Development of Hormonal Intravaginal Rings: Technology and Challenges

Die Entwicklung hormonhaltiger Vaginalringe: Technologie und Herausforderungen

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ABSTRACT

Intravaginal rings (IVRs) are minimally invasive polymeric devices specifically designed to be used for the sustained and prolonged release of various type of drugs such as hormones. One of the benefits of using topical drug delivery systems (e.g., IVRs) is the fact that systemic drug delivery may cause drug resistance due to elevated drug levels. Topical drug delivery also provides higher concentrations of the drug to the target site and has fewer side effects. In addition, when a drug is administered vaginally, the hepatic first-pass effect is avoided, resulting in higher absorption. Contraception and treatments for specific diseases such as endometriosis and hormone deficiencies can be improved by the administration of hormones via an IVR. This article aims to classify and compare various designs of commercially available and non-commercial hormonal IVRs and to analyze their performance. Current challenges affecting the development of IVRs are investigated, and proposed solutions are discussed. A comprehensive search of publications in MEDLINE/PubMed and of commercial product data of IVRs was performed, and the materials, designs, performance, and applications (e.g., contraception, endometriosis, estrogen deficiency and urogenital atrophy) of hormonal IVRs were thoroughly evaluated. Most hormonal IVRs administer female sex hormones, i.e., estrogen and progestogens. In terms of material, IVRs are divided into 3 main groups: silicone, polyurethane, and polyethylene-co-vinyl acetate IVRs. As regards their design, there are 4 major designs for IVRs which strongly affect their performance and the timing and rate of hormone release. Important challenges include reducing the burst release and maintaining the bioavail-

ability of hormones at their site of action over a prolonged period of administration as well as lowering production costs. Hormonal IVRs are a promising method which could be used to facilitate combination therapies by administering multiple drugs in a single IVR while eliminating the side effects of conventional drug administration methods. IVRs could considerably improve women's quality of life all over the world within a short period of time.

ZUSAMMENFASSUNG

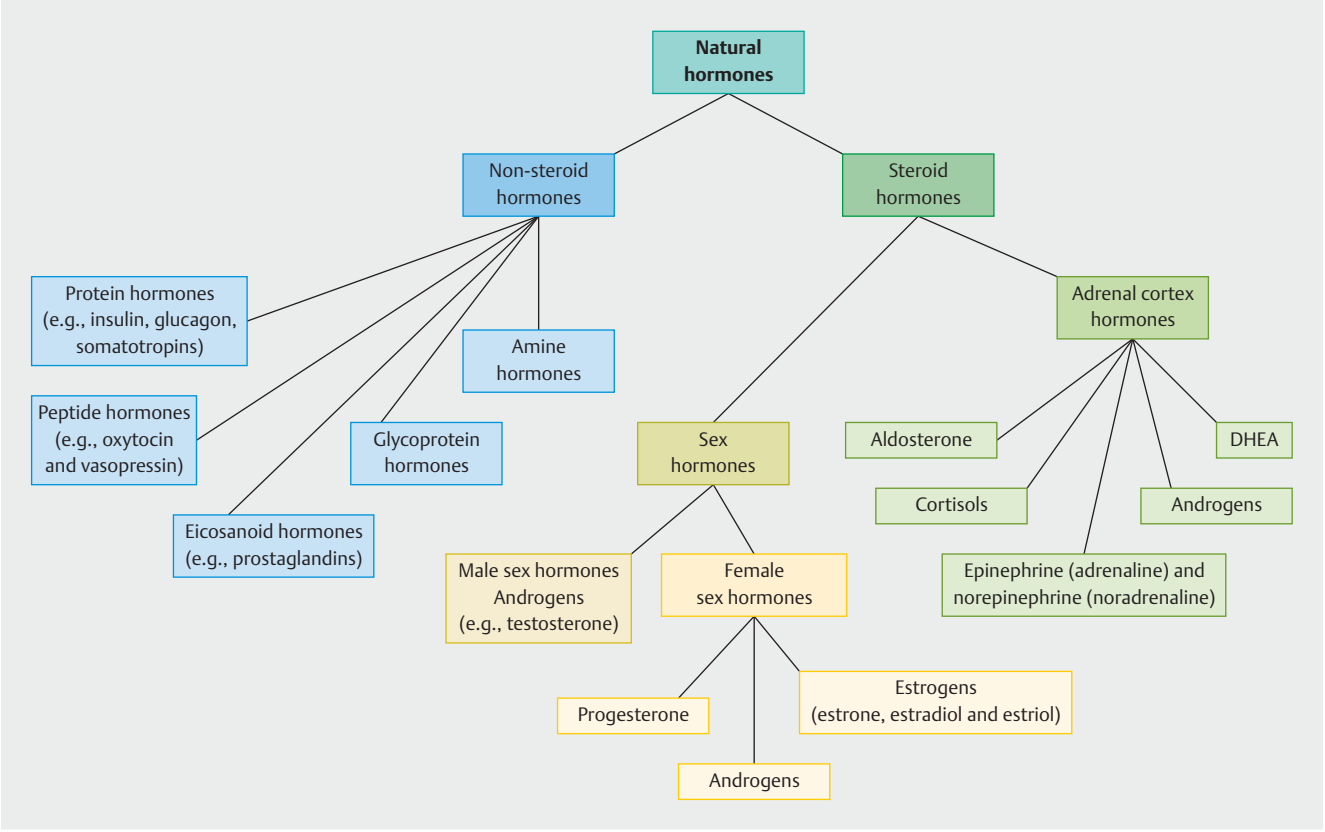
Vaginalringe (IVRs) sind minimalinvasive polymere Vorrichtungen, die speziell für die langfristige und anhaltende Gabe von spezifischen Medikamenten wie Hormonen entwickelt wurden. Der Vorteil eines örtlichen Wirkstoffabgabesystems (z. B. eines IVR) liegt darin, dass die systemische Wirkstoffabgabe wegen des erhöhten Medikamentenspiegels zu einer Medikamentenresistenz führen kann. Hinzu kommt noch, dass eine örtliche Gabe von Medikamenten zu einer höheren Medikamentenkonzentration im Zielgewebe führt und mit geringeren Nebenwirkungen behaftet ist. Außerdem wird durch die intravaginale Gabe von Medikamenten der First-Pass-Effekt vermieden, was zu einer höheren Medikamentenaufnahme führt. Verhütungsmethoden und Behandlungen von bestimmten Erkrankungen wie Endometriose und Hormondefizite profitieren von dem Einsatz hormoneller IVRs. Ziel dieser Studie war es, verschiedene kommerzielle und nicht kommerzielle hormonelle IVR-Modelle zu klassifizieren, zu vergleichen und ihre Leistungen zu analysieren. Es wurden auch die aktuellen Herausforderungen bei der Entwicklung von IVR-Modelle untersucht und grundlegende Lösungsvorschläge ausführlich besprochen. Zunächst wurde eine umfassende Recherche in MEDLINE/PubMed durchgeführt und die Daten kommerzieller IVR-Produkte wurden gesichtet, um danach die Materialien, Modelle, Leistungen und Anwendungsgebiete (z. B. Verhütung, Endometriose, Östogenmangel und urogenitale Atrophie) von hormonellen IVRs eingehend zu untersuchen. Die meisten hormonellen IVRs werden zur Verabreichung von weiblichen Sexualhormonen, d. h. Östrogenen und Gestagenen, eingesetzt. IVRs können anhand ihrer Grundmaterialien in 3 Hauptgruppen unterteilt werden: Es gibt IVRs aus Silikon, aus Polyurethan und aus Ethylen-Vinylacetat-Copolymere. Was die Ausformung angeht, gibt es im Wesentlichen 4 IVR-Modelle, wobei die jeweilige Form sich stark auf die Leistung sowie den Zeitpunkt und die Geschwindigkeit der Hormonfreisetzung auswirkt. Die wichtigsten Herausforderungen bestehen darin, einen plötzlichen Wirkstoffschub zu verhindern, die Bioverfügbarkeit der Hormone im Zielgebiet über einen längeren Zeitraum aufrechtzuhalten und die Herstellkosten zu senken. Hormonelle IVRs versprechen, aktuelle Herausforderungen mithilfe innovativer Entwicklungen zu bewältigen, indem sie den zielgenauen Transport biomedizinischer Wirkstoffe an den Wirkort und dadurch eine Kombinationstherapie aus mehreren Medikamenten in einem einzigen IVR ermöglichen, ohne die Nebenwirkungen von konventionellen Methoden der Medikamentengabe. Auf längere Sicht könnten IVRs innerhalb kurzer Zeit zu einer erheblichen Verbesserung der Lebensqualität von Frauen weltweit beitragen.

Introduction

Intravaginal rings (IVRs) are drug delivery systems (DDS) for the systemic or topical administration of one or more drugs [1]. They are doughnut-shaped polymeric devices that can stay in the vagina between 1 and 12 months. This method of drug delivery overcomes many of the challenges associated with more conventional methods, such as gastrointestinal side effects when drugs are administered orally or the hepatic first-pass effect. Another major advantage of IVRs is their ability to deliver drugs at a constant rate. Using IVRs as DDS can eliminate the need for minor surgical procedures required for other implantable drug delivery methods, making IVRs less invasive and more attractive for patients [2, 3].

The first reports on hormonal vaginal rings were published in 1970. The IVR in question was used to deliver the contraceptive drug medroxyprogesterone acetate, but it was not until the 1980s that the first contraceptive trials with vaginal rings were conducted in the United States [4–6]. Hormonal IVRs are used to deliver many different types of hormones, particularly steroids, for a number of medical reasons including the treatment of urogenital atrophy and contraception [7–9]. Several IVRs are in commercial use today. NuvaRing® is a hormonal IVR used for contraception which contains a combination of two steroids [10]. Estring® is another hormonal IVR and is used to treat urogenital atrophy [11]. Annovera® is a silicone IVR used for contraception and containing segesterone acetate and ethinylestradiol [12]. Some evaluated IVRs are not being marketed [13].

Sustained release means that a drug is released over a prolonged period of time, while controlled release indicates a predetermined drug release rate resulting in controlled drug concentrations in blood plasma. Such systems mimic drug infusion pumps which maintain stable drug levels in blood plasma by balancing the kinetics of release and elimination. Hormonal IVRs are beneficial in many ways. Using this type of DDS allows a constant and continuous delivery of hormones. Some local (vaginal) side effects of IVRs have been reported such as a slight increase in vaginal discharge [14]. The use of IVRs makes it possible to administer lower hormone doses, leading to fewer systemic side effects from high levels of hormones in the body [15]. In addition, a combination of different hormones to regulate and improve women's menstrual cycles can be administered using IVRs [16]. However, vaginal rings have some drawbacks such as increased vaginal secretions, the potential for unintended IVR expulsion, differences in drug absorption, and cultural sensitivities [17]. Most women who use IVRs report that they do not feel any sexual discomfort when using it. Studies reported no signs of erosion or bacterial invasion in the vaginal tissue of women who used IVRs over a long period of time [14]. Although loss of the ring has not been specifically reported in recent publications, it is to be expected due to the dif-



▶ **Fig. 1** Classification of hormones according to their chemical nature.

ferences in anatomy and 3D structures of the vaginal cavity in females of different ages and ethnicities.

Various types of hormonal IVRs have been designed to date. Selection of the material used to produce the IVR is critical. The rings are made from different polymers such as silicone, EVA, and PU. The design specifications for IVRs vary depending on the application (e.g., matrix IVR, core IVR, sandwich IVR, etc.). The hormones used in IVRs are usually steroid hormones and can either be natural or synthetic. A combination of two or more hormones is used in many IVRs.

The challenges of designing and optimizing IVRs include burst release, costs, and efficacy. This article looks at these general challenges and categorizes the reported solutions. Eliminating surprises when manufacturing IVRs should result in more efficient rings.

To develop optimized, efficient, and novel future applications for IVRs used in combination therapies, it is important to have a comprehensive knowledge and understanding of all types and performances of vaginal rings. The information on hormonal IVRs was collected from various publications and evaluated and summarized in this paper. The purpose of this paper was to evaluate IVRs in terms of their different design specifications and selected materials to suggest a better approach when designing intravaginal rings.

Characteristics of Hormonal IVRs

Hormone classification

For many years, hormones were divided into three groups: peptide and protein-based hormones, acid-based hormones and steroid hormones [18]. More recent discoveries have shown that not all types of hormones fit neatly into these categories. Prostaglandins, for example, are made of small fatty acids [19]. Hormones can also be categorized according to their chemical nature, their mechanism of action, or the effects they trigger. As regards their chemical nature, hormones can be divided into two groups, namely, steroid and non-steroid hormones. Non-steroid hormones consist of five different groups: amines, peptides, proteins, glycoproteins, and eicosanoids (▶ **Fig. 1**) [20].

Another way of classifying hormones is to categorize them as natural or synthesized. Natural hormones are produced in the human body while synthesized hormones are produced by synthesis and their chemical structure is not identical to that of natural hormones. Nowadays, natural hormones can also be produced by synthesis.

Modified amino acids in the body make up amine hormones that include thyroid hormones. Modification of amino acids happens when the carboxyl group of amino acids is removed while the amine group remains intact [20]. Thyroid hormones have two major effects on the body. The first effect is on cellular differ-

entiation and development, while the second effect affects the metabolic pathways [18]. Glycoprotein hormones such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (CG) hormone control and regulate numerous reproductive and metabolic functions in the human body. Stimulation from the hypothalamus affects gonadotropin release more than negative feedback from the ovaries. Glycoprotein hormones have various therapeutic potentials due to their extensive regulation roles [21, 22]. Protein and peptide hormones are both made from amino acid residues. Protein hormones include insulin, glucagon, and somatotropins while oxytocin and vasopressin are considered peptide hormones [20]. Despite the common belief that androgens are purely male sex hormones, androgens are also produced by the ovaries and adrenal glands in women. Dehydroepiandrosterone (DHEA) is one of the most common adrenal steroids in the human body [23].

Some steroid hormones are produced by the human adrenal cortex in response to specific stimuli. Cortisol is a hormone that is secreted in response to stress as is aldosterone, another stress hormone. These hormones play an essential role in regulating the water balance and blood pressure levels [18, 24]. The other group of steroid hormones are the sex hormones, produced in the testes in males and the ovaries in females [20]. The sexual differentiation of males prior to birth and maturation during puberty is prompted by androgens. Functioning of the male genitals in adult men is also maintained by these hormones. The role of androgens in other organs such as the central nervous system, the immune system, and muscle tissue is less recognized [25, 26].

Progestogens and estrogen play an important role in controlling the secretion of gonadotropins in the body. The most important female sex hormones are estradiol and progesterone. Estrone and estriol are less potent estrogens which become more prominent in pregnancy [27].

The hormones most commonly used in IVRs are female sex hormones. The capacity of the vaginal epithelium to absorb steroids is one of the reasons why IVRs are so efficient [28, 29]. Both natural and synthesized hormones are used in IVRs. Progering® is a marketed IVR that delivers progesterone, while NuvaRing contains a synthesized type of progestogen called etonogestrel [30].

Progestogens, levonorgestrel, estradiol acetate, estradiol, segesterone acetate (Nestorone®), ethinylestradiol, etonogestrel, megestrol, norgestrienone, and norethindrone acetate are female sex hormones which are used alone or in combination in various commercially available and non-commercial IVRs.

Selection of material

Selecting the proper material for IVRs is one of the most important and critical steps in the modification of the drug release mechanism. Because of how IVRs are applied and the length of time they remain in the body, the characteristics of the IVR material which need to be considered when designing IVRs for the controlled release of drugs are the solubility, diffusion coefficient, initial drug loading and stability of the polymer in addition to the polymer's biocompatibility [31].

Certain properties and physical processes which occur when manufacturing IVRs are limiting factors which influence the rate of drug release. Flexibility and transparency are important physical attributes that need to be considered when designing intravaginal rings [32]. Polymer materials are selected to manufacture IVRs because of their flexibility; their use depends on the grade and composition of the polymer [33].

Polymers are a mix of amorphous and crystalline structures, and this affects their level of transparency. With transparency one of the factors determining the choice of materials [34], polymers are a perfect option as the level of transparency can be adjusted. The chains of more transparent polymers are tightly matched [35]. Transparency is an esthetic criterion which can enhance patient compliance [36]. The benefits of using polymeric materials for drug delivery systems are ease of manufacture, flexibility, biocompatibility, transparency, and low cost. Elastomers and thermoplastics are good candidate materials for IVRs. The mechanical properties of IVRs are evaluated based on their function and the duration of drug release. IVRs need to be flexible enough for insertion into the vaginal cavity, rigid enough to stay in place, and soft enough to avoid abrasion to the vaginal epithelium [37, 38], as well as having low vaginal expulsion rates [39, 40]. Polymer structures play a critical role in engineering the controlled release of drugs [41].

The only polymers currently used to manufacture commercially available hormonal IVRs are polyethylene-co-vinyl acetate (EVA, used in NuvaRing), polydimethylsiloxane (silicone used in Estring and Femring®) [41] and polyurethane (PU used in Ornibel®) [31, 42 – 47].

Silicone

Silicones are a class of synthetic polymers with a backbone made of repeating silicon-oxygen bonds; the main repeating unit is known as a siloxane. Silicon atoms bond to organic groups, usually methyl groups. The most common silicone is polydimethylsiloxane (PDMS). Other groups such as phenyl, vinyl, and trifluoropropyl may be used as methyl substituents. Silicones are used as fluids, emulsions, resins or elastomers, depending on the concurrent presence of organic groups attached to the inorganic backbone [48].

Because of their flexibility and biocompatibility, silicone elastomers are widely used in medical devices and drug delivery systems and in the cosmetic and food industries [43, 44]. The main characteristics of silicones are chemical stability, low surface energy, and hydrophobicity. Because of their biocompatibility and low toxicity, silicones are widely used in the manufacture of medical products that come into direct contact with the human body [50].

PU

Polyurethanes (PUs) were first developed by Bayer in 1937. They are a class of condensed polymers which contain urethanes in their molecular backbone [51 – 53]. Polyurethanes are synthesized by a polymerization reaction between isocyanates and polyols in the presence of a catalyst or ultraviolet light activation [54]. Polyurethanes have segmented polymeric characteristics, i.e., hard and soft parts. The hard part is composed of isocyanate components and the soft part of polyol. The mechanical strength of the polymer relies on the hard part and its flexibility depends on

the weight percentage of the soft part [53]. Because of its segmented polymeric structure, range of physical properties, and good biocompatibility, PU is used in many biomedical devices including catheters, pacemakers, wound dressings, and drug implants [55].

In some studies, PU was the base material used in the manufacture of vaginal rings, and the sustained drug release through its polymeric chain was measured [31, 41, 56]. Ornibel is a commercially available, polyurethane-based intravaginal ring used for contraception.

EVA

Elastomeric polymers such as ethylene-vinyl acetate copolymers (EVA) are a good material for IVRs, due to their rate-controlling properties. EVA is a transparent copolymer made of ethylene and vinyl acetate monomers. The vinyl acetate content plays a key role in determining the mechanical properties, ease of manufacture, and drug release rates from the copolymer [1, 57]. The rigidity of the polymer increases as the level of the vinyl acetate decreases. Reduction of the content also leads to an increase in the relative amounts of amorphous structures and reduces the degree of crystallinity, resulting in a rubbery and more permeable polymer which allows drugs to be released more rapidly from the substrate. Accordingly, the release rate of drug increases with EVA [58, 59].

In addition to these properties, EVA is biocompatible, nontoxic, does not stimulate inflammatory reactions, and can be easily processed. More importantly, the solubility and diffusion coefficient of each drug through the EVA polymeric chain can be tailored by changing the amount of vinyl acetate [60].

Various commercial medical devices make use of the drug delivery properties of EVA. Well-known EVA-based devices include Ocusert® (an ophthalmologic DDS) to treat glaucoma [61], Implanon®/Nexplanon® which are long-acting implants for the continuous release of etonogestrel [63, 64], Vitrasert® (an eye implant containing antiviral agents), and ganciclovir to treat cytomegalovirus infection [65].

Nuvaring is a commercially available contraceptive IVR made from EVA [66]. In some studies, EVA has been used to manufacture IVR prototypes for the sustained release of various active pharmaceutical ingredients (APIs), for example, UC781 (a type of nonnucleoside reverse transcriptase inhibitor used to prevent the transmission of HIV) [67], MIV-150 (a nonnucleoside reverse transcriptase inhibitor), zinc acetate (ZA), carrageenan (CG) and levonorgestrel (LNG) [68]. In some cases, such as UC781, the release rate from EVA-based IVRs was found to be higher than that of silicone IVRs [67].

▶ **Table 1** compares some of physicochemical and biological properties of the three polymers. It shows that silicone, PU and EVA have almost similar physicochemical and biological properties. However, the molecular weight of PU is lower than that of silicone and EVA. In terms of recycling, EVA and PU are more environmentally friendly than silicone.

▶ **Table 1** Comparison of important physicochemical and biological properties of polymers generally used for IVR manufacture.

Property	Material		
	Silicone	PU	EVA
Biocompatibility	✓ [69, 70]	✓ [54, 71]	✓ [57]
Biostability	✓ [49]	✓ [71]	✓ [41]
Reshaping capabilities	✓ [69, 70]	✓ [71]	✓ [72]
Crystallinity	✓ [73]	✓ [74]	✓ [57]
Low cost	✓ [75]	✓ [54]	✓ [70]
Transparency	✓ [76]	✓ [54, 74]	✓ [57]
Low weight	✗ [75]	✓ [54]	✗ [77]
Hydrophilic nature	✗ [78]	✗ [71]	✗ [57, 79]
Recycling	✗ [70]	✓ [54, 71]	✓ [54, 71]

Design

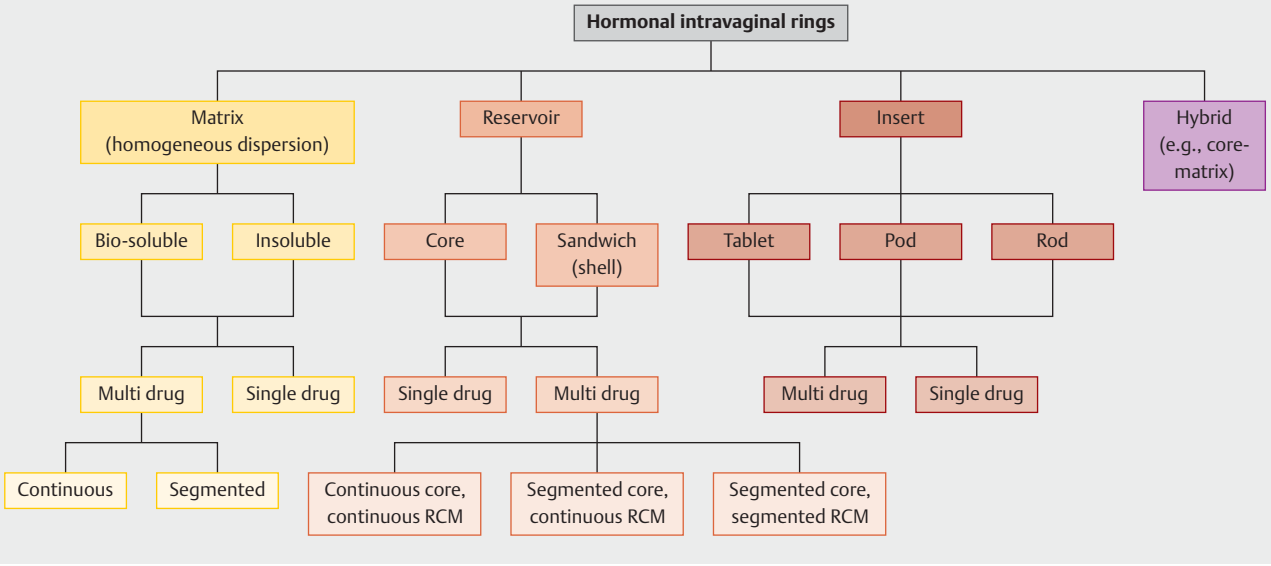
Delivering steroid hormones via the female reproductive tract bypasses the first-pass hepatic metabolism and provides constant steroid levels, both of which increase the bioavailability of the steroid hormones [28]. The most common DDS that provide sustained and controlled release are osmotic pressure, reservoir (using a rate-controlling membrane [RCM]), and matrix systems [81]. IVRs are designed either in the form of a matrix (homogeneous dispersion), a reservoir or a hybrid (a combination of matrix and reservoir). IVRs can also be used as a casing for vaginal tablets or rods, and are then referred to as insert IVRs. ▶ **Fig. 2** shows a comprehensive classification of these four types of IVR design which are commercially available or have been proposed in the literature.

The cross-sections of the various types of IVRs shown in ▶ **Fig. 2** are displayed in ▶ **Fig. 3**, which differentiates between the types of drug distribution through the polymeric substrates.

Matrix (homogeneous dispersion) IVR

Insoluble

A single injection of an elastomer mix containing drug molecules that are dispersed homogeneously in the matrix of the polymer results in a matrix IVR. The solubility of the polymer is lower than the loaded drug in insoluble matrix IVRs [1]. The entire surface area of matrix IVRs is exposed to vaginal tissue/fluid. In the first stage, burst release occurs due to the presence of immobilized drug particles separated from the crystal lattice at the surface of the intravaginal ring. This results in the creation of a concentration gradient that drives the release process thermodynamically. In the second stage, the drug molecules closest to the surface of the ring are diffused through the polymer and released into the medium (i.e., the vaginal fluid and/or interstitial fluid of the vaginal tissue). As the drug release continues, the unmedicated surface is separated from the inner drug-loaded segment of the matrix ring by the creation of a drug exhaustion zone. As the thickness of the unmedicated zone increases, the surface area of the inward-moving depletion border decreases. Consequently, the pathway from where the remaining drug is diffused increases as the amount of the released drug reduces over time and the drug near the surface of the ring becomes depleted. In vitro, the re-



▶ **Fig. 2** Intravaginal ring designs.

lease from a matrix IVR under sink conditions can be explained by the Higuchi equation (Eq. 1) [2, 82, 83].

$$Q = \sqrt{D_p(2A - C_p)C_p t} \quad (1)$$

Where Q denotes cumulative release per unit area, D_p signifies the drug diffusion coefficient of the polymer, C_p represents drug solubility in the polymer, A designates drug loading per unit volume, and t is time.

Insoluble matrix IVRs can be designed as either multi or single-drug systems. Multi-drug insoluble matrix IVRs can be segmented or continuous. Segmented IVRs are designed for multiple drugs using multiple polymers, while in continuous multi-drug IVRs, different drugs are homogeneously dispersed using one type of polymer. Segmented multi-drug IVRs, shown in ▶ **Fig. 3 b**, provide additional advantages, including the ability to control the release rate of each segment individually, compared to continuous multi-drug IVRs [1, 84].

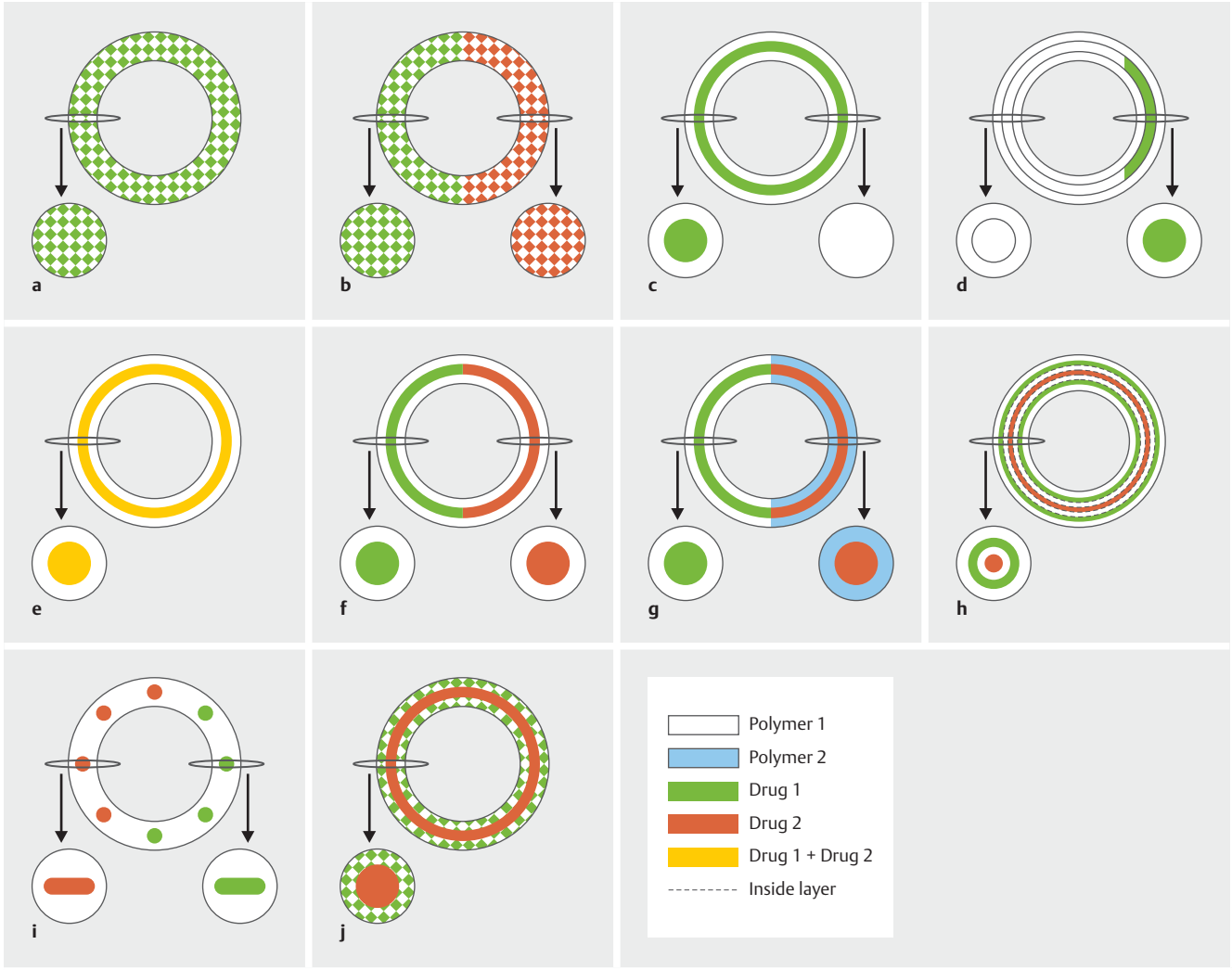
Bio-soluble

Silicone elastomers, EVA, and PU are biostable polymers which are used to create insoluble homogeneous dispersion matrix IVRs. However, scientists have proposed using certain bio-soluble biocompatible polymers to manufacture IVRs. In a study by Vartiainen et al., matrix rings manufactured from bio-soluble styrene-butadiene block copolymers were tested for their capacity to deliver 17β-estradiol to treat postmenopausal symptoms [85]. Bio-soluble polymers can control the release of drugs by means of degradation mechanisms instead of diffusion. This enables the delivery of both hydrophilic and hydrophobic APIs, including those with large molecular weights, to vaginal tissue. In another study by Han et al., non-hormonal intravaginal rings were manufactured from bio-soluble acacia gum and sodium methacrylate to deliver a combination of antiretroviral HIV microbicides for 28 days [84, 86]. This type of IVR can be manufactured as a multi or single-drug device, as shown in ▶ **Fig. 2** [1].

Reservoir IVR

Core

During the manufacture of core IVRs, a drug is placed in a central zone and surrounded by a drug-free polymeric rate-controlling membrane (RCM). The drug carrier at the core of a reservoir IVR can be either a polymer (the same as the RCM or a different polymer) or another type of biomaterial, e.g., paraffin. Core type IVRs can be designed and manufactured as either single or multi-drug delivery systems. Multi-drug reservoir IVRs can potentially be designed in one of three ways, i.e., as continuous core continuous RCM; segmented core continuous RCM; or segmented core segmented RCM. The core part of reservoir IVRs can vary in length. Depending on the application of the IVR and the amount of the drug required for treatment, the full core can be divided into smaller core lengths (▶ **Fig. 3 c, d,** and **f**) [1]. The molecules of the drug have to first detach themselves from the core crystal lattice, then diffuse into the drug-free RCM and then disseminate into the medium surrounding the IVR. The drug is constantly released until the drug's concentration at the core is depleted. One advantage of core IVRs is that release of drugs occurs in zero order compared to matrix IVRs. Aside from that, the release characteristics of this type of IVR can be easily modified. Modifications can be achieved by changing the thickness of the RCM (h) or by varying the length of the core (L). A reduction in RCM thickness leads to an enhanced release rate, due to the shorter diffusion pathway [2, 87].



▶ **Fig. 3** **a** Single-drug matrix IVR, **b** multi-drug segmented matrix IVR, **c** single-drug core IVR, **d** single-drug incomplete core IVR, **e** multi-drug continuous core continuous RCM, **f** multi-drug segmented core continuous RCM, **g** multi-drug segmented core segmented RCM, **h** sandwich IVR, **i** tablet/pod/rod insert IVR, **j** core-matrix (hybrid) IVR.

$$Q = \frac{D_p C_p t}{h} \qquad 2$$

The ratio of core to RCM diameter (b/a) affects the cumulative release rate and is represented by Crank's equation [88].

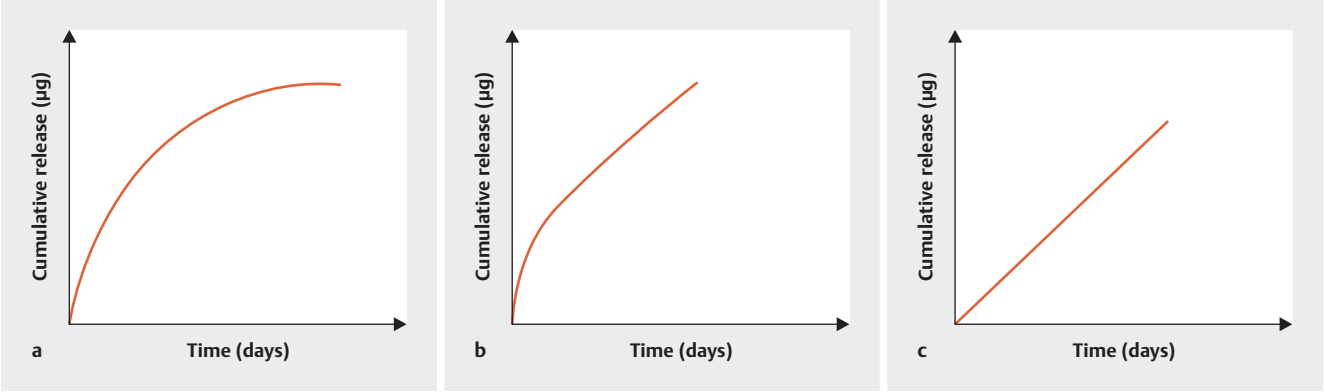
$$Q = \frac{2\pi D_p C_p L t}{\ln(b/a)} \qquad 3$$

Where L denotes core length, a represents the cross-sectional diameter of the core, and b signifies the cross-sectional diameter of the RCM.

As equation 3 shows, when the core length decreases, the rate of drug release also decreases. This type of IVR can be manufactured either by reaction injection molding or by using an extrusion process. A burst release may be observed in the first few days, especially in condensation-cured silicone IVRs, due to the presence of solid drugs in the RCM [2, 89].

Sandwich (shell)

In sandwich IVRs a layer containing the drug is located below the surface of the IVR. This layer can be located between a nonmedicated polymer surface and a central core that may or may not contain a second drug (▶ **Fig. 3h**). Since the drug layer is located a fraction of a millimeter below the surface, this particular IVR is suitable for delivering drugs with poor polymer diffusion characteristics. The manufacture of shell IVRs is less costly due to the lower drug concentrations in the drug layers compared with matrix-type IVRs where the drug is homogeneously dispersed throughout the whole IVR. As shown in ▶ **Fig. 4**, a sandwich IVR can minimize side effects due to the constant drug release compared to other types such as matrix and core IVRs [2, 90]. These types of reservoir IVRs can also be manufactured as both multi or single-drug delivery systems. Multi-drug sandwich IVRs can be designed as continuous core continuous RCM, segmented core continuous RCM, and segmented core segmented RCM [1].



▶ **Fig. 4** Cumulative release profile of **a** matrix (homogeneous dispersion) IVRs, **b** core reservoir and pod IVRs, and **c** sandwich reservoir IVRs.

Insert IVR

Tablet and rod

These types of IVRs are manufactured as nonmedicated polymeric bodies with cavities in which multiple drug-loaded vaginal rods or tablets can be inserted. Rods can be manufactured using several different methods. For example, a dispersed mixture of a particular type of polymer and drug can be injected into a PVC tubing using a plastic syringe. The PVC tubing is then removed and the polymeric rod can be cut into suitable sizes for insertion into the body of the ring [91]. These types of insert IVRs can be used as single or multi-drug delivery systems by the insertion of different tablets or drug-loaded rods into a single IVR.

Pod

Single or multi-drug release is achievable using IVRs with several small drug-containing sectors, called pods, which can be loaded with the same or different drugs [2]. Although matrix IVR designs have been developed for clinical trials, pod IVRs can provide sustained drug release over longer periods as indicated by the drug release profile shown in ▶ **Fig. 4b** [92].

Pods are made from polymers containing homogeneously dispersed drugs coated with a layer of polymer to create a drug pod. These pods, which can have identical or different geometries, are then incorporated in a nonmedicated continuous or segmented IVR. The release rate of pod IVRs is controlled by their nonmedicated polymeric membrane, the characteristics of the sectors, and the number of pods in each IVR [1,93], resulting in an independent delivery of drugs in pseudo-zero order from each pod. Pod design also eliminates the initial burst release, which is one of the challenges associated with other IVR designs [93]. The release profile of pod IVRs is similar to that of core IVRs [94]. The safety of pod IVRs has been investigated in both rabbits and humans [95], and pod IVRs have been shown to be a harmless and efficient drug delivery system [96,97]. Pod IVRs can be manufactured for the delivery of single or multiple drugs.

Hybrid IVR

Using an IVR which is a combination of conventional IVR types, i.e., matrix, reservoir, or insert, is a novel approach suggested by current research. It could be considered a hybrid IVR. It has been proposed that core-matrix hybrid IVRs could be manufactured using a core embedded in a hot-melt extruded polymer containing the active agent [1,68]. Another possible design for a hybrid IVR could be an insert-matrix IVR consisting of a medicated polymeric body with cavities for the insertion of vaginal rods, tablets, or pods (▶ **Fig. 3j**).

The drug release profiles of the major IVR types (matrix, core, and sandwich) are shown in ▶ **Fig. 4**.

Some studies have reported on the in vitro cumulative release profiles of matrix and reservoir [12,68]. Another study has discussed the release profile of a reservoir-type IVR releasing different amounts of drug [98].

Commercially available and non-commercial rings are listed in ▶ **Tables 2** and **3**.

Hormonal Ring Applications

Contraception

Contraceptive vaginal rings have been the focus of many gynecological studies for more than 40 years [28,29].

Steroids, whether alone or in combination, diffuse at a constant rate through the ring and are directly absorbed through the vaginal epithelium into the systemic circulation. Progestogens are not normally used alone in such contraception methods as skin patches, rings, pills, etc. A combination of hormones, for example a combination of estrogen and progestin [112], etonogestrel/ethinylestradiol (ENG/EE) [28], segesterone acetate/ethinylestradiol (SA/EE) rings, LNG/E2, norethindrone acetate (NETAc)/EE IVRs [28], and norelgestromin/ethinylestradiol skin patches [113] and levonorgestrel/ethinylestradiol pills [114] are preferably used in contraceptive DDS. Since progesterone is one of the most important hormones in the menstrual cycle, it has significant uses in contraception. The cyclic release of luteinizing hormone is inhibited by the increased concentration of progesterone in nonpregnant women, with production of the follicle-stimulating hormone inhibited by higher levels of progesterone [115]. There are two methods by which progestins prevent pregnancy:

▶ **Table 2** List of commercially available hormonal IVRs.

IVR Name	Company	Hormone	Release rate Application period	IVR material	IVR type	Application	Ref.
ANNOVERA®	Therapeutics MD	Nestorone (segesterone acetate) and ethinylestradiol	segesterone acetate: 150 µg ethinylestradiol: 13 µg 1 year	silicone elastomer	pod	contraception	[99 – 101]
Estring	Pfizer Inc., USA	Estradiol	7.5 µg/day 90 days	silicone elastomer	core reservoir	urogenital atrophy	[4, 84]
Femring	Warner Chilcott/ Actavis, UK	estradiol acetate	0.5 µg/day 3 months	silicone elastomer	core reservoir	urogenital atrophy, estrogen replacement therapy (ERT), contraception	[30, 84, 102, 103]
Fertiring®	Silesia Laboratories	progesterone	variable 3 months	silicone elastomer	insoluble matrix	contraception	[80, 84, 104]
NuvaRing	NV Organon Co in the Netherlands/Merck & Co., USA	etonogestrel and ethinylestradiol	8 µg/day 21 days	EVA	core reservoir	contraception	[84, 105, 106]
Ornibel	Exeltis Healthcare	etonogestrel and ethinylestradiol	8 µg/day 21 days	PU core and EVA external membrane	core reservoir	contraception	[105]
Progering	Silesia Laboratories	progesterone	10 mg/day 90 days	silicone elastomer	insoluble matrix	contraception	[80, 84, 103]

▶ **Table 3** List of non-commercial hormonal IVRs.

Hormones	IVR materials	IVR type	Application	Release rate Intended duration in situ	Ref.
Levonorgestrel	silicone elastomer	core reservoir	contraception	20 µg/day 90 days	[107]
Nestorone	elastomer LSR (liquid silicone rubber)	core reservoir	contraception	50, 75, or 100 µg/day 6 months	[108]
Nestorone and ethinylestradiol	silicone elastomer	rod insert	contraception	10, ~ 13.5 and 7.5 µg/day 1 year	[109 – 111]

1. by preventing sperm from reaching the egg by changing the cervical mucus,
2. by preventing implantation of the fertilized oocyte through changes to the uterine lining [116].

A combination of etonogestrel and ethinylestradiol are used in contraceptive vaginal rings. Contraceptive IVRs containing etonogestrel (a progestin) and ethinylestradiol (an estrogen) function by preventing ovulation [105].

Contraceptive IVRs have several advantages compared with other conventional contraceptive methods: convenience of use, fewer premenstrual symptoms, lighter and more regular menstrual cycles, as well as reducing the risk of certain cancers such as breast cancer because of the lower hormone doses [118].

Three rings containing only progestogens have been evaluated. These rings contain progesterone, levonorgestrel (LNG), and the progestin Nestorone (NES). Progestogen-only rings are specifically designed for continuous use compared to combination drug IVRs which are designed for cyclic use (3 weeks in/1 week out) [28].

NuvaRing, a commercially available contraceptive IVR, contains a combination of etonogestrel and ethinylestradiol [16, 119, 120]. These APIs are loaded in an EVA core with an outer diameter of 54 mm and a cross-section of 4 mm [121]. Using NuvaRing for the recommended 3-week period completely inhibits ovulation with an efficacy of 98 % [112, 122].

Progering is another contraceptive ring, manufactured by Silesia SA Laboratories, Chile. A silicone elastomer is used in the manufacture of this ring, and progesterone is homogeneously dispersed inside the matrix IVR. The cross-sectional diameter of Progering is 8.4 mm and the overall diameter is 58 mm. Progesterone is released at an average rate of 10 mg per day over three months

[115, 123]. Other commercially available contraceptive IVRs are listed in ▶ **Table 2**.

Research is being conducted into a contraceptive IVR containing Nestorone and ethinylestradiol. The drugs are loaded into two rods, with one rod containing only Nestorone while the other contains both drugs. This ring can be used for 1 year, which makes it an efficient contraceptive method [110, 124]. Some of the other non-commercial contraceptive IVRs which are currently being developed are presented in ▶ **Table 3**.

Endometriosis

Endometriosis is an estrogen-dependent medical condition caused by the ectopic growth of endometrial tissue in women of reproductive age. It occurs when tissue similar to the lining of the uterus or endometrium forms outside the uterine cavity [125, 126]. Endometriosis is usually found in the pelvic cavity and can attach to any of the female reproductive organs such as the uterus, fallopian tubes, ovaries, uterosacral ligaments, peritoneum, or any of the spaces between the bladder, uterus, bowel, vagina, and rectum [15, 125, 128]. The diagnosis of endometriosis in primary care is mainly clinical. There is currently no cure for endometriosis, so medical care has focused on pain reduction. The pituitary gland releases gonadotropins, hormones that stimulate the production of gonadal steroids such as estrogen which aggravate the symptoms of endometriosis and uterine fibroids [15].

Elagolix is a gonadotropin-releasing hormone (GnRH) antagonist that reduces gonadotropin levels, which in turn suppresses estradiol. This decreases dysmenorrhea, dyspareunia, and endometriosis-related pain [127]. Initial treatment consists of the administration of common agents used for primary dysmenorrhea, such as nonsteroidal anti-inflammatory drugs (NSAIDs), estrogen/progestin combination contraceptives, or progestin-only contraceptives [131]. There is some evidence that these agents are helpful and have few adverse effects. NSAIDs are often the first-line treatment for endometriosis, followed by hormone therapy [132]. Hormonal treatments that decrease estrogen and progesterone production are used to treat endometriosis [127]. The inhibition of aromatase in premenopausal women reduces estrogen production, resulting in counter-regulation by the pituitary. This eventually leads to an increase in gonadotropin levels and stimulates follicular development, which may lead to the formation of ovarian cysts. This can be a drawback when treating premenopausal women [131]. Vaginally administered ethinylestradiol and etonogestrel can be used either for contraception or to treat dysmenorrhea resulting from endometriosis [110].

IVRs are an ideal method to treat women suffering from endometriosis. The use of IVRs instead of other conventional therapies for endometriosis-associated pain such as transdermal patches was observed to be more effective as they were better at reducing dysmenorrhea. IVRs were noticeably more accepted by patients because of their convenience of use, which resulted in higher user satisfaction [133]. There are currently no IVRs to treat endometriosis on the market; however, research is being conducted into the use of hormonal IVRs to treat this disease. An IVR containing a combination of the aromatase inhibitor anastrozole and progestin has been developed for the treatment of recurrent endometriosis in women of reproductive age [127, 131]. In another study, an ethinylestradiol and etonogestrel-loaded IVR, which inhibits ovulation, was observed to be effective to treat women with endometriosis, dysmenorrhea, and polycystic ovarian syndrome [110].

Estrogen deficiency

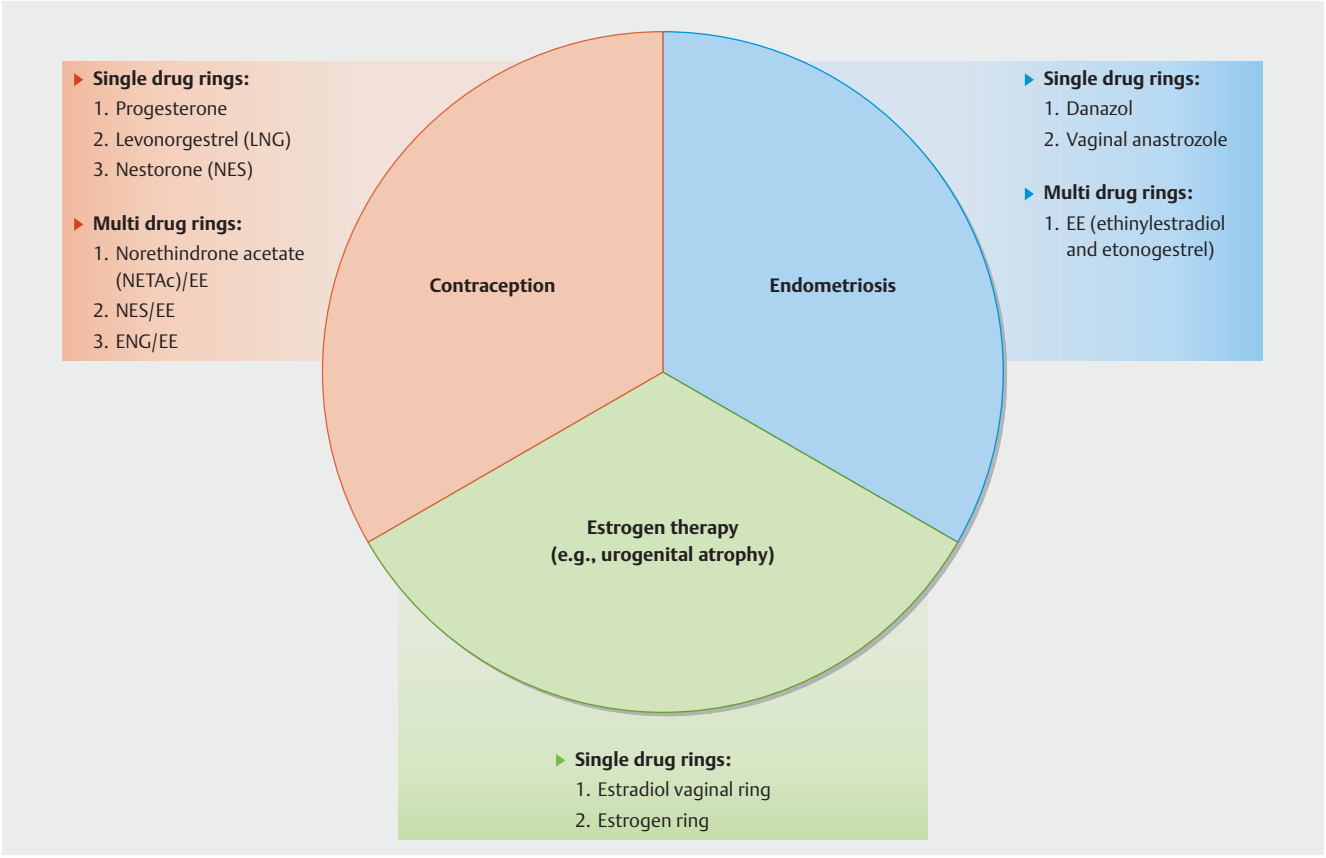
A decline in the levels of the primary sex hormone in women (estrogen) is referred to as estrogen deficiency. Lower estrogen levels in the body cause changes to the breasts, genitals, urinary tract, and even the skin [134, 135].

Oral estrogens are not absorbed effectively, and about seventy percent is metabolized during the first pass through the liver [2, 136]. In addition to the gastrointestinal side effects of oral estrogen, a further challenge of administering estrogen orally is bolus estrogen doses which result in undesirably high levels of estrogen after each dose and the necessity of administering recurrent doses. Transdermal drug delivery systems such as skin patches are the most commonly used estrogen replacement therapies and reduce the risks associated with high doses of estrogen such as thromboembolism. However, studies have reported that excessive estrogen exposure is higher when using transdermal drug delivery systems compared with IVRs or low-dose oral contraceptives [133]. Side effects of high estrogen doses include breast and endometrial cancer, heart attacks, blood clots, and stroke [137, 138]. Some of the methods used to ensure constant estrogen levels in the body are aggressive and require surgical insertion and removal. More importantly, these methods are not able to provide suitable doses of estrogen over a long period [139].

Vaginal estrogen therapy has many advantages such as a direct vaginal impact, the high bioavailability of the administered drugs, the option to use low doses of drugs compared to oral and parenteral administration, higher acceptance by patients, and fewer side effects such as endometrial stimulation, hyperplasia, breast tenderness, and adenocarcinoma [140, 141]. Among the estrogens, 17 β-estradiol (E2), is often used to treat estrogen deficiency. This specific type of estrogen compensates for a deficiency of endogenous estrogens caused by ovarian failure. In comparison with other natural estrogens, E2 has proven to be more efficient for estrogen replacement therapy (ERT) and hormone replacement therapy (HT). E2 has fewer side effects, specifically prevents blood clots and decreases the risk of venous thrombosis. This type of natural estrogen is broadly used to treat estrogen deficiency-associated disorders such as urogenital atrophy, and menopausal and postmenopausal symptoms [139].

ERT was long considered the cornerstone of therapy for postmenopausal women with osteoporosis [142]. Studies in vitro and in vivo have supported the hypothesis that estrogen works by slowing bone resorption by preventing the production of pro-osteoclastogenic cytokines mediated by osteoblast lineage cells. This impedes the formation of osteoclasts and also increases bone mineral density [143 – 145]. In one study, women who underwent estrogen replacement therapy for longer than 1 year after menopause had an 80% lower incidence risk of Alzheimer's disease compared to women who did not have the therapy [146].

Vaginal creams, tablets, and rings deliver drugs via the vagina, and so far, three creams, two rings, and one vaginal tablet have been approved by FDA for the treatment of urogenital atrophy



▶ **Fig. 5** Diagram showing applications for IVRs.

[147, 148]. Estrace [149], Premarin [150], and Estragyn [151] are commercially available vaginal creams; Vagifem [152] is the only commercially available vaginal tablet. Estring [153] and Femring [154] are two commercially available vaginal rings to treat urogenital atrophy.

Many patients believe that vaginal creams and tablets are hard to use and sometimes forget to apply the cream or tablet, which needs to be administered at specific times. Other disadvantages of using creams or tablets are their low and uneven absorption capacity. Therefore, a long-acting DDS is ideal for releasing hormones such as estradiol, estriol, and conjugated estrogens [155–159]. Estring and Femring vaginal rings, which offer sustained and controlled release of hormones, provide such conditions.

The risks of systemic estrogen or estrogen plus progestogen administration include stroke, venous thromboembolism, and invasive breast cancer. Low-dose vaginal estrogens have been approved by the FDA. They bypass the hepatic first-pass effect and there is no evidence that they cause the above-mentioned side effects, but they carry the same warnings about health risks (e.g., breast and endometrial cancer, cardiovascular disorder and probable dementia) as estrogens administered systemically [160]. Estradiol levels which are higher than postmenopausal levels lead to endometrial proliferation, which does not occur when vaginal estrogens are used. However, if there is a systemic absorption of estrogen it is suggested that progestogens should be used simultaneously [161].

Urogenital atrophy

Menopause usually occurs in women between the ages of 49 and 52, when the egg is no longer released from ovaries [142]. Estrogen levels play an essential role in maintaining the mucopolysaccharide and collagen content of the mucosa and in preserving the thickness and moisture of urogenital tract tissue. Changes in the structure and function of the genitourinary system after menopause are the result of decreased estrogen levels. The reduction of estrogen levels leads to physiological, histological, and anatomical changes to the genitourinary system, also known as urogenital atrophy [135, 162]. Effects of estrogen deficiency include thinning of the vaginal epithelium, decreased vaginal elasticity and blood flow, and decreased secretion by the Bartholin glands, resulting in damage to the vaginal mucosa [163]. Symptoms of urogenital atrophy include genital symptoms such as dryness, burning, and vaginal irritation; sexual symptoms such as painful intercourse and postpartum hemorrhage; and urinary symptoms including nocturia, recurrent urinary tract infection, urinary incontinence, urinary urgency, etc. In total, these symptoms are referred to as the genitourinary syndrome of menopause [135, 147, 164–167].

HT treats urogenital atrophy by increasing estrogen levels in the body. There are three ways to administer the drug: oral, transdermal, and intravaginal [168]. FDA-approved estrogen-loaded IVRs are suitable to treat postmenopausal urogenital atrophy and lower urinary tract symptoms. These IVRs are usually loaded with low dosages of estradiol and may not need attendant progestogens [155, 158, 168]. However, symptoms of urogenital atrophy can also occur in women with low estrogen levels for other reasons, for example, due to breastfeeding or drugs that lower estrogen levels [19]. The treatment of urogenital atrophy is highly dependent on the symptoms of the disease. Initially, non-pharmacological treatments can be used; for example, sexual activity can help maintain vaginal health during menopause [169]. Vaginal estrogen therapy can lead to higher levels of estrogen in serum; however, they will not exceed normal postmenopausal ranges. Moreover, high systemic levels of estrogen can have side effects such as venous thromboembolism and stroke [160].

Estring is a commercially available 17 β-estradiol-loaded IVR developed to treat urogenital atrophy. The IVR is designed to release a low dose of estrogen continuously for 3 months [2].

Vaginal estradiol therapy can increase the risk of recurrence in patients diagnosed with breast cancer. The use of estradiol-containing vaginal rings and tablets results in a significant increase in estradiol serum levels, indicating systemic absorption in the first few weeks of HT [170].

The schematic diagram of hormonal IVR applications is demonstrated in ▶ **Fig. 5**.

Current Challenges and Possible Solutions

Reduction of burst release

One of the most important challenges complicating the medical use of intravaginal rings is burst release due to Fickian or non-Fickian drug diffusion. In addition to the negative economic effect of higher doses, burst release can have unwelcome side effects [171].

A number of studies used membranes made of different polymers as coatings for different types of drug delivery devices [17]. One example of this is Nuvaring, which has a membrane of ethylene-vinyl acetate copolymer (EVA) surrounding an EVA core (with a different vinyl acetate content) impregnated with etonogestrel and ethinylestradiol [14]. A high burst release rate of 20–40 percent was observed during in vitro tests of IVRs manufactured from EVA. Cellulose membranes are employed to prevent the initial burst release in IVRs. The release rates of EVA rings can be efficiently controlled using membranes [172].

The release rate can be adjusted to specific required values by modifying the membrane thickness. Membranes have specific permeabilities which control drug release in a DDS. As the membrane becomes thicker, the release rate of the drugs decreases. In summary, the goal is to delay the diffusion of API through the polymeric device to reduce the amount delivered [173].

Another method for a controlled DDS is to manufacture a system that releases the loaded drug at a prearranged time or in pulses. Such a system can also be manufactured in response to environmental changes [174].

Long-term drug delivery

The drug delivery times of currently available contraceptive IVRs range from three weeks to one year [175, 176].

The primary argument for a longer delivery duration is to make the product more affordable. Microbicide IVRs are therefore designed for one to three months' use [177]. The impact of the duration of IVR use on user acceptance, device performance, and biocompatibility has not yet been comprehensively reported and is worth further evaluation.

A long-term polymeric DDS can be created by many methods, including osmotic pumps [178], matrices with controllable swelling [179], diffusion [180], erosion [181], different drug-loading profiles [182 – 184], and the use of multilayered membranes as matrices [174, 185]. As regards diffusion, drug release increases when the drug has a higher diffusion coefficient [186]. A diffusion barrier such as an empty polymeric barrier can be used to create a long-term DDS [187]. Swelling of the polymer results in an increase in the length of the diffusion pathway. The drug release rate decreases due to a reduction in the drug concentration gradient [53]. Drug delivery systems designed for long-term use should have low erosion and degradation rates. To achieve this goal, water-repellent surfaces can be used to manufacture such systems [55].

Sustained bioavailability

Drug bioavailability varies as it depends on factors such as the drug's solubility in the elastomer and vaginal fluid, the drug's diffusion coefficient in the elastomer, the volume of vaginal fluid, the drug's partition coefficient between the IVR and the vaginal fluid and tissue, the rate of diffusion and drug removal through vaginal tissue, and the rate of anterior to posterior advection of the vaginal fluid [188].

One method of achieving sustained bioavailability is to design drug delivery systems that respond to environmental changes. These systems change their drug release rate according to different stimuli such as light, temperature, specific molecules, mechanical forces, etc. to which they are exposed. Drug delivery systems can also be designed to respond to environmental changes. These are all methods which can be used to manufacture controlled drug delivery systems with reduced burst release [174].

Maximizing efficacy

Increasing the bioavailability of a drug can increase its efficacy. However, if the drug is lipid-soluble, as most hormones are, increasing bioavailability can be difficult. The Population Council is collaborating with HRA Pharma (Paris, France) and the NICHD to develop a 3-month contraceptive IVR which releases a progesterone receptor modulator. The aim is to provide an estrogen-free contraceptive that does not require daily oral intake. Ulipristal acetate, a derivative of 19-norprogesterone, binds specifically to the human progesterone receptor [8, 189]. One study reported inhibition of ovulation in 68% of the cycles studied and concluded that further testing with higher release rates of ulipristal acetate was required to achieve ovulation suppression in a higher percentage of cycles [189].

Using microbicides that contain one or more APIs is another way to increase the efficacy of IVRs. In some studies, drug levels

have been shown to correlate best in tissue with microbicide efficacy [190 – 193].

Choosing a suitable polymer for IVRs based on the polymer's solubility and stability and the required API release rate is another way to maximize the efficacy of IVRs [193].

Cost reduction

Price is one of the parameters at the commercialization stage. The price of the rings is affected by the choice of materials, method of manufacture, and type of loaded drug. Using different low-cost techniques can help reduce the costs of manufacturing drug delivery systems [194, 195]. Using low-cost materials such as bio-based polymers is another way to manufacture more economical drug delivery systems [194] (▶ **Table 4**).

Future Direction

Intravaginal rings are promising methods for the prolonged delivery of hormones for various purposes. IVRs are currently mainly used for contraception; however, they can also be used to treat diseases such as endometriosis and urogenital atrophy and for estrogen therapy. IVRs will soon also be used in combination therapies, e.g., for HIV prevention and contraception, making IVRs a highly efficient treatment for women alongside implants. In addition to hormones, other drugs can also be delivered systemically through the vaginal tract. Although there are many commercially available IVRs on the market, there are still some challenges which must be overcome for IVRs to become more efficient. One major challenge is to make IVRs that are able to deliver different types of drugs for a long period of time. Other challenges include manufacturing IVRs that are low-cost, as this will make them accessible for larger female populations. Solving these challenges will make IVRs the most efficient drug delivery system, not only specifically for female diseases but to deliver drugs that need to be systemically absorbed.

Conclusion

Hormonal intravaginal rings are highly efficient systems for delivering hormones. The advantages of IVRs are their efficacy in delivering drugs, their ability to bypass the hepatic first-pass effect, prolonged drug release, ease of administration, and a reduction in the number of required appointments with a physician. However, women will still need to see a physician to obtain a prescription and guidance on how to use IVRs. The sustained release of hormones from IVRs and the possibility of using multiple hormones and drugs at the same time can be highly efficient for many patients. Silicone elastomer is one of the most commonly used polymers for the manufacture of different drug delivery systems as it is highly biocompatible. Therefore, silicone is probably the most efficient polymer for IVRs. Various IVR manufacturing designs such as pod, sandwich, and core are used for different therapeutic purposes to maximize the efficiency of the IVR.

Hormonal IVRs are among the most efficient and effective methods to treat a wide range of diseases. These novel drug delivery systems can enhance women's lives in a number of ways and improve their quality of life.

▶ **Table 4** Major challenges in development of hormonal IVRs and proposed solutions.

Challenge	Possible solutions
Reduction of burst release	▪ Additional membranes ▪ Modification of membrane thickness ▪ Drug released at a prearranged time
Long-term drug delivery	▪ Osmotically driven pumps ▪ Matrices with controllable swelling ▪ Diffusion rates ▪ Erosion rates (using water-repellent surface) ▪ Non-uniform drug-loading profiles ▪ Multilayered matrices
Sustained bioavailability	▪ Changes in the drug release rate when faced with different stimuli
Maximizing efficacy	▪ Using selective hormone receptors ▪ Using microbicides ▪ Using the appropriate polymer for the required API
Cost reduction	▪ Low-cost techniques ▪ Low-cost materials such as bio-based polymers

Informed Consent

Informed consent was not required for this study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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