# Intravaginal Delivery Approaches for Contraception: An Overview with Emphasis on Gels

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**ABSTRACT-** The rising population with grave ramifications for the future is a fundamental issue, demanding for newer and better contraceptive modalities. Also, in order to achieve the contraceptive purpose, the choice of the most suitable delivery system is of unquestionable importance. Out of all dosage forms, vaginal gel formulations present indubitable benefits for contraceptive administration. Therefore, this review summarizes the history of research in the field of vaginal delivery systems with special emphasis on the development of vaginal gels containing safer and more effective contraceptive agents.



## INTRODUCTION

The United Nations Population Division expects world population to attain staggeringly elevated peaks at over 10 billion at the end of the 21st century (1). The population is increasing exponentially, thus it needs to be assertively controlled in order for human race to suffice.

Contraception is considered as the key solution to control the menace of rising world population. An array of methods is known for female contraception, which include barrier methods (female condoms, cervical cap, and diaphragm), hormonal methods (oral contraceptive pills, injectable contraceptives, and emergency contraceptives), intrauterine methods (IUDs), sterilization (tubal ligation) and natural methods (2). Despite their existence for decades, various drawbacks are still associated with these approaches. Barrier methods are difficult and may cause discomfort. Various adverse effects are associated with oral hormonal methods of contraception like vomiting, diarrhoea, hypertension, cervix carcinoma and gall bladder disease. Although in the hope of reducing these side effects, new contraceptive pills have been developed by replacing ethinyl oestradiol with oestradiol, yet daily intake of pills is problematical (3, 4). IUDs being the long acting reversible contraceptive method (LARC) improve compliance (5, 6) but have to be inserted by trained health care providers. They may also cause irregular menstrual bleeding and increase chances of upper genital tract infections (7). Sterilization, being an irreversible method, is only useful in females who don't want further children (8). Many women have irregular cycles, so it can be difficult to identify their likely productive time in every cycle. Each women's menstrual cycle is unique to her. If a woman has sex without using any contraceptive, she might get pregnant at a point in her cycle when she thought she was safe.

Despite existence of these methods of contraception since decades ago, there is still a quest for alternative means. To overcome these issues, exploitation of topical vaginal contraceptives is gaining clinical significance. Owing to the fact that they are employed just before the sexual activity is in the offing, the vaginal contraceptives have earned another name for themselves i.e., coitus related or episodic products, as opposed to the agents that are taken orally or implanted in the body. With this, women are not burdened to bear the agent throughout the month as is the case with oral contraceptives, intrauterine devices (IUDs), implanted inserts and depot injections, thereby freeing them from adverse effects that are caused by systemic exposure to the contraceptive agents. Besides this, they offer various other advantages which include uninterrupted sexual pleasure, no requirement of supervision by health personnel, comfort, easy affordability and most importantly, defense against sexually transmitted

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diseases (STDs). Last but not least, since these preparations usually enhance vaginal lubrication, can be used instantly after childbirth and have no hormonal side effects. Hence, vaginal contraception can prove to be a blessing for women over 40, lactating mothers and those with contraindications to oral contraceptives and IUDs (9). Less advancement in this area leading to high failure rate proved to be the nemesis of vaginal contraceptives which are the only devices that may afford some protection during emergency situations.

However, in order to administer drugs intravaginally, it is essential to incorporate them into suitable vehicles. History demonstrates that beginning from the earliest starting point till today, choice of proper delivery platform to deliver the drug in vagina for particular condition is a critical component for therapeutic adequacy. An abundant cluster of pharmaceutical modalities are presently available for delivering spermicidal agents into the vagina. There are traditional forms, such as vaginal rings, effervescent tablets, suppositories, sponges, foams, films, creams and ointments, with many improvements since their inception. There are newer forms, such as gels, and more recently, the hydrogels. This review manifests a brief discussion on the different vaginal delivery platforms, emphasizing on vaginal gels pertaining to the delivery of spermicides.

## SYSTEMS FOR VAGINAL DELIVERY

### Vaginal rings

Intravaginal rings are torus-shaped polymeric systems that are intended to supply a controlled delivery of drugs to the vagina for prolonged periods. They have a diameter of 5.5 cm with a circular cross sectional measurement of 4-9 mm, where drugs are evenly distributed (10). Intravaginal rings release active substances, mostly hormones, at uniform concentrations; they allow lower doses to be used, and can still be user controlled (11). The materials put together to form vaginal rings are mainly polymeric in nature *viz.* poly (dimethylsiloxane) or silicon devices. However, various other elastomeric polymers such as ethylene vinyl acetate (EVA) and styrene butandiene block copolymer have also been tried in recent past. The hormone(s) which show contraceptive efficacy, merged with an elastomer, form cores which are finally implanted in the ring's body and from there, a constant and slow release takes place. The steroids are then quenched from the vaginal epithelium and circulated systemically (12). Some other rings are designed as an amalgamation of steroid and elastomer matrix and injected in the body of ring. Alternatively, rings may also contain steroid(s) homogeneously distributed throughout the ring's core or in a circular system throughout the centre of the doughnut (13). For instance, medroxyprogesterone acetate upon impregnation into a silastic vaginal ring has been used as a contraceptive device (14). In today's times, two contraceptive rings are available commercially: the NuvaRing (available in more than 40 countries globally), and the Progering (available in Chile, Peru, Bolivia, Ecuador, Guatemala, and Honduras) (15). The first one i.e. Nuvaring, a doughnut-shaped combined contraceptive (etonorgestrel/ ethinyl oestradiol) vaginal ring made up of EVA, is worn intravaginally continuously for 3 weeks and removed for one week. The contraceptive efficacy is almost 99.4% and the ring has been well received with good user compliance. However, a study which used vaginal ultrasound and serum progesterone as ovulation markers supports that Nuvaring curbs ovulation for 5 weeks (16). However, the other is Progering, which is a 3-month ring containing only natural progesterone, delivers 10 mg of progesterone per day for 3 months. It is made up of silicone elastomer and has been found to be safe for use by lactating women. The only thing where they score above over other long-acting contraceptive systems (e.g. IUD and hormonal implants) is that they can be inserted and removed easily by the users and women find the ring to be a simple method of birth control. But these also face a major challenge in that they are not suitable for the delivery of peptide and protein drugs because of the conditions which are required for their manufacture. Also, they cause vaginal wall erosion, ring expulsion, interference with coitus, repulsive odour, storage and sanitation issues, premature discontinuation because of vaginal discomfort and device related events, including foreign body sensation (17).

### Vaginal tablets

Vaginal tablet ingredients might be similar to those of conventional oral tablets *viz.* binders, disintegrates and other excipients, yet, they are primed in such a way that they will melt, or disintegrate and release the drug in the vaginal cavity only. A direct compression method is employed for their preparation and the factors like swellabilty and release of drug are checked by adding effervescent

agents into the formulations. Briefly, the manufacturing process of these matrix tablets involves the blending of a matrix mixture with a pharmaceutically acceptable excipient. However, the rate of drug release depends on ability of drug to diffuse through the swollen polymers and the progressive erosion or dissolution of the gel matrix (18). By and large, they offer an ease in manufacture and insertion, great stability and are less messy to handle, still it has been found that highly hydrophobic drugs do not cater to as vaginal tablets. To name a few, Clotrimazole vaginal tablet has been found effective in preventing vaginal candidiasis in comparison to oral flucanazole tablets (19). Extremely low doses of Estriol and *Lactobacillus acidophilus* vaginal tablets (Gynoflor) have been reported to be very effective in treatment of vaginal atrophy in breast cancer patients who have attained their post menopausal age (20). Vagifem, a vaginal tablet containing estradiol, has been indicated for the treatment of atrophic vaginitis (21). Also, to increase the retention time in vagina, various mucoadhesive polymers are being utilized for tablet formulation such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (Na CMC), ethyl cellulose (EC), guar gum, xanthan gum, etc. This mucoadhesive property can be improved by using mucoadhesive polymers like chitosan, polycarbophil, etc. such tablets have proved to be used in the past eg. bioadhesive vaginal tablets comprising cyclodextrin complex of itraconazole in preventing vaginal candidiasis and Tenofovir vaginal tablet, to deliver tenofovir, as a HIV microbicide (22, 23).

**Vaginal suppositories**

Suppositories, also known as pessaries or vagitories, are of two types: water-soluble form which is gelatin based and water-insoluble which is wax-based. Generally, these are available as torpedo-shaped dosage forms; however, to be used in vagina, oval is the shape of choice. The composition of the vaginal suppositories to be used is based on the physicochemical properties of the drug and the required drug release profile. As already reported, these systems can be used for contraceptive drug administration and cervical ripening prior to childbirth. They can also act as delivery method for local administration of anti fungal drugs in case of vaginal candidiasis and for progesterone in case of hormonal replacement therapy (24). The base which is generally used for preparation of vaginal suppositories is made by blending different molecular weight polyethylene glycols, surfactants and preservatives. They are designed in a way such that they dissolve at body temperature when pH is buffered to about 4.5. As a result, suppositories liberate active ingredients to cover the vagina and cervix when positioned high against the vaginal cavity. For maximum efficacy, these suppositories must be inserted about 15 minutes before sexual intercourse and the protection given ranges from about 20 minutes to one hour. These must be protected from humidity and heat to prevent its deterioration.

The contraceptive suppositories that are currently accessible to women in the United States have Nonoxynol-9 as the active spermicidal agent. These include Encare, that contains 2.27% of N-9, Koromex Inserts containing 125 mg of N-9, and Semicid that comprises 100 mg of N-9 (25). Hatem et al (26) have also developed a vaginal suppository containing combination of zinc acetate and N-9 to minimize the vaginal irritation rates caused by using N-9 alone. Moreover, vaginal suppositories containing lactobacillus were also developed which served to reduce the chances of relapse of urinary tract infections after antimicrobial treatment (27). Amphotericin B vaginal suppositories were also used by women for curing non-albicans *Candida* vaginitis (28). Other types of vaginal suppositories comprising Prostaglandin E2 were found to be successful in treating the persistent postpartum uterine atony.

The major advantages of using vaginal suppositories include evasion of the first pass metabolism, ease of formulation, and self-administration. However, they are also associated with certain disadvantages such as they may lead to untidiness, have low bioadhesive properties and contradiction in pregnancy (14).

**Vaginal sponges**

Vaginal sponge and its variants are possibly the oldest intravaginal devices utilized for contraception. Wads of cloth, cotton tufts, sea sponges, powder puffs, and so forth have been utilized all through history and are still being used everywhere throughout the world, either alone or in blend with various solutions, probably spermicides. The sponge is a delicate, round barrier method that is around two inches in measurement. It comprises solid polyurethane froth with a nylon loop connected to the base for expulsion. The sponge provides both mechanical and chemical hindrances to sperm. It is

self-managed and does not necessitate a pelvic fitting; one size fits all. There are no contraindications, with the exception of persons hypersensitive to the sponge material or the spermicide or persons reluctant to touch their genitals (25). Accessible without prescription, the vaginal sponge can be personally obtained, embedded, and expelled. After insertion, there is no waiting time for sponge to be effective. It can be embedded hours before a sexual intercourse, keeping away from any interference in sexual act, while maintaining privacy. No additional doses are necessary before engaging in repeated coitus. Sponge may offer defense against a few STDs and is an effective alternative that does not require special skills. The disposable Today sponge (Synova, Media, PA) was introduced in United States of America in 1983 which was later on withdrawn due to compliance issues by US FDA. After FDA consent in 2005, it was reintroduced. The sponge is made up of molded polyurethane soft foam impregnated with 1 gram of N-9. An indentation on one side allows the sponge to fit against the cervix, while another end encloses a ribbon to facilitate removal. The sponge should be wet with tap water prior to insertion. In Europe and Canada, Protectaid (Pirri Pharma, Canada) and Pharmatex (Innotech International, France) are the two contraceptive sponges that are being marketed. Protectaid consists of polyurethane impregnated with three spermicides i.e. benzalkonium chloride, sodium cholate, and N-9 in low concentrations (29). The Pharmatex sponge is impregnated with only one spermicide i.e 60 mg of benzalkonium chloride (30).

There are certain drawbacks of using sponge as a contraceptive that include vaginal dryness, increase in vaginal sores that caused viral infection, mucosal abrasions and the danger of developing TSS. The risk was associated with its use during the puerperium and extended retention of the sponge (31).

**Vaginal foams**

The currently available foam products are present in either tablet form or in pressurized containers. Foam tablets are generally made up of tartaric acid and sodium bicarbonate with a powder base in which the spermicide is amalgamated. When inserted, they react with vaginal secretions, leading to release of carbon dioxide and thus producing foam. Based on the product used, the time taken ranges from three to ten minutes. As per manufacturer's advice, before inserting, tablet can be moistened with little quantity of saliva or water, so that the foaming act can be hastened. Foam containing the spermicide when spread over a wide vaginal surface area, an evident amount of heat is generated. Although no separate applicator is required, but packing must be moisture-proof. These are not marketed in the United States; however, these are widely accessible as the Japanese vaginal foaming tablet NeoSampoon (Eisai Co., Tokyo, Japan). In this tablet, menfegol is present as main spermicide. The Eisai Company, Japan has also industrialized small foam tablets containing a novel surface active agent, p-methanylphenyl polyoxyethylene (8.8) ether, commonly called TS-88. These tablets are round in shape with central hole and they foam rapidly. Also, their spermicidal impact is powerful.

Pressurized foam products, also termed as aerosol foams, are made up of oil and water emulsion kept under gas pressure. When the liquefied gas propellant is loosened, foam is generated. This foam contains spermicidal agent that kills the sperm, thus averting conception. This leads to a barrier amid the sperm and the egg. On the basis of type of container used, either the foam is directly placed into an applicator or, in case of modern designs, discharged rightly into the vagina, there the foam diffuses extensively and gives an instant contraception. Certain foams can be introduced approximately one hour before copulation. Emko (The Emko Co., USA), a type of aerosol contraceptive foam comprising N-9 and benzethonium chloride in a pressurized container, was developed by Joseph Sunnen in late 1950s. Being next in order was Ortho Pharmaceuticals in 1963, with Delfen contraceptive foam. Jensen et al (32) demonstrated that a single dose of foam containing polidocanol prevented pregnancy in female baboons. However, there are various shortcomings linked with its practice like messiness, unsuccessful against STDs, vaginal irritation, swelling, and for better outcome, it is to be used together with some other contraceptives.

**Vaginal films**

Vaginal films are dosage systems which are polymeric in nature, prepared in the form of thin strips with thickness ranging from 220 to 240 μm. These dosage forms are generally square in shape, colorless and smooth with a homogenous surface (33). The film rapidly disintegrates on coming in contact with fluids in vagina to distribute the active agent. These films do not require any applicator or

additional obtrusive and inconvenient administration method. The film is folded once, placed over the dry finger and inserted high into the vagina. Besides, they offer various other advantages that include ease in use, no messiness, comfort, unimpeded sexual activity and reduced cost (34). The major components employed to develop vaginal films include active pharmaceutical ingredient (API), polymers that form water soluble film and plasticizers to increase elasticity (35). To accomplish desirable attributes, polymers that are used should possess certain properties such as superior wetting and spreadability, moderate tensile strength, good peelability, less manufacturing cost, nontoxicity, non irritability and without any leachable contaminants (36). Polymers that are exploited in this capacity are polyacrylates, polyethylene glycol, PVA, and cellulose based derivatives. Certain other excipients such as disintegration agents, coloring and flavoring substances and stabilizers are also sometimes incorporated in these vaginal films. These dosage formulations are used to deliver broad range of drug candidates to attain local or systemic effects. The vaginal contraceptive film (VCF) manufactured and marketed by Apothecus Pharmaceutical in New York (USA), is a transparent and water-soluble ultra thin film measuring four cm square, incorporated with 28% N-9 that acts as an active spermicide and PVA as water soluble polymer. No particular application device is required. Instead, it is folded and placed high in the vagina against the cervix by making the use of fingers. It is advised to place the film in the vagina not less than 15 minutes and not beyond 1 hour prior to intercourse as mentioned in the manufacturer recommendations (37, 38). Another vaginal film is the one reported by Garg et al. (39) formulated using Polystyrene sulphonate (PSS), PVA and sorbitol in the proportion of 3:1:2, where PSS is an active ingredient that hinders sperm function and possesses antimicrobial property. It is colorless, smooth and tough, dissolves rapidly in physiological fluids and has pleasing aesthetic and pharmaceutical properties. Inspite of possessing various desirable attributes, use of these dosage forms is at a halt. Factors that limit its use are the local side effects, amount of active agent that could be incorporated in this dosage form and variability in drug permeation (40, 41).

**Vaginal creams**

Vaginal creams are the delivery platforms in the form of semi-solid emulsions incorporated with one or more active drugs formulated using a suitable base. Generally pharmaceutical creams are prepared as oil in water emulsions or as water washable dispersions of long chain fatty acids or alcohol. These creams most of the times comprise oil phase in dispersed form, constant water phase, a set of structure shaping excipients, responsible for its semisolid nature (42). To curtail bacterial contamination, frequently used preservatives in the creams are methylparabens, propylparabens, benzyl alcohol, germaben and sodium benzoate. Creams offer certain advantages such as they are easy to use, readily accessible and can be formulated effortlessely. Creams are usually employed for releasing contraceptives, antimicrobial drugs and anti-inflammatory compounds, either topically or systemically across the vaginal mucosa. National Institute of Immunology has developed a spermicidal formulation in the form of polyherbal cream named as Praneem. It is formulated by making the use of three synergistic spermicides namely Praneem (an extract purified from the desiccated seeds of *Azadirachta indica*), saponins extracted from the fruit pericarp of *Sapindus* species and quinine hydrochloride (43). Pharmaceutically suitable polymer base is used to formulate these ingredients into water soluble cream. Antioxidants and preservatives are also added to stabilize the product. This formulation showed antifertility effect on precoital intravaginal administration in rabbits and monkeys without causing vaginal irritation. Similarly, Consap is a water dispersible contraceptive cream comprising saponin fraction extracted from *Sapindus mukorosii.* When applied intravaginally before intercourse, it kills all the spermatozoa instantly. It is free from any adverse effects such as vomiting and disturbance in menstrual cycle as observed with oral contraceptive methods (44). There are some other vaginal creams that are indicated for purposes other than contraception. “Premarin” cream is specified for the management of patients suffering with refractory endometria (45). Two other vaginal creams: Metronidazole and clindamycin vaginal dosage forms have already been verified for the cure of bacterial vaginosis when given intravaginally. Out of these two, clindamycin dosage cream has been found to be more effective when compared to the other one (46). For the treatment of vaginal candidiasis, itraconazole formulated into cyclodextrin-based formulation showed good therapeutic efficacy (47). Dienoestrol (non-steroidal estrogen) formulated in a

cream base is indicated for the treatment of vaginal atrophy, a condition that occurs mostly after menopause (48). Two other vaginal creams: ovestin and Estrace have also been developed for treating atrophic vaginitis (49). Creams have certain drawbacks that include messiness, inconvenience, and inability to deliver an exact dose due to non uniform distribution and leakage (14).

These above described vaginal contraceptive formulations comprising of creams, foams, pessaries and jellies, are susceptible to leakage and their efficacy is compromised due to meagre retention at the site of delivery. To overcome the mentioned shortcomings, there is a necessity for the development of vaginal formulation that adheres to vaginal mucosa for an adequate time period (50, 51).

**Vaginal gels**

Gels are a kind of semi-solid delivery forms containing little quantity of solid, dispersed in generally a lot of liquid, yet displaying more solid-like nature (52). Because of high extent of physical or chemical reticulation, these platforms shape a three-dimensional, polymeric network (53). They comprise elongated, tangled chains that are associated at particular points; however the associations must be reversible. The molecular methods of gelation are inadequately understood, but researchers are endeavoring to design and upgrade molecules with these characteristics. Gels have an edge over the other vaginal dosage forms owing to ease in preparation, convenience in usage, safety, greater bioavailability, the capability to accomplish close contact with mucosal surface of vagina and affordability (18). Moreover, gels introduce the further point of interest of a hydrating and greasing up activity because of their rheology and high water content, which is especially valuable in pathological conditions portrayed by dryness of the vaginal mucosa. A noteworthy favorable property of gels is their configuration, which can furnish them with characteristics like those of biological tissues keeping up their mechanical integrity. Also, gel offers better drug delivery because of its elasticity when they are swollen. Based on the proposed application, gels are utilized as a part of numerous viewpoints as drug dosage platforms to bring local or systemic effects. They are often utilized clinically for various therapeutic applications, for example, contraception, microbial infections, end of pregnancy, pain reliever, and urge incontinence. They can be applied on the surface of skin, in vaginal cavity, intracutaneously as inserts and utilized as part of other biomedical applications (54).

**Formulation of vaginal gels**

A formulation can be considered as a system in which an active substance is amalgamated with some inert ingredients to produce the final product (Fig 1). According to the International Pharmaceutical Excipients Council (IPEC), “Excipients are the natural or synthetic substances, supplementary to the pharmacologically active ingredient, that have been suitably assessed for safety and are present in a finished product to perform particular functions”. This definition suggests that excipients play an important role in manufacturing process of the drug delivery systems, enabling bioavailability, stabilization, protection of active ingredient from biodegradation, and improvement of product compliance (55).

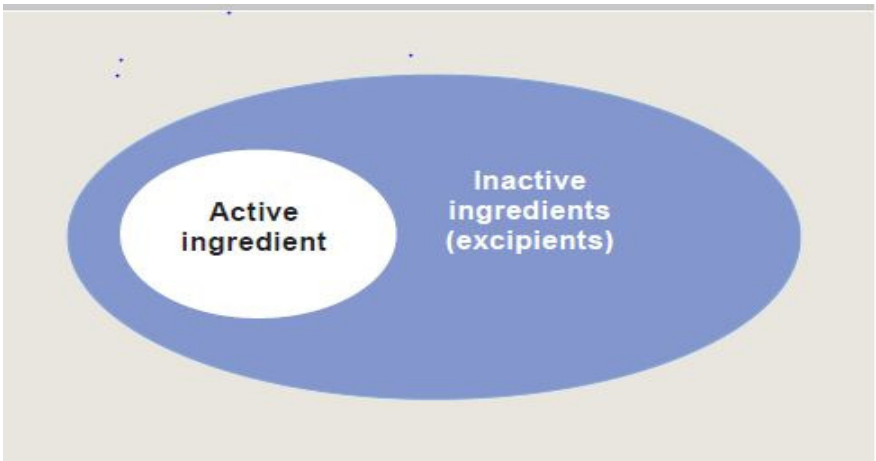


**Figure 1.** Concept of a formulation (Adapted from Garg *et al*., 2001)

Categories of excipients that are generally used to formulate vaginal gels comprise gelling agents, diluents, humectants, preservatives and vehicles.

Gelling excipients are the type of polymers that are used to formulate gels. When hydrated and dissolved in the dispersing medium, these substances experience a high level of cross-connection which adjusts the viscosity of the medium in which it is dispersed. The customary commercial gel formulations are known to have low retention time in the vaginal vault attributable to the self-cleaning mechanism of the vaginal cavity, and frequently entail multiple doses on the daily basis to guarantee the preferred therapeutic impact (52). Moreover, it must be recalled that the vaginal epithelium does not have goblet cells that produce mucus. In this manner, mucoadhesion is a proper procedure to be considered. In this appreciation, mucoadhesive polymers are often incorporated in the gel formulations to improve its biological properties.

**Mucoadhesives gelling polymers**

Mucoadhesives are usually natural or synthetic polymers whose function is to interrelate with the mucous layer that covers the surface of mucosal epithelium. At physiological pH, there is a significant negative charge on the surface of mucus owing to the occurrence of acid residues, leading to a considerable bioadhesion (56). Bioadhesion might be characterized as a state in which two materials are bonded together for amplified timeframes by interfacial forces, implying achievement of the inimate contact between the delivery system and a biological surface, thereby extending the residence time in the vaginal cavity. Varied types of polymers have been scrutinized as mucoadhesives to formulate vaginal dosage systems. These include naturally occurring polymers such as carrageenan, chitosan, hyaluronic acid, sodium alginate, and starch, as well as synthetic polymers such as cellulose derivatives, polyacrylic acid, poly vinyl alcohol etc (57).

**Natural polymers**

***Carrageenan***

Carrageenan is generally extracted from edible seaweeds of Irish moss i.e Red alga. Its chemical structure is comprised of repeating units of galactose and 3, 6-anhydrogalactose (3, 6-AG) copolymer (both sulfated and non-sulfated). Alternating α-1,3 and β-1,4 glycosidic linkages join these units (58). High flexibility and double helical structure of carrageenans enable them to shape a range of diverse gels at room temperature. There are various benefits offered by carrageanan such as safety, affordability, easy accessibility and efficacy over a broad range of pH. Even at high temperature, carrageenan maintains its properties and effectiveness within the vaginal cavity for hours. Therefore, it can be utilized to provide protection during coitus (59). Carrageenans undergo thinning under shear stress, a property termed as thixotropy, allowing it to recover its viscosity after the removal of stress (60). The carrageenan-based formulation containing N-9 was found to protect against transmission of HSV-2 and HIV infections in vagina, therefore could be established as the vehicle for the delivery of antiretrovirals in future experiments (42). However, itching in vagina, burning sensation and pain caused by carrageenan on prolonged application limits its use in pregnant women (61).

***Chitosan***

Chitosan is a natural and safe copolymer comprising units of glucosamine and N-acetylglucosamine, synthesized from chitin through the process of deacetylation. On the account of various interesting features presented by chitosan such as greater penetrating ability, mucoadhesion, biodegradability, and antimicrobial activity, it is currently being paid a great attention for the development of various pharmaceutical delivery platforms (62). Owing to the presence of primary amino groups, chitosan presents cationic character, a property probably responsible for its association with vaginal mucosa and augmenting penetrating ability (63). High molecular weight derivatives such as 5-methyl-pyrrolidinone chitosan, possess ability to increase penetration making it the most promising derivative to improve the absorption of hydrophilic drugs through the vaginal mucosa (64). Chitosan citrate is also endowed with penetration enhancing power and mucoadhesive property, which could be further improved by adding thiol group (65). Further being hydrophilic, it possesses capability to form gel when exposed to acidic pH making it an ideal candidate for the formulation of controlled release delivery systems (66). Gel formulation prepared using chitosan for administering insulin intravaginally, has been found to be suitable for longer release (67). The single drawback associated with the utilization of chitosan is its dependence on pH and rapid dissolution rates (68).

***Hyaluronic acid derivatives***

Hyaluronic acid also termed as Hyaluronan, is a linear polysaccharide consisting of polyanionic disaccharide units in which glucuronic acid (GlcUA) and *N*-acetyl glucosamine (GlcNAc) are bonded by β-1-3 and β-1-4 glycosidic linkages, arranged alternately. It is a natural polymer, generally extracted from the tissue of higher animals, with properties of biodegradability, viscoelasticity and biocompatibility. Being viscoelastic, it is employed as a biomaterial whose viscosity is managed by the amount and molecular mass of its chains. Being easily soluble in water, it is readily formulated into a gel. These polymers are exploited for the formulation of gels to deliver drugs to various cavities (69).

***Sodium alginate***

Sodium alginate is a linear polysaccharide that occurs naturally, isolated from seaweeds and bacteria. This sodium salt of alginic acid is a combination of uronic acid molecules, either in the form of homopolymers or heteropolymers, consisting of units of (1–4)-β-D-mannuronic acid and (1–4)-α-L-guluronic acid (70). In the view of various characteristics possessed by alginate and its sodium salts such as less toxicity, biodegradability, affordability, solubility in water, ability to form gel with greater viscosity, they are extensively utilized for drug delivery by various pharmaceutical companies (71). Moreover, in contrast to other acids utilized as spermicides, alginic acid does not dissolve at an acidic pH as that of human vagina, resulting in long-term protection. Additionally, its adhesiveness can further be enhanced by increasing the polymer concentration (72). To deliver spermicide intravaginally, a 3% alginate gel containing N-9 has been studied (33, 73). However, application of sodium alginate as an effective mucoadhesive is limited because of some aspects such as pH and shear sensitivity (74).

***Starch or starch based derivatives***

Starch is a polymer that occurs naturally, consisting of mixture of amylose, a linear D (1, 4′)-glucan and amylopectin, a branched polymer with more of α-1, 6′ linkages (75). It has various practical applications such as a simple binder (76) or as an excipient in the preparation of various formulations including capsules (77), tablets (78), coatings (79) and subcutaneous implants (80). Starch possesses hydrophilic character due to its structure having hydroxyl functional groups. This property of hydrophilicity can be used to perk up the disintegration rate of some hydrophobic polymers. Starch is not used in its native form, because end products in this case have meager processability and mechanical features (81). So to upgrade its characteristics, it is modified either chemically or physically in such a way that it retains its biodegradability. To prepare a stable gel using starch, it is chemically remodelled through hydroxypropylation resulting in better clarity and cold-storage stability. Hydroxypropylation reaction does not let starch chains to reassociate and augments water holding capacity (82). Biodegradeable polymers based on starch with modified properties possess superior biocompatibility, biodegradability, non-toxicity and better mechanical properties (83). Owing to these properties, starch is broadly employed in tissue engineering and drug delivery either in the form of microspheres or hydrogels (84).

**Synthetic polymers**

***Poly Acrylic Acid***

Polyacrylic acid (PAA) is a water soluble, high molecular weight polymer that has been extensively utilized as a vehicle for vaginal drug delivery (85). Carbopol and polycarbophil, derivatives of PAA with high molecular weight, are the two most commonly utilized mucoadhesive polymers for the formulation of vaginal delivery systems (52). In order to formulate the gels, Carbopol is a most frequently employed gelling polymer on account of various unique features it possess such as anionic character, greater mucoadhesiveness and has also been permitted for human use (86). Chemically, it is synthetic polymer manufactured from PAA by cross linkage. Based upon the developing conditions and the extent of cross linkage, Carbopol provides a portfolio of grades, with each one having its own significance for application in pharmaceutics. Out of these, the most frequently utilized polymer in the pharmaceutical delivery systems is the grade Carbopol 934P NF which is cross connected with allyl sucrose (87). In view of the presence of carboxylic acid groups on the carbomer, its pH in water at a concentration of 1% is 2.5~3.0 (88). On increasing the pH, carboxylic acid moieties neutralize leading to the formation of soluble salt, and on this mechanism, its gelation is based. Being hydrophilic in nature, Carbopol produces clear, homogenous, sparkling gels upon neutralization. In addition, they display the further preferred

standpoint of a hydrating and greasing up activity owing to their greater water content and rheological profile. Replens gel formulated using 1-3 % polycarbophil is a mucoadhesive gel that retains in the vaginal vault for 3-4 days (89). It helps replenish vaginal moisture and rejuvenate dry vaginal cells by increasing the blood flow at the vaginal surface. It forms a kind of moist film at the epithelial surface of vagina, resulting in lubrication of the vaginal wall and hence, reduces vaginal irritation (90). Gel formulations are also essential candidates to act as vehicles for the delivery of microbicides (91). SPL7013 Gel, manufactured by Starpharma, is a vaginal gel formulated using Carbopol 971P, for the delivery of microbicide SPL7013 in order to prevent HIV and HSV infections (92). This gel formulation showed no signs of vaginal/ vulvar/ cervical irritation. Another gel formulated using mucoadhesive polymers namely 1.0–1.5% Carbopol® 974P and hydroxypropylmethylcellulose (HPMC) was found to be an ideal gel base for controlled delivery of microbicides against STDs (93).

Some Carbopol based gels have also been formulated for contraception, particularly those containing spermicides. One such contraceptive gel formulation, Advantage S® developed using polycarbophil and carbomer as gelling agents contain N-9 as spermicidal agent. This is a bioadhesive gel, which delivers the spermicide into the cervix by using a dosing device specially designed for this purpose. It releases the trace effective spermicide slowly and continuously within 24h (94).

***Cellulose Derivatives***

Cellulose is the most plentiful biopolymer that occurs naturally and is the primary constituent of cotton and other higher plants. It comprises elongated chains of anhydro-D-glucopyranose units (AGU), each unit containing three hydroxyl groups, exempting the terminal ends (75). Owing to the presence of intramolecular hydrogen bonding, pure cellulose is water insoluble. To make it water soluble, it is converted to cellulose ethers. These cellulose ethers with different molecular weights are subjected to varying levels of substitution in their cellulose chains (95). These cellulose derivatives can be further modified to prepare a myriad of products with various applications due to the properties such as enhanced capacity to retain water, biocompatibility, safety, affordability, flexibility, pseudoplasticity and absence of taste as well as odour (96). Degree of substitution, the type of substituents, molecular mass and particle size differentiates these derivatives from one another. For intravaginal drug delivery platforms, cellulose ethers that are commonly studied include hydroxy ethylcellulose (HEC), hydroxy propyl cellulose (HPC), HPMC and sodium carboxy methylcellulose (Na-CMC). Sodium CMC is an excellent bioadhesive polymer. Out of all the above mentioned ones, two vaginal contraceptive gels formulated using Na-CMC as bioadhesive polymers containing N-9 as active spermicidal agent are commercially available by the trade name of Conceptrol (Advanced Care Products, Raritan, NJ) and Gynol II (Janssen–Cilag).

Similarly, HPMC, water soluble cellulose ether in virtue of its hydrating action, bioadhesiveness and ability to form thicker gels, can be used for controlled delivery of the active ingredient (97). High swellability, one of its most significant features, is responsible for controlling release kinetics of a drug to be delivered. Drug diffuses into the polymer system on making a contact with biological fluid or water, causing increase in volume along with loosening of polymer chains (98). As a consequence, the drug once incorporated, disseminate out of the polymer gel system. Other worth mentioning properties of HPMC include biodegradability, biocompatibility, non toxicity and little price (99). HEC and HPMC were assessed as mucoadhesive polymers for the formulation of the bioadhesive vaginal gel containing sodium polystyrene sulfonate, a novel contraceptive antimicrobial agent, as an active component. Poly (sodium 4-styrene sulphonate) (T-PSS) gel formulation exhibited effectiveness and safety as a contraceptive in rabbits (100). T-PSS gel formulations tested comprised 5–10% of T-PSS, HEC, propylene glycol, benzoic acid, glycerine, sodium hydroxide and methyl paraben. However, the use of certain cellulose derivatives is restricted due to sensitivity to temperature and pH (101).

Although, various vaginal gels are still available over the counter for contraceptive use, but most of these products contain a surfactant such as N-9 as an active spermicidal agent, which causes lethal effects on vaginal epithelium, making the women more prone to HIV and other microbial infections. Nonetheless, the detrimental consequences of the attempts to develop N-9 as vaginal contraceptive directed the interest to search for alternative

contraceptive means. On this account, microbial factors have flared up as the most reliable replacement to the chemical ingredients. In our laboratory, in pursuit of a newer contraceptive agent, a sperm immobilizing factor (SIF) has been extracted and purified from *Staphylococcus aureus*, isolated from a woman suffering from unexplained infertility (102). SIF having sperm immobilizing property, when administered *in vivo*, indicated complete blockage of conception in mouse model. Therefore, an endeavor was made to create gel formulation containing SIF as an active contraceptive agent using 1% Carbopol 934P. SIF in the proposed gel formulation showed 100% contraceptive effect in female mice when used at amount as low as 10μg, thus confirming the possibility to develop it as a potent vaginal contraceptive for future use (103).

## CONCLUSION

The above facts and the foregoing literature highlight that though a lot of exploration work has been done on the delivery platforms for vaginal contraceptives, a colossal task is yet to be done. The difficulties confronted by the conventional vaginal delivery systems have been addressed by utilizing mucoadhesive polymers for formulating vaginal gels. These gels have been proven to be safe, effective, efficient, acceptable, nontoxic, and easy to be administered via the vaginal route. Their continued use in research for contraception confirms their potential as an intravaginal delivery system. Though various chemical spermicidal agents have been used for quite a long time as a contraceptive agent in most of the commercially available vaginal gels, various drawbacks (vaginal irritation, cytotoxic impact on vaginal epithelial cells, inactivation of normal vaginal flora and increased risk of STDs) associated with them leave a lacuna in the field of contraceptive research. This has provided the impetus for an increased emphasis on the development of safe, highly effective and inexpensive sperm impairing agents as vaginal contraceptives.

**Table 1.** List of some of the commonly used contraceptive formulations

| Formulation (Brand name) | Type | Active ingredient | Company |
|---|---|---|---|
| Advantage-S® | Gel | Nonoxynol-9 | Columbia laboratories, USA |
| NuvaRing | Ring | Ethinyl oestradiol | Merck & Co., Inc, USA |
| Progering | Ring | Progesterone | Silesia laboratories, USA |
| Encare | Suppository | Nonoxynol-9 | Blairex laboratories., Inc, USA |
| Koromex | Suppository | Nonoxynol-9 | Meridian Enterprises Pvt. Ltd, Mumbai, India |
| Today sponge | Sponge | Nonoxynol-9 | Synova, New York, USA |
| Protectaid | Sponge | Benzalkonium chloride, sodium cholate, and N-9 | Pirri Pharma, Canada |
| Pharmatex | Sponge | Benzalkonium chloride | Innotech International, France |
| Neosampoon | Foaming tablet | Menfegol | Eisai Co., Tokyo, Japan |
| Emko | Aerosol foam | Nonoxynol-9 and benzethonium chloride | Emko Co., USA |
| Delfen | Aerosol foam | Polidocanol | Ortho pharmaceuticals, USA |
| Vaginal contraceptive film | Film | Nonoxynol-9 | Apothecus Pharmaceutical, New York, USA |
| Praneem | Cream | An extract purified from the desiccated seeds of *Azadirachta indica*, saponins extracted from the fruit pericarp of *Sapindus* species and quinine hydrochloride | NII, Pune, India |
| Consap | Cream | Saponin fraction extracted from *Sapindus mukorosii* | HLL Lifecare Ltd., India |
| Gynol II® | Gel | Nonoxynol-9 | Janssen-Cilag, UK |
| Conceptrol® | Gel | Nonoxynol-9 | Advanced care products, UK |

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