring (requires administration every 4 w), intrauterine progestin system (given every 3-5 y), and injectable progestin (given every 8-13 w) [17].

The prevalence of contraceptive implants usage

Although there have been millions of implants worldwide, it still has the low prevalence usage. The prevalence of implants usage in women is 18% worldwide, and the highest prevalence of it was in India, about 36%[18]. At 2010, only 2.6% of women (<30 y) used the implants in France [19]. Meanwhile, in 2008, women of childbearing age in the United Kingdom that used the implant for their contraception were about 1–2% [20]. Columbia, Burkina Faso, Norway, Rwanda, and Ethiopia have succeeded countries in increasing the prevalence of contraceptive implants usage more than 3% of women of childbearing age [18].

Advantages of Implant Contraception

The advantage of implants is high effectivity (miscarriage rate: <1%) and easiness of use. After the insertion procedure, there is no further handling up to removal procedure time. Therefore, the implant is suitable contraception technique for women who are difficult to recall the time of use, such as pills. In addition, the implant does not interfere with the copulatory activity, because it is inserted on the subdermal of the upper arm. Even though the implant is tangible below the skin and gives a small scar, providing contraceptive supplies at home is not required. The user also does not need to refill the contraception or follow-up for contraception in the short term. Contraceptive implants are free from estrogen influences. Women with estrogen hormone contraindications, very appropriate to use contraceptive implants. As a consequence women that have certain medical conditions such as hypertension, venous thrombotic or family history of inherited thrombophilia may still use this contraception method [21,22].

The woman that use implant can get the fertility back quickly. Most women recover their normal ovulatory cycle within the first month after the removal procedure. Pregnancy rates in the first year after removal procedure equals to pregnancy rates in women who do not use contraceptive methods and attempt to pregnant. There is no effect on long-term fertility in the future. In addition, implants do not constrain breast milk. Implants are the best method for breastfeeding women. There is no effect on the quality and quantity of breast milk, and the baby grows normally. If the newly breastfed mother does not have time to (within three months), the implant can be dispersed immediately Postpartum. Another benefit of the implant is blood loss when period reduced, so it can help prevent anemia [22].

Summary of implant benefit [9]:

- Patient compliance — patient does not worry about dosing interval.
- Fewer side effects — drug release in the body is controlled and the dose usually is lower with better control at the target site; side effects are reduced; drug concentration in the plasma is constant.
- Lower dose — the drug does not meet first pass hepatic effects, before approaching the receptor.
- Drug stability improved — the drug is protected from rapid metabolism.
- Drug allergy — if the patient has an allergy or shows an adverse reaction to the drug, the implant could remove immediately.

Disadvantages of implant contraception

The main disadvantage of implants is an unscheduled period. Although for most women, the implant could reduce blood loss when the period, in uncommon cases it could prolong the period time [21]. There was a study evaluated bleeding after ENG implantation, the result showed that 22% had amenorrhea, 34% were rarely bleeding (bleeding or spotting), 7% were frequent bleeding, and 18% were excessive bleeding [23].

Women who use implants more often complain about weight gain. Assessment of weight change in implant users is disrupted by changes in exercise, diet, and aging. Although appetite enhancement may be associated with the androgenic activity of levonorgestrel, low levels of implants may not have any clinical implications. In addition, continuous monitoring of 75 women using Norplant® showed no body mass index improvement after five years [22, 24].

In addition, the prevalence of acne, dysmenorrhea, and endometriosis are increased in women with contraceptive implants. Acne is caused by the androgenic activity of levonorgestrel directly and it also decreases sex hormone binding globulin (SHBG), leading to elevated free steroids level (levonorgestrel or testosterone). Compared to combined oral contraceptives containing levonorgestrel, the estrogen increases SHBG levels, so free androgens is decreased. The literature stated that women who used ENG implants for 2 y, 16% of them experienced the incidence of new acne [25]. In another study that investigates the effect of ENG implants in endometriosis women, the mean score for dysmenorrhea increased from 7.08 to 0.84 at 12 w after implantation of ENG [21]. Other side effects include dizziness, headaches, nausea, rashes, and mood changes. In rare cases, the implant user may experience severe headaches or a migraine [22].

Contraceptive implant types

a. Levonorgestrel implants (LNG implants)

LNG Implant consists of two rods that were inserted using a disposable V trocar. Two products available were Sino-implant (II)® and Jadelle®. The size of rods was 2.5 × 43 mm and each rod containing 75 mg of LNG. Thin silicon (Silastic®) wrapped the embedded LNG in siloxane copolymer. The original license of Jadelle® was last for 3 y; but now in most countries, it was extended for 5 y, while the license of Sino-implant (II)® was last for four years [5, 26].

b. Etonogestrel implants (ENG implants)

Implanon NXT®/Nexplanon® was single rod-shaped ENG implants (2 × 40 mm) that could be inserted easily because of its

special applicator. ENG microcrystal was embedded in a 68 mg matrix of EVAc copolymer, then it was covered by a membrane (thickness: 0.6 mm). Implanon NXT®/Nexplanon® contained 15 mg of $BaSO_4$; this radio-opaque implant was bioequivalent to Implanon®[27]. ENG implant was very effective and safer. However, comparing the pregnancy rate between LNG and ENG implants, there was no significant difference between them [28, 29].

Table 1: Products of contraceptive implant in the market

Products	Polymer	Drug	Ref.
Norplant®	Silicone	Levonorgestrel	[30, 31]
Jadelle®	Silicon	Levonorgestrel	[31]
Implanon®	EVAc	Etonogestrel	[32, 33]
Sino-implant (II) ®	Silicone	Levonorgestrel	[5]
Nexplanon®	Silicon	Etonogestrel	[6]
Capronor®	PCL	Levonorgestrel	[34]

Pharmacology

The mechanism of action of the sub-dermal implant was included to prevent the ovulation, the sperm penetration in cervical mucus, and the implantation by attenuating the endometrium [35].

Minimum effect concentration (MEC) of ENG was 90 pg/ml, and it was achieved within a few hours after insertion. After four to six months from insertion, the remaining plasma levels was almost constant. The study indicates that when ENG plasma levels were higher than MEC, it would inhibit the ovulation in 97% of women; this condition could be achieved within 8 h from insertion. So, it means that the effectivity could be ascertained since insertion. ENG plasma concentrations decreased slightly for 3 y (1,000 pg/ml to 100 pg/ml) [26]. After the release, ENG plasma levels fall quickly, below the threshold for detection (20 pg/ml) over four days. Drug release of LNG implant generally similar to the ENG implant, causing their pharmacokinetic profile were almost identical [36].

Progestin contraceptive implants effectivity might be reduced by inducers such as antiretroviral therapy, some antibiotics, and some antiepileptic drugs [37]. Contraceptive implants should not be initiated in women who use narcotics for long-term. Additional precautions are recommended in patients with the use of inducer for 28 d after termination.

Insertion

Timing of insertion

Implants in women are used to avoid pregnancy; implant implantation can be used at any time during the woman's cycle. Implants are very effectively used/inserted during the first 5 d of the menstrual cycle, starting from the first day of menstruation. If the woman who is implanted is impaired by her menstrual cycle, a pregnancy test should be performed after 3 w. This implant is effective after 7 d if inserted at the time of the menstrual cycle. Thus, if the woman is having sexual intercourse, need to use another contraceptive like a condom for 7 d after installation. Alternative contraceptives are used with caution if need to be extended to 2 w [28].

If postpartum implantation is performed, implant insertion may be performed after 21 d postpartum. In this condition, there is no need for an extra precaution such as women with normal menstrual cycles. 15 Women who are breastfeeding for up to 6 mo postpartum, it can be assumed that the woman is not pregnant. Similarly, in women who have both first and second density abortions, implants can be performed within 5 d [28].

Insertion technique

Early initial implant insertion is by local anesthesia; this is done so that insertion can be more effective. Implant insertion should be done carefully to avoid insertion into a muscle or nerve or blood vessel injury. Use of the applicator should be used with a 30 ° slope to the skin and thereafter immediately after the needle penetrates the dermis is lowered to the horizontal position. After the needle penetrates the skin, careful withdrawal of the needle until the subdermal plane is shallow. Then adjust the depth of the implant below the skin surface. After insertion, the health professional will verify the presence of the implant by palpation. Palpation is a method of examination in which the tester feels the size, strength, or location of something (from the part of the body where the examiner is a health practitioner). Documentation is ensured that the implant has been successfully inserted into the arm [28].

Side effects of insertion

Side effects after insertion of contraceptive implants include bruising, pain, redness, or irritation. Infectious lesions (cellulitis) after insertion are not reported in an ENG implant trial, but sometimes cases of wound infections due to the implant insertion process need treatment with antibiotics. Side effects that occur after implantation can occur changes in vaginal bleeding patterns, including the absence of menstruation (amenorrhea), decreased sex drive, dizziness, inflammation experienced mood swings and depression, nausea or abdominal pain and weight gain [38].

Site of insertion

For implant insertion regions ENG (Norplant) is recommended to be between the biceps and triceps muscles. The insertion is carried out 8 to 10 cm above the medial humerus epicondyle area. For insertion of NXT Implanon inserted inside the upper arm to avoid large blood vessels and nerves located deeper in connective tissue. The insertion is carried out with low depth subdermal, to avoid the risk of neurovascular damage done by insertion or implant release [28].

Timing of remove

After 3 y after insertion or after the implant has finished, the implant should be removed because the effectiveness of the implant is reduced. The implant release process performed is a similarly minor surgical process performed as in the implant insertion process [38].

Polymers of implant dosage forms

Polymers used in implants broadly divided into two groups, namely non-degradable and degradable polymers. The non-degradable polymer used because it is relatively inert and biocompatible, and mechanism of the drug release system was diffusion or swelling [7,39]. Diffusion-controlled systems can be divided into the type of reservoir and matrix, while the systems swelling-controlled produced from water-soluble polymers which have cross-link bonds. Examples of non-degradable polymers were silicon, cellulose derivatives, and acrylic [7]. These polymers are suitable for long-term use as bones and teeth implants [40].

Degradable polymer is safer to use because it can be degraded into monomers and by-products that are non-toxic for the body so that it can be cleared efficiently by the body. It didn't need surgery for implants removal after the treatment is completed [7, 41]. Biodegradable implants with PLA and PLGA-based can flabbergast the weaknesses of non-degradable implants. This type of polymer is widely used as a surgical polymer and has been approved by the USFDA for parenteral administration. PLGA and PLA as the biodegradable carrier could be designed into an implant easily with some of the techniques [42]. These polymers also have disadvantages. The acidic by-products can undergo unwanted reaction. In addition, the cost of the implant with the biodegradable polymer is higher than non-degradable polymer [43]. Until now,

some pharmaceutical products using degradable polymers have been approved by the USFDA. This system has been delivering various types of drugs such as hormones, antitumor, and antibiotics with complex drug release include diffusion and erosion [44, 45].

The physicochemical properties of the drug are the main key to determining drug release mechanism of PLA or PLGA-based implants. Implants show a large burst in initial release followed by a quick release. Drug loading also affects the drug release rate. As higher drug loading, as faster drug release from the polymer. Some drugs assimilated into the PLA or PLGA implants are purposed to be released at the target site, which is a benefit of drug delivery of PLA or PLGA-based implant [46].

a. Polyethylene (PE)

Polyethylene can be classified based on molecular weight, the high-density (HDPE) and low-density (LDPE). As molecular weight increased, the material strength increased, but its elasticity decreased [47]. Porous HDPE has good elasticity, biocompatibility, and its anti-infective properties were strong enough to be used as the material in rhinoplasty surgery [48]. However, PE has a "plastic feel" when applied to the skin. Another PE that is often used in the controlled release system is poly (ethylene-co-vinyl acetate) or EVAc. It could deliver drugs with wide range molecular weight and also specifically used as a drug elution matrix. Products using EVAc as a polymer were Ocusert® (pilocarpine implant for glaucoma, from Johnson and Johnson) and Implanon® (etonogestrel implant, from Organon).

b. Polyurethane (PU)

Polyurethane widely used in implants and degraded in the body for a long time. However, if handled properly, the degradation can facilitate the growth of new tissue [49]. PU has a low water permeability, but this can be reduced with the addition of a low concentration of isopropyl myristate [50].

c. Silicone

Silicone is an inert compound used in various applications and forms [47]. Silicon included into the most suitable polymer for the encapsulation of the body for the long-term period compared with polyurethane and other resins because of its surface energy was low and the topography was more subtle [51].

Because of these characteristics, absorption of the cells and molecules by the polymer itself could be prevented. The most widely used of silicone derivative compounds in biomedical implants were parylene and polydimethylsiloxane (PDMS) [47].

d. Polycaprolactone (PCL)

Polycaprolactone, a semi-crystalline polyester, was highly-soluble in organic solvents, the glass transition temperature was-54 °C, and the melting point is 55-60 °C [52]. It's *in vivo* degradation rate was low but the drug permeability was high, so PCL would be suitable for long-term drug delivery [53].

Table 2: Advantages and disadvantages of polymer

Polymer	Advantages	Disadvantages	Ref.
PE	▪ Resistant against chemical reactions ▪ Mechanical properties can be modified based on its molecular weight ▪ low melting point ▪ HDPE porous are anti-infective, biocompatible, and elastic	▪ Less comfortable due to 'plastic feel' when applied ▪ Hard to dye ▪ High coefficient of friction	[47]
PP	▪ Good dielectric properties ▪ two forms (copolymers and homopolymers) have different mechanical strengths ▪ Non-toxic ▪ High melting point	▪ Non-degradable ▪ semi-rigid → local discomfort to the patient ▪ yet confirmed whether it was biocompatible or not	[47]
Silicone	▪ biocompatible ▪ low toxicity ▪ chemically inert ▪ excellent electrical insulation ▪ high gas permeability ▪ heat stability ▪ Hydrophobic ▪ low thermal conductivity ▪ PDMS o Clear o No flame ▪ Parylene o Good conformation o Could form a thin layer with low coefficient of friction	▪ Long-term effect was unknown ▪ High coefficient of friction ▪ PDMS o cyclic silicone monomer can contaminate the product o Hydrophobic o Tend to absorb protein ▪ Parylene o high absorption rate o poor adhesion o low mechanical strength	[47]
PU	▪ high durability ▪ biocompatible and hemocompatible ▪ low water permeability ▪ good biostability ▪ low coefficient of friction	▪ *in vivo* degradation ▪ metal oxidation	[47]

Contraceptive implant development

The first contraceptive implant was established by The Population Council and permitted in 1983 in Finland, namely Norplant®. Norplant® consists of six-rods, each rod contained levonorgestrel with dose of 36 mg. Levonorgestrel was a progestin produced synthetically that have similarity with the natural progesterone in females. At 2008, production of Norplant® was stopped because of the launching of new generation product. Those products were two-rods implants (Sino-implant (II)® and Jadelle®) and single-rod implants, (Nexplanon®/Implanon NXT® and Implanon®). Those new implants were easier to be inserted and retrieved [29, 54].

At 1996, Jadelle® was agreed by the United States Food and Drug Administration (USFDA). It comprises two rods; each rod contained levonorgestrel with dose 75 mg. At the same year, a similar product (number of rod and amount of levonorgestrel) was introduced in China, namely Sino-implant (II)®. Two years later, Implanon® first introduced but USFDA approval announced in 2006. It contains 68 mg of etonogestrel (also progestin) [33, 55].

The new generation single-rod implant, Implanon NXT®, have the similarity with Implanon® in design but it was more radio-opaque. Because of radio-opacity of Implanon NXT®, if the implant inserted too deep in the skin and when removal procedure the rod was very

difficult to trace, it can be easily detected using x-ray. Implanon NXT® also has a trocar, the operating instruments used to insert the rod [6].

In situ forming implants is one of the latest implant developments. Rapid development of this implants was because of its several advantages, such as ease of application, prolong of drug duration, reduced the dosage, improve patient compliance, and the main advantage is to reduce the invasive procedure. Prior to injection, the implant is in a liquid state, whereas once injected into the body, the polymer solution solidified to semisolid state and release the drug slowly. There were several ways in solidifying process of the implant, including cross-linking, solvent-removal, temperature change, pH, and more [56, 57].

PLGA is the most widely used biodegradable and biocompatible polymer as a carrier in a sustained drug delivery system. PLGA dissolves completely in N-methyl-2-pyrrolidone (NMP) or other organic solvents and precipitates when injected into the water environment, in this case, body fluids. This is because the organic solvent diffuses out and the water penetrates into the polymer matrix. Both hydrophilic drugs and hydrophobic drugs can be easily dissolved or suspended into the PLGA solution, and no other treatment is required for in situ compound forming implants, which is particularly suitable for delivery of drugs of proteins and peptides [56].

Table 3: Recent advances in implant technology

Product	API	Polymer	Principle	Ref.
In research	Thymosin alpha 1 (Tα1)	PLGA	Tα1 was encapsulated by chitosan and mixed with a high concentration of PLGA to form a stable in situ forming implant. The half-life of Tα1 was successfully extended up to 4 w.	[56]
In research	Asenapine maleate	PLGA	PLGA as biodegradable polymer was used to prolong the activity of asenapine maleate in Schizoprenia and bipolar disorder treatment. The drug was released for 21 d and showed an antipsychotic effect.	[58]
Lupron	Leuprolide	Saber Depot Technology	Saber delivery system used a highly viscous carrier (i.e. sucrose acetate isobutyrate). It can be injected in a liquid form after mixed with the drug and solidified in the body. Because the polymer used are biodegradable, it was not required for removal procedures.	[59]
Atridox	Doxycycline	Atrigel system	Atridox was designed as a locally applied antibiotic for periodontal management. There was 2 coupled syringe contained atrigel and drug powder (doxycycline). When the syringes were mixed, Atridox becomes a gel and easy to apply in the target area. Doxycycline would release for 21 d, and Atridox would be absorbed into the body, thus removal procedure was not required.	[59]
OncoGel	Paclitaxel	Regel depot technology	The product reconstituted using ReGel and formed a liquid because it was below the gelation temperature. After injection, Regel system quickly changes into biodegradable implants. Polymer used in this system was thermosensitive polymers.	[59]

Opportunities to develop contraceptive implant dosage forms

Nowadays, most preparations are designed relatively easily and made into oral dosage forms. However, this design still causes some problems such as patient compliance, design complexity, and also cost system that would control the rate, dosage, and delivery towards specific targets. In the end, we need to design a dosage form that didn't have a fluctuation of plasma concentration of the drug due to patient non-compliance. Finally, the implant could overcome that problem. But the challenge was how to design the implant that more effective in terms of cost and patient-friendly (smaller, non-invasive, and specific targets) [9]. There were challenges in designing implant such as:

- Operating time: duration of action needs to be longer, especially for chronic disorders treatment [60].
- Loading volume and drug reservoir size: it is impossible to surge the device size to put up a large reservoir. The device should be designed as small as possible thus the side effects into surrounding tissues are fewer [61].
- Biocompatibility: the material should be well-respond to the immune system so the risks (allergy, inflammation) could be reduced [62,63]

Application of contraceptive implants requires a trained person because it is still invasive, where the implant should be inserted and removed. The new generation of contraceptive implants, Implanon NXT®, added the ease of detection of the implant site. The opportunities that can be developed from the contraceptive implant such as by using the concept of in situ forming implants so insertion by the operative procedure can be replaced only by an injection. Then we should develop the implants using biodegradable polymers to solve implant removal problem.

CONCLUSION

Contraceptives implant are hormonal contraceptives containing low-dose progestin,which is inserted subdermally with long-term duration. Contraceptive implants prevent the occurrence of pregnancy by making the cervical mucus thicker and disrupting the formation of the endometrium. Some of the benefits of implant contraception include its very high effectivity. Thus, contraceptive implants are still on a great demand in the market to overcome unintended pregnancies and control human growth population. And in the end, its benefit is to improve the quality of life. Contraceptive implants in the future can undergo technological developments by using the concept of in situ forming implants and biodegradable polymers as the carrier so that no removal action is required.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Pleaner M, Morroni C, Smit J, Lince Deroche N, Chersich MF, Mullick S, *et al.* Lessons learnt from the introduction of the contraceptive implant in South Africa. SAMJ South African Med J 2017;107:933–8.
2. Hubacher D, Mavranezouli I, McGinn E. Unintended pregnancy in sub-Saharan Africa: magnitude of the problem and potential role of contraceptive implants to alleviate it. Contraception 2008;78:73–8.
3. Hardee K, Harris S, Rodriguez M, Kumar J, Bakamjian L, Newman K, *et al.* Achieving the goal of the london summit on family planning by adhering to voluntary, Rights-based family planning: what can we learn from past experiences with coercion? Int Perspect Sex Reprod Health 2014; 40:206–14.
4. Hubacher D, Dorflinger L. Avoiding controversy in international provision of subdermal contraceptive implants. Contraception Elsevier Inc 2012;85:432–3.
5. Steiner MJ, Lopez LM, Grimes DA, Cheng L, Shelton J, Trussell J, *et al.* Sino-implant (II) a levonorgestrel-releasing two-rod implant: systematic review of the randomized controlled trials. Contraception 2010;81:197–201.
6. Mansour D. Nexplanon®: what Implanon® did next. BMJ Sex Reprod Heal. Br Med J Publishing Group 2010;36:187–9.

7. Santos A, Sinn Aw M, Bariana M, Kumeria T, Wang Y, Los. Drug-releasing implants: current progress, challenges and perspectives. J Mater Chem B; 2014. p. 1–28.
8. C Wright J, S Hoffman A. Long acting injections and implants. Long Act Inject Implant; 2012.
9. Kleiner LW, Wright JC, Wang Y. Evolution of implantable and insertable drug delivery systems. J Controlled Release 2014;181:1–10.
10. Folkman J, Long DM. The use of silicone rubber as a carrier for prolonged drug therapy. J Surg Res 1964;4:139–42.
11. Hoffman AS. The origins and evolution of "controlled" drug delivery systems. J Controlled Release 2008;132:153–63.
12. Vernon B, Wegner M. Controlled release. Encycl Biomater Biomed Eng. Taylor and Francis; 2004. p. 384–91.
13. Wright JC, Burgess DJ. Long acting injections and implants. Springer; 2011.
14. NHS Choices. Contraceptive implant; 2014. p. 1–2.
15. Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, et al. The prevalence of unplanned pregnancy and associated factors in Britain: Findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). Lancet 2013;382:1807–16.
16. Cameron ST, Glasier A, Chen ZE, Johnstone A, Dunlop C, Heller R. Effect of contraception provided at termination of pregnancy and incidence of subsequent termination of pregnancy. Int J Obstet Gynaecol 2012;119:1074–80.
17. Excellence C. Guideline-LARC guideline consultation table consultation; 2014. 2014. p. 1–25.
18. Nations U. World Family Planning; 2017. p. 1–43.
19. Moreau C, Bohet A, Hassoun D, Teboul M, Bajos N. Trends and determinants of use of long-acting reversible contraception use among young women in France: Results from three national surveys conducted between 2000 and 2010. Fertil Steril 2013;100:451–8.
20. Lader D. Opinions Survey Report No. 41 Contraception and Sexual Heath, 2008/09; 2009. p. 1–105.
21. Stoddard A, McNicholas C, Peipert JF. Efficacy and safety of long-acting reversible contraception. Drugs 2011;71:969–80.
22. Russo JA, Miller E, Gold MA. Myths and misconceptions about long-acting reversible contraception (LARC). J Adolesc Health 2013;52:S14-21.
23. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon® on menstrual bleeding patterns. Eur J Contracept Reprod Heal Care 2008;13:13–28.
24. Darney P, Patel A, Rosen K, Shapiro LS, Kaunitz AM. Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertil Steril 2009;91:1646–53.
25. Funk S, Miller MM, Mishell DR, Archer DF, Poindexter A, Schmidt J, *et al.* Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 2005;71:319–26.
26. Rowlands S, Searle S. Contraceptive implants: current perspectives. Open Access J Contracept 2014;5:73–84.
27. Schnabel P, Merki-Feld GS, Malvy A, Duijkers I, Mommers E, Van Den Heuvel MW. Bioequivalence and X-ray visibility of a radiopaque etonogestrel implant versus a non-radiopaque implant: A 3-year, randomized, double-blind study. Clin Drug Investig 2012;32:413–22.
28. Faculty of Sexual and Reproductive Healthcare. Introduction: Efectiveness of Contraceptive Method. UK Med Eligibility Criteria Contracept. UK: Faculty of Sexual and Reproductive Healthcare; 2016. p. 1–7.
29. Power J, French R, Cowan FM. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy. Cochrane Libr. Wiley Online Library; 2007.
30. Glantz S, Glantz JC, Campbell-Heider N, Schaff E. Norplant® use among urban minority women in the United States. Contraception 2000;61:83–90.
31. Brache V, Faundes A, Alvarez F, García AG. Transition from Norplant to Jadelle in a clinic with extensive experience providing contraceptive implants. Contraception 2006;73:364–7.
32. Alam S, Baldwin JB, Tombros KA, Rinehart B, Shields WC, Swann AM. The single-rod contraceptive implant. Clin from Assoc Reprod Heal Prof; 2008. p. 7–9.
33. Fischer MA. Implanon: a new contraceptive implant. J Obstet Gynecol Neonatal Nurs 2008;37:361–8.
34. Darney PD, Monroe SE, Klaisle CM, Alvarado A. Clinical evaluation of the capronor contraceptive implant: preliminary report. Am J Obstet Gynecol 1989;160:1292–5.
35. Jacobstein R, Polis CB. Progestin-only contraception: Injectables and implants. Best Pract Res Clin Obstet Gynaecol 2014;28:795–806.
36. Reproductive Health Supplies Coalition. Caucus on New and Underused Reproductive Health Technologies. Cochrane Database Syst Rev; 2011. p. 12–4.
37. Faculty of Sexual and Reproductive Healthcare. Clinical Guidance: Drug Interactions with Hormonal Contraception Drug Interactions with Hormonal Contraception; 2017. p. 1–12.
38. Mansour HM, Sohn MJ, Al-Ghananeem A, DeLuca PP. Materials for pharmaceutical dosage forms: molecular pharmaceutics and controlled release drug delivery aspects. Int J Mol Sci 2010;11:3298–322.
39. Solorio L, Carlson A, Zhou H, Exner AA. Implantable drug delivery systems. In: Bader RA, Putnam DA. editors. Eng Polym Syst Improv Drug Deliv. First Edit. John Wiley and Sons, Inc; 2014. p. 191–225.
40. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opin Drug Delivery 2010;7:429–44.
41. Gad HA, El-Nabarawi MA, El-Hady SSA. Formulation and evaluation of PLA and PLGA in situ implants containing secnidazole and/or doxycycline for treatment of periodontitis. Aaps Pharmscitech 2008;9:878.
42. Lü JM, Wang X, Marin Muller C, Wang H, Lin PH, Yao Q, *et al.* Current advances in research and clinical applications of PLGA-based nanotechnology. Expert Rev Mol Diagn 2009;9:325–41.
43. Shuwisitkul D. Biodegradable implants with different drug release profiles. Freie Universitat Berlin; 2011.
44. Patel B, Chakraborty S. Biodegradable polymers: emerging excipients for the pharmaceutical and medical device industries. J Excipients Food Chem 2013;4:126-57.
45. Dorati R, Conti B, Colzani B, Dondi D, Lazzaroni S, Modena T, *et al.* Ivermectin controlled release implants based on poly-D,L-lactide and poly-ε-caprolactone. J Drug Delivery Sci Technol 2018;46:101–10.
46. Wischke C, Schwendeman SP. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. Int J Pharm 2008;364:298–327.
47. Teo AJT, Mishra A, Park I, Kim YJ, Park WT, Yoon YJ. Polymeric biomaterials for medical implants and devices. ACS Biomater Sci Eng 2016;2:454–72.
48. Zhou J, Huang X, Zheng D, Li H, Herrler T, Li Q. Oriental nose elongation using an L-shaped polyethylene sheet implant for combined septal spreading and extension. Aesthetic Plast Surg 2014;38:295–302.
49. Rahimi A, Mashak A. Review on rubbers in medicine: natural, silicone and polyurethane rubbers. Plast Rubber Compos 2013;42:223–30.
50. Roohpour N, Wasikiewicz JM, Moshaverinia A, Paul D, Grahn MF, Rehman IU, *et al.* Polyurethane membranes modified with isopropyl myristate as a potential candidate for encapsulating electronic implants: a study of biocompatibility and water permeability. Polymers (Basel) 2010;2:102–19.
51. Kirsten S, Uhlemann J, Braunschweig M, Wolter KJ. Packaging of electronic devices for long-term implantation. Electron Technol (ISSE), 2012 35th Int Spring Semin. IEEE; 2012. p. 123–7.
52. Patlolla A, Collins G, Livingston Arinzeh T. Solvent-dependent properties of electrospun fibrous composites for bone tissue regeneration. Acta Biomater 2010;6:90–101.
53. Ulery BD, Nair LS, Laurencin TC. Biomedical applications of biodegradable polymers. J Environ Polym Degrad 1993;49:65–80.
54. Ramchandran D, Upadhyay UD. Implants: the next generation. Popul Reports Ser K Inject Implant; 2007. p. 1–19.
55. Hohmann H, Creinin MD. The contraceptive implant. Clin Obstet Gynecol 2007;50:907–17.
56. Liu Q, Zhang H, Zhou G, Xie S, Zou H, Yu Y, *et al. In vitro* and *in vivo* study of thymosin alpha1 biodegradable in situ forming poly(lactide-co-glycolide) implants. Int J Pharm 2010;397:122–9.

57. Li H, Liu T, Zhu Y, Fu Q, Wu W, Deng J, *et al.* An in situ-forming phospholipid-based phase transition gel prolongs the duration of local anesthesia for ropivacaine with minimal toxicity. Acta Biomater 2017;58:136–45.
58. Avachat AM, Kapure SS. Asenapine maleate in situ forming biodegradable implant: an approach to enhance bioavailability. Int J Pharm 2014;477:64–72.
59. Solanki HK, Thakkar JH, Jani GK. Recent advances in implantable drug delivery tm. Int J Pharm Sci Rev Res 2010;4:168–77.
60. Tsai NC, Sue CY. Review of MEMS-based drug delivery and dosing systems. Sensors Actuators A Phys 2007;134:555–64.
61. Kotzar G, Freas M, Abel P, Fleischman A, Roy S, Zorman C, *et al.* Evaluation of MEMS materials of construction for implantable medical devices. Biomaterials 2002;23:2737–50.
62. Dash AK, Cudworth GC. Therapeutic applications of implantable drug delivery systems. J Pharmacol Toxicol Methods 1998;40:1–12.
63. Abel PU, Von Woedtke T. Biosensors for *in vivo* glucose measurement: can we cross the experimental stage. Biosens Bioelectron 2002;17:1059–70.