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(Review)

Applications of advanced biomaterials for the development of contraception

Mohamed Ashraf [1], Hossam S. El-Sawy [1, *]

[1] *Pharmaceutics and Pharmaceutical Technology Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo-Suez Road, 11829, Cairo, Egypt.*

*Corresponding author(s): Hossam S El-Sawy, E-mail: hossam-elsawy@eru.edu.eg

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ABSTRACT

Unplanned pregnancy incidence is currently a staggering number, which almost represents half of the total population worldwide according to what reported from the United Nation Population Fund (UNFPA) in 2022. Several factors could contribute to the unintended pregnancy including lack of reproductive health care and contraceptive options that don't suit all family circumstances, in addition to related side effects, menstrual disorder and lifelong infertility. Biomaterial-based contraception has gained much attention in the last few years due to its improved role in controlling drug delivery routes. In this mini review, we will discuss and mention the recent interventions and progress of conventional and advanced biomaterials-based contraceptives for long acting contraception goals. This includes subcutaneous implants, transdermal patches and microneedles, orally administered contraceptive loaded delivery systems, intravenous administration and intrauterine devices. In addition, the role of biomaterials in improving sterilization methods such as tubal ligation and vasectomy, has been also emphasized in this review.

Keywords: contraception, biomaterial, biodegradable, controlled drug delivery.

Introduction

Unintended pregnancy is a global challenge, which has significant impact on family future and, consequently, their quality of life. Although several contraceptive method are used widely nowadays, there are still major drawbacks that hinder their full effectiveness and satisfactory results. Long term usage of oral hormonal contraception is associated with many unpleasant events such as mood swings, depression and bleeding [1]. Moreover, oral contraception that requires daily administration may lead to variable plasma concentrations. Intrauterine devices (IUDs), implants, and transdermal patches were designed to overcome the limitations of other contraception forms in terms of patient compliance. However, they may suffer some drawbacks regarding patient discomfort, high cost and non-biodegradability that mandate surgical intervention for their removal [2]. Condoms, one of the most convenient and non-invasive pregnancy preventions, have marginal contraceptive efficacy and poor long-term compliance, which leads to contraceptive failure, in addition to probability of latex-material allergic reactions [3]. Sterilization methods have efficacy in reducing the rate of pregnancy but there are drawbacks related to post-contraceptive desire of reproduction [4]. Biomaterials have attracted great significance in practical and scientific applications to develop safe, effective and reversible methods of contraception and controlling drug release. Biomaterials can be modified to attain new physical and biological properties and to provide more flexibility in their usage of biomedical devices [5]. So, the utilized controllable biodegradability, as well as photothermal or chemical responses of advanced biomaterials of various delivery routes are addressed in this review with mentioning their significant enhanced efficacy, safety and compliance as contraceptive method, alongside their future aspects of development.

1. Conventional contraception approaches

Contraception methods depend mainly on prevention of either secretion of hormones, maturation of fusion between egg and sperm or implantation of fertilized egg even after fusion [6]. Many factors including accessibility, affordability and correct usage participate in the choice of appropriate contraception method. The undeniable ugly truth is that no method can assure 100% efficacy till present time [7]. Methods of contraception are summarized in table 1.

Table 1. Methods of conventional contraception [8].

Method	Device	Mechanism
Hormonal	**Implants**	Disruption of normal ovulation and thickening mucus at uterus by progesterone released slowly from silicone rod implants inserted surgically for 3 years.
	Injections	Same mechanism as implants, intramuscular injection of synthetic depot of progesterone with efficacy for 3 months.
	Patches	Progesterone is absorbed through skin of lower abdomen and upper body to inhibit normal ovulation, thickening mucus of uterus hindering movement of sperms. It is also easier to operate.
	Pills	Can be progesterone only or estrogen-progesterone combined pills, they are highly effective in disrupting normal ovulation. Suitable for women under 50 years to relieve symptoms of menstruation.
Intrauterine Device (IUD)	**Hormonal or copper**	Progesterone hinders mobility of sperms by thickening of mucus at uterus entrance or disruption of normal ovulation while copper is toxic to sperms and disrupts the implantation of fertilized egg by changing the endometrium.
Sterilization	**Tubal ligation Vasectomy**	Permanent contraception by blocking the pathway of egg fertilization, ejaculation or tubal ligation for women.
Barrier method	**Condoms**	Prevention of body fluids from passing as it is considered as physical barrier.
	Spermicidal forms (creams, gels, foams, suppository)	Kill sperms and preventing egg fertilization.

2. Applications of advanced biomaterials for different contraception approaches

In the following sections, the different methods of contraception with application of advanced biomaterials are discussed, and also summarized in Figure 1, with mentioning how to defeat possible faced challenges.

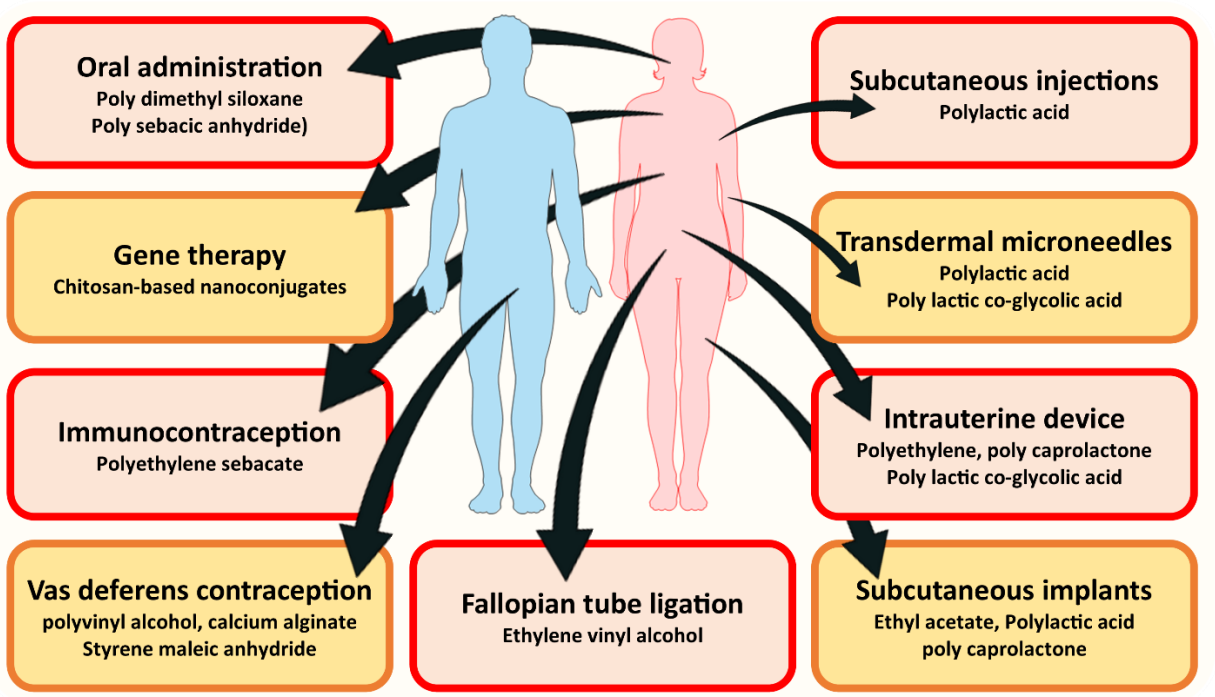

Figure 1. Examples of advanced biomaterials utilized in different contraception approaches.

2.1. Subcutaneous implants

They are inserted under the skin in order to release drug constantly, they can be designed in form of small silicone rods. Although silicone has excellent characters, it still considered a foreign substance to the human tissues and its reaction with body may lead to many difficulties. Extended release delivery systems and increasing drug dose are options to reduce the number of implants and become easier to remove [9]. Many biomaterials can be employed for the purpose of extending drug release. Ethyl acetate is used with Impalnon® as a carrier system and can be also modified with $BaSO_4$ to aid in the positioning of implants using x-rays. However, devices still need to be removed. Therefore, further development was directed towards biodegradable devices. Extensive studies were applied to avoid the necessity to remove foreign body of implant after ending of its usage. The biodegradable biomaterial must ensure constant and steady release of the drug in biodegradable manner, in addition to being non-harmful and not accumulating in the body. Polylactic acid (PLA), a biomaterial good example, is synthesized through agricultural resources fermentation. It is a hydrophobic polymer which is characterized by appropriate mechanical strength and its degradation produce CO_2 and H_2O [10]. Capronor® is subcutaneous commercial implant containing levonorgesterel (LNG) and poly caprolactone (PCL). PCL maintain its physical integrity until the drug is completely released then it degraded into

oligomers and finally to water and carbon dioxide. Clinical phase 1 showed constant level of plasma LNG without fluctuations [11].

2.2. Subcutaneous injections

Octapeptide (OP) is a synthetic peptide which upon binding to follicle stimulating hormones (FSH) receptor, it causes its inhibition. In a previous study, it is aimed to avoid repeated drug administration and increase patient compliance by formulation of OP-loaded PLA biodegradable polymer nanoparticles *via* multiple-emulsion technique. The *in-vitro* release profile showed a sustained release pattern of OP over treatment cycle with negligible initial burst release, which indicated equivalent distribution of OP. The anti-fertility studies were also indicated significant efficacy of formulation in 66% of animals [12].

2.3. Transdermal patches/microneedles

They are non-invasive drug delivery systems applied on the skin, which provide sustained drug release with avoided first pass metabolism and subsequent increased patient compliance. Stable plasma drug concentration is required in order to avoid side effects resulted from burst release.

Dissolving microneedles composed of biocompatible/biodegradable matrix have been developed to allow passing of large molecules by puncturing skin layer. Major drawback is the limited dissolving capacity of the carrier which would hinder the drug release steadily. In an earlier work, LNG was loaded into hydroxyl propyl beta cyclodextrin to improve drug release pattern and enhance its physicochemical characters [13]. PLA and poly lactic co-glycolic acid (PLGA) were used to construct biodegradable, biocompatible microneedle maintaining constant drug release [14].

2.4. Oral administration

Progesterone pills need to be taken continuously for 21 days. Missing doses can potentially lead to unplanned pregnancy due to the lowered levels of progesterone and the consequent thinning of the cervical mucus. Biomaterial-based oral contraceptive pills have been developed to increase patient compliance and reduce dosing frequency. They also provide a controlled drug release pattern *via* tailoring the monomers used for polymer synthesis.

Polydimethylsiloxane (PDMS) and poly (sebacic anhydride) were used/designed into V-shaped with elastomer core to load LNG. The system recoil larger than pylorus to be fixed/retained in the stomach and start drug release at constant rate for 1 month. Arms composed

of 2 parts, outer rigid polymer that provide mechanical strength and integrity, and drug polymer matrix. This dosage form allowed more compliance of contraceptive method as only one dose, self –administrated oral biomaterial-based dosage form [15].

2.5. Intrauterine device (IUD)

It can be categorized into two types hormonal and copper. IUD possess several advantages including but not limited to its low cost, high efficacy and easiness of reversible fertility after removing. Its action relies on disturbance and prevention of sperm fertilization of egg or its implantation. Main drawbacks of the device can be expressed by the risk of uterine bleeding and changing of vaginal discharge after application of the device [16].

Concerning Copper-IUD (Cu-IUD), its mechanism depends on the suppression and inactivation of sperms by Cu^{+2}. Unstable release of Cu^{+2} and initial burst of Cu^{+2} after its insertion represent a limiting problem of usage of IUD. Stable controlled effective release of Cu^{+2} over a long period is required to achieve the aim of method of contraception and avoid vaginal or uterus bleeding or excessive muscles spasm. To overcome this limitation, copper nanoparticles were distributed uniformly into the composite of low-density polyethylene (LDPE). Internal spacing provides channels for copper ions to be released in constant effective rate. Studies to evaluate toxicity of the designed device showed no sign of systemic toxicity or bleeding or any effect on food consumption and biochemical parameters [17].

Tailoring the initial burst release of copper ion can be also achieved by addition of preferentially dissolved Mg with ultra-fine copper, as this alloy hinder the initial release in a bursting manner and thus keep the level of copper ion constant over the period of contraceptive action. Moreover, Mg can be considered biocompatible with safely biodegradable profile [18]. PLGA is also used to coat copper intrauterine device, which participated in reduction of initial burst copper release compared to uncoated devices [19]. Another design of system is directed toward relieving the pain caused by insertion of copper intrauterine device. A polyelectrolyte multilayered film was designed containing indomethacin (IDM) and composed mainly of chitosan and alginate. This delivery system was used to coat the surface of copper/LDPE composite. This system provided controlled release of IDM with minimized side effects of pain and avoided initial burst release of cupric ions after insertion [20].

Regarding hormonal-IUD, it depends on both the normal contraceptive mechanism of IUD as well as the hormonal release from IUD in the uterus. It suppresses ovulation and

thickening of cervical mucus which will lead to the prevention of the entry of sperms and thus egg fertilization. Polyethylene (PE) was the material of choice as the matrix of hormone due to its reasonable release of hormone and appropriate surface area. Main problem regarding its usage is the fluctuation of hormones released from the IUD insertion along the period of contraception [21]. Upcoming trend for treatment of this problem is the personalized 3D printing of contraception implants and devices. Fused deposition modeling adapting the body structure is designed using PCL for encapsulation of estrogen and progesterone. As we mentioned before, PCL possess mechanical strength character, along with its safe profile of biocompatibility and biodegradability into metabolized by-products, in addition to the stable thermal properties of hormones and PCL without degradation during addition process. Release studies on this 3D printed IUD showed extended and stable hormone release over contraception period [22].

2.6. Fallopian tube ligation

Previously, fertilization process can be prevented completely by removing of fallopian tube or by its occlusion *via* injection of materials have corrosive action on mucus membrane that lead to its scarring. Several related side effects including pain, disrupted menstrual cycles and increased risk of cancer are associated with fallopian tube ligation [23]. To overcome these limitations, tubal plug of nickel-titanium is constructed with silicone rubber framework. This scaffold showed good biocompatibility and shape reversibility [24]. The Ethylene vinyl alcohol (EVOH) copolymer has been utilized in such plugs, as upon its contact with aqueous media, it solidifies and forms spongy plug, which consequently prevents fertilized egg from implantation [25].

2.7. Vas deferens contraception

It is established as an effective method of contraception for men. Nevertheless, it is an irreversible procedure with hormonal side effects. Therefore, a novel/reversible/low side effects method is required to overcome limitations of the conventional method. Choice of suitable biomaterial is crucial in order to avoid using of hormonal treatment as well as permitting one-time intervention with effective results, little impact on sexual life and ease of administration. Reversible filtering-type intra-vas device (IVD) has been developed to overcome the limitation of the conventional vasectomy. IVD composed of copper wires or threads as copper has spermicidal activity. However, the drawback of initial burst release of Cu^{+2} appears again as we mentioned before in earlier section. Composite of CuCl, polyvinyl alcohol (PVA) and

nanoparticle of silica proved to efficiently filter the sperms with avoiding the complete occlusion of vas deferens [26].

Reversible inhibition of sperms under guidance (RISUG®) is reported one of the male contraceptive methods with reversible vas occlusion. Styrene maleic anhydride (SMA) is injected causing pH reduction and positive charge disrupting acrosome function and hindering egg fertilization. It showed high efficacy of contraception and it could be reversed within 30 days by injection of $NaHCO_3$ or DMSO, which have the ability to dissolve SMA enabling recovery of fertility [27]. Sequential injection of calcium alginate hydrogel PEG-Au nanoparticles and ethylene diamine tetra acetic acid (EDTA) were also utilized. Both calcium alginate and EDTA deactivate sperms in addition to that calcium alginate acts as a physical carrier. Sequentially, PEG-Au nanoparticles solidifies at body temperature with blocking both ends of EDTA. For fertility recovery, PEG-Au nanoparticles are melted *via* near infrared light irradiation in order to unblock vas deferens [28].

Another smart novel RISUG method of contraception is currently adapted by designing iron oxide copper linked to SMA under the action of pulsed magnetic field (PMF). The novel system can reach the membrane of sperm at PMF magnitude 760Mt in around 50 seconds with no need for surgical intervention. Reduction of sperm motility by more than 70% and sperm count by 30% resulted from the application of this contraceptive system at dose lower than conventional RISUG [29]. From another study performed for the assessment of RISUG efficacy on 25 subjects by intravasal injection of new male contraceptive prepared from copolymer styrene maleic anhydride dissolved in dimethyl sulphoxide (DMSO). Polymer delivered into vas deference affecting the sperm head leading to leaching of acrosin and hyalouronidase making sperms incapable of fertilization. Results showed that 24% of subjects were found to be azoospermic after only 1 month, 60% after 2 months, 12% after 3 months, 4% after 4 months with no pregnancy incidence in the same study period [30].

2.8. Immunocontraception

Although it is considered as effective, long term and stable method, immunocontraception faces a lot of challenges regarding the reversibility of immune response towards the reproductive system. It can be explained as the main utilized mechanism of action is *via* inducing high level of luteinizing hormone releasing hormone (LHRH) antibodies. System of nanoparticles based on modified chitosan was engineered with modification by choloracetyl

group to allow attaching of peptide-based protein and antigen to exaggerate the immune action after being retained by lymph nodes. Results showed high level of antibodies equivalent to amount produced by freund's adjuvant and successful contraceptive effect [31]. Polyethylene sebacate (PES) was used to incorporate sperm specific 80 kDa human sperm antigen (HSA). Inter dermal injection of formulation was found to produce high titer of antibodies reaching 1:3200 and specific immune reactions, in addition to the high safety, biodegradability and non-mutagenicity of PES [32].

2.9. Gene therapy contraception

Gene therapy is known to be employed by using of nucleic acid as a therapeutic agent and directing it towards targeted cells using a vector for treatment of gene associated diseases. Modified chitosan was used here as a potential vector for delivering gene to gonadotropin releasing hormone receptor expression cells. Nanoparticles of positive charge physiognomy were designed using synthetic gonadotropin releasing hormone as a targeting moiety conjugated to chitosan condensing the required DNA for achieving contraceptive action. Results showed successful targeting with high transfection efficiency and non-toxicity reactions [33]. Another study aimed to induce sterility by delivering of RNAi for silencing the gene involved in controlling reproduction. This procedure was found to disrupt the ovulation process and introduce means of silencing genes, which successfully induced sterility in dogs and cats [34].

3. Conclusion

Scientific research is devoted to develop different methods of contraception to satisfy all people's needs and maintain its effective goals regarding effectiveness, lower side effects and maintain normal daily life. Biomaterials provided promising solutions to overcome many limitations associated with conventional methods of contraception. Biomaterials with their modifications aimed to produce sensitive materials to respond to different microenvironment conditions and avoid initial burst release of drug or cupric ions. Moreover, they participated greatly in restoring of fertility after removal of contraception method with enhancing the concept of reversible long term contraception. They also satisfied the need for sustained constant level of hormones in case of using hormonal contraceptives and avoided its level fluctuations that could lead to contraception failure. Biomaterials was also used for the development of personalized 3D printing devices to satisfy all goals of contraception. Despite the groundbreaking effectiveness of these biomaterials, further research is still required till reaching the complete prevention of

pregnancy incidence with reversibility characteristics and as well as having lowest possible side effects.

- **Conflict of Interest**

The authors declare that they have no competing interests.

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