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Implications of advance biomaterials in development of new contraceptive devices

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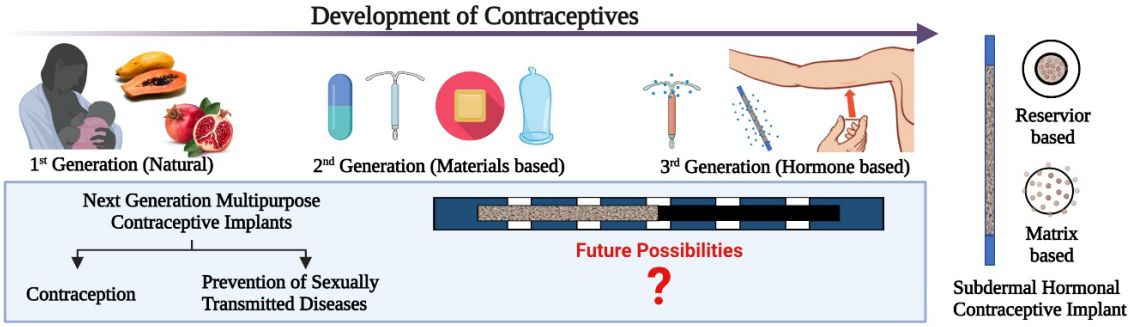
Review Article

ABSTRACT



Contraceptives are playing an integral role in maintaining human reproductive and sexual health in present society. Currently available contraceptives are based on the ease of applying, comfort during use, and activity period. The materials used in the development of contraceptives can be a determining factor towards the desired features for possible adoption. Here, in this review, we have discussed the important and futuristic contraceptives in terms of biomaterials used in the production and techniques which can be used as inspiration for better contraceptives in the future. Especially, this review discusses long-acting reversible hormonal contraceptives, Intrauterine Devices (IUDs), oral pills, vaginal rings, and patches along with the comparison of these with several polymer-composite-based implants for contraception. The overall analysis indicated possible development of better contraception devices in near future, particularly with further improvements in biomaterials that are used for the production of advanced multipurpose polymer-composite-based contraceptive implants.

Keywords: Contraceptive Agents, Male Contraceptive Devices, Female Contraceptive Devices, Hormonal contraception, Reproduction

INTRODUCTION

Alarmingly high rates of unintended and unwanted pregnancies have been reported in various scientific survey reports. High number of unexpected pregnancies occur despite considerably significant advances in the field of contraceptive technologies in recent years. Data shows that in the period of 2015-19, 121 million unintended pregnancies occurred annually and around 61% of these pregnancies resulted in abortions.[1] Added to this, global decline in general reproductive health has been reported; mostly due to the rapid increase in the spread of sexually transmitted infections (STIs). According to some recent studies, more than one million sexually transmitted infections are occurring every day worldwide.[2] It also revealed that some of the sexually transmitting diseases like syphilis occurred to 988,000 pregnant women in 2016, which resulted in more than 350,000 unnatural birth outcomes including 200,000 stillbirths and newborn deaths.[3] These enormous number of unintended pregnancies and STIs are concerning and have adverse effect on the mental and physical health of the society.[4–6] This highlights the importance of the use of contraceptives and the development of better technologies.

According to WHO data for the year 2019, among the 1.1 billion women who needed family planning, around 76% (842 million) women were using contraceptive methods, and the rest 24% i.e., around 270 million women were recognized as having an unmet need for contraception. The progress made in the recent past has been slow and modern contraceptive prevalence increased by only 2.1% i.e., from 55.0% to 57.1% between 2000 and 2019.[7] Regional disparities are even worse and are masked in the global data provided. For example, in the case of contraceptive prevalence in Sub-Saharan Africa, it is observed to be at 28%, against the contraceptive prevalence of around 60% in Eastern and South-Eastern Asia, which is far less than the

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global figure of 57.1%.[8] These disparities can arise from numerous factors like region dependant awareness and accessibility issues (reachability and costs).[9,10] Some of these issues like the cost factor can be resolved by advancement in contraceptive and biomaterial technologies to make them more accessible.

Out of the various contraceptive methods known around the world, use of modern contraceptive technologies were observed to be around 27% (including injectable contraceptives 8%, implants 2%, and Intrauterine Devices (IUDs) 17%). Female sterilization (24%) and male condoms (21%) were the most widely used contraceptive methods, even oral pills with their numerous side effects accounted for 16% of the total contraceptives used.[8] These low percentages of modern contraceptive usage despite their high rates of effectiveness (Table 1) can be explained by the unawareness and lack of comfort, accessibility, and fear of using these methods.[11–13] There is also a huge disparity among geographical regions on the most prevalent type of contraceptive method used, for instance, the high prevalence of female sterilization in central and southern Asia[14] as opposed to the high prevalence of oral contraceptive pills in Europe and North America.[8] This implies a need for the development of better contraception technologies, which can be addressed through improved biomaterials selection and design. There is also a need for better awareness and accessibility of these technologies.

The evolution of contraceptive technologies can be divided into three generations (Table 1). The first generation primarily belongs to behavioral methods while the second and third generations were based on improvised biomaterials and hormone-based contraceptives. In the current review, a summary of third-generation contraceptive devices has been presented in the light of biomaterials used in the development of these devices. For designing a particular contraceptive device of advanced generation and futuristic approach, the constituent biomaterials need to have desirable properties such as low Young's moduli and higher yield stress which can be attributed to the elastomer class of polymers. The proper choice of biomaterial can go a long way in making a contraceptive device more robust, effective, efficient, and user-friendly. Furthermore, improving the materialistic constitution of a contraceptive device can greatly increase its biocompatibility, and lower the production cost which will make the device more available and accessible to the common population. The mechanism of action, the significance of the biomaterials used, and the drug release pattern of various hormonal contraceptive devices and contraceptive implants have been discussed here to understand the fundamental characterstics of materials required in the development of these methods/devices by biomaterial scientists. The molecular details and chemical synthesis processes adopted for the synthesis of the biomaterials that are utilized in these implants have been included to further help in understanding the structure-activity relationship (SAR). Further discussion includes the current progress in long-term reversible male contraceptives, especially implants, and multipurpose prevention technologies, which includes anti-microbial properties along with their contraceptive action. This review intend to summarize the recent developments in contraceptive technologies and devices with respect to biomaterials used in their construction along with their properties, and further discusses the avenues of improvements to achieve futuristic contraceptives with desired properties and benefits.

Table 1: Period of intended use and effectiveness of various contraceptives.

Contraceptives	Effectiveness*	Period of Use
Barrier contraceptives (2nd generation)		
Condoms (male)	82-98%	Single use
Condoms (female)	79-95%	Single use
Diaphragm (w/ spermicide)	92-94%	24 hours
Cervical cap (w/ spermicide)	92-96%	48 hours
Spermicidal contraceptives		
Sponge	88-91%	24 hours
Gel/film/Suppository	72-82%	1-3 hours
Inert IUD	>99%	10 years
Hormonal Devices (3rd generation)		
Oral Pills	91-99.7%	1 day
Transdermal patch	91-99.7%	1 week
Intravaginal ring	91-99.7%	3 weeks
Subdermal Implant	> 99%	3-5 years
Hormonal IUD	>99%	3-5 years
Sterilization		
Tubal litigation	99.5%	Permanent

Advanced Contraceptive Devices

Among three generations of the contraceptions, first generation can be associated with behavioral methods, where many of them being proved ineffective later on.[15] One of the earliest known oral contraceptives was pomegranate.[16] Evidence of the use of such natural contraceptives like papaya[17] in India and Sri Lanka, silphium in North Africa, pine, pennyroyal, and vitex in Greece are also found in ancient records.[18] Women also used extended breastfeeding to space pregnancies as it can postpone ovulation and menstruation, also known as lactational amenorrhea.[18] The second generation of contraceptive methods were brought about in the 19th century by the advancements in material technology, mainly by the single innovation of vulcanization of rubber.[18–20] These methods were primarily

physical barrier methods like male and female condoms, cervical caps, and diaphragms. The third-generation contraceptives are characterized by the use of hormones to regulate ovulation cycles and incite physiological changes to the reproductive tract that could affect the migration and survivability of sperms. Further advances to these basic contracentives[21–25] have generated new classes of contraceptives including Short-Acting Reversible Contraceptives, Long-Acting Reversible Contraceptives, Male Contraceptives and multipurpose contraceptive implants, etc.

Short-Acting Reversible Contraceptives: Short-acting reversible contraceptives are known to provide better control over their contraception period to users. They are non-invasive in application which makes them safer and more reliable to use.

(i) Oral Contraceptive Pills

Oral contraceptive pills are the earliest and the basic form of hormonal contraceptive. It is an oral method of hormonal delivery, due to which some properties need to be ensured in the design strategy. The major issue that the pill should overcome is ensuring proper absorption of the drug into the bloodstream. The pill should survive the pH conditions in the stomach and only dissolve in the intestine to ensure maximum absorption efficiency. Oral contraceptive pills have a typical use case failure rate of ~9 %.[26] A major issue with contraceptive pills is the need for punctuality and regularity. Women often miss their doses.[27,28] This may result in the requirement of emergency contraceptives, unwanted pregnancy, miscarriage, abortion, etc.[29] Among other drug delivery systems, microspheres have been implemented to ensure the adequate release profile of the hormone.[30] The drug is generally delivered in a burst (very rapidly) with serum levels of hormone reaching well above the required levels. The release profiles are also very unstable, which leads to higher risk and severity of occurrence to the side effects.[31,32]

(ii)Transdermal delivery contraceptives

Transdermal delivery contraceptives are based on the release of hormones into the bloodstream through the skin. The delivery system used for the delivery of the hormones have to be carefully designed to achieve transdermal diffusion. Hormones with small molecular sizes/weights and low therapeutic levels are ideal as they are the easiest to deliver as per Lipinski's rule of five.[33] Higher lipophilicity of the hormonal molecules also help them permeate easily through the skin.[34] Generally, matrix-based delivery systems are used in these contraceptives, where the hormone is suspended in a polymeric matrix.[23] The hydrophobicity of the hormones in comparison to the matrix is very important to determine the rates of diffusion in the matrix.[35] It creates a hormone gradient across the skin and generates the driving force for the hormone diffusion into the skin. Polyesters and polyethylenes are used to manufacture the membranes in Xulane, a commercially available transdermal contraceptive.[23] A modified micro-needle system has been recently reported to be used for transdermal delivery of levonorgestrel successfully. Chitosan and beta-sodium glycerophosphate were included in the formulation of microneedles along with dexamethasone (DEX) solution. This formulation increased the drug loading in the implant and bioavailability in the bloodstream.[36] Most of the side effects seen in these transdermal patches are similar to those observed in contraceptive pills like nausea, headache, emotional lability, and breast discomfort.

(iii) Inter-Vaginal Rings (IVRs)

Inter-vaginal rings are flexible rings loaded with hormones that are designed such that they can be inserted into the vagina near the cervix, where they remain and release hormone(s) over a period of time.[37] These rings can have a matrix or reservoir design inside/on which the intended hormone can be loaded and delivered based on constant zero-order kinetics. The release rate is dictated and can be controlled by relative quantity and solubility of hormone in the matrix, diffusivity in the matrix, and the surface area of the ring.[23,38]

(iv) Injectable Contraceptives

Injectable contraceptives are drug delivery formulations containing hormones that can be injected intramuscularly for contraception purposes. These injectable hormone delivery systems are generally matrix-based oil-in-water formulations in the form of microspheres, which can release the hormones at a steady rate into the bloodstream for an extended period.[39] Another kind of delivery system generally used is in-situ depot (ISD) which contains a solution or suspension of a hormone loaded in biodegradable polymers. When injected into the human body it forms a solid phase material due to solvent exchange with aqueous body fluids.[40] The carrier materials in these systems are desired to have low degradation rates and high hydrophobicity for a better release profile over longer periods of use. Polycaprolactone (PCL), polylactic acid (PLA), and poly lactic-co-glycolic acid (PLGA) microspheres are some of the major delivery systems used in this method.[24]

LONG-ACTING REVERSIBLE CONTRACEPTIVES (LARCS)

Long-acting reversible contraceptives (LARCs) are highly effective techniques preferred by users who want reliable contraception over longer periods. LARCs utilize both 'reservoir based' and 'matrix based' drug delivery systems.[41] The reservoir-based implants possess a compact drug core surrounded by a non-degradable and permeable membrane which allows controlled diffusion of the drug from the implant. The matrix-based system on the other hand consists of a polymer matrix in which the drug is homogeneously dispersed.[42] An outer layer of a polymer or copolymer controls the release rate, and the release follows zero-order kinetics[43,44] with the rate dependent on initial hormone load and the outer layer properties.[23,45]

(i) Intrauterine delivery

In this method, hormonal IUDs are placed in the uterus to prevent fertilization by delivering hormones consistently. The hormonal IUD is a flexible T-shaped polyethylene device with the shaft of the "T" acting as a reservoir for containing the desired hormone. Hormonal IUDs have a low failure rate of only 0.2% within the first year of use.[46] The procedure for insertion of IUDs is uncomplicated and short but can be slightly painful and is accompanied by cramps in some users.[47,48] During the placement, uterine size, mobility, and position must be accurately assessed to minimize the risk of perforation and expulsion. Even in cases of perfect placement, there are many potential side effects

associated with the IUDs like bleeding pattern changes, expulsion (at a later stage), and pelvic inflammatory disease (more probable to occur in the first 21 days after insertion).[23]

(ii) Contraceptive Implants

This class of devices uses the subdermal delivery method to achieve contraception. Subdermal contraceptive devices are generally small, flexible, and non-biodegradable rod-shaped implants that use a matrix or drug-reservoir-based design for hormonal delivery (figure 1). Implantable drug delivery systems can be classified into two broad categories, passive and active implants. Passive implants are devices where drug release occurs by passive diffusion. They can further be classified into two categories including biodegradable and non-biodegradable systems. Active implants are devices that rely on energy-dependent methods like osmotic pressure gradient or electromechanical drives to provide the driving force for drug release. These implants are very costly and are not widely used. Biodegradable type passive implants are made of polymers or block copolymers. They can be degraded and then excreted or absorbed by the body. Polymers such as PLA, PLGA, and PCL are used in these implants. The drug delivery mechanism in these implants is a combination of matrix degradation and diffusion-dependent drug release with matrix degradation being the main driving force. Their main advantage over non-degradable implants is that they do not require extraction procedures after their intended period of use. These delivery systems are not commercially used in contraceptive devices currently due to the smaller spectrum of polymers available to be used and strict regulatory requirements.[49,50]

(a) Levonorgestrel based implants

Norplant can be considered as the first contraceptive implant being made available in the market which was approved by the Food and Drug Administration (FDA) in 1990. Originally, Norplant was manufactured as a set of six capsules, 34 mm long and having a diameter of 2.4 mm made up of medical grade silicone (used in catheters and valves) and sealed with polydimethylsiloxane adhesive on both ends (figure 1). The capsules were reservoirs each filled with 36mg of levonorgestrel (LNG) microcrystals (total of 216 mg) implanted under the skin in the upper arm of the user and were effective for 5 years.[51] Later on, the amount of inert silica in the silicone tubes was reduced making it softer (or less crystalline) which enhanced the linkage with levonorgestrel and its diffusion through the thin-walled silicone membrane. Probably, less crystallinity meant that the atoms in the silicone tube were less ordered which increases the ease of diffusion through the medium. Soft tubing also enhanced the long-term release rates in the implant, which led to a significant decrease in observed pregnancy rates in users.[52] Though originally recommended for a period of 5 years, Norplant has been shown to have 69% of the original hormone left and is observed to have sustained LNG serum levels above the threshold for about 8 years after implantation. This has led to the exploration of the possibility of extending the period of use to 7 years.[51]

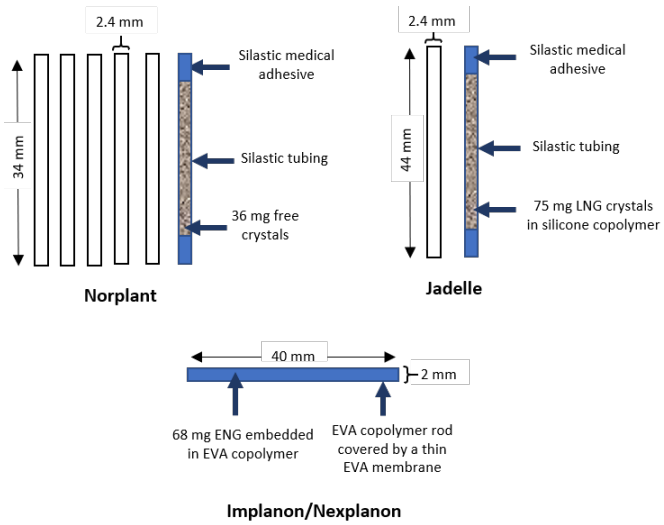

Figure 1. Schematic of commercially available subdermal contraceptive implants.

The idea of using Silastic®, silicone, or dimethylsiloxane for implantable contraceptives was proposed by Croxato and Segel in 1967. They visioned that this polymer, which had been previously utilized as a heart valve and many other biomedical applications, can become the basis of implantable contraceptives.[53] Silastic elastomer refers to the long chain of silicates (Si-O) with the branching of two methyl groups, containing 25 weight percent of amorphous fumed silica fillers.[54] Replacing the methyl group with other hydrophobic groups like trifluoropropyl and phenyl vinyl can lead to a wide variation in physical properties.[55] The Jadelle implant is a copolymer of dimethylsiloxane and methyl vinyl siloxane enclosed in a thin layer of the silicone tube and sealed by Silastic – a silicone adhesive.[56,57] High molecular weight poly dimethyl siloxane PDMS (~600kDa) gives it the characteristics of a solid. The elastomeric properties are achieved with the crosslinking of the vinyl-containing derivative of PDMS with PDMS containing Si-H bond. This reaction is generally catalyzed by H_2PtCl_6 (figure 2A). Amorphous silica is added as a filler to enhance the tensile strength of silastic.[54]

The large bond length and bond angle between Silicon and oxygen give rise to a flexible implant. The inorganic backbone of the Si-O bond makes the implant biocompatible and inert. The inertness not only reduces the chances of a chemical reaction between the body fluid and the implant but also makes it non-biodegradable.[58] Resistance to biodegradability enhances its shelf life. As compared to other organic polymers, implants made of silicone rubbers are less affected by the living tissues.[55] The release properties of silicone rubber tubing enhance the passage of biological fluids through the implant. The strong inorganic bond makes it robust towards extreme environments such as very low and high temperatures (-100℃ to 300℃).[59] Due to this property, the implant can be easily sterilized by autoclaving. In short, inertness and stable mechanical properties of silicone rubber make the implant suitable for long-term use in the body.

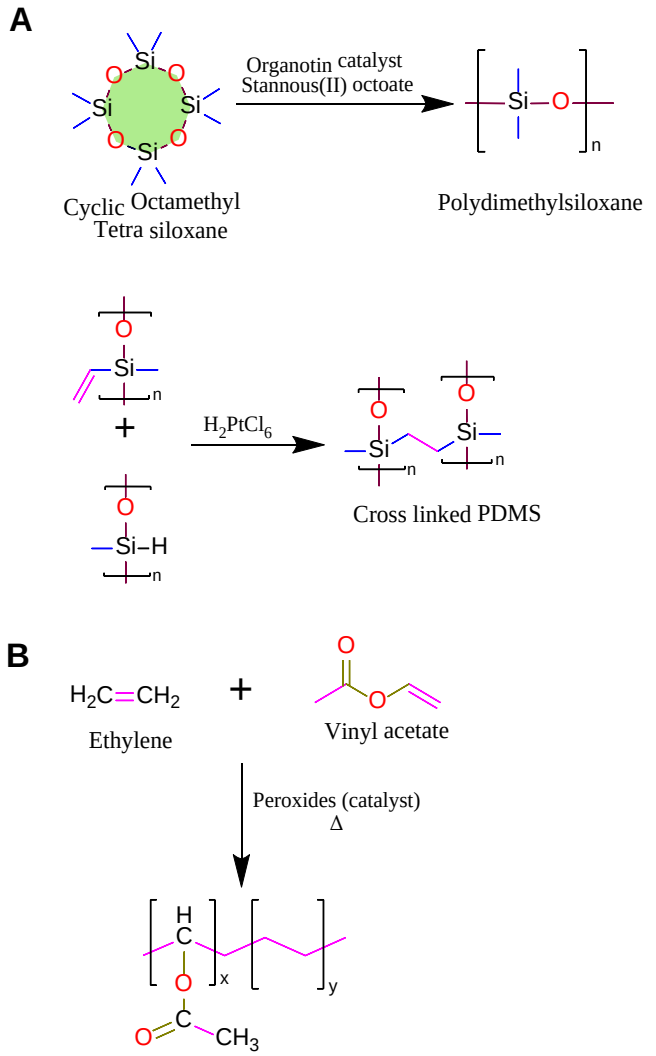

Figure 2. (A) Synthesis of a linear polymer of PDMS using cyclic octamethyl tetrasiloxane as a monomer and crosslinking of PDMS using H_2PtCl_6 as a catalyst, via hydrosilylation reaction. (B) Co-polymerisation of ethylene and vinyl acetate to synthesize polyethylene vinyl acetate.

Both Jadelle and Norplant may ensure approximately 100% bioavailability of the hormone because they are implanted subdermally and hence do not need to go through the hepatic drug metabolism.[60] It is also important to note that both Jadelle and Norplant surpass the threshold hormone serum level for contraception within a few hours after implantation.[51]

(b) Etonogestrel based implants

It has been reported that levonorgestrel-based implants could not release the appropriate therapeutic levels to reliably suppress ovulation in all users throughout their intended period of use.[61,62] So, it was desired to develop an implant that could reliably suppress ovulation for a longer time. There were two design problems to overcome, first, improving therapeutic levels without increasing the number and size of the implants, and second, ensuring a stable release profile for a longer period of time. Both of these effects (increase in size/number of implants and decrease in the period of use) were not desired, hence the solution found was a hormone that could suppress ovulation at lower therapeutic levels in a shorter time. This gave rise to the development of etonogestrel-based implants. Along with having lower required therapeutic levels for suppression of ovulation, etonogestrel is also less androgenic than levonorgestrel.[56] But etonogestrel implants have been observed to cause a higher incidence of break-through bleeding and amenorrhea.[63] The use of etonogestrel in place of levonorgestrel was not sufficient for overcoming the design problems completely. The manufacturing of commercially viable etonogestrel implants was made possible by the novel co-extrusion technique of EVA polymers patented by De Nijs in 1990 for the preparation of Implanon and Nexplanon.[64]

The biomaterial used in this case was the same for the core and the rate-controlling membrane. The core material was made using poly ethylene-co-vinyl acetate (PEVA) synthesized by free radical polymerization of vinyl acetate and ethylene gas (see figure 2B).[54] By varying the ratio of the two monomers the hardness of the material could be tuned. The implant polymer had a higher molecular weight and a vinyl acetate content of 20% w/w or more. The membrane was made using the same PEVA material of lower molecular weight and 20% w/w or less, vinyl acetate content (figure 1).[64,65] As a result of the material used in the core and membrane being similar, there was a very small diffusion barrier for the hormone, which resulted in a better diffusion rate per unit surface area and a more stable release profile (as compared to Jadelle) due to better continuity in the concentration gradient in the implant. Here the release profile of the implant (Table 2) is very easily and precisely controlled by the amount of vinyl acetate in the membrane. There have been studies reporting that Implanon is viable for a period of up to 5 years, which may form the future basis for its approval as a 5-year implant.[63,66] Implanon NXT (refers to the next generation of Implanon) or Nexplanon are implants that have the same mechanism and composition as Implanon but were developed to improve localization of the implant by including radiopaque materials like barium sulphate in its composition.[67] Nexplanon also provided a next generation 'use and throw' applicator which could be single-handedly implanted by the doctors. Previous applicators needed both the hands of an expert clinician to implant the rod and were reusable and needed proper sterilization after every use.[68]

Table 2: Serum concentration levels of hormones in different contraceptive implants

Contraceptive	Peak value (within 1 week)	End of 1 year	End of intended period of use
Norplant	1400 pg/ml	466 pg/ml	315 pg/ml
Jadelle	770 pg/ml	341 pg/ml	275 pg/ml
Implanon	813 pg/ml	186 pg/ml	156 pg/ml

Both the silastic and PEVA based implants are non-biodegradable and hence do not leave residues in the biological

Table 3: Comparative evaluation of various biomaterials used in different contraceptives

Biomaterials	Advantages	Disadvantages	Recommendation
Silastic	Physical properties can be controlled by the extent of polymerization and introducing amorphous silica (containing methyl groups).[54] Silastic implants can be easily sterilized by autoclaving, as silastic is stable at extreme temperatures (-100°C to 300°C).[75] Silastic has a successful medical history. It has been used as a facial reconstruction implant, dialysis tubing, blood, and urethral catheters, etc.[54]	Potential source of toxicity: cyclic siloxane, platinum complexes, low molecular weight PDMS and amorphous silica.[54] More costly material, and has a higher thermal cost and time-consuming process for curing and bonding.[76] It has been extensively studied as a biomaterial and some contrary studies suggest that it can induce an immune response in the host. Although later reports discourage this finding.[54]	
Ethylene-co-vinyl acetate (EVA)	Physical properties can be tuned by altering the ratio of the co-monomers.[54] EVA can be used both as a rate-controlling membrane and as a matrix for loading the hormone.[64] EVA has lower production cost and an easier production process.[76] According to the studies done so far, EVA possess no health risks.[54]	Potential source of toxicity: vinyl acetate, organic peroxides, polyvinyl acetate, and alcohol.[54] Melting point of PEVA lies below 100°C, which means it is not very stable at higher temperatures.[77] Only a limited number of safety studies have been done on EVA so far.[54]	EVA is recommended for use in long term implantable contraceptives as it has very good biocompatibility and a stable release profile for a long period of time. EVA is recommended over Silastic as: EVA can be used both as a hormone loading matrix and outer membrane, which leads to better release kinetics and a more stable profile, which can be observed in Implanon vs Jadelle. EVA is easier and is cheaper to manufacture than Silastic.

environment. Although some of the studies have suggested that they can leach out residues at a very minute scale. It is important to consider them if the leach-out product concentration is above the threshold. The threshold here refers to the concentration that can be tolerated by the body. The possible leachants include an unreacted or residual monomer, low molecular weight polymer, catalysts, fillers, etc. In the case of Norplant and Jadelle, cyclic siloxane, platinum complexes, low molecular weight PDMS and amorphous silica and in Implanon and Nexplanon, vinyl acetate, organic peroxides, polyvinyl acetate, and alcohol can play the role of leachants.[54] Studies have shown that 40-100ng of platinum per gram of silastic can leach out every day from implants.[69] As shown in figure 1, platinic acid is used to catalyze the hydrosilylation reaction in crosslinking of PDMS. If the removal of the catalyst is improper or incomplete it may cause cellular toxicity and hence pose some health risks.[69,70] The 6 micrograms of tin per gram of silastics and particulate silica debris have been observed in some of the silastic based implants.[71–74] Unreacted monomer residues – cyclic siloxanes – have also been found to be leaching out in some silastic based implants although deleterious effects have not been observed.[35]

Various advantages and disadvantages of the biomaterials used in contraceptive implants have been summarised in table 3. Commonly two types of biomaterials are used in the synthesis of contraceptive implants – Silastic (silicone) and EVA. Silastic refers to poly dimethyl siloxane and EVA is a copolymer of Ethylene-co-vinyl acetate. Norplant and its derivatives (Jadelle and Uniplant) utilises silastic as their primary biomaterial while Implanon/Nexplanon employs EVA as their primary biomaterial. The Norplant implants are generally reservoir based and consist of silicone capsules loaded with levonorgestrel (drug). Some other levonorgestrel based implants also come in the form of rods in which a mixture of levonorgestrel and silicone elastomer is cured and skinned with a thin wall of silicone tubing. Implanon/Nexplanon, on the other hand, comes in the form of matrix of the copolymer (ethylene/vinyl acetate), containing the drug, and the core is surrounded by EVA skin. Thus, Norplant has an outer layer of silicone but not all the contraceptive implants have silicone capsule (or outer silicone layer).

A major advantage of subdermal implants over any other kind of implants is their prolonged duration of stable drug release, which is not possible by any other hormonal contraceptive. Another very apparent advantage is their high effectiveness compared to other contraceptive methods. The subdermal method of delivery ensures that the bioavailability of hormones is higher as they do not get metabolized by the liver. This ensures that a big proportion of the total amount of hormone will be effectively utilized for contraception and will not go in vain.[78,79]

MALE CONTRACEPTIVES

While there are numerous non-biodegradable LARCs developed to protect women for an extended period, male contraception development encounters slow progress despite the hype. Currently, there is no hormonal male contraceptive available in the market.[80–84] However, there are several novel approaches shown to be effective in trials and could provide a range of options other than male condoms and vasectomy. Male contraceptives may be considered to function by either hormonal method (hypothalamic-pituitary-testicular axis) or through non-hormonal techniques that act anytime during spermatogenesis targeting sperm development, separation, or motility.

(i) Non-Hormonal long term reversible male contraceptives

Reversible Inhibition of Sperm Under Guidance (RISUG) is a contraceptive injection that contains a co-polymer, stericmaleic anhydride (SMA), dissolved in dimethyl sulphoxide (DMSO), and creates a chemical and physical barrier when injected in each vas deferens. This contraceptive can be reversed if RISUG is flushed out with injections containing dimethyl sulfoxide or sodium bicarbonate ($NaHCO_3$). The RISUG forms charged precipitates to create an acidic environment in the lumen and further implanting precipitated layers in the micro folds on the inner longitudinal layer of vas deferens.[85] When RISUG comes in contact with sperm in the vas deferens, it dissolves the plasma membrane of the sperm by ionic as well as pH stress, thus, rendering them incapable to fertilize the oocytes (figure 3A-C).[86]

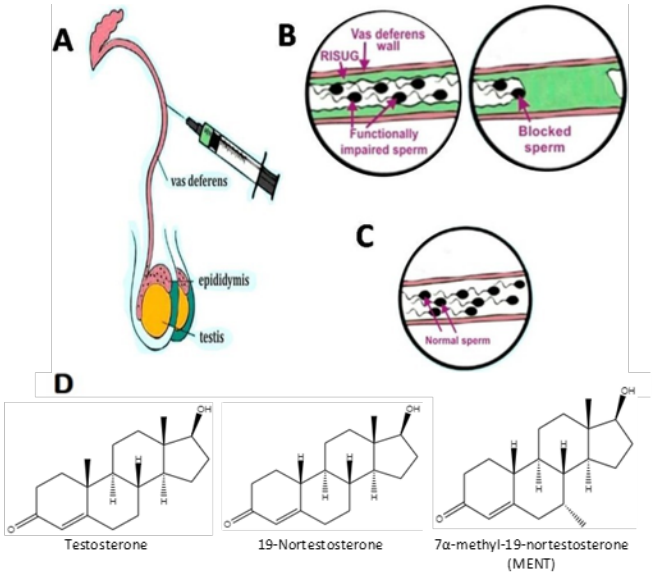

Figure 3. (A) RISUG is injected in both vas deferens (B) Action of RISUG by coating the wall of the vas deferens blocking sperm movement as well as the formation of a chemical barrier. (C) Complete reversal of infertility effects obtained after DMSO/NAHCO3 is injected. Adapted from Khilwani, B., Badar, A., Ansari, A.S. et al. RISUG® as a male contraceptive: journey from bench to bedside. Basic Clin. Androl. 30, 2 (2020), under the terms of the Creative Commons Attribution 4.0 International License. 41 (D) Molecular structures of i) Testosterone ii) 19-Nortestosterone iii) 7α-methyl-19-nortestosterone (MENT).

Another approach towards nonhormonal-based contraceptives implants is small-molecule inhibitors and protein targets.[87] Epididymal Protease Inhibitor (Eppin) is a serine protease-like inhibitor on the surface of spermatozoa that modulates the proteolysis activity of prostat specific antigens (PSA). A small organic compound, inhibiting Eppin activity that acts on ejaculated spermatozoa by binding to seminal vesicle protein semenogelin (SMEG1) on the sperm surface, can thereby inhibit sperm motility.[88] Macrophage migration inhibitory factor (MMIF) (a pro-inflammatory cytokine) is involved in sperm motility acquisition during transit through the epididymis. MMIF has been demonstrated to support sperm capacitation at low concentrations while inhibiting it at higher concentrations.[89] Sperm motility inhibiting factor (SMIF) (plasmatic peptide) inhibits the cAMP-dependent motility function of spermatozoa.[90] Lower levels of Epidermal Growth Factor (EGF) significantly reduced the human sperm penetration rates.[91] Soon some contraceptive implants based on these molecule targets might be available.

(ii) Hormonal contraceptive implants

Testosterone alone as well as combination therapy of testosterone and progestins is considered for male hormonal contraception by inhibiting the hypothalamus (Gonadotropin-releasing hormone, GnRH) and pituitary (luteinizing hormone, LH; follicle-stimulating hormone, FSH) action resulting in spermatogenesis.

(a) Testosterone plus progestin

Several pilot trials have been carried out to study synergic and additive effects using depot medroxyprogesterone acetate (MPA), levonorgestrel implants, and testosterone. The use of progestin coupled with androgen supports the suppression of spermatogenesis and reduces the required androgen concentration, in turn reducing potential androgenic side effects.[92] In 2008, a multicentre trial involving 354 men used 750 mg or 1000 mg of Testosterone undecanoate (TU) subcutaneous implants combined with etonogestrel every 10–12 weeks to obtain adequate sperm suppression of 1 million/ml. This treatment did not exhibit any serious side effects and offered effective and reversible spermatogenesis inhibition.[93]

In 2003, an efficacy study of four 200 mg testosterone implants (every four to six months) plus 300 mg depot MPA (injected every three months) provided adequate short-term safety and complete recovery of spermatogenesis in all except one person. No pregnancies occurred in 426 person-months (35.5 person-years); confidence limit 95% for contraceptive failure rate: 0–8% per annum. Participants reported fewer androgenic effects; however, the implant extrusion rate was about 10%, and the variable pharmacokinetics of testosterone implants led to the termination of further studies.[94]

(b) MENT (7α-Methyl-19-nortestosterone)

MENT is one of the recently developed products in this category. The short half-life of testosterone and the discouraging results from self-administered hormonal male contraceptives led to the development of synthetic progestins. Derivatives of 19-Nortestosterone (formed by removing Carbon-19 from testosterone) with the differing extent of achieving azoospermia

are currently being explored. A promising androgen implant MENT is a selective androgen receptor modulator (SARM) with an anabolic: androgenic ratio of 12 which does not convert to dihydrotestosterone by enzyme 5α-reductase, therefore not stimulating prostate growth, while providing similar health benefits of testosterone (figure 3D). A clinical trial with sustained delivery of MENT in ethylene-vinyl acetate implants has been going. The used implant has a length of 4.9 cm with a diameter of 2.7 cm and contains 171mg of MENT acetate. The serum levels are found to reach 1-3nmol/L.[95]

Multipurpose Contraceptive Implants

Contraception prevents unintended pregnancy using the existing methods, but those existing strategies do not protect the subject from different harmful sexually transmitted diseases (STDs).[96] New contraceptive designs that can provide contraception along with prevention of STDs are now being focussed upon. Multipurpose prevention methods are used for providing long-acting contraception and prevention from STD either by subdermal contraceptive implants or intrauterine devices (IUDs). However, it has been reported that IUDs are less preferred than subdermal implants due to the discomfort during intercourse and some IUDs have a deleterious effect on the uterine upper layer and normal uterine physiology.

(i) Antimicrobial peptide LL-37 as a potential contraceptive and microbicides

Antimicrobial peptide LL-37 is a class of cathelicidins peptides, which triggers the host's innate immune system by activating neutrophils and macrophages. LL-37 peptide has a wide range of antimicrobial activities against most STD-causing microorganisms.[96] It interacts with the negatively charged surface of microorganisms and enables the host to trigger an immune response. The peptide also has spermicidal activities which makes it a potential contraceptive and microbicide. Mammalian sperm head membrane has a special kind of lipid called sulfo galactosyl glycerolipid (SGG), in its lipid rafts. SGG is crucial for sperm capacitation and it makes lipid rafts negatively charged. The peptide LL-37 interacts with SGG non-specifically and prevents sperm capacitation.[97,98] LL-37 is an active peptide part of human cationic anti-microbial (hCAP-18) protein that is secreted from the epithelial cells, neutrophils, and seminal fluid. It is also the active part of hCAP-18 protein that can be obtained by cleaving it using proteinase 3.[99] It has been observed that no cross-reactions occur with vaginal tissues in the *in vivo* studies in mice while using LL-37 as a contraceptive. Studies report that 36 and 10.8 µM concentration of LL-37 is required for the inactivation of sperms of mice and humans, respectively.[97]

(ii) Use of antiviral drugs for specific harmful viral STD

HIV is one of the harmful viral STDs which can transfer to a healthy partner from the infected one. As long-acting contraceptives may not be the most suitable method for protection against HIV infection, the use of Tenofovir in contraceptive implants can inhibit reverse transcriptase function to prevent the transmission.[99]

(iii) The design approach of multipurpose contraceptive implant

The main challenge of designing the multipurpose contraceptive implant is to select appropriate biomaterial for the implant framework. As per the collected learning from various reports, the intended implant should be permeable to both, the steroid hormone and the antimicrobial drugs (LL-37 and Tenofovir) for contraception and preventing STDs respectively. Additionally, the kinetics of payload release should fall under zero-order kinetics. PDMS is a suitable biocompatible polymer that is generally used in most biomedical devices. Due to the hydrophobic characters of the PDMS, the steroid contraceptive hormones can easily diffuse through polymers. But antiviral drugs (Tenofovir) can't permeate through PDMS because of their hydrophilic nature. Polyvinyl alcohol (PVA) polymer has also been added to the design for releasing hydrophilic drugs in a controlled manner in the design proposed by Gunawardana et.al.[100] In an improved strategy, the implant was fabricated using a PDMS-PVA polymer combination. A hollow cylindrical PDMS backbone of length 40mm having tiny holes of 1mm diameter was fabricated. Two silica plugs were inserted each on its ends to close them. The implant backbone was treated with 5% (w/w) followed by 10% (w/w) PVA solution. One of the silica plugs was removed and TVF (Tenofovir Alafenamide), a drug used for HIV treatment, was loaded. The plug was restored after loading the drug.[100] Application of multiple drug delivery systems has become a common approach for treating various diseases in the last couple of decades.[101–105] A multidrug vaginal ring containing two drugs acyclovir (ACV) and Tenofovir (TFV) was proposed for the treatment of sexually transmitted diseases in 2012.[106] A multipurpose vaginal ring with the ability to prevent STDs as well as providing contraception had been proposed by the same group of researchers in 2013.[99] A crucial advantage of their system was that an independent release of multiple drugs could be achieved. The rate of delivery of different drugs could be controlled as per requirement.

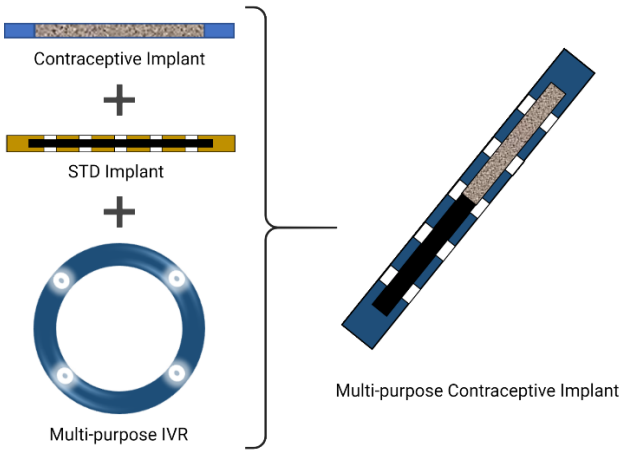

Figure 4. Design ideas of contraceptive implants, STD implants [100], and multipurpose IVRs [106] can be utilized to make a multi-purpose long-acting subcutaneous contraceptive implant.

Currently, no literature is available to claim any research on the multipurpose long-acting subcutaneous implant with an ability to provide contraception as well as prevention from STDs. Although, the studies on multipurpose drug delivery systems, more specifically on multipurpose vaginal rings suggest that multipurpose contraceptive implants are not very far-fetched. Present studies on contraceptive implants, STD implants, and multipurpose vaginal rings can be useful in overcoming design challenges to make a multipurpose contraceptive implant (figure 4).

CONCLUSION

The idea of contraception is of paramount importance for a woman planning for both personal, family health, and welfare. Contraception not only addresses the issues of unwanted pregnancies but also can protect one from sexually transmitted infections. Biomaterials used in a contraceptive generally play a major role in maintaining homeostasis and reducing immune responses. Chemically inert properties of implant biomaterials help in reducing the interaction with the surrounding tissues. Optimized flexibility and strength make them suitable for subdermal application and robust to stay longer in extreme conditions, respectively. The methods utilizing matrix have tried to improve this issue to a certain extent. Researchers have reported similar patterns leading to failure among existing devices that utilize different systems of hormonal delivery. New technologies, which are currently being studied and developed, must focus on addressing not only biomaterial functionalities but also the physiological and anatomical criteria that have obstructed the successful fabrication of the device along with user compliance. Other angles to view the possibility of designing hybrid systems might be to account for both hormonal deliveries bringing about contraception as well as highly regulated antimicrobial drug delivery through polymeric coatings over the implants. It can thereby bring about protection from STDs along with effective contraception. Considering the present developments in physiology, structural biomaterials, molecular biology, and nanotechnology, better strategies for contraception can be achieved through interdisciplinary research and synchronization for customizing user requirements. Most importantly, to overcome the lack of available product varieties, an equal impetus should be given to the field of male contraception to reduce the load on the other half of the world population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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