WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

2025
Volume: 02
Issue: 01
Page: 184-204

# A NOVEL APPROACH TO MANAGING POLYCYSTIC OVARY SYNDROME USING A VAGINAL RING LOADED WITH HERBAL PHYTOCONSTITUENTS: A REVIEW

**Abinaya[1], Gugan Raj[1]*, Harish Kumar[1], Manivasagan[1], Stephia[1], Vaishali[1], Nandhakumar L.[2], Ashokkumar P.[3]**

[1]Department of Pharmacy, Kasthooribha Gandhi Pharmacy College, Namakkal, Tamil Nadu, India Pincode-637401.

[2]Department of Pharrmaceutics, Kasthooribha Gandhi Pharmacy College, Namakkal, Tamil Nadu, India Pincode-637401.

[3]Department of Pharmaceutical Chemistry, Kasthooribha Gandhi Pharmacy College, Namakkal, Tamil Nadu, India Pincode-637401.

**Received: 03 December 2024** **Revised: 23 December 2024** **Accepted: 13 January 2025**

**Corresponding Author: Gugan Raj**

**Address:** Department of Pharmacy, Kasthooribha Gandhi Pharmacy College, Namakkal, Tamil Nadu, India Pincode-637401.

## ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that affects women of reproductive age, with a prevalence estimated at 8–13%. This translates to approximately 66 million women worldwide living with PCOS. Current treatment options for PCOS have limitations, emphasizing the need for innovative therapeutic approaches. This review explores the potential of *Caesalpinia bonducella* in managing PCOS, proposing a novel vaginal ring formulation containing *C. bonducella* extract as a delivery system for treatment. The review highlights the pharmacological properties of *C. bonducella* and its potential therapeutic benefits in PCOS. An intra-vaginal controlled-release drug delivery system is suggested as an effective method for continuous administration of therapeutic agents. Compared to traditional oral administration, intra-vaginal drug delivery offers systemic absorption due to the dense network of blood vessels in the vaginal wall. Various drug delivery platforms suitable for intra-vaginal administration include hydrogels, vaginal tablets,

pessaries/suppositories, particulate systems, and intra-vaginal rings. The vaginal route is particularly effective for administering drugs such as contraceptive steroids, metronidazole, and antiretrovirals.

**KEYWORDS:** Polycystic ovary syndrome (PCOS), *Caesalphinia bonducella*, Vaginal ring formulation, Novel therapeutic approach.

## 1.0 INTRODUCTION

Polycystic ovarian syndrome (PCOS), first identified by Stein and Leventhal in 1935, is the most prevalent heterogeneous reproductive disorder in women, affecting up to 10% of the female population. It is a multifactorial condition with a strong genetic component and is observed across all ethnicities (Stein and Leventhal, 1935).[1] The primary diagnostic features include hyperandrogenism, menstrual irregularities (oligo/anovulation), and polycystic ovarian morphology detected via ultrasound. However, women with irregular menstrual bleeding and polycystic ovaries may be diagnosed with PCOS even in the absence of clinical or biochemical evidence of androgen excess (illustrated in Fig. 1).

The clinical presentation of PCOS is highly variable, with patients exhibiting a range of signs and symptoms. This heterogeneity is influenced by multiple factors, including prenatal androgen exposure, uterine nutritional status, genetic predisposition, ethnicity, puberty-associated insulin resistance, exaggerated adrenarche, and changes in body weight.

Caesalpinia bonducella, also known by synonyms such as Caesalpinia bonduc, Caesalpinia crista, and Guilandina bonduc, belongs to the Caesalpiniaceae family and is a prickly shrub commonly found in tropical regions of India, Sri Lanka, and the Andaman and Nicobar Islands. Widely distributed across the globe, this plant is recognized for its effectiveness in treating PCOS and its extensive pharmacological properties, including antiseptic, antibacterial, anti-inflammatory, antidiabetic, antidiuretic, anthelmintic, antipyretic, anticonvulsant, antidiarrheal, antiviral, antiasthmatic, antianaphylactic, antiamoebic, and antiestrogenic activities.[2]

Pharmacognostic and phytochemical studies, along with quality evaluations such as microscopic and macroscopic analyses, have revealed that ethanolic extracts of C. bonducella contain various bioactive compounds, including flavonoids, saponins, alkaloids, steroids, and resins. PCOS is a leading cause of infertility among affected individuals, and the intake of C.

bonducella seed kernels has been reported by Ayurvedic and Siddha practitioners to reverse PCOS conditions in numerous patients.

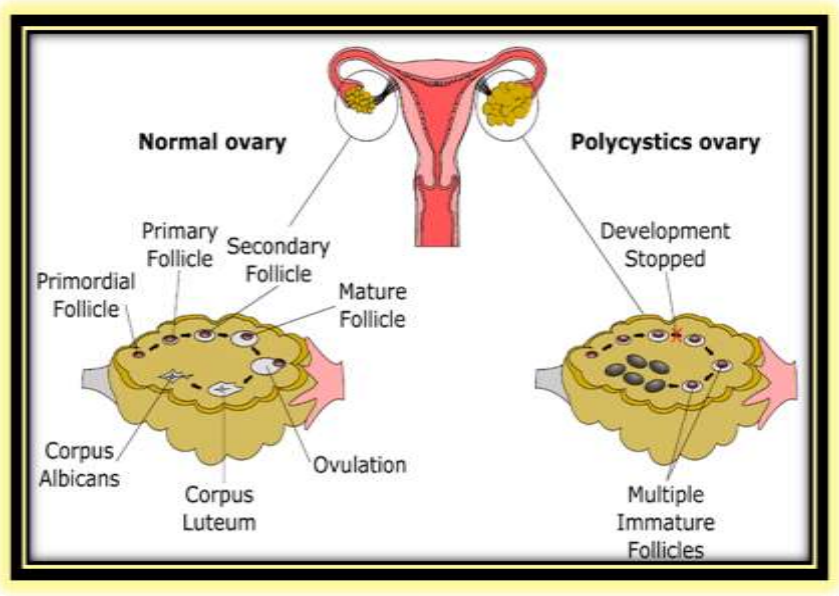


**Figure 1: Female reproductive system disorder.**

### 1.1 Etiology

High insulin levels lead the ovarian cells to produce more testosterone, less FSH, and have a greater LH/FSH ratio, which in turn contributes to poor follicular development and ovarian abnormalities. The LH/FSH ratio may also be impacted by changes in the hypothalamus's ability to generate gonadotropin- releasing hormone (GnRH). GnRH stimulates the pulsatile LH and FSH secretion by the pituitary gland. In certain PCOS individuals, there is low testosterone and too much oestrogen. negative feedback inhibition, brought on by high oestrogen levels, stops FSH from being released through the GnRH route. Low FSH and high LH impair follicle maturation. The incidence of PCOS has been closely related to oxidative stress and chronic low-grade inflammation. Recent 33 studies have demonstrated that the core aetiology and primary endocrine characteristic 34 of PCOS are hyperandrogenaemia (HA) and insulin resistance (IR).[2]

**The fundamental driver of PCOS[3]**

- ✓ Genetic inclination
- ✓ Life style
- ✓ Increase insulin
- ✓ Increase androgens

- ✓ Increase oestrogen
- ✓ Irregular periods
- ✓ Weakened resistant framework
- ✓ Bead dietary
- ✓ Dirty nourishment
- ✓ Hormonal awkwardness

### 1.2 Pathophysiology

With a 70% concordance rate in monozygotic twins, PCOS is a highly heritable illness, which raises the possibility that genetics may play a role in its pathophysiology. It has been established that PCOS patients' first-degree male and female relative both suffer metabolic and reproductive problem. More specifically, in girls with such genetics, glucose-stimulated hyper-insulinaemia starts to appear as early as age four and lasts into puberty. Furthermore, fasting indices of insulin resistance and insulin responses during an intravenous glucose tolerance test for the evaluation of b-cell function were used to demonstrate insulin resistance and b-cell dysfunction in such premenarchal girls between the ages of 8 and 14. A deficiency in pancreatic b-cell activity was suggested by a longitudinal follow-up of peripubertal adolescent girls whose mothers had PCOS, which revealed a significantly lower disposition index that remained over 2 years.one potential genetic reason is the connection between the type 2 diabetes TCF7L2 susceptibility locus and the evidence of b-cell malfunction in adult PCOS women. Epigenetic changes, such as those of the PDXI gene involved in the regulation of pancreatic development, are also through to be connected to the b-cell malfunction in girls who are first-degree relatives of people with PCOS. High levels of the adaptor protein LnK, which suppresses the phosphatidylinositol 3-kinase-AKT and MAPK-ERK signalling response to insulin, are another hereditary factor that may contribute to IR in PCOS patient. While the role of oxidative stress in the pathogenesis of PCOS is still under study, it was shown to cause altered steroidogenesis in the ovaries, by increasing androgen levels, disturbing follicular development, leading to infertility, obesity, insulin resistance, and cardiovascular risks were also related to oxidative stress in PCOS women. In multiple investigations, oxidative stress in the pathogenesis of PCOS women. In multiple investigation, oxidative stress- associated inflammation markers were positively correlated with androgen levels in PCOS patients. ROS exert both negative and positive effects on mammalian ovaries (Fig. 2).[4]

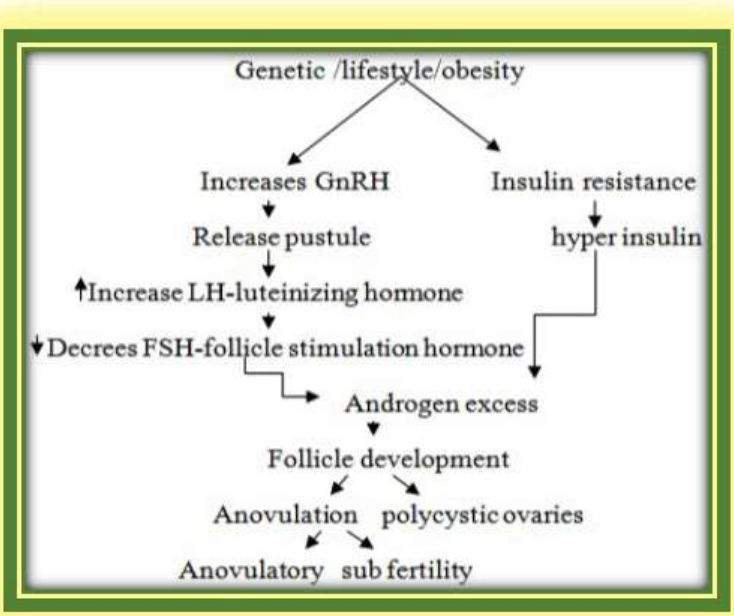


**Figure 2: Flow chart for pathophysiology of PCOS[3].**

### 1.3 Anovulation

Anovulation is decreased progesterone release and increases the oestrogen. Via endometrial releases and increase the endometrial cancer.[3]

### 1.4 Symptoms

Symptoms of polycystic ovary syndrome can differ from person to person. Symptoms may change over time and often occur without a clear trigger (Fig. 3).

**Possible symptoms include**

- ❖ Irregular periods
- ❖ Acne
- ❖ Hair loss or hair thinning on scalp
- ❖ Excessive bleeding during the periods
- ❖ No periods


**Figure 3: Symptoms of PCOS.**

People with PCOS are more likely to have other health condition including:

✓ Type 2 diabetes

✓ Hypertension (high blood pressure)

✓ High cholesterol

✓ Heart disease

✓ Endometrial cancer (cancer of the inner lining of the uterus).[5]

### 1.5 Diagnosis

There's no test to definitively diagnose PCOS. A physical exam will include checking for signs of excess hair growth insulin resistance and acne.

A pelvic exam: manually inspects reproductive organs for masses, growths or other abnormalities.

Blood tests

✓ Blood may be analyzed to measure hormone levels. This testing can exclude possible causes of menstrual abnormalities or androgen excess that mimics PCOS.

✓ Additional blood testing to measure glucose tolerance and fasting cholesterol and triglyceride levels.

An ultrasound

To checks the appearance of ovaries and the thickness of the lining of uterus.

- Additional tests for complications

✓ Periodic checks of blood pressure, glucose tolerance, and cholesterol and triglyceride levels

✓ Screening for depression and anxiety

✓ Screening for obstructive sleep apnea.[3]

### 1.6 Caesalpinia bonducella

*Caesalpinia bonducella L.* plant is also known as "fever nut", belongs to family Caesalpiniaceae. *C. bonducella* is a huge thorny shrub known to be a local of south India, Burma and Ceylon, especially along the ocean drift and up to 2500ft.in hilly regions. *C. bonducella* commonly known as kalachika, karanja. It is accounted in this literature that most parts of the plant have therapeutic properties, however, much has been studied with the seed and shell. The shell is known to contain starch, fatty oil, sucrose, phytosterols, stearic, palmitic, oleic, linoceric, linolenic and a mixture of unsaturated acid. The alkaloids in *C. bonducella* are known to be found in shell, seed and twigs. The active molecule bonducin is present in the seed as an incredible glycoside also saponins and terpenoids are additionally known to be found in seed.[6]

**Figure 4*: C. bonducella (fruit).***

### 1.7 Taxonomical Classification

**The following table covers the taxonomical classifications of C. bonducella.[7]**

| **Kingdom** | **Plantae** |
|---|---|
| Phylum | Magnoliophyte |
| Division | Magnoliopsida |
| Class | Angiospermae |
| Order | Febales |
| Family | Caesalpiniaceae |
| Genus | Caesalpinia |
| Species | *C.bonducella* |
| Parts used | Seeds |

### 1.8 Vernacular Name

**Vernacular names of *C. bonducella* are including the following table.[8]**

| | |
|---|---|
| Hindi name | Kantkarej, Kantikaranja, Sagar gota. |
| English | fever nut, bonducella nut, nicker nut, nicker seed |
| Sanskrit name | Kalachika, Kantakikaranja, kantakini, karanja, krakachita, kuberaksah, kuberksi, latakaranja, pakiriya, pakrinah, putikah, putikaranja, putikaranjah, pulikaranji, tinagachhika, tirini, valli, varini, vitapakaranja |
| Urdu | Akitmakit |
| Persian name | Khayahe-i-iblas |
| Tamil name | Kalarci ver, Kalarci koluntu, Kalarcip paruppu, Kazharchikkaai, Kalarchikai, Kazarci. |
| Kanada name | Gajjiga, Kiri gejjuga, Gajikekayi |
| Malayalam name | Ban-karetti, Kaka-moullou, Kazhanji, Kalanci, Kalanchikkur |
| Telugu name | Mulluthige, Gaccakayai |

1.9 Morphological features and flowering season of *C. bonducella*

The morphological characters of *C. bonducella* plants parts are including below.[6]

#### 2.9.1. Leaves

The leaves are bipinnate, 30–60 cm in length with rachis, with hard thorns. There is a pair of reduced pinnae at the base of each leaf. There are seven pairs of pinnae with 3–8 pairs of leaflets having 1–2 small prickles between them on the lower sides (Fig. 5).

**Figure 5: *C. bonducella* (plant).**

#### 2.9.2. Stem

Vine stem diameters to 5 cm recorded. Usually grows as a vine but also flowers and fruits as a shrub. Occasional spines or numerous spines present on the stems.

### 2.9.3. Flower

The flower colour is pale yellow, thick (usually spicate), with a long peduncle terminal and supra-axillary racemes at the peak. Racemes droop downwards and are 15–25 cm long; the pedicles are very short in the bud, elongating to 5 mm in flowers and 8 mm in fruit; they are brown, downy, and oblanceolate. Filaments are declinate, compressed at the base, and clad with long white silky hairs (Fig. 6).

**Figure 6: *C. bonducella (flower)***

### 2.9.4. Seed

The fruits are inflated oblongate pods, 5 to 7.5 × 4.5 cm, covered with prickles, containing one or two seeds per pod. The pods have short stalks. The seeds are 1–2 cm in size, globular, hard, bluish-grey in colour, and have a smooth, shiny surface (Fig. 7).

**Figure 7: *C.bonducella* (seed).**

### 2.9.5. Inflorescence Rachis

Flowers showing alternate arrangement.

### 2.9.6. Fruits bearing

The shrub bears fruits by November (Fig. 4 and 7).

### 2.10 Anatomy of the Intra-Vaginal

The vaginal is the female genital organ with functions related to reproduction conception and menstruation discharge. The vagina is a fibromuscular tubular organ that 9cm.The vaginal wall consist of three layer including the epithelial layer the muscular coat and the tunica adventia. the thickness of the epithelial layer phatic vessels is abundant in the walls of varies by approximately 200-300micro meter during the menstrual cycle. The vaginal surface has numerous folds, which are known as rugae, responsible for distensibility, support and larger surface area to the vagina wall. The excellent elastic property of vagina is due to the presence of smooth elastic fibres in the muscular coat and loose connective tissue of tunica adventia that further improve its elasticity. The dense network of blood vessel supplies sufficient amount of blood to the vagina. The arteries include a plus of arteries extending from the internal iliac artery, uterine, middle rectal and internal pudendal arteries. In fact, arteries, blood vessels and lymph vagina. furthermore, the absorbed drug from the vagina by passes first pass metabolism as blood leaving the vagina enters the peripheral circulation via a rich venous plexus, which empties directly into the internal iliac veins.[9] There is some drainage to the hemorrhoidal veins as well. The lower part of the vagina receives its nerve annervation and impulse supply from the pudendal nerve and from the inferior hypogastric and utero vaginal plexuses. They give rise to the cervicovaginal artery which branches to supply the cervix and the anterior and posterior surfaces of the vagina. The vagina is surrounded by a rich venous plexus which eventually into the internal iliac veins. The vaginal wall is devoid of glands but is usually covered by a surface film of moisture. This consists mainly of cervical mucus and of fluid exuded from the rich, vascular lamina propria. vaginal fluid may also contain secretions from the uterus and from Bartholin's glands. The pH of the vagina is usually between 4 and 5 and is maintained by the action of bacteria which convert glycogen from exfoliated cells into lactic acid. the vaginal tract exhibits a pH gradient where the pH is lowest nearest the cervix. Menstrual blood, cervical and uterine secretion and semen will all act as alkalinising agents and increase the vaginal pH.[11]

### 2.10 Factors Affecting the Vaginal Absorption of Drug

In common with other mucosal routes, drugs administered vaginally will be transported across the vaginal membrane by a number of different mechanisms.[12]

- ✓ By diffusion through the cell due to a concentration gradient (transcellular route);
- ✓ By a vesicular or receptor-mediated transport mechanism; or
- ✓ By diffusion between the cells through the tight junctions (intercellular route).

### 2.10.1 Physiological Factors

One of the main factors that could potentially alter the rate of released medication absorption and impact drug release from any intravaginal delivery device is the physiological component. This includes variations in the fluid volume, cyclical fluctuations, thickness of the epithelial layer, hormone and enzyme levels, vaginal pH changes, and sexual excitement. For instance, the thickness of the vaginal epithelium makes it easier for the vaginal to absorb steroids. A case study indicates that compared to premenopausal women, postmenopausal women absorb noticeably more oestrogen through their vagina. Due to an increase in progesterone absorption, women receiving vaginal oestrogen therapy who were low in oestrogen may have seen an increase in vaginal epithelium thickness. because of the high volume of vaginal fluid, a medicine that is not very water soluble may be absorbed more easily. Additional investigation into the microstructure of cervical mucus indicates that a glycoprotein gel may improve vaginal medication administration when paired with a bio adhesive drug delivery method. However, it also blocks the permeability of several potential medication and subsequently, it has been proven that the pH of the media in an in vitro setting can impact the release of PGE2 from vaginal preparations. Furthermore, change in pH can affect the release profile of a drug that is sensitive to changes in pH.[12]

### 2.10.2 Physiochemical properties of drugs

The physicochemical characteristics of the drugs and polymer i.e. lipophilicity, ionization, surface charge, chemical nature can influence vaginal drug absorption. The vaginal permeability of straight chain aliphatic alcohols increases linearly in a chain length dependent manner. Similarly, the lipophilic steroids such as hydrocortisone and testosterone. It is widely accepted that generally low molecular weight lipophilic drug is more absorbed than large molecular weight lipophilic or hydrophilic. Vaginal fluid contains a large amount of water, any drug intended for vaginal delivery requires to be soluble before it is absorbed.[12]

### 2.11 Ideal characters of intravaginal drug delivery system

- Component should melt at vaginal temperature (36 c), the device may be nontoxic and non-irritating and stable on storage

- It should not have any meta-stable from
- The preparation must have high water number
- It should possess easy wetting and emulsifying properties.
- The preparation should be non-sensitized on vaginal pH (i.e.3.5-4.9)
- The preparation should have proper viscosity
- The preparation should have proper bio adhesive/mucoadhesive properties, so their residence time may be increased between the membrane and preparation.[13]

### 2.12 Advantages of intravaginal route of administration

- The avoidance of hepatic first-pass metabolism.eg. the bioavailability of propranolol was higher after vaginal administration compared with oral delivery.
- The reduction in the incidence and severity of gastrointestinal side effects observed during the vaginal delivery of bromocriptine.
- Reduction in hepatic side effects of steroids used in hormone replacement therapy or contraception.
- Easy self-insertion and removal of the dosage from is possible.
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by other parenteral routes.
- Contact with digestive fluid is avoided, thereby preventing enzymatic degradation of some drug.[13]

### 2.13 Limitations of intravaginal route of administration

- ✓ Some drugs are sensitive at the vaginal pH.
- ✓ Few drugs may be causing the local irritation
- ✓ Influence of sexual intercourses
- ✓ Gender specificity
- ✓ Personal hygiene
- ✓ Sometime leakage of drugs from vagina.[13]

### 2.14 Various delivery systems for intravaginal administration

- ✓ Vaginal ring
- ✓ Creams and gels
- ✓ Vaginal tablets and suppositories
- ✓ Bio adhesive delivery systems

- ✓ Other novel delivery systems

The important criterion for intravaginal delivery is that drugs it should be based on adequate vehicles. Their development should consider and address anatomical and physiological features of the vagina.[14] The ideal intravaginal drug delivery system has potentials for selective regional therapeutic administration and offers localized effect where needed, while rest of the body may remain unaffected. This effect is highly desirable and critical for steroid, which are administered to or through vagina for the treatment of urogenital atrophic complaints. Several drug delivery systems have reportedly been developed for vaginal administration including semi-solid, tablets, capsules, pessaries, liquid preparation, vaginal films, vaginal rings, and foams[15] The liquid formulations seen inappropriate owing to their short residence time in the vaginal cavity, and hence fail to provide controlled release. Although solid dosage forms are easy and in expensive to manufacture with their easy mode f application, the vaginal residence time however remain still poor, necessitating frequent application. Therefore, the most widely accepted conventional semi-solid preparation for vaginal drug delivery include creams, ointments, and gels. Their consistency as well as ability to adhere onto surfaces for sufficient duration, unless removed by washing or by natural factor is some common features. In addition, the benefits of these formulations are acceptability, feasibility, and low cost while messiness, discomfort and leakage are their main problems. Indeed, convention vaginal drug delivery systems show the rapid removal from the application site[14]

### 2.15 Vaginal Ring

They are flexible, tours-shaped, elastomeric drug delivery devices that may be sustained or controlled released of drug to or through the vagina for either local or systemic effect. The sustained release implicates to release of active contents over a prolonged time while controlled release refers to constant rate of release of bioactive following zero-order kinetics (16). In 1970, it was discovered for the very first time that vaginal rings may be able for sustained/controlled delivery to the human vagina and a range of molecules, including steroid could delivered using silicone elastomer in a predictable manner.[17]

**Figure 9: Vaginal ring.**

It eliminates the need of daily dosing, lowers the adverse effects and improves patient compliance.[16] Although the exact position of ring placement is not so critical for their clinical effects, it only addresses the comfort in some women. The basic design of vaginal ring possesses solid drug dispersed throughout a polymer matrix where release rate is dependent on both the drug loading as well as surface area of the device.

**Drug release from these matrices follows a permeation mechanism.**

1. The dissolution of the solid drug within the polymer,
2. Diffusion of the solubilized drug through the polymer matrix, and
3. Partition of the drug from the polymer into the surrounding vaginal fluid /tissue.

In the matrix ring, surficial drug is released first forming a drug depletion zone through which solubilized drug could diffuse and finally released. As the time proceeds, the thickness of drug depletion zone increases consequently the surface area of the inner moving boundary layer decrease. Hence, the continuous amount of drug released may reduce with time as the drug near to the surface of the ring becomes exhausted and the diffusional pathway for the remaining drug increase. Release kinetics may follow a root time kinetics or $t^{1/2}$ and are calculated when the corresponding cumulative drug release versus root time plot is linear.[18] The other variations of vaginal ring such as sandwich type rings consist of a narrow drug containing layer present below the surface of the ring and located between nonmedicated central core and nonmedicated outer band; while in reservoir type ring, drug is dispersed in a central core and surrounded by a polymer. The main advantage is being several cores containing various drugs and allowing co-administration of several drugs using the same

device. The main benefits and their complication associated with vaginal ring. the rate of drug release can be modulated by changing the core diameter or thickness of coating. The polymeric materials commonly used for vaginal ring designing and construction are poly (dimethyl siloxane) or silicone devices, although other elastomeric polymers i.e. ethylene vinyl acetate and styrene butadiene block copolymer have been tested in recent years. Moreover, the clinical applicability of rings made of ethylene vinyl acetate is very high attributed to higher flexibility, improved optical properties, greater adhesion, and increased impact and puncture resistance. Vaginal rings are used for both contraceptive and hormone replacement therapy. The contraceptive rings prevent pregnancy involving hormonal mechanism, either suppression of ovulation or by changing in cervical mucus. These rings are simply inserted into the vagina so that they remain appropriately in intimate contact with vaginal epithelium. For most contraceptive applications, these rings are applied or placed for 21 days and then removed for a period of 7days to allow for menstrual cycle. The first vaginal ring developed for contraception contained medroxyprogesterone acetate. Other progestogens have also been explored including; norethindrone and norgestrel, however, the best studied is levonorgestrel ring developed by the world health organization and the population councils. these vaginal systems however do not completely suppress ovulation and reportedly associated with variable bleeding patterns (vaginal ring as shown in the figure 9.).[12]

### 2.16 Benefits of Vaginal Ring

- ✓ Higher efficacy compared to oral contraceptives
- ✓ Controlled release formulation allows continuous delivery
- ✓ Low dose, so patient compliance
- ✓ Option to administer both oestrogens and progestogens
- ✓ Easily inserted and removed by the user herself
- ✓ It will continue to inhibit ovulation for an additional two weeks
- ✓ No hepatic first-pass metabolism of the progestin
- ✓ Ovulation returns quickly after a woman stops using the ring
- ✓ Vaginal administration precludes gastro intestinal interference with absorption.[12]

### 2.17 Drawbacks

- Unable to protect against STDs
- Not recommended for women with cystocele, rectocele or uterine prolapsed

- Side effect include vaginal infections and irritation, discharge, headache, weight gain, and nausea
- Premature discontinuation
- The women who are pregnant or may be pregnant, or have blood clots, severe high blood pressure, certain cancer or a history of heart attacks and strokes, not suggested.
- Women who use the ring are strongly advised not to smoke, as doing so can increase the risk of severe cardiovascular side effects.[12]

### 3.6 Formulation of vaginal ring

Silicone elastomer rings, comprising cores loaded with HPMC and either lysozyme (a model protein) or lyophilised 5P12-RANTES powder and with the cores partially exposed to the external environment by an overmolded silicone elastomer sheath containing one or more discrete windows, were manufactured using a simple two-step injection molding process. ¼- or full-length cores (cross-sectional diameter, 4.2 mm) were first manufactured using a temperature-controlled laboratory-scale injection molding machine fitted with a custom mold assembly (as shown in the Fig.10). DDU-4320 addition-cured silicone elastomer kit is comprised of two parts. Both parts contain a basic silicone formulation, primarily vinylfunctionalized and hydroxy terminated poly (dimethyl siloxane) s. Part A also contains a platinum catalyst and part B contains a hydridefunctionalizedpoly(dimethyl siloxane) crosslinker which when mixed react via a hydrosilylation addition reaction. Here, Part A and Part B DDU-4320 silicone elastomer premixes containing 8.58% w/w lysozyme and 17.2% w/w of 10 kDa or 120 kDa HPMC (bulk,>125 μm, 90–125 μm, 53–90 μm or < 53μm particle size) were prepared by adding weighed quantities of the powdered materials into a screw-cap polypropylene container, followed by addition of the silicone elastomer parts, and then mixed using a Dual Asymmetric Centrifuge (DAC) mixer (30 s, 3000 rpm; SpeedMixer™ DAC 150 FVZeK, Hauschild, Germany) (as shown in the Fig.10A). A and B premixes were then combined in a 1:1 ratio, according to the following procedure: (i) equal weights of each premix were added to a screw-cap polypropylene container to a final batch weight, (ii) the material was hand-mixed for 30 s and then DAC mixed (15 s at 1500 rpm). The active mix was transferred to a 75 g polypropylene SEMCO injection cartridge designed for use with the SEMCO Model-850 injection system. Full-length ring cores (outer diameter, 54.0 mm) were prepared by injecting the active mix into the heated ring mold assembly (85 °C) and curing for 3 min (as shown in the Fig.10B). The resulting lysozyme-loaded cores were subsequently overmolded with drug-free DDU-4320 silicone elastomer in a further injection molding step,

using a custom mold assembly designed to introduce 24 circular orifices in the sheath (Fig. 10C and D3). Rings were subsequently demolded, deflashed (where necessary) and stored at ambient temperature until further testing. ¼-length DDU-4320 silicone elastomer cores containing 8.58% w/w freeze-dried 5P12-RANTES and 17.2% w/w 120 kDa HPMC (not sieved) were similarly manufactured and overmolded (as shown in the fig.10 C). Using custom mold assemblies, three alternative sheath designs were prepared to expose different fractions of the underlying ¼-length core. The final rings contained a ¼-length core having one or six discrete 3.0mm diameter circular orifices (Fig. 10D1 and D2), one ¼ core with two large windows (Fig.10 D4; 210.9mm2), or two ¼- length cores with four large windows (see graphical abstract; 421.8mm2).[32]

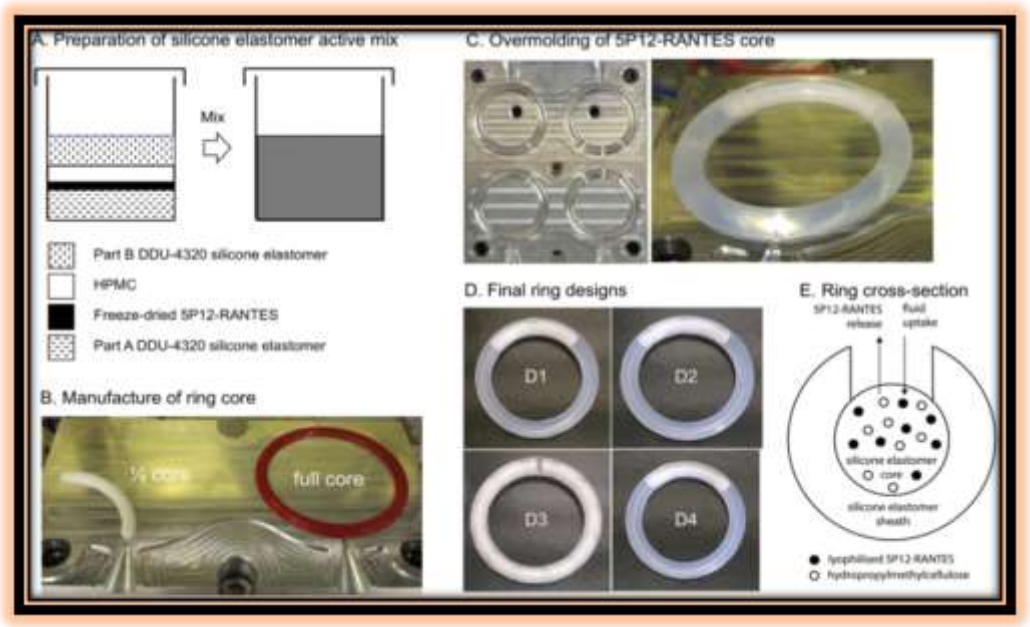


**Figure 10: Formulation of vaginal ring.[32]**

## Evaluation

Testing should be conducted to evaluate a wide range of mechanical parameters, including durometer, tensile strength, elongation at break, compression strength, fatigue due to cyclic loading, seal integrity following cyclic loading or bond strength (for rings with cores or pods inserted into the ring body) and aging studies to determine changes to the mechanical properties with time.[32]

## Stability studies

A stability study was conducted to evaluate the in vitro release and mechanical properties of rings stored at 40 °C and 75% relative humidity (RH), following the schedule outlined in the

Table. For content and in vitro release testing, three rings were analyzed shortly after manufacture (T0) and after 15 weeks (T15). Mechanical testing involved six rings at T0 and T15, with an additional three rings tested at 4 weeks (T4). Prior to testing or storage, the rings were weighed and inspected for surface defects.[32] For storage, the rings were left unpackaged in individually labelled plastic weigh boats and placed in a Binder KBF115 stability chamber set at 40 °C and 75% RH.

| Test | Stability time point | | |
|---|---|---|---|
| | 0 | 4 weeks | 15 weeks |
| Ring content | × | × | × |
| Shore M hardness | × | × | × |
| Twist during compression | × | × | × |
| 5–20 mm compression | × | × | × |
| 1000 cycle compression | × | - | × |
| 28-day static compression | × | - | × |

## 4.0 CONCLUSION

At this juncture, the vaginal route, conventionally used for the local application of drugs, is now emerging as a promising method for non-invasive, controlled trans-mucosal delivery of therapeutically active compounds for both local and systemic effects. Innovative vaginal delivery systems address many of the limitations associated with conventional vaginal drug delivery. This approach holds significant potential for advancing research into the delivery of microbicides aimed at preventing the transmission of sexually transmitted diseases, including HIV.

## ACKNOWLEDGMENT

We would like to extend our deepest gratitude to the managements, principal, staff members and our team members. whose support, guidance, and encouragement have been instrumental in the completion of this research review work.

## REFERENCES

1. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol, 2018; 14(5): 270-284. doi: 10.1038/nrendo.2018.24. Epub 2018 Mar 23. PMID: 29569621.
2. Hayder abbas, insights on fever nut: the next generation treatment of PCOS Journal of cardiovascular disease research (14). 12.2023.

3. Miss Dipamoni Morang, Pankaj Chasta and Mr. Kaushal K.Chandrul "A Review on “Polycystic Overy Syndrome (PCOS)”" Published in International Journal of Trend in Scientific Research and Development, 2019; 3(4): 60-66.
4. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, Kumar M. Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. J Clin Med, 2023; 12(4): 1454. doi: 10.3390/jcm12041454. PMID: 36835989; PMCID: PMC9964744.
5. Rasquin LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. 2022 In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024.
6. Shikhar Verma. Review of C. bonducella. J. pharm, 2020; 64(2): 1-7. DOI link: http://dx.doi.org/10.47583/ijpsrr.2020. v64i02.001.
7. Vellingiri Vadivel, Pemaiah Brindha l. C. bonducella L. A nutaceutical plant. Journal of chemical and pharmaceutical research, 2015; 7(12): 137.
8. Juvatkar PV and Jadhav AG. *Caesalpinia bonducella*: A medicinal potential value Phyto pharm. JPP, 2021; 10(4): 206-214.
9. Sjoberg, I., Cajander, S., & Rylander, E. Morphometric Characteristics of the Vaginal Epithelium during the Menstrual Cycle. Gynecologic and Obstetric Investigation, 1988; 26(2): 136–144. doi:10.1159/000293685.
10. Richardson J.L. Vagina: An Ideal site of drug delivery. Research and Journal of Pharmacy and Technology. Adv. Drug Deliv. Rev., 8: 341.
11. Paavonen J. Physiology and ecology og vagina. scand. J.Infect. Dis., Suppl., 1983; 40: 31.
12. Hussain A. and Ahsan F. Vagina as a route for systemic drug delivery. J. Control. Rel., 2005; 103: 301.
13. Chatterjee A. and Kumar L. J. Pharm. Res., 2009; 2: 698.
14. Baloglu E., Senyigit ZA.,. Karavana S.Y. and Bernkop- Schnurch A. strategies to prolong the residence time of drug delivery systems. J. Pharm. Pharmaceut. sci, 2009; 12: 312.
15. Vermani K. and Garg S. The scope and potential of vaginal drug delivery. Pharm. Sci. Technol, 2000; 3: 359.
16. Barnhart K. T., Timbers K. and Shaunik A. In vivo assessment of NuvaRing placement, 2005; 72: 196.
17. Dzuik P.J. and Cook B. Passage of steroids through silicone rubber, 1966; 78: 208.
18. Malcolm R.K. and Smith TJ. Adavaces in microbicide vaginal ring, 2010; 88S-S30.

19. Pritom Kurmi, Konwar M, Das S. *In-vitro* anticataract activity of ethanolic extract of seed kernel of *Caesalpinia bonducella* (L.) Fleming on goat. Pharma Science Monitor, an International Journal of Pharmaceutical Sciences, 2015; 6(1): 244-253.
20. Ogunlana OO, Ogunlana OE, Ntube CA, Olagunju JA, Akindahunsi AA. Phytochemical Screening and *in vivo* Antioxidant Activity of Ethanolic Extract of *Caesalpinia bonduc* (L.) Roxb, Global research journal of Pharmaceutical Sciences, 2012; 1(1): 1-5.
21. Yadav PP, Maurya R, Sarkar J, Arora A, Kanojiya S, Sinha S. Cassane diterpenes from *Caesalpinia bonduc*, journal of Phytochemistry, 2009; 70(2): 256-61.
22. Gupta M, Mazumder UK, Kumar RS, Sivakumar T, Vamsi MLM. Antitumor activity and antioxidant status of *Caesalpinia bonducella* against Ehrlich ascites carcinoma in Swiss albino mice. Journal of Pharmacological Sciences, 2004; 94(2): 177-184.
23. Md. Mahfoozurrahman, Hifzul Kabir, Asif M. Analgesic and Anti-Inflammatory Activities of Aqua Form of *Caesalpinia Bonducella* Seed in Rats, international journal of pharmaceutical sciences and research, 2012; 3(11): 4235-4241.
24. Muruganantham N, Basavaraj KH, Dhanabal SP, Praveen TK, Shamasundar NM, Rao KS. Screening of *Caesalpinia bonduc* leaves for antipsoriatic activity. Journal of Ethnopharmacology, 2011; 133(2): 897- 901.
25. Lilaram RNA. Abortifacient potential of ethanolic seed extract of *Caesalpinia bonducella* in female albino rats. J Basic Clin Physiol Pharmacol, 2014; 25: 445-451.
26. Ansari JA, Ahmad S, Jameel M. Effect of *Caesalpinia Bonducella* L. on ulcer and gastric secretions in pylorus legated rat model. J Drug deliv Ther, 2012; 2: 102-104.
27. Salunke KR, Ahmed RN, Marigoudar SR. Effect of graded doses of *Caesalpinia bonducella* seed extract on ovary and uterus in albino rats. J Basic Clin Physiol Pharmacol, 2011; 22: 49-53.
28. Shukla S, Mehta P, Mehta A, Vyas SP, Bajpai VK. Preliminary phytochemical and antifungal screening of various organic extracts of Caesalpinia bonducella seeds. Romanian Biotechnological Letters, 2011; 16(4): 6384- 6389.
29. Khan HU, Ali I, Khan AU, Naz R, Gilani AH. Antibacterial, antifungal, antispasmodic and Ca++ antagonist effects of Caesalpinia bonducella, Nat Prod Res, 2011; 25: 444-449.
30. Usha Balasundaram. *Caesalpinia bonduc* (L.) Roxb. as a promising source of pharmacological compounds to treat Poly Cystic Ovary Syndrome (PCOS): A review. Journal of Ethnopharmacology, 2021.
31. John W. McBride. Vaginal rings with exposed cores for sustained delivery of the HIV CCR5 inhiobitor 5P12-RANTES. Journal of Controlled Release, 2019; 298: 1-11.

32. Dallal Bashi Y.H., Murphy D.J., McCoy C.F., Boyd P., Brown L., Kihara M., Martin F., McMullen N., Kleinbeck K., Dangi B., Spence P., Hansraj B., Devlin B., Malcolm R.K. Silicone elastomer formulations for improved performance of a multipurpose vaginal ring releasing dapivirine and levonorgestrel. Int. J. Pharmaceut. X., 2021; 3. doi: 10.1016/j.ijpx.2021.100091.