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Recent Trends in Formulation Strategies for Vaginal Drug Delivery System

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ABSTRACT

The present review gives special particulars about Anatomy, Dosage forms, Polymers used and some Patents of Vaginal Drug Delivery System. The concept of mucoadhesion has gained considerable interest in pharmaceutical technology. The vaginal microbiome is an intricate and dynamic microecosystem that constantly undergoes fluctuations during the female menstrual cycle and the woman's entire life. The vagina is highly vascular; a plexus of arteries and veins is located round the vagina. The venous blood supply from the vagina does not enter the portal system and therefore first-pass metabolism does not occur. The mucus membrane is continually lining the uterus. More recently, the vaginal ring was introduced for hormone replacement and contraceptive therapy. Drug distribution and coverage of vaginal tissue varies considerably with the nature of the delivery system. For vaginal drug delivery purposes, starch as well as its derivatives are investigated mainly as the component of tablets, micro- or nanoparticles, gels, etc. Polyacrylates can also be used to form the basis for semisolid, transdermal, vaginal and rectal drug delivery systems.

INTRODUCTION

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology.[1] Mucoadhesive drug delivery systems are delivery systems that utilize the property of Bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time.[2]

Bioadhesion' widely encompasses adhesive interactions with any biological or biologically derived substance. 'Mucoadhesion' can be used when the bond with a mucosal surface is formed. Mucoadhesion may be defined as a state in which two components, one from the biological source, are joined together for prolonged periods by the aid of interfacial forces. Bioadhesion can be classified into 3 types:

- Adhesion between two different biological phases.
- Adhesion of a biological phase to an artificial substrate.
- Adhesion of an artificial material to a biological substrate.[3]

Mucous membranes (mucosae) are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the upper part of which is made moist usually due to the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine, and bronchi) or multilayered/ stratified (e.g. in the esophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present as either a gel layer sticking to the mucosal surface or as a soluble or suspended lumenal entity. The primary components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter comprising more than 95% of its weight, making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, which provide the mucous with its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies at different mucosal surfaces, from 50 to 450 μm in the stomach, to less than 1 μm in

the oral cavity. The major functions of mucus include protection and lubrication (anti-adherents).

COMPOSITION OF MUCUS LAYER

The mucus is translucent and viscous secretion which forms a thin, continuous gel layer sticking to the mucosal epithelial surface. Mucus glycoproteins are high molecular weight proteins possessing attached oligosaccharide units containing, L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and Sialic acid.

Functions of the mucous layer

- Mucous layer is protective because of its hydrophobicity.
- It influences the bioavailability of drugs as it acts as a barrier in tissue absorption of drugs and other substrates.
- It strongly bonds with the epithelial cell surface as a continuous gel layer.
- It plays a major role in the lubrication of the mucosal membrane and maintenance of its moisture.[4]

DRUG DELIVERY SYSTEMS

- Nasal drug delivery systems
- Buccal drug delivery systems
- Vaginal drug delivery systems
- Ocular drug delivery systems
- Oral drug delivery systems [5]

VAGINA

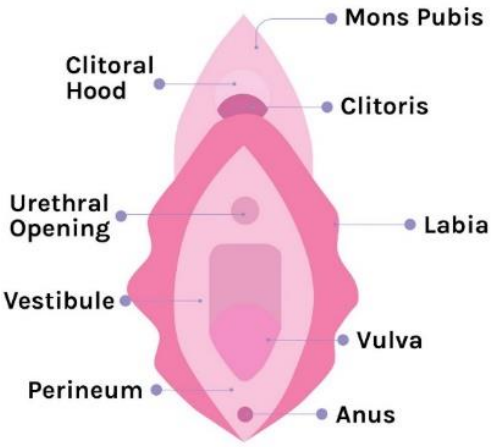

Fig 1: Different anatomical parts of Vagina

The vagina is a female reproductive organ. In the literature, vagina is described as a slightly S- shape fibro-muscular, tubular organ about 6-10 cm extended from the cervix of the uterus to the vestibule. The anterior surface of the vagina is in relation with the fundus of the bladder, and with the urethra and the posterior surface is separated from the rectum.

Histologically vagina consists of an internal mucous lining and a muscular coat separated by a layer of erectile tissue **fig 2**. The mucus membrane is continually lining the uterus **(Table1)** The epithelium covering the mucus membrane is of stratified squamous cells similar to those of buccal mucosa. The vaginal epithelium is comprised of five different cell layers- (i) superficial layer whose thickness varies with age and hormonal activities. (ii) the next is lamina propria or tunica, made of dense connective tissues consisting of collagen and cells such as macrophage, mast cells, lymphocytes, neutrophils, eosinophils etc. It contains a network of nerve fibres, lymphatic drainage system and blood supply.

It is suggested that the drugs can gain entry into the systemic circulation through the blood vessels of lamina propria. The submucous tissue is very loose and contains numerous large veins. The surface of mucosa has a number of folds or also called as rugae which increases the surface area of the vaginal wall (iii) the muscular coat consists of two layers- an external longitudinal, and an internal circular layer. (iv) external to muscular coat is a layer of connective tissue containing large plexus of blood vessels The surface of vagina has many folds (called as rugae). The rugae increases the surface area of the vaginal wall. The vagina is highly vascular; a plexus of arteries and veins is located around the vagina. The venous blood

supply from the vagina does not enter the portal system and therefore first-pass metabolism does not occur. This makes the vagina is an useful site for the systemic administration of the therapeutic agent.

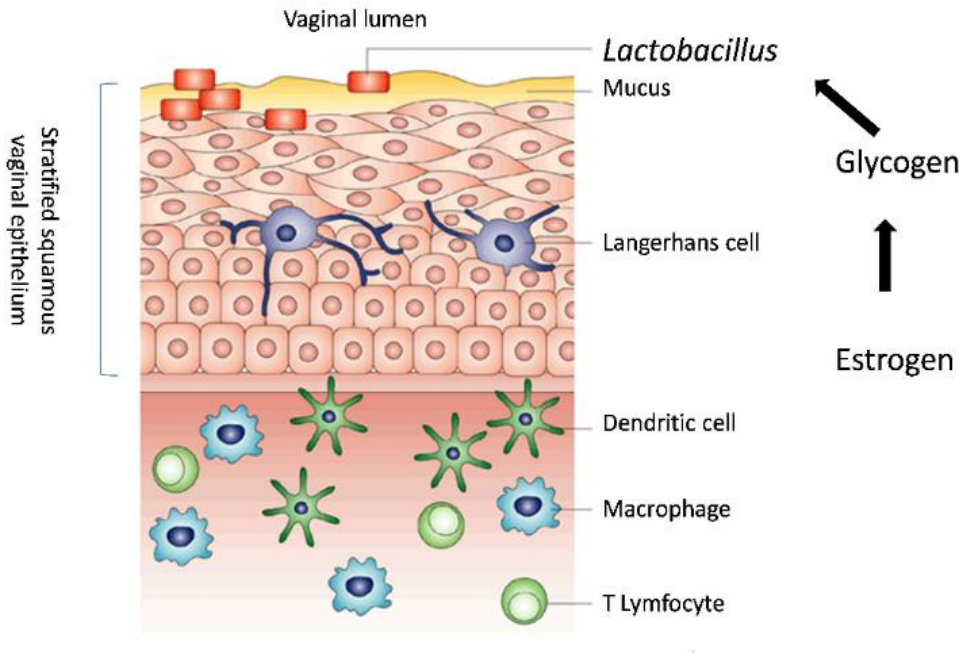

Fig 2: Different Layers of vaginal Mucosa

Table 1: Layers, sublayers and Historical Description of Mucosa

LAYERS	SUB-LAYERS	HISTORICAL DESCRIPTION
Mucosa	Epithelium	Multiple layers thick made up of non-keratinized stratified squamous cells of five different types viz., basal cells; parabasal cells; transitional cells; intermediate largest cells and superficial outermost layer
-	Lamina propria	Consists of loose connective tissues that contain blood vessels and lymphatics.
-	Submucosa	Consists of connective tissue made of collagen fibres, elastic fibres and blood vessels.
Muscularis	-	Consists of muscle fibers arranged in outer longitudinal layer and an inner circular layer.
Adventitia	-	Consists of thin fibrous layer made of collagen fibres, elastic fibres and blood vessels.

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HEALTHY VAGINAL MICROBIOME

The vaginal microbiome is an intricate and dynamic microecosystem that constantly undergoes fluctuations during the female menstrual cycle and the woman's entire life. The vagina houses a complex microbial community that subsists in a symbiotic relationship with the host. Thus, the indigenous environment, microorganisms, and their genomes jointly compose the entire habitat, also known as the vaginal microbiome. In women of reproductive age, physiological changes, such as changes in hormone levels, cause fluctuations in the vaginal microbiome. Marked differences have been reported between non-pregnant and pregnant women in terms of the vaginal microbiome. According to the comparison results, a sharp decline in the diversity and abundance of the vaginal microbiome is observed in pregnant women.

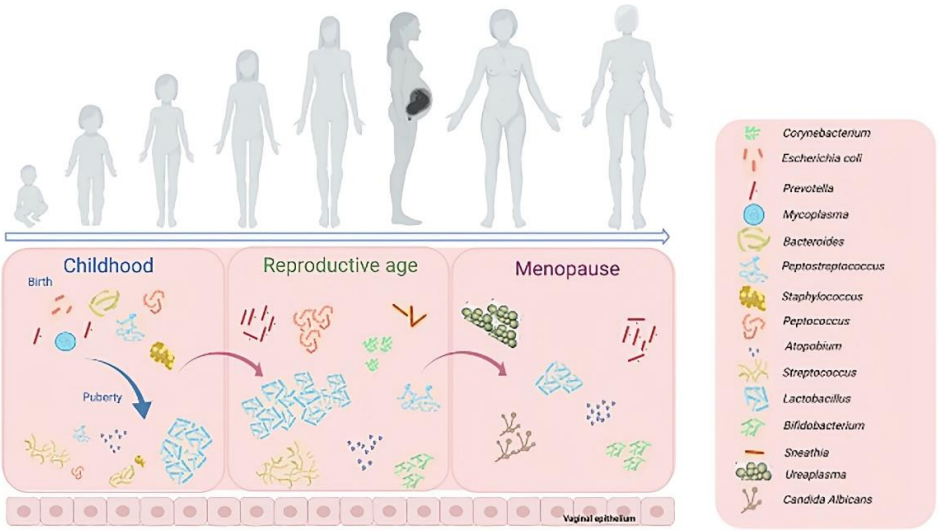

Fig 3: The vaginal microbiome throughout a woman life

Moreover, the predominance of Lactobacillus spp., Actinomycetales, Clostridiales, and Bacteroidales is observed in pregnant women. In non-pregnant women, the predominance of Lactobacillus spp., Actinobacteria, Prevotella, Veillonellaceae, Streptococcus, Proteobacteria, Bifidobacteriaceae, Bacteroides, and Burkholderiales is observed. Thus, the vaginal microbiome would change temporally in a single person. In addition, the vaginal microbiome differs largely among individuals, and the differences are due to variations in sexual activity, douching, chronic stress, regional disparity, race and other factors. The differences in the vaginal microbiome by race of women might be driven by host genetic factors, such as immune system, ligands on the surface of epithelial cell, and the quantity and components of

vaginal discharge. Compared to behavioral and cultural differences, host factors might play a more crucial role in shaping the vaginal microbiome among races.

Lactobacillus species flourish in the vaginal anaerobic environment and produce various antimicrobial compounds, such as lactic acid, hydrogen peroxide (H2O2), and bacteriocins, thereby contributing to a healthy vaginal microbiome and establishing a defense against invading pathogens. Lactobacillus species are the main source of L-lactic acid and D-lactic acid that keep the pH value of the habitat lower than 4.5.[7]

The vagina provides a promising site for local effect as well as systemic drug delivery because of its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs and self-insertion. The currently available vaginal delivery systems, such as creams, foams, gels, irrigations, and tablets, have some limitations, such as leakage, messiness and relatively low residence time owing to the self-cleaning action of the vaginal tract and often require multiple daily doses to ensure the desired therapeutic effect [8]. In recent years vaginal Bioadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for an extended period including day hours and night, thereby enabling lower dosing frequencies. The concept of controlled-release drug delivery has also been successfully applied to the intra-vaginal administration of a systemic prostaglandin derivative for abortion indication. Intra-vaginal controlled release drug delivery system is an effective means of continuing delivery of therapeutically active agents such as contraceptive steroids and prostaglandins.[9]

FACTORS AFFECTING THE VAGINAL ABSORPTION OF DRUGS

Like other mucosal routes of administration, drugs administered via vaginal route are absorbed (i) transcellularly via concentration-dependent diffusion through the cells, (ii) paracellularly mediated by tight junctions and (iii) vesicularly or receptor mediated transport as pointed out by Richardson and Illum. Absorption of drug from vaginal delivery systems occurs in two main steps: drug dissolution in the vaginal lumen and membrane penetration. Any biological or formulation factor that affects drug dissolution and membrane transport could potentially affect the absorption profile from vaginal drug delivery systems. Overall,

vast and multifarious factors and processes are involved in drug absorption from the vaginal route.

Physiological factors

Cyclic changes in the thickness of vaginal epithelium, fluid volume and composition, pH and sexual arousal could potentially affect drug release from intravaginal delivery systems. For example, the vaginal absorption of steroids is affected by the thickness of the vaginal epithelium. Vidarabine has been shown to have a 5–100 times higher permeability coefficient during the early dioestrus stage than during the oestrus stage in guinea pigs. Vaginal absorption of estrogen is higher in postmenopausal women compared to premenopausal women. There have been some conflicting reports as to the change in drug absorption with the increase in vaginal epithelium. Studies have shown that the vaginal absorption of steroids is influenced by the thickness of vaginal epithelium and the epithelial thickness is therefore reduced by long-term estrogen therapy. However, the vaginal progesterone absorption in estrogen-deficient women who were receiving vaginal estrogen therapy was found to be increased, although prior estradiol therapy should have caused an increase in the vaginal epithelium thickness.

This anomalous finding was explained by the fact that the absorption of progesterone was increased with increased vascularity of the vagina. Further cervical mucus of the vagina, which is a glycoprotein gel, could possibly be exploited for bioadhesive drug delivery. However, the presence of cervical mucus could also serve as a permeability barrier to prospective drug candidates The volume, viscosity and pH of vaginal fluid may have either negative or positive impact on vaginal drug absorption. The absorption of a drug that is poorly water-soluble may be increased when the fluid volume is higher. However, the presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from the vaginal cavity and subsequently reduce absorption. Since many drugs are weak electrolytes, the pH may change their degree of ionization and affect the absorption of the drug. In vitro study has showed that release of PGE2 from vaginal preparations may vary depending on the pH of the media. Any change in the vaginal pH may affect the release profiles of pH sensitive drugs from vaginal drug delivery systems.

Physicochemical properties of drugs

Physicochemical properties such as molecular weight, lipophilicity, ionization, surface charge, chemical nature can influence vaginal drug absorption. For example, the vaginal permeability of straight-chain aliphatic alcohols increase in a chain length dependent manner. Similarly, vaginal permeability is A. Hussain, F. Ahsan / Journal of Controlled Release 103 (2005) 301–313 303 much greater to lipophilic steroid such as progesterone and estrone than to hydrophilic steroid such as hydrocortisone and testosterone. However, it is generally accepted that low molecular weight lipophilic drugs are likely to be absorbed more than large molecular weight lipophilic or hydrophilic drugs. A study on vaginal absorption of polyvinyl alcohol suggested that the molecular weight cut-off above which compounds are not absorbed may be higher for the vagina than other mucosal surfaces. Since vaginal fluid contains a large amount of water, any drug intended for vaginal delivery requires a certain degree of solubility in water. Data on the human vaginal permeability to drugs with different physicochemical properties is very limited; much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption.[10]

NOVEL CONCEPTS IN VAGINAL DRUG DELIVERY

Several aesthetic and functional qualities must be incorporated into VDFs. NVDDS need to be designed with desirable distribution, Bioadhesion, retention and release characteristics. Conventional VDFs, such as suppositories, gels, creams and foams can meet some but not all of these requirements. These features can be achieved by the use of bioadhesive and other novel delivery systems.

Bioadhesive delivery systems

Bioadhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate have been developed and studied recently. In a study on postmenopausal women, a bioadhesive formulation, Replens gel (1–3% polycarbophil gel), was shown to be retained in the vaginal cavity for 3–4 days. However, conflicting reports were obtained when the same formulation was studied for retention in the human vagina. There was a lack of significant retention of the gel in five out of the six volunteers studied. Another polycarbophil-based bioadhesive vaginal gel, Crinone®, provided a prolonged release of progesterone in postmenopausal women. An acid buffering gel, Acid form, was found to form a thin bioadhesive layer over the genital tract surface in Phase I clinical

studies. Some bioadhesive formulations have been found to reduce the conventional treatment time of fungal infections by at least 25%. For systemic delivery, insulin suspended in a polyacrylic acid gel base was observed to facilitate the rate of vaginal absorption in alloxan diabetic rats and rabbits.

In addition to semi-solids, polycarbophil-based bioadhesive tablets of metronidazole were tested for adhesion to bovine vaginal tissue. In another study, metronidazole tablets in a modified starch–polyacrylic acid mixture showed an increased potential for curing bacterial vaginosis. A bioadhesive formulation might not necessarily contain a therapeutic agent and can be used as a moisturizer for the treatment of dry vaginas. Several bioadhesive polymers have been reported for different mucosal sites such as the buccal cavity, stomach and intestine. In most of vaginal preparations, either carbopol or polycarbophil has been used as the bioadhesive polymer. The necessary assemblies have been designed to measure the bioadhesion characteristics of polymers and formulations in a simulated vaginal environment, and these have been used to select the appropriate polymers in terms of adhesion in a vaginal environment.

Other novel delivery systems

Phase change polymers such as poloxamers exhibit sol–gel transition in response to body temperature, pH and specific ions, and they prolong the residence time of the dosage form in the vagina. However, these can interfere with sexual intercourse. Formulations based on a thermoplastic graft copolymer have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins in a vaginal environment. non-aqueous solutions of the copolymer in hydrophilic excipients undergo in situ gelation in a short period after application. These in situ gelling liquid formulations can provide: (1) the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and (2) retention owing to the formation of a mucoadhesive gel. Although studied to a limited extent, liposomes also have the potential to provide the controlled release of a drug after vaginal administration.[11]

DOSAGE FORMS

Fig 4: Different Dosage forms of VDDS

Traditionally, vaginal formulations comprised creams, gels, tablets, pessaries, foams, ointments, and douches. More recently, the vaginal ring was introduced for hormone replacement and contraceptive therapy. Drug distribution and coverage of vaginal tissue varies considerably with the nature of the delivery system. Solutions, suspensions, and foam show greater absorption than the tablet form. The choice of vaginal drug administration depends on the intended effect of therapy; i.e., local, topical, or systemic. Drugs intended for local effect should distribute uniformly throughout the vaginal cavity, and a semisolid or fast-dissolving solid system is thus preferable. For a topical effect, a bioadhesive dosage form or intravaginal ring system is more suitable.

Creams and gels

Some contraceptives and antibacterial agents are available in this form. However, these forms are limited by the fact that they can be messy to apply, are uncomfortable, and may leak onto clothes. However, they can be as effective as orally administered medication in the treatment of bacterial vaginosis. Other medications available as a vaginal gel include intravaginal vaccine delivery, drugs for cervical ripening and labor induction, as well as abortifacients.

Suppositories and vaginal tablets

These forms are most commonly used to administer drugs for cervical ripening before childbirth and for local delivery of drugs. Some examples of vaginal suppositories are dehydroepiandrosterone sulfate for cervical ripening, miconazole for vaginal candidiasis, and progesterone for hormonal replacement therapy. Drugs administered as vaginal tablets include itraconazole, clotrimazole, prostaglandins, and estrogens for urogenital atrophy.

Vaginal rings

Vaginal rings are circular drug delivery devices designed to release the drug in a controlled fashion after the ring's insertion into the vagina. These are an alternative route of drug delivery for systemic application. Vaginal rings were developed in 1966, initially as contraceptive devices, after the demonstration that hormones could diffuse through silastic tubes or solid discs at a constant rate. Since then, vaginal rings have been made from flexible polysiloxane and then ethylene vinyl acetate copolymer. Contraceptive rings have been used for years, both to deliver progestogens alone or in combination with estrogen.

Contraceptive rings do not act as a physical barrier to sperm but prevent pregnancy by hormonal mechanisms, either by suppressing ovulation or changing cervical mucus. These rings, unlike the cervical cap or diaphragm, do not need to be fitted or placed over the cervix. The ring is simply inserted into the vagina, in contact with the vaginal epithelium. Contraceptive hormones are absorbed through the vaginal epithelium into the systemic circulation. The best-studied ring is the levonorgestrel ring developed by the World Health Organization. However, as with other progestogen-only methods, progestogen-only vaginal rings do not completely suppress ovulation and have been associated with variable bleeding patterns, which led to the development of combined rings because the estrogen component maintains the endometrium and prevents breakthrough bleeding.[12]

ADVANTAGES OF INTRA-VAGINAL DRUG DELIVERY SYSTEM

1. Prolonged-release
2. Minimal systemic side effects
3. An increase in bioavailability
4. Use of less total drug than an oral dose.
5. First-pass metabolism can be avoided.
6. Self-medication is possible.
7. Contact with digestive fluid is avoided and degradation of drug is minimized.
8. Nausea, vomiting, and emesis induced through oral administration is avoided.

9. Quick onset of action.

DISADVANTAGES

1. Gender specificity

2. Patient in compliance

3. Only a few drugs are administered by this route.[13]

POLYMERS USED IN VAGINAL DRUG DELIVERY SYSTEM

Mucoadhesive polymers are either water-soluble or insoluble, which are swellable networks, connected by cross-linking agents.

Properties of an ideal mucoadhesive polymer

- The polymer and its degradation products should be nontoxic, non-irritant and non-absorbable from the GIT.
- Possess high viscosity, proper degree of cross-linking and proper spatial conformation of polymer is must.
- It should have site specificity and adhere rapidly to most tissues.
- It must not degrade during the shelf life of the dosage form.
- Strong H-bonding groups (-OH, -COOH) should be present in polymer for bonding with mucous membrane.
- Polymer should have strong anionic charges and high molecular weight.
- It should be sufficiently flexible to interpenetrate the mucus membrane or tissue crevices.
- It should have correct surface tension characteristics suitable for moistening of mucus surface.[14]

POLYMERS USED IN VAGINAL DRUG DELIVERY SYSTEMS

Polymers of Natural Origin

1. Polymers from Plant Sources

2. Cellulose and Its Derivatives

Cellulose is regarded as the most abundant organic compound in the world. It is an unbranched polysaccharide, built of 3000–14,000 glucose molecules linked by linear β-1,4-glycosidic bonds. It is the scaffold component of cell walls and tissues in most plants. Pure and unmodified cellulose is insoluble in water and most organic solvents. To obtain solubility and achieve swelling properties, the hydroxyl groups of the main backbone are subjected to esterification or etherification. The semisynthetic cellulose derivatives constitute a large and diverse group of compounds differing in terms of polarity, water solubility, swelling properties, and thus possible pharmaceutical and biomedical applications. The most commonly used cellulose derivatives are microcrystalline cellulose (MCC), methylcellulose (MC), ethylcellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), and sodium carboxymethyl cellulose (Na-CMC).

Pectin

Pectin is usually defined as a diverse and complex group of oligosaccharides and polysaccharides abundantly occurring in plant cell walls. Its main component is the esterified D-galacturonic chain. In the case of natural pectin, the acid groups are esterified with methoxy residues. The free hydroxyl groups can also occur in the acetylated form, and additionally, the galacturonic acid main chain can be substituted with rhamnose groups. The presence of the latter disrupts the chain helix formation. Depending on the source, pectin can also contain other xylose, galactose, or arabinose residues, located in side chains. Pectins are differentiated mainly due to methoxy group content and classified as high methoxy- (>50% esterified) and low methoxy pectins (< 3.5, usually in the presence of an additional substance (e.g., sucrose), decreasing water molecules activity. In vaginal drug delivery studies, pectins are mainly investigated as mucoadhesive components of various formulations. Their pH dependent behavior can also strongly influence the drug release mechanism.

Alginates

Alginates are biocompatible and biodegradable anionic polysaccharides occurring naturally in brown seaweeds (Phaeophyceae). Among the whole group, sodium alginate is the one most commonly used for pharmaceutical and biomedical purposes. Alginic acid is a copolymer containing D-mannuronic and L-guluronic acids organized in blocks separated with sequences of the same units organized randomly. The exact composition of the compound depends on its source of origin. Alginates reveal a high water binding capacity due to their hydrophilic nature. In the presence of divalent and multivalent cations, the alginate solution undergoes an ionotropic gelation process. The properties of the obtained gel depend mostly on the composition of the polymer. Gel strength is higher in the case of compounds with a higher guluronic acid content. Alginates can be applied as thickeners and stabilizers in liquid and semisolid pharmaceutical formulations. They are also investigated as binders and hydrophilic matrix-forming agents in prolonged-release solid dosage forms. Moreover, the ability to undergo ionotropic gelation may be advantageous in terms of in situ gelling system formulations.

Starch

Starch is one of the most abundant plant polysaccharides and the main carbohydrate in the human diet. It consists of two compounds: linear amylose (25%) and branched amylopectin (75%), both composed of multiple α-D-glucose units. In the first one, structural elements are linked with α-1,4 bonds, while in the other one, α-1,4, α-1,3, andα-1,6 bonds are observed. Starch is insoluble in cold water, while at higher temperatures reveals a tendency to swell and form gels. For vaginal drug delivery purposes, starch, as well as its derivatives, are investigated mainly as the component of tablets, micro- or nanoparticles, gels, etc.

Microbial Polymers

Gellan Gum

Gellan is an anionic polysaccharide secreted by Sphingomonas (formerly Pseudomonas) elodea bacteria as a product of the fermentation process. Gellan molecules are linear and consist of repeating tetrasaccharide units containing L-rhamnose, D-glucose, and D glucuronic acid moieties in the molar ratio 1:2:1. In the native form gellan main backbone is substituted with acetyl and L-glyceryl moieties, which can be removed in a hydrolysis

process leading to obtaining the low-acetyl gellan gum. Both forms are commercially available.

The most important feature of gellan gum is its ability to form gels in the presence of monovalent, divalent and trivalent cations, which can form coordinate bonds with carboxylic groups of the polymer and stabilize the three-dimensional structure. The properties of the obtained physical gels depend on the acetylation degree of the polymer. In the case of the low-acetylated form, the rigid and brittle product is obtained, while in the case of high-acetylated gellan soft semisolid gels are observed. The described feature is favorable in terms of in situ gelling systems forming upon contact with physiological fluids containing mentioned cations.

Xanthan Gum

Xanthan gum is a microbial polysaccharide obtained in a fermentation process of the cabbage plant bacterium Xanthomonas campestris. The biopolymer has been produced industrially since 1964, and in the late 1960s, it was granted the approval of the FDA as a food additive. Currently, it is employed in several areas, e.g., the food industry, personal care products and pharmaceutics. It may act as a stabilizer in disperse systems such as emulsions and suspensions, and because of excellent swelling properties and a shear thinning behavior, it may be used as a thickening agent in topical drug dosage forms and cosmetics, as well as a structure-enhancing additive in food products.

The most important structural element of the xanthan molecule is a backbone consisting of glucose moieties connected with β-1,4-glycosidic bonds also observed in cellulose molecules. The cellulose backbone is connected to side chains consisting of two mannose and one glucuronic acid moiety. The side chains are attached to the main structural element through β-1,3-glycosidic bonds, and some of them are terminated with a pyruvic acid residue. Moreover, the hydroxyl group in position 6 of one or both mannose moieties may be esterified with acetic acid. The conformation of xanthan molecules depends on the temperature.

At physiological conditions, they occur in the form of a helix, while at higher temperatures, the transition into a disordered state is observed. The same process can also be induced by dilution.

Synthetic Polymers

Poloxamers

Poloxamers are synthetic block copolymers composed of hydrophobic poly (propylene oxide) (PPO) units with two hydrophilic blocks of poly (ethylene oxide) (PEO). The building blocks of poloxamer reveal different polarities, and the presence of both elements in the molecule makes it amphiphilic. The hydrophilic-lipophilic balance (HLB) value characterizing amphiphilic properties of poloxamer depends on the molar ratio of propylene oxide and ethylene oxide blocks. Their solubility in water increases with the content of more hydrophilic ethylene oxide units and decreases at higher molecular weights. One of the most important properties of poloxamer is its thermosensitivity. It was demonstrated that the increase in temperature resulted in an increase in the viscosity and the transformation from a liquid system into a semisolid one. As the temperature increases polarity of more hydrophobic PPO blocks decreases results in their further dehydration. In these conditions, poloxamer molecules form spherical micelles with a hydrophobic core composed of PPO units and a hydrophilic shell built of PEO chains. With a further increase in temperature, micelles organize into a three-dimensional network, which is related to gelation. This process is fully reversible and takes place at a certain temperature, depending on the polymer concentration, molecular weight and structure.

Polyacrylates

Polyacrylates are a group of cationic and anionic synthetic esters of acrylic and methacrylic acids, with different structures and physicochemical properties. They are available in different forms (powders, granules, organic solutions, aqueous dispersions). Specific polyacrylates differ in terms of their abilities of dissolve and swell. Depending on the structure, they may form coating films with different solubilities at different pH values. Mostly they are used as film-forming and coating components in the preparation of tablets, enteric-coated capsules, and oral dosage forms with a modified release. Polyacrylates can also be used to form the basis for semisolid, transdermal, vaginal, and rectal drug delivery systems. A copolymer of methacrylic acid with methyl ester of this acid (Eudispert®) is especially useful in these kinds of formulations because of its bioadhesive properties.

Polyvinylpyrrolidone

Povidone is a synthetic polymer formed by the linearly arranged 1-vinyl-2-pyrrolidone. The degree of polymerization determines the molecular weight of the compound, which influences the properties of polyvinylpyrrolidone. Higher molecular weight causes an increase in viscosity and a decrease in solubility of this substance. Povidone is a white, hygroscopic powder with no specific odor, and it is easily soluble in water and many organic solvents. After oral application, it is not absorbed from the gastrointestinal tract and, when applied to the skin, does not cause irritation or sensitization. The polymer has been used as a stabilizer and thickener of the suspensions and solutions used orally and topically. It is also used as a solubilizer in oral and parenteral formulations, as a binding agent in the wet granulation process, and as a disintegrant in tablet technology.

Polyethylene Glycol

Polyethylene glycols are also known as macrogols. Depending on the degree of polymerization, they differ in molecular weight and consistency. With molecular weight increase, the increase in the viscosity may be observed, and the physical form can range from liquid to hard wax. All kinds of polyethylene glycols are soluble in water and miscible with each other. They are stable, hydrophilic substances exhibiting no skin irritation. Furthermore, their removal from the skin is very easy, so they are often used as an ointment base and to prepare suppositories. Macrogols have also been applied in ocular and oral formulations, as well as injections.[15]

TABLE 2- SOME OF THE PATENTED CONVENTIONAL VAGINAL DRUG DELIVERY FORMS [16-32]

Formulation	Summary of Invention	Drug Candidate	Patent No.	Inventor/Assignee
Tablet	Vaginal progesterone tablet that delivers progesterone for at least about 48h	Progesterone	US5084277	Greco, J.C., McGinity, J.W.
Suppository	Medicated suppository comprising a medicament, a mixture of triglycerides of fatty acids, a gel forming agent and a gel dispersing agent	Econazole nitrate/miconazole Nitrate/terconazole /clotrimazole	US4698359	Niederer, R.R., Zulliger, H.W.
Suppository	Novel pharmaceutical compositions as suppositories, ointments, vaginal drops and talc powders, and painting solutions	Sulfadimidine, nystatin, Metronidazole	US6432935	Milankovits, M.
Cream	A long-lasting antifungal vaginal cream composition having stable viscosity at human body temperature	Imidazoles	US5514698	Ahmad, N., Brummer, B., Dalal, N.M., Toddywala, R.
Gel	Vaginal pharmaceutical composition containing an antimicrobial imidazole used in treating bacterial vaginosis	Metronidazole	US7456207	Bentley, C.L., Feldtmose, K
Gel	A vaginal treatment composition that employs a therapeutic agent to inhibit and/or treat vaginal infection	Xylitol	US7619008	Yang, S.P., Huang, L., Martin, S.M., Villanueva, J., Sharon, G., Kelly, A., Curtis, S., Robert, B.J
Gel	A vaginal gel of tenofovir or a physiologically functional derivative used in the prevention of HIV infections	Tenofovir	EP1773296	Dahl, T.C.

Ointment	Gamma-linolenic and/or dihomo-gamma-linolenic acid-containing ointment for the treatment of vulvar dystrophy	Gamma-linolenic acid and Dihomo-gamma-linolenic acid	US5380757	Horrobin, D.F.
Sponges	A compressible, smooth surfaced, plastic sponge used for dispensing medicaments and controlling the flow of menstrual blood or seminal fluid	Copper salts	US3762414	Burnhill, M.S.
Sponges	A sponge impregnated with a liquid containing an effective amount of an active pharmaceutical agent	Nonylphenoxypoly - (Ethyleneoxy)-ethanol Benzalkonium chloride, And Povidone-iodine	US5527534	Myhling, J.
Foam	Vaginal foam containing rifaximin, useful in the treatment of vaginal infections	Rifaximin	US5314904	Egidio, M., Gabriele, R.L., Desai, S., Massimo, G.
Patch	Patches used in a variety of pelvic floor reconstruction or stabilization procedures	Bacitracin	US6197036	Tripp, H.A., Rackley, R.
Medicated Tampons	Tampon which carries a medicament into vaginal cavities	Antibiotics/contraceptive	US4318405	Sneider, V.R.
Medicated Tampons	Rod-shaped medical tampon for releasing an active substance including a tampon core of compressed fibres	Triglycerides and partial glycerides	US5201326	Kubicki, J., Rink, R.
Medicated Tampons	Vaginal device for delivery of an anti-migraine/antinausea drug to the uterus or the general circulation through vaginal mucosa	Ergotamine, ketoprofen Domperidone, dexamethasone	US7744916	Pauletti, G.M., Wilson, M., Soderstrom, R., Kishorkumar, D.J., Ritschel, W.A.
Vaginal Rings	The solid pharmaceutical device formed of a nontoxic resilient polymer and medication releasable there from during residence in a living mammal	Medroxyprogesterone acetate.	US3920805	Roseman, R.J.

REFERENCES

1. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. J of adv pharm tech & res. 2010 Oct;1(4):381.
2. Mohite B, Patel R, Kayande N, Thenge R. Vaginal Mucoadhesive Drug Delivery System. J of Pharm Res Int. 2021 Nov 22;33(51A):123-33.
3. Parmar HK, Pandya KK, Pardasani LJ, Panchal VS, Tandel T. A systematic review on mucoadhesive drug delivery system. World J Pharm Res. 2017 Jun 30;6(9):337-66.
4. Khan AB, Mahamana R, Pal E. Review on mucoadhesive drug delivery system: novel approaches in modern era. RGUHS J Pharm Sci. 2014 Oct;4(4):128-41.
5. Schafer-Korting M, editor. Drug delivery. Springer Science & Business Media; 2010 Mar 10.
6. Kale VV, Ubgade A. Vaginal Mucosa–A Promising Site for Drug Therapy. 3(4): 983-1000, 2013
7. Chen X, Lu Y, Chen T, Li R. The female vaginal microbiome in health and bacterial vaginosis. Frontiers in cellular and infection microbiology. 2021 Apr 7; 11:631972.
8. Acarturk F. Mucoadhesive vaginal drug delivery systems. Rec pat on dru deli & form. 2009 Nov 1;3(3):193-205.
9. Krishna SV, Ashok V, Chatterjee A. A review on vaginal drug delivery systems. Int J Biol Pharm Allied Sci. 2012;1(2):152-67.
10. Hussain A, Ahsan F. The vagina is a route for systemic drug delivery. J of cont rele. 2005 Mar 21;103(2):301-13.
11. Vermani K, Garg S. The scope and potential of vaginal drug delivery. Pharm sci & tech tod. 2000 Oct 1;3(10):359-64.
12. Srikrishna S, Cardozo L. The vagina as a route for drug delivery: a review. Int urogy jou. 2013; 24:537-43.
13. Sahoo CK, Nayak PK, Sarangi DK, Sahoo TK. Intra vaginal drug delivery system: an overview. Am. J. Adv. Drug Deliv. 2013; 1:43-55.
14. Parmar HK, Pandya KK, Pardasani LJ, Panchal VS, Tandel T. A systematic review on mucoadhesive drug delivery system. World J Pharm Res. 2017 Jun 30;6(9):337-66.
15. Osmałek T, Froelich A, Jadach B, Tatarek A, Gadziński P, Falana A, Gralińska K, Ekert M, Puri V, Wrotynska- Barczynska J, Michniak-Kohn B. Rec adv in poly vaginal drug delivery syst. Pharm. 2021;13(6):884.
16. Greco, J.C., McGinity, J.W. Vaginal progesterone tablet. US5084277 (1992).
17. Niederer, R.R., Zulliger, H.W. Medicated suppository. US4698359 (1987).
18. Milankovits, M. Pharmaceutical compositions, mainly vaginal suppository, containing many different active ingredients. US6432935 (2002).
19. Ahmad, N., Brummer, B., Dalal, N.M., Toddywala, R. Antifungal vaginal cream composition. US5514698 (1996).
20. Bentley, C.L., Feldtmose, K. Vaginal pharmaceutical compositions and methods for preparing them. US7456207 (2008).
21. Yang, S.P., Huang, L., Martin, S.M., Villanueva, J., Greene, S., Arehart, K., Sayre, C., Johnson, R.B. Xylitol for treatment of vaginal infections. US7619008 (2009).
22. Dahl, T.C. Pharmaceutical vaginal gel comprising tenofovir. EP1773296 (2009).
23. Horrobin, D.F. Method of treating vulvar dystrophy and vaginal dryness. US5380757 (1995).
24. Burnhill, M.S. Vaginal Sponge. US3762414 (1973).
25. Myhling, J. Vaginal sponge delivery system. US5527534 (1996).
26. Egidio M, Gabriele R L, Desai, S, Massimo, G. Pharmaceutical compositions containing Rifaximin for treatment of vaginal infections. US5314904 (1994).
27. Tripp, H.A., Rackley, R. Pelvic floor reconstruction. US6197036 (2001).
28. Sneider, V.R. Tampon and drug delivery device. US4318405 (1982).
29. Kubicki, J., Rink, R. Tampon for medical or hygienic purposes and method of making the same. US5201326 (1993).
30. Pauletti, G.M., Wilson M., Soderstrom R., Kishorkumar D.J., Ritschel, W.A. Coated vaginal device for delivery of anti-migraine and anti-nausea drugs. US7744916 (2010).

31. Roseman, R.J. Pharmaceutical devices and method. US3920805 (1975).
32. Schopflin, G., Laudahn, G., Muhe, B., Hartmann, H., Windt, F. Vaginal ring. US4155991 (1979)