EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 3
106-128
Year: 2022

A REVIEW ON MUCOADHESIVE VAGINAL TABLETS

Amatullah Taskin*

India.

***Corresponding Author: Amatullah Taskin**
India.

Article Received on 06/01/2022 **Article Revised on 27/01/2022** **Article Accepted on 18/02/2022**

ABSTRACT
Conventional drug delivery system (CDDS) is one of the classical methods for the delivery of drug into the body. Despite of benefits and ease associated with these systems, there are certain serious drawbacks such as poor absorption, first pass metabolism, bitter taste, patient compliance, dosing frequency, dose dumping, toxicity, interaction and many more. That is why exploration of other routes for delivery of medication have been an important topic of discussion. Earlier the use of vaginal route was only restricted to the delivery of contraceptives and steroids. Apart from these traditional purposes, this route has been exploited for delivering a wide variety of drugs including antimicrobials, antifungals, contraceptives, anticancer drugs and labor inducing drugs. Among various explored routes, one of the finest, effective and non-invasive routes is Vaginal route. The large surface area, rich vascularization, high permeability of vaginal epithelium, rich blood supply, avoidance of first pass metabolism, access to the lymphatic system and potential for drug delivery throughout the female reproductive tract makes the vagina a desirable route of administration. A wide range of dosage forms have been designed for this route which allows for both immediate and sustained drug delivery with ease of administration. This review highlights the benefits and limitations of intravaginal delivery, factors affecting vaginal absorption and distribution, and the novel approaches for better drug delivery through vagina. The main aim of this review is to mention the importance and effectiveness of mucoadhesive vaginal tablets over other available dosage form and to bring up the growth and expansion in this field to improve the delivery of drugs via this route.

KEYWORDS: Vaginal drug delivery; mucoadhesion; mucoadhesive vaginal tablets; mucoadhesive polymers; novel approaches.

1. Anatomy and Physiology of Vagina

In the pharmaceutical literature, human vagina is usually described as slightly S shaped fibro muscular collapsible tubes between 6 and 10 cm long extending from the cervix of the uterus.[1,2] The lower part is convex, and the wider upper portion is almost horizontal in the upright posture.[3] Histologically, the vaginal wall consists of three layers: the epithelial layer, the muscular coat and the tunica adventina.[4] Each layer has its own specific function. During the menstrual cycle, the thickness of the vaginal epithelial cell layer changes by approximately 200-300 Am.[5] The vagina has an excellent elasticity because of the presence of smooth elastic fibres in the muscular coat. Loose connective of tunica advent further increases the elasticity of this organ. The surface of the vagina is composed of numerous folds, which are often called rugae. The rugae provide dispensability, support and an increased surface area of the vaginal wall. The presence of vaginal folds and micro elevations on the epithelial cell surface permits the vagina to expand and allow the placement of vaginal formulation and also improves the drug absorption.[6]

The network of blood vessels that supply blood to the vagina include a plexus of arteries extending from the internal iliac artery, uterine, middle rectal and internal prudential arteries. In fact, arteries, blood vessels and lymphatic vessels are abundant in the walls of the vagina.[6]

1.1 Drainage system: Drugs absorbed from the vagina does not undergo first pass metabolism because vaginal veins form venous plexus along the sides of the vagina and within its mucosa and communicate with the vesical, uterine and rectal venous plexus and ultimately drain into the internal iliac veins.[7] In addition, vaginal, uterine, vesical and rectosigmoid veins from the middle and upper vagina drain directly into the inferior vena cava. A "first uterine ass effect" has been postulated when hormones are administered vaginally owing to the extensive vascular connections between the vagina and uterus.

The lymphatic drainage of the vagina is interesting in regard to its embryologically different compartments. The lower third of the vagina drains to the inguinal

lymph nodes and the upper two thirds to the pelvic and para-aortic lymph nodes.[8]

1.2 Vaginal secretions: although the vagina does not possess any gland, it secretes a large amount of fluid. transudation from the blood vessels, cervical secretions, desquamated vaginal cells and leucocytes mainly constitute the vaginal fluid.[9] Secretions from the endometrium and fallopian tubes also contribute to the vaginal fluid. The vaginal discharge is a mixture of multiple secretions that collect in the vagina from peritoneal, follicular tubal, uterine, Bartholin's and Skene's glands.[10] Sexual arousal may affect the volume and composition of vaginal fluids and that can alter the drug release pattern from the vaginal delivery system.[11]

1.3 Vaginal pH: Lactobacillus acidophilus produces lactic acid which is present in the vagina and thereby plays an important role by keeping the vaginal pH between 3.8 to 4.2. As both ejaculate and vaginal transudate are alkaline, the increase in vaginal pH was observed during menstruation and sexual intercourse. The pH also changes with age, health conditions, estrogen levels, levels of cervical mucus, infections and many more.[1] The control of vaginal pH is a critical point of consideration in designing successful intravaginal preparation.

2. BENEFITS OF VAGINAL DRUG ADMINISTRATION

- In the vagina, arteries and veins form a dense network which provides a rich blood supply and consequently the vagina is well suited for the rapid and steady uptake of hormones.[12]
- Avoid nausea and vomiting associated with certain drugs, for instance, administration of bromocriptine vaginally in treatment of hyperprolactinemia in women who suffer from nausea and vomiting following oral administration.[12]
- Drugs administered intravaginally do not face the first pass effect, which metabolizes the major part of the medication.[13]
- Irritation to the stomach and small intestine associated with certain drugs can be avoided.[13]
- Targeted delivery of drug can be achieved.
- Rapid drug absorption and quick onset of action is one of the most important benefit of intravaginal route as it helps in accomplishing earlier therapeutic benefit in emergency condition.[7]

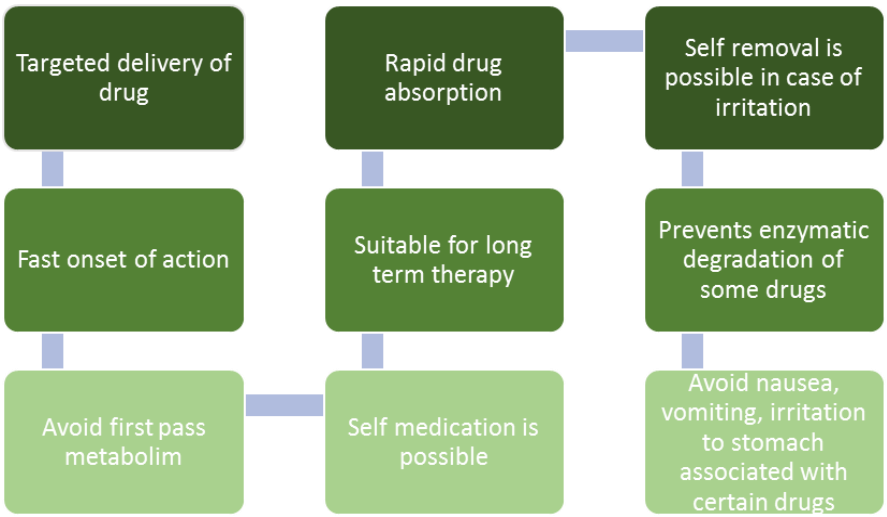

Fig. 1: Advantages of vaginal drug delivery.

- Contact with digestive fluid is avoided, thereby preventing enzymatic degradation of some drugs.
- In case of long-term therapy, this route is more agreeable for the patients as compared to oral/ parenteral medication.[13]
- Self-medication is possible.[7]
- The vaginal bioavailability of smaller drug molecules is good. Some drugs, such as propranolol show greater bioavailability after vaginal administration compared with oral delivery.[7]
- The bioavailability of larger drug molecules can be improved by means of other novel approaches.
- Vaginal drug therapy facilitates the use of prolonged dosing regimens, lower daily doses, continuous and sustained medication release.
- In terms of contraception, vaginal contraceptive ring has the advantage of being nondaily while maintaining constant serum levels over the oral pills.
- Vaginal drug therapy can also allow for selective local administration, leading to little or no systemic changes. for instance, the use of vaginal estrogen therapy in urogenital atrophy.[14]
- Some drugs are known to be more efficacious when administered vaginally, ad compared to other routes. A prime example is administration of misoprostol intravaginally to induce labor.
- Vaginal therapy also avoids the inconvenience that may be caused by pain, tissue damage, and potential for infection by other parenteral routes.

- This form of therapy is amenable self-removal of the drug, which reduces the burden of repeated hospital/ physician appointments.[14]

3. Vaginal Routes of Drug Absorption

Drugs are delivered into the vagina via two routes: intravaginally to the vaginal epithelium or transvaginally through the vaginal mucosa to uterus and systemic circulation.[15] Absorption of drugs through vaginal route occurs in two steps, initially the drugs get dissolve in the lumen and finally the drug enters into systemic circulation by membrane penetration[1]. The vagina has specific blood flow characteristics, either by a portal type circulation or by venous and lymphatic channels, that allow bypassing the gastrointestinal tract absorption and liver detoxification and permit preferential transport of drug molecules from the vagina to the uterus and systemic circulation.[16] Most commonly used drugs in vaginal route are contraceptive steroid hormones. Certain antifungal agents are topically administered to treat urinary tract infections or vaginal yeast infections. This route is known to be effective for the treatment of HIV. Vaginal route has proved to be efficacious for delivery of hormones. By using the novel concepts in vaginal drug delivery, researchers are exploring this route for treatment of many more other conditions successfully.

4. Factors Affecting Vaginal Drug Delivery

4.1. Physiological Factors

4.1.1. Vaginal pH

In case of drugs intended for vaginal administration, at the vaginal pH, the majority of the weak bases are found in the ionized form (more than 50% of the weak bases have a pKa=8.5-10.5). In the case of weak acids, about 40% have a pKa<5.5; this means that they will be found unionized at the vaginal pH.[17] From the above data, we can conclude that weakly acidic drugs show better vaginal absorption than weak bases at a normal pH; however, presumably the absorption profile may change if the pH is modified in certain illness. For instance, the effect of the vaginal pH over the induction of labor with misoprostol and dinoprostone was studied by Chandia et. al.[18] and Kurion et al.[19], respectively. No effect was observed when misoprostol was employed (pKa=14.68) while the pH was a positive factor for the effectiveness of dinoprostone (pKa=4.9).

4.1.2. Thickness of Vaginal Epithelium

Absorption of steroids via vaginal route is affected by the thickness of vaginal epithelium. Vidarabine has been shown to have a 5-100 times higher permeability coefficient during the early disastrous stage than during the estrus stage in guinea pigs. In postmenopausal women, the vaginal absorption of estrogen has been reported to be higher as compared in premenopausal women. 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. These findings were explained by the fact that the vaginal absorption of progesterone was increased with increased vascularity of the vagina.

4.1.3. Vaginal Microbiota

Changes in the vaginal microbiota can influence the entire vaginal microenvironment, thus affecting the absorption, distribution and therapeutic action of drugs in the vaginal cavity. For instance, topical drugs such as tenofovir, a vaginal antiretroviral gel, can be metabolized by certain vaginal species.[20] A recent study in African women concluded that, tenofovir shows higher effectiveness in women with lactobacillus-dominant microbiota and HIV incidence was reduced by 61% whereas in women with predominant Gardnerella vaginalis, the incidence of reduction reached only 18%, a 3-fold difference in efficacy.[21] On the other hand, statins have shown less effectiveness in reducing low density lipoprotein in African women than in European women.[22]

4.1.4. Vaginal Fluid

In healthy women, vaginal fluid is constituted of cervical secretion and transudation from blood vessels, desquamated vaginal cells and leukocytes, it also contains enzymes, proteins, carbohydrates, amino acids and other molecules. The volume and viscosity of the vaginal fluid may also affect the drug release and absorption of the drugs. Although any drug intended for vaginal delivery requires a certain degree of solubility in water, the absorption of a drug that is poorly water soluble may be increased when the fluid volume is higher.[23] Thus, if there is a large volume of vaginal fluid, then low hydro soluble drugs will dissolve effectively, but this increases the feasibility of the drug being expelled due to gravity.

4.1.5. Vaginal Mucus

It acts as a lubricant and protection barrier against pathogens and other harmful substances. Despite its pivotal roles, the viscosity of the mucus can be hurdle in diffusion of the drug from the formulation or drug delivery system; the higher the viscosity, the lower the rate of release. However, too low viscosity may increase the removal of the formulation and decreases the bioavailability of drugs administered via vaginal route. Therefore, it is important to alter the quantity and viscosity of the mucus for the successful intravaginal delivery. This can be achieved by utilizing mucoadhesive polymers or materials with gelling ability.[24]

4.2 Physicochemical Factors

Physicochemical properties of drug such as molecular weight, lipophilicity, ionization, surface charge, chemical nature can influence vaginal drug absorption.[25]

4.2.1. Molecular Weight

It is reported that small molecules show better vaginal absorption and acceptance as compared to large molecules. For example, the vaginal permeability of

straight chain aliphatic alcohols increases in a chain length dependent manner.[25] The nanotechnology for vaginal drug delivery and targeting was developed with the aim of beating the challenges related to molecular size. These nanostructures can maximize the accumulation of therapeutics within the non-healthy cells / tissues or in deep contact with biological membranes before absorption into the bloodstream.

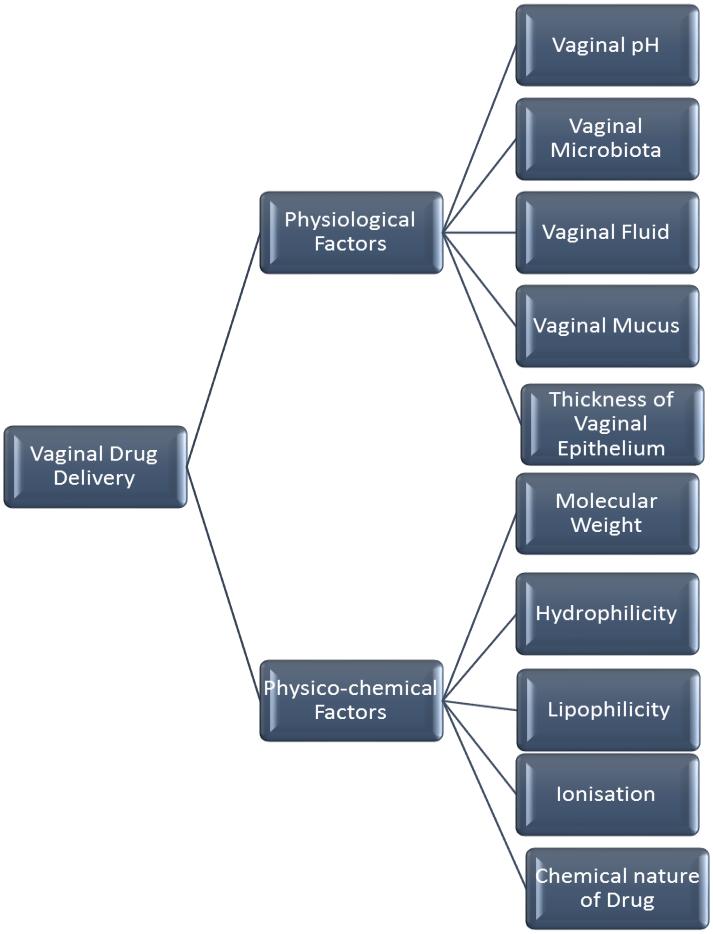

Fig.2: Factors Affecting Vaginal Drug Delivery.

4.2.2. Lipophilicity and Hydrophilicity

Since vaginal fluid contain a large amount of water, any drug intended for vaginal delivery require a certain degree of solubility in water. According to the fact, low molecular weight lipophilic drugs are likely to be absorbed more than large molecular weight lipophilic / hydrophilic drugs. Vaginal permeability is much greater to lipophilic steroid such as progesterone than to hydrophilic steroid such as hydrocortisone and testosterone.[26]

4.2.3. Ionization and Chemical Nature of Drug

Drugs with different nature, ionizes at particular pH, and possess respective pKa's (dissociation constant). The effect of these factors on intravaginal delivery of drugs have been already discussed under the previous section of vaginal pH.

5. Intravaginal Dosage Forms

5.1. Vaginal Rings

Vaginal rings are circular ring type drug delivery devices designed to release the drug in a controlled fashion after insertion into the vagina. They are approximately 5.5cm diameter with a circular cross section diameter of 4-9 mm. these are flexible with improved optical properties, greater adhesion, increased impact and puncture resistance. in simple vaginal rings, drug is homogenously dispersed within a polymeric ring. Drug at the surface of the ring is released faster than drug in the inner layer of the ring. To obtain a constant release of drug from vaginal ring, sandwich or reservoir type rings has been developed.[27,28]

Fig.3: Vaginal Ring.

5.2. Vaginal Capsules

It is prepared by filling the medicated powder into capsules. These are inserted into the vagina just like a pessary.

Fig. 4 Vaginal Capsules.

5.3. Vaginal Powder

It is prepared by dissolving hydroxypropyl cellulose in water with heat. The mixture is slightly cooled and the bisphosphonate is added. The mixture is then lyophilized.[29]

5.4. Vaginal Ointment

Vaginal ointment according to the invention comprises an oil and an aqueous phase. For preparation of the ointment, suitable drug is selected and dissolved in the aqueous phase and finally the oil phase is added. Both phases are mixed properly.[30]

5.5. Vaginal Creams, Gels and Foams

Creams, gels and foams are intended for quick distribution of contraceptives and antibacterial agents.[31] Vaginal creams and gels are formulated on the principle of liquid emulsion or hydrogel-based drug delivery system. When these hydrogels are placed in aqueous environment they swell and retain large amount of water in their enlarged structure and finally release the drug in controlled fashion.[32] They are acceptable, feasible, effective as orally administered drug, easy to use, non-toxic and non-irritating to mucus membrane. Despite of having many advantages, these are uncomfortable, messy to apply, not provide exact dose and sometime embarrassing when hey leak into the undergarments.[31]

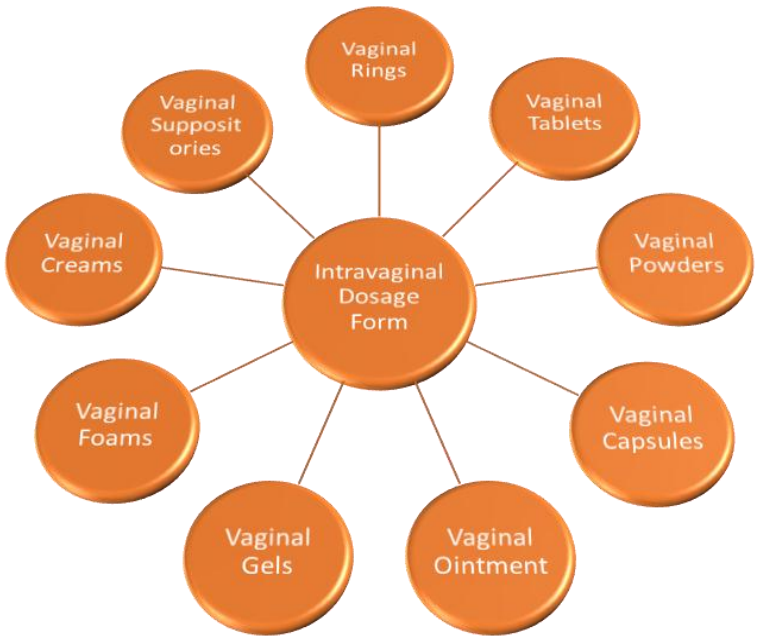

Fig.5: Intravaginal Dosage Forms.

5.6. Vaginal Suppositories

These are also called pessaries, weigh about 3 to 5 g and usually are molded in the globular or oviform shape or compressed on a tablet press into modified conical shapes. These are designed to melt in the vaginal cavity and release the drug for several hours. Vaginal suppositories are usually used for topical therapy or for introducing drugs with systemic effects.[33]

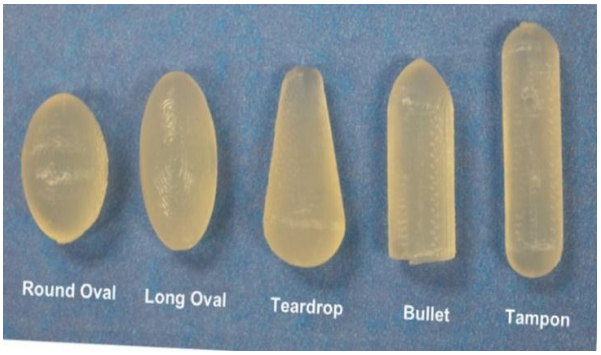

Fig.6: Vaginal Suppositories.

5.7. Vaginal Tablets

Vaginal tablets refer to tablets that are uncoated bullet shaped, ovoid, or pear shaped, designed to be kept into the vagina. These are usually manufactured by direct compression technique. They can often dispense faster therapeutic action and more targeted delivery of concerned drug to the actual site of action making it more effective for vaginal use than oral medication. The vaginal tablets can be inserted into the vagina via suitable applicator, where they dissolve, melt (as they reach body temperature), disintegrates, release the drug and get directly absorbed into the tissue or bloodstream via vaginal mucosa. These are mainly used for local anti-inflammatory, sterilizing effects and contraception purposes. Besides these, the vaginal tablets are now frequently used for delivering sex hormones, anti-infectives and anti-fungal drugs.

They can be categorized as

- Ordinary vaginal tablets
- Effervescent vaginal tablets
- Vaginal sustained release tablets
- Double layer vaginal tablets
- Bioadhesive/mucoadhesive vaginal tablets

A list of marketed vaginal tablets, their active agent, and their uses are listed below.

Fig. 7: Marketed Vaginal Tablets.

Brand Name	Therapeutically Active Agent	Manufactured/ Marketed by	Treatment/Use
Aabab	Quesrcus Infectuous & Argilla vitriolutum	Ayurved Research Foundation	Vaginal Tightening
Betadine Vaginal pessaries	Povidone – Iodine vaginal pessaries	Marketed by – Win Medicare	Fungicidal, Bactericidal, Trichomonocidal
Candid V3	Clotrimazole	Glenmark Pharmaceutical Ltd.	Treatment of vaginal candidiasis caused by candida albicans
Clocip	Clotrimazole 100 mg	Cipla	Anti-fungal, Anti-trichomonal
Candid V	Clotrimazole 100 mg	Glenmark Pharmaceutical Ltd.	Anti-fungal
Candifem	Miconazole, Ordinazole	Meyer Organics Pvt. Ltd.	Treatment of Ringworm, Athelete's foot, jock itch & other fungal infections
Candistat	Clotrimazole B.P. 100 mg	Elys Chemical Industries Ltd.	Antimycotic with fungicidal action
Candid V6 ER	Clotrimazole	Glenmark	Antifungal
Canesten V1	Clotrimazole 500 mg	Piramal Pharma Ltd.	Treatment of vaginal candidiasis
Canazole V	Clorimazole 100 mg	Lupin Ltd.	Treatment of Ringworm Athelete's foot, jock itch& other skin infections such as burning, itching & cracking of skin.
Colposeptine	Chlorquinaldol, promutriene 200 mg + 10 mg	Mecechem	Bactericidal & treatment of abnormal vaginal discharge
Clotry 500	Clotrimazole 500 (USP)	Healthy Life Pharma Pvt. Ltd.	Antifungal
Cloginal	Metronidazole, Clotrimazole, Lactic acid bacillus	SG Pharma	Antibacterial
Dazolac-V	Tinidazole, Clotrimazole & Lactic acid Bacillus V.T.	Peenak	Antifungal
Donystatin, Nystatin	Donystatin, Nystatin	Dony-triumph	Antifungal
EvaNew	Lactobacillus Salivarius (50%), Lactobacillus Brevis (30%)	Zuventus Healthcare Pvt. Ltd.	
Enfometrin	Progesterone	New Era Pharmacy	Treatment of Assisted Reproductive Technology (ART) Program
Feprox CTP	Clotrimazole, Tinidazole, Povidone Iodine vaginal tablets	Solitaire Pharmacia Pvt. Ltd.	Antifungal, Antibacterial, anti trichomonal
Fluomizin	Dequalinium chloride	Rottendorf Pharma for Medinova	Treatment of bacterial vaginosis
Ginlac V	Clotrimazole 200 mg + Lactobacillus 150 million spores + tinidazole 500 mg	Rapross Pharmaceuticals Pvt. Ltd.	Antifungal

Gogunax	Clotrimazole 100mg	Shalima Healthcare	Antifungal
Gynoflor	Estriol (estrogen), Lactobacillus acidophilus (probiotic)	EP Plus for Medinova	Treatment of vaginal atrophy, for restoration of vaginal flora
Gynocid	Clotrimazole	Southshourne Corporation India	Antifungal
Gynostat	Clotrimazole	SG Pharma	Antifungal
Gyno tiocosid	Ticonazole 100 mg	Neimeth	Treatment of vaginal yeast infection
Krema Rosa	Clotrimazole 100 mg	Epico	Antifungal
Myprox CTP	Clotrimazole, Tinidazole, Povidone Iodine vaginal tablets	Radix Solitaire Pharmacia	Anti-fungal, prevents fungal growth on the skin
Megmazole V	Clotrimazole 250 mg + Tinidazole 500 mg	Megma Healthcare Pvt. Ltd.	Antifungal
Mycoten	Clotrimazole	Padek Health Care Pharmacy	Antifungal
Mycoten Plus	Clotrimazole 200 mg + Clyndamycin 100 mg	OneHealth NG	Treats vaginal yeast infection.
Nistan	Nystatin Vaginal Tablets USP 1,00,000 I.U.	UniMed India	Antifungal
NYST V	Nystatin Vaginal Tablets USP	Lexine Technochem Pvt. Ltd.	Antifungal
Nystene vaginal tablets	Nystatin 1,00,000 units	Prawil Laboratories Ltd.	Antifungal
Pilzole V6	Clotrimazole, Tinidazole, Povidone Iodine	Psychotropics India Ltd.	Antifungal, Antibacterial, anti trichomonal
Prostin E2	Dinoprostone	Pfizer Pakistan	Induction of labour
Trigyno	Metonidazole, Neomycin sulphate, Clotrimazole V.T.	SG Pharma	Treatment of Bacterial vaginitis.
Triginal V.T.	Tinidazole 500 mg, Miconazole 100 mg, Neomycin 20 mg	Vitapure Corporation	Provide local treatment of the mixed gynecological infections due to the bacterial, mycosis & protozoal cause
Vagifem	Estradiol		Relieves vaginal irritation & dryness.
Vagirux	Estradiol hemihydrate 10 mcg	Gedeon Ritcher Ltd.	Treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women
Yuvafem	Estradiol	Amneal	Help to reduce vaginal symptoms of menopause (such as vaginal dryness, burning, itching, etc)

6. NOVEL APPROACHES

6.1. Thermosensitive Dosage Forms

Thermosensitive gels refer to stimuli responsive systems, which thickens upon certain physiological conditions. These systems remain liquid at room temperature and transform into liquid when inserted into vagina. These formulations include thermosensitive polymers such as poloxamer. A disadvantage regarding poloxamer based system in vaginal drug delivery system is their poor mucoadhesive strength, for this, additional bioadhesive excipients are need to be added. It is to be noted that gelation temperature and characteristics of gel depends on formulation of the system.[34]

Advantages

- Easy vaginal administration
- Suitable contact with folds and crevices of the vaginal mucus membrane
- Improves retention time at the site of administration
- Prolonged release of active ingredient[34]

Liu et. al.[35] showed the effect of carrageenan addition to poloxamer system in sustained release formulation (vaginal gel) for the delivery of acyclovir (antiviral drug used in the therapy of genital herpes). Rheological studies disclosed that the incorporation of carrageenan does not change the gelation temperature. In vitro data revealed that the process was slower in the presence of carrageenan. The prepared formulation has higher residence time as compared to the plain poloxamer based gel. Rossi et. al.[36] investigated that addition of chitosan lactate to poloxamer 407 in the system loaded with amoxicillin trihydrate increases the gelation temperature of poloxamer. Gelation time of mixture was increased after dilution with vaginal fluid. Deshkarand Palve[37] briefly studied poloxamer based (Poloxamer 407 and Poloxamer 188) in situ forming thermosensitive gel incorporated with cyclodextrin complex. The active ingredient used was variconazole, an antifungal drug having low solubility in water. It was revealed that the inclusion of poloxamer 188 increases the gelation

temperature, whereas addition of mucoadhesive agents decreases the same. Rencber et. al.[38] preformed a study focused on the system composed of poloxamer 407, poloxamer 188 forming a vaginal gel loaded with clotrimazole, an antifungal agent used in the treatment of vaginal candidiasis. The gel remained for 24 hours at the site of administration.

6.2. Pellets

Pellets are a kind of granules, of size range 300-1000 microns. It can be anticipated, that due to their small size they can retain in vaginal mucosa for more period of time as compared to vaginal tablets after vaginal application. Santosh et. al.[39] studied the carrier nature of starch-based pellets and lyophilized lactose-based pellets, with probiotic bacteria. After vaginal application of gelatin capsules filled with these pellets, it was concluded that fast disintegrating starch pellets and lyophilized lactose pellets are suitable carriers for probiotics intended for vaginal delivery. Poelvoorde et. al.[40] investigated the characteristics of disintegrating microcrystalline cellulose. The researchers concluded that slowly disintegrating capsules would restrict the drug release. As a result of faster disintegration of starch-based pellets, the formulation would easily spreadable over vaginal mucosa. Hiorth et. al.[41] prepared bioadhesive pellets containing hexyl ester 5 aminolevulinic acid, with a faster release following vaginal administration. Pellets were manufactured by extrusion/ spheronization technique, Carbopol 934 was incorporated to achieve bioadhesion that helps to retain the formulation in vaginal tract for prolonged period of time. It was found that 8% of Carbopol exhibited good mucoadhesion. The pellets were mechanically stable and release drug within 20 minutes in phosphate buffer at pH=4.0 and 6.8 in the in vitro dissolution test.

6.3. Microspheres

For 20 years, microspheres were examined as a carrier for drugs for vaginal administration. Rochina et. al.[42] produced microspheres made up of hyaluronic acid esters containing salmon calcitonin. The microsphere preparation process (solvent extraction method) has no effect on biological action of calcitonin. Pliszczak et. al.[43] developed a novel vaginal bioadhesive microspheres based on pectinate hyaluronic acid for delivery of probiotics and prebiotics. It was shown that the effect of Lactobacillus species could enhance upon encapsulation. The diameter of microparticles were 137 µm. it was found that the microsphere released the drug (probiotics strain) after 16 hours in vaginal fluid. The microparticles based on calcium chloride as cross-linking agent was prepared by Maestrelli et. al.[44] using ionic gelation technique for vaginal delivery of cefixime to overcome the drawbacks associated with its oral administration. With the increase in the amount of drug entrapped, the swelling behavior of microspheres enhances. The correlation between microsphere water uptake and the release rate of drug showed that the microspheres formulated with 30 mg/ml cefixime was the best formulation. Zhang et. al.[45] studied the spray dried mucoadhesive and pH sensitive microspheres based on poly-methacrylate salt for the delivery of tenofovir, an agent used in the treatment of HIV. It has been concluded that microspheres manufactured using Eudragit L-100 and S-100 (sodium or potassium salt of methacrylate polymers) releases the drug over 90% within 1 hour and readily respond to pH change. The further study revealed the non-cytotoxic and non-immunogenic nature of microspheres in respect to vaginal/endocervical epithelial cells. The vaginal tablets in the form of microspheres were formulated by Gupta et. al.[46] using methacrylic acid copolymers containing clotrimazole. Hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (sod. CMC) and Carbopol 934 were used as additives to impart mucoadhesive properties to obtain prolonged therapeutic effect. Eudragit RS100 and Eudragit RL100 were used. The study revealed the controlled drug release from the above formulation.

6.4. Nanoparticles

In recent years, polymeric nanoparticles (NPs) have been broadly studied as the drug carrier for vaginal administration for local and systemic effect.[47] The main objective behind use of nanoparticles in vaginal drug delivery system is the fast onset of action, targeted and efficient delivery of drug (mainly antibiotics and antifungals) and treatment of sexually transmitted diseases.[48-51] They can be formulated using natural and synthetic polymers. They can entrap active pharmaceutical agent (API) and provide controlled, prolonged and targeted delivery. There are some problems associated with NPs such as poor oil/water solubility, degradation of API, toxicity or unpleasant organoleptic properties.[52-55]

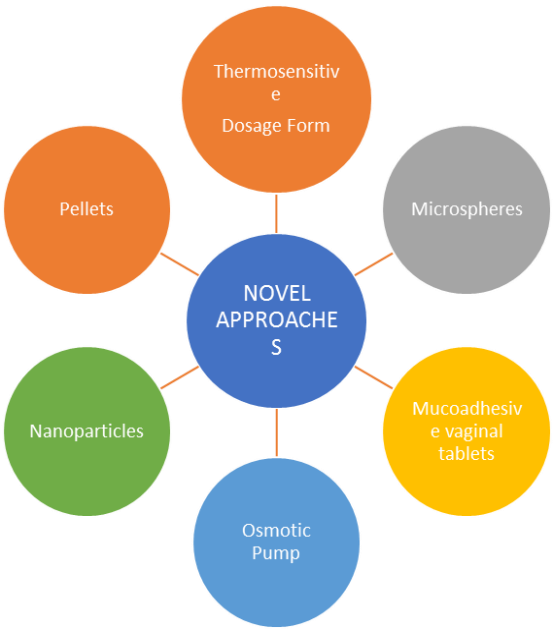

Fig.8: Novel Approaches in Vaginal Drug Delivery System.

6.5. Osmotic Pump

According to Rastogi et. al.[56] the osmotic pump tablets (OPTs) can be formulated for vaginal drug delivery. The team prepared vaginal tablets of an antiretroviral drug IQP-0582 coated with a mucoadhesive polymer (cellulose acetate/cellulose acetate phthalate) with a proper mechanism for water intake and drug release via an orifice. It was found that these tablets can release drug for 2-5 days in the vagina. In these type of dosage forms, the release of drug also depends on pH. It is found that OTPs could improve the effectiveness and adherence of drug in vaginal canal for desired period of time.

6.6. Mucoadhesive Vaginal Drug Delivery System

In recent years mucoadhesive vaginal dosage form holds an important place in the field of pharmaceutical research.[57] Mucoadhesion occurs when the formulation components gels adhere on mucus, or specifically vaginal mucosa in case of vaginal dosage form. The prime element of mucus are mucins, whose subunits are connected with disulphide bridges. Basically, mucus are water soluble glycoproteins that are responsible for formation of 3-D gel structures. Let us discuss in brief about mucoadhesive vaginal drug delivery and the novel approaches regarding the same.[58,59]

7. Mucoadhesive Vaginal Drug Delivery System

The traditional commercial preparations, such as creams, foams, gels, rings, ointments, suppositories and tablets are known to reside in the vaginal cavity for a relatively short period of time owing to the self-cleaning action of the vaginal tract, and often require multiple daily doses to ensure the desired therapeutic effect [60]. Many different approaches have been tested to develop novel vaginal drug delivery systems that can meet both the clinical and the patients' requirements. One interesting group of auxiliary agents is the mucoadhesive polymers, which are the basis of newly designed systems.[61] Bioadhesion may be defined as the state in which two materials, at least one of which is biologic in nature, are held together for extended periods of time by interfacial forces. If this attachment is due to a mucus coating, the phenomenon is sometimes referred to as mucoadhesion.[62-64] Mucoadhesion is the interaction between a synthetic or natural polymer and a mucin surface, leading to a net attraction.[65] It increases the intimacy and duration of contact between a drug containing polymer and a mucous surface results in prolonged residence time of the drug at the specific site and extended therapeutic effect.

The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems. To prolong the residence time in the vaginal cavity, mucoadhesive drug delivery systems have been developed in the form of semi-solid and solid dosage forms. The main advantages of the bioadhesive systems over the existing solid and semi-solid preparations are as follows.[62]

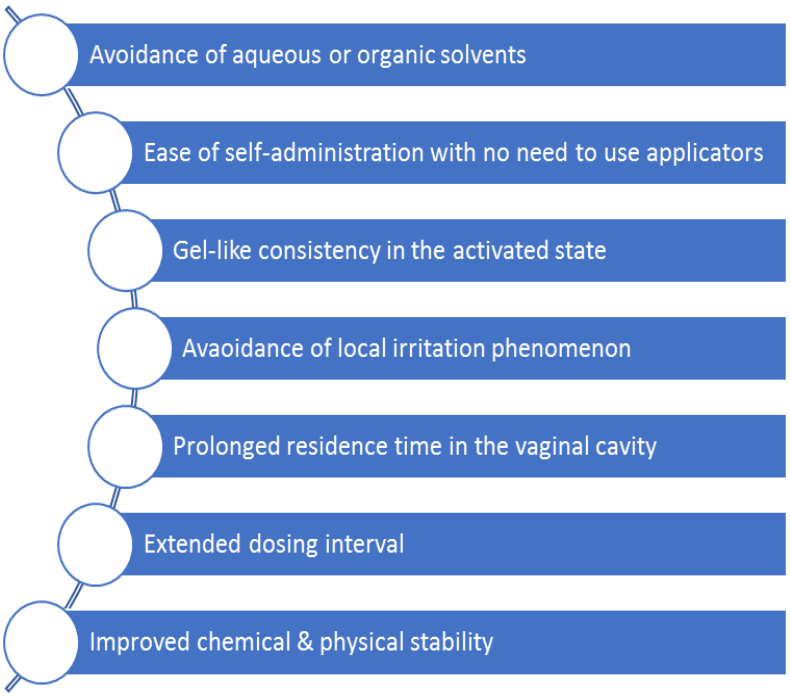

Fig. 9: Benefits of vaginal MDDS.

Mucoadhesive formulation contains one or more hydrophilic polymers along with drug. Mucoadhesion is usually obtained by using both synthetic and natural bioadhesive polymers. The polymers used for the development of Mucoadhesive systems and their significances will be discussed later. Mucoadhesive vaginal drug delivery systems can be categorized as follows:

1) Mucoadhesive gels
2) Mucoadhesive tablets

3) Mucoadhesive films
4) Emulsion type mucoadhesive systems[66]

Among these formulations, mucoadhesive vaginal tablets are considered as the most convenient delivery system as others are messy to apply, uncomfortable and sometimes desirable distribution of drug remain a point of concern. This review reflects the advantages, working and development in mucoadhesive vaginal tablets.

8. Mucoadhesive Vaginal Tablets

Mucoadhesive vaginal tablets are one of the solid dosage forms which adheres to the vaginal mucus resulting in release of drug in a controlled fashion when administered via vagina. Mucoadhesive tablets increases the intimacy and duration of contact between a drug containing polymer and a mucous surface at the site of application to achieve improved and maximum therapeutic effect for long period of time. Mucoadhesive vaginal tablets offers localization of drug at specific site as well as systemic control of drug release.

8.1. Advantages

- A prolonged residence time at the site of action or absorption
- Localization of the drug delivery system at a given target site
- Increase in the drug concentration gradient due to the intestinal contact of the particles with the mucosal surface
- Direct contact with the intestinal cells, which is the step earlier to particle absorption[7]
- improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels
- Easy and convenient to use as compared to other vaginal dosage forms.
- They are stable
- Less messy to handle than creams, ointments and foams
- The tablets omit the problem of leaking or slipping out of solution or semisolid formulation and expulsion of suppositories after insertion.

8.2. Factors Affecting Mucoadhesion

There are three major factors that affect mucoadhesion in a broader sense, which include environmental factor, physiological factor and polymeric factor. Physiological factors affecting mucoadhesion between MDDS and vaginal mucus have been discussed earlier. Here, we have concentrated on the polymeric factors because polymer is the most important component of a mucoadhesive drug delivery system.[67]

8.2.1. Molecular Weight

The mucoadhesive power of a polymer increases with molecular weight above 1,00,000.[68] Beyond this range, there is no further increase in mucoadhesive strength of concerned polymer. It is shown that the interpenetration of polymer molecules is best in case of low molecular weight polymers whereas the entanglements are favoured at higher molecular weights.[69]

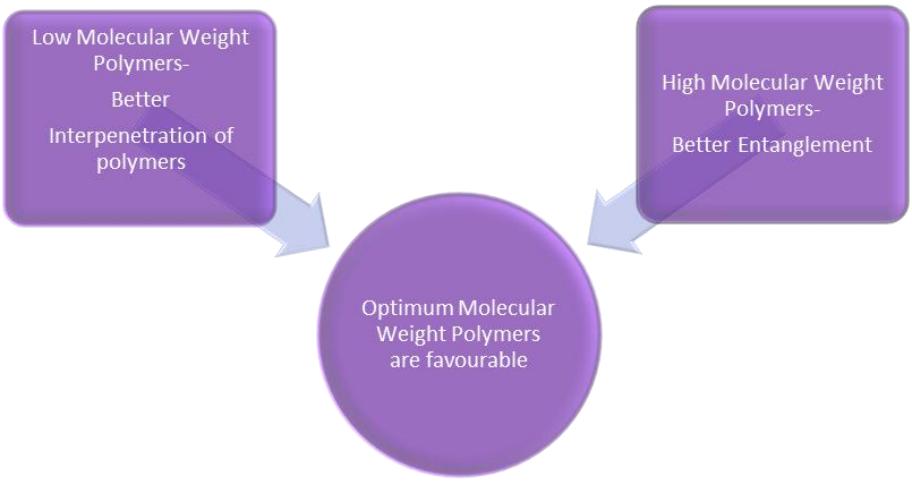

Fig.10 Effect of Molecular Weight of Polymers on Adhesion.

8.2.2. Flexibility

As mucoadhesion commences when the polymeric chains diffuse into interfacial region. Therefore, in order to get the sought entanglement of polymer with the mucus, the polymer must possess substantial degree of flexibility.[70] The higher be the flexibility of polymer, the greater it diffuses into the mucus network. Usually, the flexibility and mobility of polymers are associated to their diffusion coefficients and viscosities.[71]

8.2.3. Cross Linking

The average pore size, average molecular weight of cross-linked polymers and the degree of cross linking are three important and inter-connected structural variables of a polymer framework. The greater degree of cross

linking, lowers the rate of diffusion of water into the polymer network cause inadequate swelling of the polymer, which in turn decreases rate of interpenetration between polymer and mucin.[71] On the other hand, the lower the cross linking of polymers, the greater the flexibility, the larger the surface area of the polymer, the substantial the mucoadhesion. The mucoadhesive strength of cross-linked polymers can be increased by incorporation of adhesion enhancers in the formulation such as free polymer chains and polymers attached on the preformed network.[72] To attain a higher degree of swelling, polymers whose cross-linking density is low if favoured.[73] Cross linking is inversely proportional to degree of swelling[74]

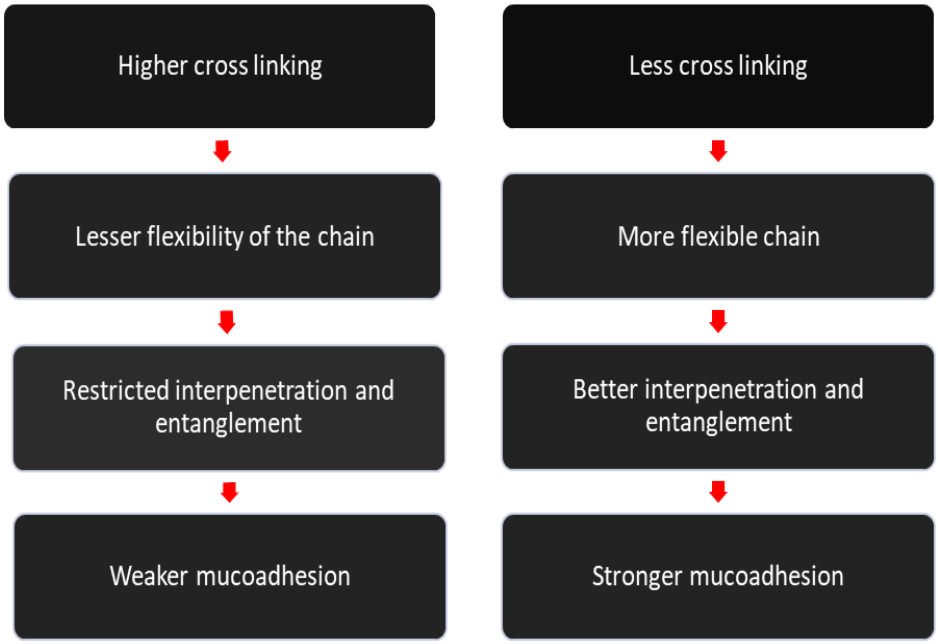

Fig.11: Effect on Cross-linking on Adhesion.

8.2.4. Hydrogen Bonding Capacity and Hydrophilicity

The concerned polymers must have such functional groups that are capable of forming hydrogen bonds to improve the hydrogen bonding potential.[71] Polymers such as poly (vinyl alcohol), hydroxylated methacrylate and poly (methacrylic acid) as well as all their copolymers, have good hydrogen bonding capacity.[75] Functional groups such as carboxyl and hydroxyl allow hydrogen bonding between the polymer and mucous membrane. More hydrophilic functional groups enable the formation of more hydrogen bonding. The degree of hydration of a polymer depends on its molecular structure. Hydration is important for polymer to swell on mucus layer, creating a maximal exposure for interpenetration between polymer and mucin as well as providing entanglement between them. However, excess hydration may reduce mucoadhesion and slippery mucilage will form instead.[64]

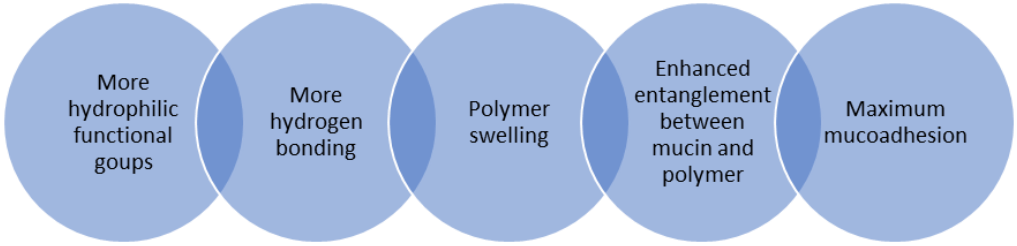

Fig. 12: Effect of Hydrophilicity on Adhesion.

8.2.5. Hydration/Swelling

Hydration or swelling is essential for expansion of mucoadhesive polymers in order to produces an appropriate macromolecular mass o desired/adequate size. Polymer swelling allows for mechanical entanglement by exposing the desired bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and mucus framework.[71] To attain a higher degree of swelling, polymers whose cross-linking density is low is considered to be favourable.[73] The optimum swelling and mucoadhesion results in critical degree of hydration of the mucoadhesive polymer.[75]

8.2.6. Spatial Conformation

It plays an important role in defining mucoadhesion. Certain polymers with high molecular weight possess less mucoadhesive strength as compared to polymers with low molecular weight due to their spatial arrangements of bonds (spatial configuration). One such example is dextran (high molecular weight of 19,500,000), they own mucoadhesive strength similar to that of PEG (molecular weight pf 2,00,000). The reason behind this is the helical confirmation of dextran that shields the active bioadhesive sites fundamentally responsible for mucoadhesion, unlike PEG polymers, which possess linear confirmation.[76]

8.2.7. Concentration of Active Polymer

Ahuja[77] has stated that there is an optimum concentration of polymer at which it shows maximum mucoadhesion at very low concentration, only little amount of polymer chains penetrates in mucus resulting in unstable interaction between mucus and polymer. There is a critical concentration for each polymer, above which the polymer creates an undisturbed state due to its coiled structure. Therefore, in highly concentrated system, polymers do not show enhancement in mucoadhesion, in spite of it, in some cases the mucoadhesive properties actually retards above critical concentration.[78] Although in general, for solid dosage forms such as tablets, the penetration in mucus and adhesion increases with increase in polymer concentration.[79]

8.2.8. Environmental Factor

Environmental factor such as pH at the mucoadhesion site affects ionizable functional group of ionic polymers that are used as an adhesive layer in the formulation such as a carboxylic group for anionic polymers. Ionic polymer provides a higher degree of mucoadhesion by interaction of the ionizable functional group with charged component of mucin layer thus promoting a strong adhesiveness. Polymer will be largely ionized if the pH at the mucoadhesion site is above the pKa value of the polymer whereas it will be largely unionized if pH at mucoadhesion site is below pKa.

Fig. 13: Effect of pH on Mucoadhesion.

8.2.9. Polymeric Factors

Apart from environmental and physiological factors, major responsible factor from the formulation point of view is the polymeric nature that present in the formulation. Polymeric factors that may affect mucoadhesion include hydrogen bonding capacity and hydrophilicity, molecular weight, cross-linking, spatial conformation and concentration of polymer.

8.3. Preparation and Working

The manufacturing process of vaginal bioadhesive controlled release matrix tablets consists of the preparation of a matrix mixture comprising the pharmaceutically acceptable excipients. The mucoadhesive vaginal tablets are prepared by direct compression technique. Direct compression tablets are easy to manufacture, has rapid disintegration and faster dissolution properties as compared to tablets manufactured via wet granulation technique. So, we can say that, these may be the reason behind manufacturing mucoadhesive vaginal tablets by direct compression technique. But there is no specific reason mentioned yet.

There are two basic stage of mucoadhesion, first is contact stage and second is consolidation stage. During contact stage, wetting will occur between dosage form and mucus surface. During consolidation stage, the plasticizing and adhesion activity of the polymers are activated by the moisture that promotes formation of hydrogen bonds and van der Waals force between vaginal tablets and vaginal mucus.[67]

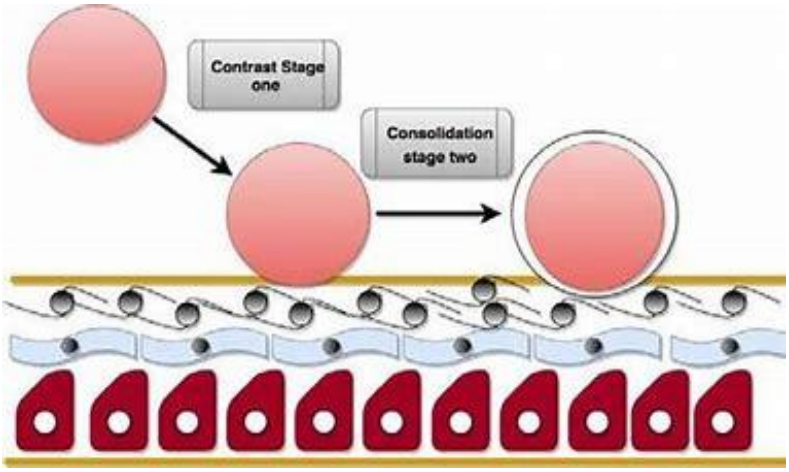

Fig.14: Stages of Mucoadhesion.

The dosage form gets adheres to the mucus surface by several mechanisms such as electronic, adsorption, wetting, diffusion, fracture or mechanical theory. Diffusion theory also explains the consolidation phase where the glycoprotein of mucus layer and the polymer molecules inter diffuses and form secondary bonds. This will strengthen and prolong adhesion.

The release mechanism is based on drug diffusion through the swollen polymers and progressive erosion / dissolution of the gel matrix. Once the dosage form gets adhered to vaginal mucus surface, it will release the drug via diffusion for desired period of time depending upon the composition of matrix and the polymers used. As the tablet comes in contact with vaginal fluid, it swells as the mucoadhesive polymers used in vaginal tablets are hydrophilic in nature. The drug is then released via diffusion mechanism for prolonged period of time to achieve sustained therapeutic effect of medicaments.

Basic mechanism of mucoadhesion	STEP 1 Wetting and swelling step occurs when polymer spreads over the surface of mucosal membrane to develop intimate contact
	STEP 2 Mucoadhesive polymer chain and the mucosal polymer chains get intermingle and entangles to form adhesive bonds
	STEP 3 Formation of weak chemical bonds between the entangled polymer chain.

The release mechanism is based on drug diffusion through the swollen polymers and progressive erosion / dissolution of the gel matrix. Once the dosage form gets adhered to vaginal mucus surface, it will release the drug via diffusion for desired period of time depending upon the composition of matrix and the polymers used. As the tablet comes in contact with vaginal fluid, it swells as the mucoadhesive polymers used in vaginal tablets are hydrophilic in nature. The drug is then released via diffusion mechanism for prolonged period of time to achieve sustained therapeutic effect of medicaments.

8.4. Polymers used in Mucoadhesive Vaginal Tablets

To design and formulate mucoadhesive drug delivery system, large number of polymers are required which are classified as anionic, non-ionic, cationic and thiolated polymers. Among various polymeric groups, acrylate polymers, cellulose derivatives, chitosan, pectin and alginates are mainly analysed as mucoadhesive polymers. Combination of two or more mucoadhesive polymers or chemically modified polymers are used for better designing of MDDS and to achieve significant mucoadhesion. Let us discuss the extensively used mucoadhesive polymers in MDDS and their mechanism of action.[67]

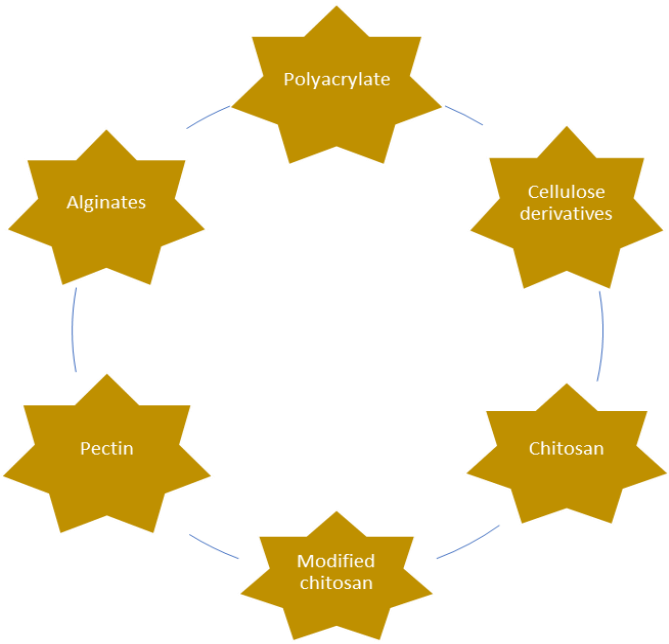

Fig. 15: Mucoadhesive Polymers.

8.4.1. Acrylic Acid Derivatives / Polyacrylate

Chemically polyacrylate is cross linked polymers of acrylic acid with divinyl glycol or polyalkenylether substitution. Methacrylate is most common type of polymer among polyacrylates. Among this group of polymers, polycarbophil and carbomer have been widely studied for their use as mucoadhesive polymers in MDDS. They differ in the cross-linked pattern and viscosity. Polycarbophil is an insoluble polymer that adheres to vaginal mucus after topical administration and also has significant swelling capacity. It usually forms H bond with the glycoproteins of mucus. Carbomer grades like 934P, 971P etc are extensively used for their mucoadhesion features.[80] The presence of frequent carboxylic groups in carbomer is makes them suitable candidate for macromolecular confirmation and also allows maximum H bond forming groups.[81] The H bond forming abilities of both polymers promotes their penetration in the mucosal area, which results in better interlinking of polymers with mucus, which in turn gives good adhesion making them suitable for their use in MDDS.[82]

Despite possessing significant mucoadhesive characteristics polyacrylates swells well in aqueous medium resulting patient inconveniences. Chemically modified, methyl group substituted acrylate, polymethacrylate is commonly used to overcome the above drawback.[83] Polyacrylates were also modified by thiolation or cysteine conjugation for better mucoadhesion. Thiolated polycarbophil is derived by neutralizing its carboxyl group with sodium hydroxide (NaOH) and covalent bonding with cysteine amino groups. The resulting thiolated polymer forms disulphide bond (S=S) with cysteine moiety of subdomains of mucus glycoprotein by either thio/disulphide exchange or oxidation of thiol group, resulting increased mucoadhesion. These mucoadhesive properties restricts thiolated polymers from getting adhere to epithelial tissue and also decreases their absorption rate. Therefore, sustained release of drug might be achieved from this type of platform in MDDS.[84]

8.4.2. Cellulose Derivatives

Cellulose is considered as polymers, found in ample amount throughout the world.[85] It is commonly found in plant cell walls and tissues.[86] Semisynthetic celluloses are often used in the formulation if vaginal dosage forms because of their mucoadhesive characteristics. These polymers are used in gels, viscous liquids, tablets and nanoparticles intended for vaginal administration.[87,88,89] Cellulose derivatives such as hydroxyl propyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), hydroxyl ethyl cellulose (HEC), carboxy methyl cellulose (CMC) are considered as first generation mucoadhesive polymers.[90] The formation of hydrogen bond between carboxylic acid group of cellulose derivatives and glycoprotein of mucin is responsible for adhesion. The stronger the H bond, the deeper and greater it attaches with the mucus membrane causing good adhesion. Among these, HPMC is widely used for their excellent mucoadhesive features and controlled release mechanism. It has been applied to deliver various drugs via different type of dosage forms.[91] Na-CMC is another most extensively used mucoadhesive polymers, and known for their better H bonding ability as it is an anionic polymer.[92] On the other hand, HPMC being a non-ionic polymer lacks proton donating group which causes formation of less hydrogen bonds resulting in comparatively weaker adhesion as compared to CMC.[93] But the mucoadhesion nature also depends upon the pH of the desired medium. At higher pH (vaginal pH), anionic polymer like CMC do not ionize and therefore unable to form more H bonds with the glycoprotein of vaginal mucin and hence not suitable for vaginal mucoadhesive drug delivery system. However, thiolated CMC shows better mucoadhesion due to disulphide bond formation like thiolated polyacrylate.[94]

8.4.3. Chitosan

Chitosan is considered as non-toxic, biodegradable and biocompatible component, that is why it is evaluated as active agent as well as an additive in pharmaceutical formulations.[95,96] Among all mucoadhesive agents, chitosan is the most abundant polysaccharide after cellulose in the world. Chitosan, a cationic mucoadhesive agent is basically a polysaccharide derived from chitin by means of deacetylation. This is a co-polymer of glucosamine and N-acetyl-glucosamine. Chitosan is insoluble in water but soluble in dilute weak acid. It offers amazing mucoadhesion and gelling properties which makes it favourable for topical preparations.[97,98,99]

There are several mechanisms which explains the mucoadhesion nature of chitosan. Due to the presence of -OH and -NH_2, it forms H bond with the glycoprotein of mucin, which makes it a mucoadhesive polymer. The mucoadhesive nature of chitosan is also attributed to its confirmational flexibility.[100] Also, electrostatic interaction between positively charged amines of chitosan and negatively charged sialic acid residue of the mucin is considered as one of the factors responsible for adhesion.[101] These interactions result in strong mechanical and chemical attachment between polymers and mucus, which is required for adhesion. The adhesive nature of chitosan depends on its physicochemical properties and physiological factors. The mucin adsorption by chitosan increases with increase in sialic acid in mucin.[102] As the amount of sialic acid in mucin vary, the mucoadhesion strength of chitosan vary depending upon the mucosa considered. Since the vaginal mucosa possess frequent sialic acid endings, chitosan adheres well to it and is therefore known for frequently used mucoadhesive polymer in vaginal MDDS.

8.4.4. Modified Chitosan

Thiolated chitosan (TC) is a disulphide substituted chitosan that might be made from reaction of chitosan

and thioglycolic acid or by cysteine conjugation. Certain studies have considered TC as improved mucoadhesive polymer with enhanced permeation properties.[103] TC forms disulphide bond with cysteine moiety of subdomains of mucin result in several advantages such as better hydrophilicity, improved uptake for macromolecules to be delivered, increased drug permeability etc.[104] It is evidenced that apart from thiolation, different modified or crosslinked chitosan is also used by scientists in order to boost its mucoadhesion strength and efficiency. For instance, N-trimethyl chitosan, a partially quaternised chitosan prepared by reacting chitosan with EDTA.[105]

8.4.5. Alginates

Alginate is a natural and biodegradable anionic polymer that is typically obtained from brown seaweed. It has low toxicity and relatively low cost thus making it extensively being investigated in numerous studies to prepare microparticles, beads with excellent bioadhesive features. Alginic acid contains molecules of D-mannuronic and L-guluronic acids separated with sequences of same units arranged randomly.[106] Its composition varies according to the source of origin. Being hydrophilic in nature, alginates subunit high water binding capacity.[107,108] Mostly sodium or calcium salt of alginate is used in pharmaceutical research. Alginate has good mucoadhesion property due to the presence of carboxylic acid moiety which causes H bonding with the glycoprotein of mucin. In acidic pH alginate does not swell much resulting much coiling of the polymeric chain. Uncoiling of polymeric chains raises possibilities of entanglement with mucous layer and hence more mucoadhesion occurs. Therefore, alginate gives comparatively less mucoadhesion in acidic pH.

Combination of alginate with different other bioadhesive carrier to design drug delivery system is very popular in pharmaceutical researchers, for example; chitosan-alginate bead for vaginal delivery of chlorhexidine digluconate. Strength of mucoadhesion by alginate depends on its molecular weight. It has been shown that low molecular weight alginate chain remains comparatively rigid than high molecular weight alginate. This nature makes low molecular weight alginate less susceptible to bridge with mucin molecule resulting lower bioadhesion than high molecular weight alginate. These may be used for various purposes such as thickeners, binders, stabilizers, hydrophilic matrix forming agents etc.[109,110] They undergoes ionotropic gelation and possess good gel strength which makes their use effective in topical gel formulations including gels intended for vaginal administration.[111,112]

8.4.6. Pectin

Pectin is a natural, biodegradable, biocompatible, nontoxic heterogenous polysaccharide that is extracted from citrus peel or apple pomace. It contains linear chains of (1–4)-linked a-D-galacturonic acid residues that have carboxyl groups.[111] The main component of pectin is the esterified D galacturonic chain.[112] In case of natural pectin, the acid groups are esterified with methoxy residues. Its acetylated form contains free hydroxyl groups. Pectin may also hold galactose, rhamnose, xylose or arabinose residues in their side chain. They may be categorised as high methoxy (>50% esterified) and low methoxy (<50% esterified).[113]

The mucoadhesion nature of pectin is attributed to two mechanism.[114] The presence of carboxylic acid group in pectin is responsible for formation of H bond with mucin which establishes good adhesion between the two. The mixture of pectin and mucin in aqueous solution causes formation of aggregates which increase upon further addition of pectin,[115] As mucin and pectin, both are negatively charged, the increase in the amount of pectin in MDDS causes electrostatic repulsion with mucin. This repulsion result in uncoiling of polymeric chain. It is evidenced that the greater uncoiling of polymer favours more entanglement and adhesion.[116] For intravaginal dosage forms, pectins are specifically used to impart mucoadhesion properties. In pectins with high methoxy group content, gel formation occurs at pH < 3.5. this pH dependent nature ca strongly influences the drug release mechanism.[117]

Thiolated pectin weas found to be a superior mucoadhesive polymer as compared to normal pectin. Sharma and Ahuja (2011), compared metformin loaded gel beads made up of thiolated pectin and normal pectin for mucoadhesive efficiency. It was revealed that the former had 2.5 folds higher mucoadhesion strength with respect to ex-vivo adhesion study. The stronger disulphide linkage between thiolated polymer and mucin is responsible for the enhanced bioadhesion.[111]

8.5. Preformulation Studies

Mucoadhesive vaginal tablets are generally prepared by direct compression technique hence micromeritics studies of powder blend were evaluated prior to its manufacturing, such as[118]

8.5.1. Angle of Repose

It is a technique for measuring resistance to particle movement. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Such measurements give at least a qualitative assessment of the internal cohesive and frictional effects which might be useful in powder mixing or in tablet die filling operations.[119]

$$\text{Tan } \Theta = 2h/D$$

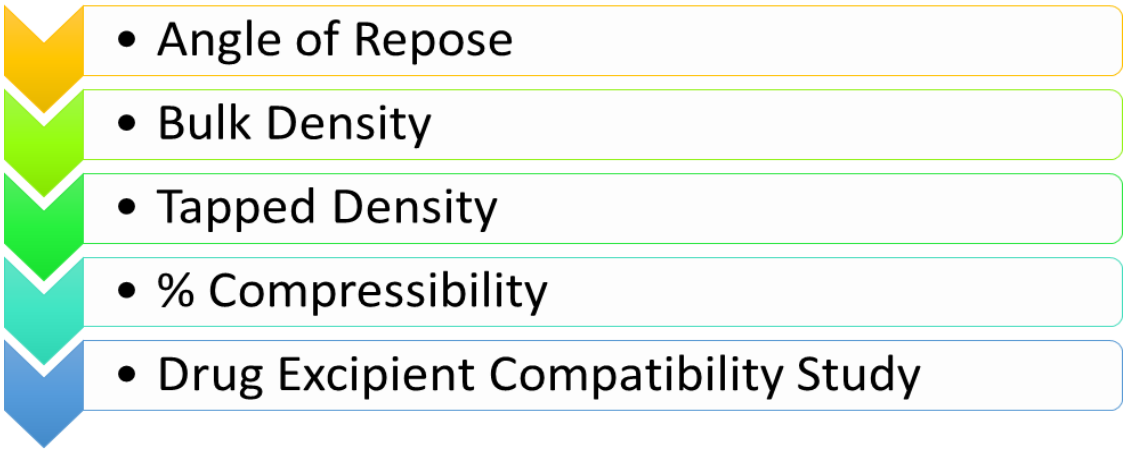

Fig. 15: Preformulation Parameters.

8.5.2. Bulk Density

It is the ratio of the mass of an untapped powder and its volume. It indicated bulking properties of powder which contains three types of air spaces or voids viz. open intraparticulate voids, closed intraparticulate voids and interparticulate voids.[119]

$$\rho_b = M_b/v_b$$

Where, ρ_b = bulk density, M_b= mass of untapped powder and v_b= bulk volume.

8.5.3. Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample for a fixed number of taps (~100) so that the powder bed volume reaches to minimum.[119]

$$\rho_t = M_t/v_t$$

Where, ρ_t = tapped density, M_t= mass of powder after 100 tapings, v_t= tapped volume

8.5.4. % Compressibility

The flow properties of powder are considered as important evaluation parameter when the tablets are prepared using direct compression method. A simple indication of the ease with which a material can be induced to flow is given by application of a compressibility index and Hausner ratio.[119]

$$\text{Carr's compressibility index} = \frac{(\text{tap density} - \text{bulk density})}{\text{Tap density}} * 100$$

$$\text{Hausner ratio} = \frac{\text{tap density}}{\text{Bulk density}}$$

Parameters like solubility and moisture content need to be examined before manufacturing to ensure the ease in designing of formulation. Studies mentioning compatibility between drug and polymer/excipient is considered as one of the essential records required in preformulation studies.[120]

8.5.5. Drug Excipient Compatibility Study

Drug excipient studies are done by FT-IR spectroscopy. The pure drug and drug with polymers were scanned separately. Drug and the polymer were taken in 1:1 ratio. FT-IR spectrum of pure drug was compared with FT-IR spectrum of drug with polymer. Appearance of additional peaks, disappearance of pure drug peaks or shifting of peaks in any spectra was studied, as it indicates the incompatibility between the two.[121]

8.6. Evaluation Parameters

8.6.1. Swelling Index

It indicates the amount of water uptake by tablets. To improve the hydration ability of a formulation, a prolonged adhesion is required. Mucoadhesive polymers are supposed to take water from the underlying mucosal tissue by absorbing, swelling and capillary effects, leading to a considerably stronger adhesion which is one of the essential factors when we talk about mucoadhesive preparations.

The swelling index for the tablets was determined in 100ml acetate buffer (pH 6) at 37±0.1℃. The weight of the tablets was determined and each tablet was placed separately in a 25ml beaker containing 10ml buffer. The beakers were stored at 37±0.1℃. the tablets were removed at different time intervals (1,2,3,4,5,6,8,10 and 12h) and weighed at each of these intervals after removing the surface water using a blotting paper. Swelling index was calculated using below equation

$$\text{Swelling index (\%)} = (W2-W1)/W1 * 100$$

Where, W1 is the original weight of the tablet before commencement of the test and W2 is the tablet weight at each swelling interval.[122]

8.6.2. Tablet Thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers.[121]

8.6.3. Hardness

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. In this, five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester.[121] The hardness is usually measured in terms of kg/cm^2.

8.6.4. Friability

The friability test was carried out to evaluate the hardness and stability instantly. In Roche Friabilator twenty tablets were weighed (W_0) initially and out in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). the percent loss in weight or friability (f) was calculated.[121]

8.6.5. Determination of Surface pH

The surface pH of prepared tablets was determined by soaking tablet in 1ml distilled water for 60 seconds. After the time of soaking, the pH of the wet surface was measured by placing the electrode in contact with the surface of the tablet.

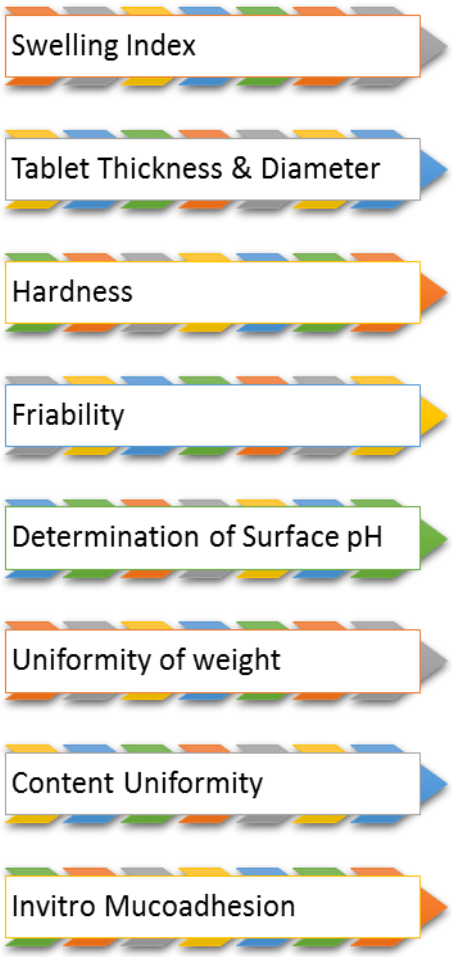

Fig. 16: Evaluation Parameters for Mucoadhesive Vaginal Tablets.

8.6.6. Uniformity of Weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage as mentioned in IP.[121]

8.6.7. Content Uniformity

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. To assure uniform potency for tablets of a low-dose drugs (below 50mg), a content uniformity test is applied. In this test, 30 tablets are randomly selected for the sample, and at least 10 of them are assayed individually. Nine of the 10 tablets must contain not less than 85% or more than 115% of the labelled drug content. The tenth tablet may not contain less than 75% or more than 125% of the labelled content. If these conditions are not met, the tablets remaining from the 30 must be assayed individually, and none may fall outside of the 85 to 115% range.[121]

8.6.8. Drug Content

10 tablets were selected randomly and crushed to form powder. Weigh powder equivalent to weight of one tablet. The weighed powder was stirred in 100ml phosphate buffer saline pH 1.2 for 2 hours in magnetic stirrer. Samples were diluted to appropriate dilutions prior to get analysed by UV spectrophotometer at 254 nm.[123]

8.6.9. In Vitro Mucoadhesion

There are several methods for examining in vitro bioadhesion. One of the methods involve chicken pouch as a model for mucosal membrane. The tissue was obtained from chicken after slaughter, its contents and surface fats are need to be removed prior to tissue collection. It is then stored frozen in simulated physiological fluid (2.38g $Na_2HPO_4.2H_2O$, 0.19g KH_2PO_4 and 8.0g NaCl/L, pH=6.8). This membrane was thawed to room temperature before use. A round piece of the tissue was cut and sticked with cyanoacrylate adhesive on the surface of the tissue holder disk made of Plexiglas (5.0cm in diameter). The tablet is placed on the upper surface of the tissue. The disk was placed in the bottom of a glass tube fitting the disk diameter. 50ml phosphate buffer pH 5.0 was poured on the tissue surface. The whole assembly was immersed in a water bath containing 900ml of buffer solution maintained at 37.0±0.5℃. The stirring rate is fixed to 50rpm. Samples of 5l are withdrawn at predetermined intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples are suitably diluted with dissolution fluid, and are analysed at specific λ_{max} by UV spectroscopy.[124]

9. Recent Developments

Abidin I.Z. et. al.[125] investigated the bilayer tablets prepared by direct compression method for the localized delivery of two chemotherapeutic agents and to evaluate their synergistic effect following the vaginal administration. The tablet contains Disulfiram and 5-fluorouracil, which acts by eradicating cancerous cells in the margin of cervical tumors. First the blends of both drugs were compressed individually (keeping pressure 20 tons for 20 seconds). The two layers were then

compressed to form a bilayer tablet, keeping the pressure 3 tons for 30 seconds. The two layers were compressed with different pressures, so as to impart good cohesion. 81% of DSF and 89% of 5-FU released within 24 hours.

Bioadhesive mini tablets, sized 1-3 mm intended for vaginal administration were evaluated by Hiorth et. al. [126] to find an adequate formulation to deliver hexyl aminolevulinate hydrochloridum (HAL), an agent used in the photodynamic therapy of cervical cancer. Hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) were used as they possess adequate mechanical properties and desired mucoadhesion features. The study revealed that the polymers caused faster disintegration and released the drug within few minutes. As mini tablets are very small in size, they might be packed into capsules, for their easy administration.

Mc. Conville[127] studied an innovative approach by forming multi-layered tablets, used to avoid pregnancy and sexually transmitted diseases (STD) simultaneously. Dapivirine (antiretroviral), levonorgestrel (contraceptive hormone) and acyclovir (anti-herpes simplex) in combination were used by researchers. They prepared tablets having 3-4 layers exhibiting immediate release of therapeutic agents. The formulated tablets showed immediate/quick release of active pharmaceutical ingredients and the therapeutic action were successfully achieved. It can be concluded that these types of multitasking multi-layered tablets can be introduced to satisfy several therapeutic effects and to reduce the number of administered forms.

Sustained release[128] mucoadhesive vaginal tablets of tenofovir, an antiretroviral drug was prepared by Fernando Notario Perez et al. it is given as antibacterial preparation to reduce the rate of sexual transmission of HIV. Mucoadhesive polymers such as HPMC (hydroxypropyl methylcellulose), chitosan, guar gum and Eudragit were used to achieve good mucoadhesion. The formulation is evaluated for their swelling behaviour, changes in crystallinity of the formulation after swelling by X-ray diffraction, size distribution by scanning electron microscopy and release rate of drug. The formulation showed satisfactory mucoadhesion and adhered to vaginal mucosa for 96 hours, releasing the drug for 72 hours. It has been also concluded that the formulation containing more chitosan as compared to HPMC, exhibits moderate swelling, which is proved to be more comfortable for women to insert it into vagina.

Preetha et.al.[121] formulated the mucoadhesive vaginal tablets of stavudineas, an antiretroviral drug, to achieve extended therapeutic effect. Several formulations were prepared and evaluated for stability, drug content, drug release profile, swelling behaviour and mucoadhesion. It was found that the formulation having HPMC K100M and HPMC K15M along with certain binders such as magnesium, PVP K30, methyl cellulose is proved to be most promising product with the in vitro drug release for 10 hours. The same formulation showed significant swelling index and maximum drug release rate. The tablets were found to release drug up to 99.2% in 7 hours. Thus, the prepared stavudineas tablets exhibited good localized action and sustained release of therapeutic agent.

Mucoadhesive vaginal tablets of sertaconazole was prepared by Anita Patel et.al.[129] to improve the stability, retention time and release characteristics. They prepared vaginal tablets by direct compression method. Hydroxypropyl methylcellulose, hydroxymethyl cellulose, Carbopol 934P, chitosan, sodium alginate, methyl cellulose, sodium carboxymethyl cellulose were used as excipients to achieve significant mucoadhesion. Effervescence was introduced into the formulation to improve swelling behaviour. The formula having 100% of effervescence keeping 1:1 ratio of HPMC and chitosan is proved to be best among all. The swelling rate of tablets increases with increased effervescence. The tablets remain adhered to vaginal mucosa for 10 hours. 98.99% drug was found to be released from formulation. It was considered as optimized formulation as it exhibits moderate mucoadhesion and good drug release.

Abeer S. Hassan et.al[130] formulated mucoadhesive vaginal tablets for Progesterone (P4) to overcome low oral bioavailability which results from hydrophobic drug and extensive hepatic metabolism. Several mucoadhesive polymers were used to achieve mucoadhesion. The tablets were then evaluated for swelling index, in vitro mucoadhesion force, ex vivo mucoadhesion time, drug release and stability. The formulation having 20% chitosan, 10% alginate were detected as most suitable as it exhibits significant swelling behaviour and mucoadhesion. The tablets exhibit sustained release of drug up to 48 hours. It was found that the prepared tablets showed 5-fold higher bioavailability as compared to its oral administration. It was proved to be a potential formulation with enhanced therapeutic efficacy.

10. CONCLUSIONS

The vaginal route is one of the traditional routes used for the delivery of steroids and contraceptives. Since past few years, it has been evolved as a promising route for delivering variety of dosage forms to give local and systemic effects. Over the years the vaginal drug delivery system was limited to vaginal pessaries, capsules, suppositories, powder, cream, gels, ointments etc. but along with advancements in this field, many novel approaches have been observed. Researchers have formulated and studied several new dosage forms to achieve improved results such as site-specific action, sustained release, quick onset of action, rapid delivery of drug to desired site, better therapeutic outcomes and many more. Thermosensitive dosage forms, pellets, microspheres, mucoadhesive vaginal tablets, osmotic pump, nanoparticles, bilayered tablets are some of the newly developed vaginal dosage form, meeting several

criteria for successful delivery of wide variety of agents along with some microparticles that presents challenges when administered via other routes. This review emphasized on the advancement in mucoadhesive vaginal tablets, their advantages over other formulations, polymers used in MDDS and its significance. It can be concluded form the above study that mucoadhesive vaginal tablets can be used as a successful dosage form for the delivery of various therapeutically active agents for both local and systemic effects. Earlier conventional polymers were used in MDDS which could not meet the desired requirements satisfactorily. It was found that by the use of sophisticated polymeric platform such as composite materials, combined polymers, modified or substituted polymers etc the frequency of achieving desired outcomes have been increased. Mucoadhesive vaginal tablets are emerging as a safe and effective means of delivering drugs via vaginal route. From this review it is quite evident that drug delivery via vaginal route can be explored to a greater extent in future by using MDDS.

REFERENCES

1. A.D. Woolfson, R.K. Malcolm, R. Gallagher, Drug delivery by the intravaginal route, Crit. Rev. Ther. Drug Carr. Syst., 2000; 17: 509–555.
2. N. Washington, C. Washington, C.G. Wilson, Vaginal and intrauterine drug delivery, in: N. Washington, C. Washington, C.G. Wilson (Eds.), Physiological pharmaceutics: barriers to drug absorption, Taylor and Francis, London, 2001; 271–281.
3. Funt MI, Thompson JD, Birch H. Normal vaginal axis. South Med J., 1978; 71: 1534-1535.
4. W. Platzner, S. Poisel, E.S.E. Hafez, Functional anatomy of the human vagina, in: E.S.E. Hafez, T.N. Evans (Eds.), Human reproductive medicine: the human vagina, North Holland Publishing, New York, 1978; 39–54.
5. I. Sjorberg, S. Cajander, E. Rylander, Morphometric characteristics of the vaginal epithelium during the menstrual cycle, Gynecol. Obstet. Invest., 1988; 26: 136–144.
6. J.L. Richardson, L. Illum, Routes of drug delivery: case studies (8) The vaginal route of peptide and protein drug delivery, Adv. Drug Deliv. Rev., 1992; 8: 341 – 366.
7. Richardson, J.L.; Illum, L. Routes of drug delivery: case studies (8) The vaginal route of peptide and protein drug delivery, Adv. Drug Deliv. Rev., 1992; 8: 341-366.
8. Washington, N.; Washington, C.; Wilson, C.G. Vaginal and intrauterine drug delivery, 2001 In: Washington N, Washington C, Wilson CG (eds) Physiological pharmaceutics: Barrier to drug absorption. Taylor and Francis, London, 271-281.
9. Burgos, M.H.; Roig de Vargas-Linares, C.E. Ultrastructe of the vaginal mucosa, In: E.S.E. Hafez, T.N. Evans (eds) Human Reproductive Medicine: the human vagina, North Holland Publishing, New York, 1978; 63-93.
10. Moghissi, K.S. Vaginal Fluid Constituents. In the Biology of the Fluids of the Female Genital Tract, Elsevier, North Holland. 1979; 13-23
11. Masters, W.H.; Johnson, V.E. Human sexual response, Little Brown, Boston, 1966.
12. Sitruk-ware, R. Expert Opi. Drug Deliv., 2005; 729-736.
13. Varmesh, M. vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. Obstet Gynecol, 72: 693-698.
14. Chatterjee, A.; Bhowmik, B.B.; Kumar, L. An Overview of Intravaginal Drug Delivery: case studies, Adv. Drug Del. Rev., 1992; 8: 341-366.
15. D'Augustine, M.A.; Liu, J.H.; Harrison, D.C. U.S. Patent, July 11, 2000; 6, 416, 779.
16. Cicinelli, E. Fertil. Steril., 1998; 69: 471-473.
17. Manallack, D.T. The pKa Distribution of Drugs: Application to Drug Discovery. Perspect. Med. Chem., 2007; 1: 25-38.
18. Allen, V.; Lee, W.; Chandra, S; Fanning, C.; Young, D. The effect of vaginal pH on labour induction with vaginal misoprostol. J. Matern Neonatal Med., 2007; 17: 387-391.
19. Kurian, M.; Rao, B.; Rao, A.A.S. Effect of vaginal pH on efficacy of dinoprostone gel for labor induction. Int. J. Reprod. Contracept. Obstet. Gynecol, 2016; 5: 1196-1770.
20. Carlson, R.D.; Sheth, A.N.; Read, T.D.; Frisch, M.B.; Mehta, C.C.; Martin, A.; Haaland, R.E.; Patel, A.S.; Pau, C.P.; Kraft, C.S. The female genital tract microbiome is associated with vaginal antiretroviral drug concentrations in HIV- Infected women on antiretroviral therapy. J. Infect. Dis., 2017; 216: 990-999.
21. Klatt, N.R.; Cheu, R.; Birse, K.; Zevin, A.S.; Perner, M.; Noel-Romas, L.; Grobler, A.; Westmacott, G.; Xie, I.Y.; Butler, J. Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women. Science, 2017; 356: 938-945.
22. Simon, J.A.; Lin, F.; Hulley, S.B.; Blanche, P.J.; Waters, D.; Shiboski, S.; Rotter, J.I.; Nickerson, D.A.; Yang, H.; Saad, M. Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: The cholesterol and pharmacogenetics (CAP) Study. Am. J. Cardiol., 2006; 97: 843-850.
23. Hussain, A.; Ahsan, F. The vagina as a route for systemic drug delivery. J. Control. Release, 2005; 103: 301-313.
24. De Araujo Pereira, R.R.; Bruschi, M.L. Vaginal mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm., 2012; 38: 643-652.
25. Hwang, S.; Wada, E.O.; Yotsuanagi, T.; Suhardja, I.; Ho, N.F.H.; Flynn, G.L.; Higuchi, W.I. Systems approach to vaginal delivery of drugs: II. In situ vaginal absorption of unbranched aliphatic alcohols, J. Pharmm. Sci., 1997; 65: 1574-1578.

26. Brannon-Peppas, L. Novel vaginal drug release applications, Adv. Drug. Deliv. Rev., 1992; 11: 169-177.
27. Roumen, F.J.M.E.; Dieben, T.O.M. Clinical acceptability of an ethylene-vinyl-acetate non-medicated vaginal ring, Contraception, 1999; 59: 59-62.
28. Van Laarhoven, J.A.H.; Kruft, M.A.B.; Vromans, H. In vitro properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring, Int. J. Pharm., 2002; 232: 163-173.
29. Krishna, S.V.; Ashok, V.; Chatterjee, A. A review on vaginal drug delivery systems, Int. J. Bio. Pharm. Alli. Sci., 2012; 1(2): 152-167.
30. Kuklin, N.; Daheshia, M.; Karem, K.; Manickan, E.; Rouse, B.T. Induction of mucosal immunity aginst herpes simplex virus by Plasmid DNA Immunization, J> Virol, 1997; 71: 3138-3145.
31. DuBouchet, L.; McGregor, J.A.; Ismail, M.; McCormack, W.M.A pilot study of metronidazole vaginal gel versus oral metronidazole for the treatment of trichomonas vaginalis vaginitis, Sex. Transm. Dis., 1998; 25: 176-179.
32. Mandal, T.K. Swelling controlled release system for the vaginal delivery of miconazole, *Eur. J. Pharm. Biopharm*, 2000; 50: 337-343.
33. Chore, S.A.; Dighade, S.J. A review on mucoadhesive vaginal drug delivery system, *Int. J. Res. Pharm. Chem*., 2020; 10(4): 350-364.
34. Russo, E.; Villa, C. Poloxamer hydrogels for biomedical applications. *Pharmaceutics*, 2019; 11: 671.
35. Liu, Y.; Zhu, Y.; Wei, G.; Lu, W. Effect of carrageenan on poloxamer based In situ gel for vaginal use: Improved in vitro and in vivo sustained release properties. *Eur. J. Pharm. Sci*., 2009; 37: 306-312.
36. Rossi, S.; Ferrari, F.; Bonferoni, M.C.; Sandri, G.; Faccendini, A.; Puccio, A.; Caramella, C. Comparision of poloxamer and chitosan based thermally sensitive gels for the treatment of vaginal mucositis. *Drug. Dev. Ind. Pharm.*, 2013; 40: 352-360.
37. Deshkar, S.S.; Palve, V.K. Formulation and development of thermosensitive cyclodextrin based in situ gel of voriconazole for vaginal delivery. *J. Drug. Deliv. Sci. Technol*, 2019; 49: 277-285.
38. Rencber, S.; Karavana, S.Y.; Senyigit, Z.A.; Erac, B.; Limoncu, M.H.; Baloglu, E. Mucoadhesive in situ gel formulation for vaginal delivery of clotrimazole: Formulation, preparation, and in vitro/ in vivo evaluation. *Pharm. Dev. Technol*, 2016; 22: 551-561.
39. Santiago, G.L.; Verstraelen, H.; Poelvoorda, N.; De corte, S.; Claeys, G.; Trog, M.; De Backer, E.; Saerens, B.; Vervaet, C.; De Boeck, F.; et al. A pilot study evaluating the safety of vaginal administration of a multi- particulate pellet formulation. *Eur. J. Pharm. Biopharm*., 2009; 73: 399-403.
40. Poelvoorde, N.; Verstraelen, M.; Verhelst, R.; Saerens, B.; De Backer, E.; Santiago, G.L.D.S.; Vervaet, C.; Vaneechoutte, M.; De Boeck, F.; Van Bortel, L.; et. al. In vivo evaluation of the vaginal distribution and retention of a multi-particulate pellet formulation. *Eur. J. Pharm. Biopharm*, 2009; 73: 280-284.
41. Hiorth, M.; Leireng, L.; Reinertsen, R.; Tho, I. Formulation of bioadhesive hexylaminolevulinate pellets intended for photodynamic therapy in the treatment of cervical cancer. *Int. J. Pharm.*, 2013; 441: 544-554.
42. Rochira, M.; Migleitta, M.R.; Richardson, J.L.; Ferrari, L.; Beccaro, M.; Benedetti, L. Novel vaginal delivery system for calcitonin II. Preparation and characterization of HVAFF Microspheres containing calcitonin. *Int. J. Pharm*., 1996; 144: 19-26.
43. Pliszczak, D.; Bourgeosis, S.; Bordes, C.; Valour, J.P.; Mazoyer, M.A.; Orecchioni, A.; Nakache, E.; Lanteri, P. Improvement of an encapsulated process for the preparation of probiotics and prebiotics loaded bioadhesive microparticles by using experimental design. *Eur. J. Pharm. Sci*., 2011; 44: 83-42.
44. Maestrelli, F.; Jug, M.; Cirri, M.; Kosalee, I.; Mura, P. Characterization and microbiological evaluation of chitosan alginate microspheres dor cefixime vaginal administration. *Carbohydr. Polym*., 2018; 192: 176-183.
45. Zhang, T.; Zhang, C.; Agrahari, V.; Murowchick, J.B.; Oyler, N.A.; Youan, B.B.C. Spray drying tenofovir loaded mucoadhesive and pH sensitive microspheres intended for HIV preparation. *Antivir. Res.*, 2013; 97: 334-346.
46. Gupta, N.V.; Natasha, S.; Getyala, A.; Bhat, R.S. Bioadhesive vaginal tablets containing spray dried microspheres loaded with clotrimazole for treatment of vaginal candidiasis. *Acta. Pharma*., 2013; 63: 359-372.
47. Pinto Reis, C.; Neufeld, R.J.; Ribeiro, A.J.; Veiga, F. Nanoencapsulation, I. Methods for preparation of drug loaded polymeric nanoparticles. *Nanomed. Nanotechnol. Biol. Med.*, 2006; 2: 8-12.
48. Das Neves, J.; Sarmento, B. Precise engineering of dapivirine-loaded nanoparticles for the development of anti-HIV vaginal microbicides. Acta Biomater, 2015; 18: 77–87.
49. Gu, J.; Yang, S.; Ho, E.A. Biodegradable film for the targeted delivery of siRNA-loaded nanoparticles to vaginal immune cells. Mol. Pharm., 2015; 12: 2889–2903.
50. Yang, M.; Yu, T.; Wang, Y.Y.; Lai, S.K.; Zeng, Q.; Miao, B.; Hanes, J. Vaginal delivery of paclitaxel via nanoparticles with non-mucoadhesive surfaces suppresses cervical tumor growth. Adv. Healthc. Mater, 2014; 3: 1044–1052.
51. Melo, C.M.; Cardoso, J.F.; Perassoli, F.B.; Neto, A.S.D.O.; Pinto, L.M.; Marques, M.B.D.F.; Mussel, W.D.N.; Magalhães, J.; Moura, S.A.D.L.; Araújo, M.G.D.F.; et al. Amphotericin B-loaded eudragit

RL100 nanoparticles coated with hyaluronic acid for the treatment of vulvovaginal candidiasis. Carbohydr. Polym, 2020; 230: 115608.
52. Cunha-Reis, C.; Machado, A.; Barreiros, L.; Araújo, F.; Nunes, R.; Seabra, V.; Ferreira, D.; Segundo, M.; Sarmento, B.; das Neves, J. Nanoparticles-in-film for the combined vaginal delivery of anti-HIV microbicide drugs. J. Control. Release, 2016; 243: 43–53.
53. Jøraholmen, M.W.; Basnet, P.; Acharya, G.; Škalko-Basnet, N. PEGylated liposomes for topical vaginal therapy improve delivery of interferon alpha. Eur. J. Pharm. Biopharm, 2017; 113: 132–139.
54. Santos, S.S.; Lorenzoni, A.; Pegoraro, N.S.; Denardi, L.B.; Alves, S.H.; Schaffazick, S.R.; Cruz, L. Formulation and in vitro evaluation of coconut oil-core cationic nanocapsules intended for vaginal delivery of clotrimazole. Colloids Surf. B Biointerfaces, 2014; 116: 270–276.
55. Machado, A.; Cunha-Reis, C.; Araújo, F.; Nunes, R.; Seabra, V.; Ferreira, D.; das Neves, J.; Sarmento, B. Development and in vivo safety assessment of tenofovir-loaded nanoparticles-in-film as a novel vaginal microbicide delivery system. *Acta Biomater*, 2016; 44: 332–340.
56. Rastogi, R.; Teller, R.S.; Mesquita, P.M.M.; Herold, B.C.; Kiser, P.F. Osmotic pump tablets for delivery of antiretrovirals to the vaginal mucosa. *Antivir. Res.*, 2013; 100: 255–258.
57. Mahours, G.M.; Ali Sherif, A.Y.; Shaaban, D.E.Z.; Shazly, G.A. Formulation and evaluation of fluconazole mucoadhesive vaginal tablets, *Briti. J. Pharma. Res.*, 2016; 14(2): 1-10.
58. Caramella, C.M.; Rossi, S.; Ferrari, F.; Bonferoni, M.C.; Sandri, G. Mucoadhesive and thermogelling systems for vaginal drug delivery. *Adv. Drug Deliv. Rev.*, 2015; 92: 39–52.
59. De Araújo Pereira, R.R.; Bruschi, M.L. Vaginal mucoadhesive drug delivery systems. *Drug Dev. Ind. Pharm.*, 2012; 38: 643–652.
60. Rahman, S.S.; Ahmed, A.B. Vaginal drug delivery system a promising approach for antiretroviral drug in the prevention of HIV infection: A Review. *J. Pharm. Sci. Res*., 2016; 8(12): 1330-1338.
61. Valenta, C. The use of mucoadhesive polymers in vaginal delivery. *Adv. Drug. Deliv. Res.*, 2005; 57: 1692-1712.
62. Das Neves, J.; Bahia, M.F. Gels as vaginal drug delivery systems. *Int. J. Pharm.*, 2006; 318: 1-14.
63. Park, K.; Robinson, J.R. Physicochemical properties of water insoluble polymers important to mucin/epithelial adhesion. *J. Control Release*, 1985; 2: 47-57.
64. Andrews, G.P.; Laverty, T.P.; Jones, D.S. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur. J. Pharm. Biopharm*, 2009; 71: 505-518.
65. Leung, S.; Robinson, J.R. Polymer structure features contributing to mucoadhesion. II. *J. Control Release*, 1990; 12: 187-194.
66. Acarturk, F. Mucoadhesive vaginal drug delivery system. *Rec. Pat. Drug. Deliv. Form*., 2009; 3: 193-205.
67. Chatterjee, B.; Amalina, N.; Sengupta, P.; Mandal, U.K. Mucoadhesive polymers and their mode of action: A Review. *J. Appli. Pharm. Sci.*, 2017; 7(05): 195-203.
68. Tiwari, D.; Goldman, D.; Sause, R.; Madan, P.L. Evaluation of polyoxyethylene homopolymer for buccal bioadhesive drug delivery device formulations. *AAPS Pharm. Sci*., 1999; 1: 13-21.
69. Gurny, R.; Meyer, J.M.; Peppas, N.A. Bioadesive intraoral release systems: Design, testing and analysis. *Biomaterials*, 1984; 5: 336-40.
70. Huang, Y.; Leobandung, W.; Foss, A.; Peppas, N.A. Molecular aspects of mucoadhesion and bioadhesion: Tethered structure and site-specific surfaces. *J. Control Release*, 2000; 65: 63-71.
71. Gu, J.M.; Robinson, J.R.; Leung, S.H. Binding of acrylic polymers to mucin/epithelial surfaces: Structure property relationships. *Crit. Rev. Ther. Drug carrier system*, 1998; 5: 21-67.
72. Peppas, N.A.; Little, M.D.; Huang, Y. Bioadhesive controlled release systems. In: Wise DL editor. Handbook of pharmaceutical controlled release technology. New York: Maral Dekker, 2000; 255-69.
73. Mc Carron, P.A.; Woolfson, A.D.; Donnelly, R.F.; Andrews, G.P.; Zaerislak, A.; Price. J.H. Influence of plasticizer type and storage conditions on the properties of poly (methyl vinyl ether-co-maleic anhydride) bioadhesive films. *J. Appl. Polym. Sci.*, 2004; 91: 1576-89.
74. Gudeman, L.; Peppas, N.A. Preparation and characterization of pH-sensitive, interpenetrating networks of poly (vinyl alcohol) and poly (acrylic acid). *J. Appl. Polym. Sci.*, 1995; 55: 919-28.
75. Peppas, N.A.; Buri, P.A. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. *J. Control Release*, 1985; 2: 257-75.
76. Jimenez-Castellanos, M.R.; Zia, H.; Rhodes, C.T. Mucoadhesive drug delivery systems. *Drug. Deliv. Ind. Pharm*., 1993; 19: 143-94.
77. Ahuja, A.; Khar, R.K.; Ali, J. Mucoadhesive drug delivery systems. *Drug. Deliv. Ind. Pharm.*, 1997; 23: 489-515.
78. Solomonidou, D.; Cremer, K.; Krumme, M.; Kreuter, J. Effect of carbomer concentration and degree of neutralisation on the mucoadhesive properties of polymer films. *J. Biomater. Sci. Polym. Ed*., 2001; 12: 1191-205.
79. Duchens, D.; Touchard, F.; Peppas, N.A. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. *Drug. Deliv. Ind. Pharm.*, 1988; 14: 283-18.
80. Singla, A.K.; Chawal, M.; Singh, A. Potential applications of carbomer in oral mucoadhesive controlled drug delivery systems: A Review. *Drug. Deliv. Ind. Pharm.*, 2000; 26(9): 913-24.

81. Mortazavi, S.A. A comparative study between the strength and duration of mucosa-adhesion of trans buccal carbomer based aqueous gels. *Iran. J. Pharm. Res.*, 2002; 1(1): 7-13.
82. Zhu, Z.; Zhai, Y.; Zhang, L.; Leng, D.; Ding, P. The development of polycarbophil as a bioadhesive material in pharmacy. *Asian. J. Pharm. Sci.*, 2013; 8(4): 218-27.
83. Elhady, S.S.A.; Mortada, N.D.; Awad, G.S.; Zai, N.M.; Taha, R. Development of in situ gelling and mucoadhesive mebeverine hydrochloride solution for rectal administration. *Saudi. Pharm. J.*, 2003; 11(4): 159-71.
84. Wasnik, M.N.; Godse, R.D.; Nair, H.A. Development and evaluation of buccoadhesive tablet for selegiline hydrochloride based on thiolated polycarbophil. *Drug. Deliv. Ind. Pharm.*, 2014; 40(5): 632-8.
85. Shokri, J.; Adibki, K. Application of cellulose and cellulose derivatives in pharmaceutical industries. *In. Cellulose Med. Pharm. Elec. Appl*. In Tech: London, UK, 2013.
86. Sahin, H.T.; Arslan, M.B. A study on physical and chemical properties of cellulose paper immersed in various solvent mixtures. *Int. J. Mol. Sci*., 2008; 9: 78-88.
87. Yadav, Y.K.; Gupta, A.B.; Kumar, R.; Yadav, J.S.; Kumar, B. Mucoadhesive polymers: Means of improving the mucoadhesive properties of drug delivery system. *J. Chem. Pharm. Res.*, 2010; 2: 418-432.
88. Kamel, S.; Ali, N.; Janahngir, K.; Shah, S.M.; EL-Gendy, A.A. Pharmaceutical significance of cellulose: A review. *Eupress. Polym. Lett.*, 2008; 2: 758-778.
89. Jian, S.; Sandhu, P.S.; Malvi, R.; Gupta, B. Cellulose derivatives as thermosensitive polymers. An overview. *J. Appl. Pharm. Sci.*, 2013; 3: 139-144.
90. Bade, R.A.; Putnam, D.A. Engineering polymer systems for improved drug delivery. 2013, New Jersey, USA: Wiley.
91. Baloglu, E.; Karavana, S.Y.; Hyusein, I.Y.; Kose, T. Design and formulation of mebeverine hydrochloride semisolid formulations for intraorally administration. *AAPS Phar. Sci. Tech.*, 2010; 11(1): 181-8.
92. Ramineni, S.K.; Cunningham Jr., L.L.; Dziubla, T.D.; Puleo, D.A.; Cunningham, L.L.; Dziubla, T.D. Competing properties of mucoadhesive films designed for localized delivery of imiquimod. *Biomater. Sci.*, 2013; 1(7): 753.
93. Prajapati, S.K.; Tripathi, P.; Ubaidulla, U.; Anand, V. Design and development of gliclazide mucoadhesive microcapsules: in vitro and in vivo evaluation. *AAPS Pharm. Sci. Tech.*, 2008; 9(1): 224-30.
94. Flavia, L.; Alexie, M. Development of mucoadhesive thio-carboxymethyl cellulose for application in buccal delivery of drugs. *Ther. Deliv*, 2016; 7(2): 63-71.
95. Riva, R.; Ragelle, H.; Rieux, A.D.; Duhem, N.; Jerome, C.; Preat, V. Chitosan and chitosan derivatives in drug delivery and tissue engineering. *Adv. Polym. Sci.*, 2011; 244: 19-44.
96. Baldrick, P. The safety of chitosan as a pharmaceutical excipient. *Regul. Toxicol. Pharmacol*, 2010; 56: 290-299.
97. Sogias, I.A.; Williams, A.C.; Khutoryanskiy, V.V. Why is chitosan mucoadhesive? *Biomacromolecules*, 2008; 9: 1837-1842.
98. Alsarra, I.A. Chitosan topical gel formulation in the management of burn wounds. *Int. J. Bio. Macromol*, 2009; 45: 16-21.
99. Lupo, N.; Bernkop- Schnurch, A. Entirely S-protected chitosan: A promising mucoadhesive excipient for metronidazole vaginal tablets. *Acta Biomater*, 2017; 64: 106-115.
100. Alhalaweh, A.; Vilinska, A.; Gavini, E.; Rassu, G.; Velega, S.P. Surface thermodynamics of mucoadhesive dry powder formulation of zolmitriptan. *AAPS Pharm. Sci. Tech.*, 2011; 12(4): 1186-92.
101. Jacobsen, J.; Meng-Lund, E.; Muff-Westergaard, C.; Sander, C.; Madelung, P. A mechanistic based approach for enhancing buccal mucoadhesion of chitosan. *Int. J. Pharm.*, 2014; 461(1-2): 280-5.
102. Sandri, G.; Rossi, S.; Bonferoni, M.C.; Ferrari, F.; Mori, M.; Caramella, C. Th role of chitosan as a mucoadhesive agent in mucosal drug delivery. *J. Drug. Deliv. Sci. Tech.*, 2012; 22: 275-84.
103. Peh, K.; Khan, T.; Ch'ng, H. Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. *J. Pharm. Sci.*, 2000; 3(3): 303-11.
104. Anitha, A.; Deepa, N.; Chennazhi, K.P.; Nair, S. V.; Tamura, H.; Jayakumar, R. Development of mucoadhesive thiolated chitosan nanoparticles for biomedical applications. *Carbohydr. Polym*., 2011; 83(1): 66-73.
105. Sandri, G.; Rossi, S.; Bonferoni, M.C.; Ferrari, F.; Zambito, Y.; Di Colo, G. Buccal penetration enhancement properties of N-trimethyl chitosan: Influence of quaternization degree on absorption of a high molecular weight molecule. *Int. J. Pharm.*, 2005; 297(1-2): 146-55.
106. Johnson, F.A.; Craig, D.Q.M.; Mercer, A.D. Characterization of the block structure and molecular weight of sodium alginates. *J. Pharm. Pharmacol*, 2011; 49: 639-643.
107. Tonnesen, H.H.; Karlsen, J. Alginate in drug delivery system. *Drug. Dev. Ind. Pharm.*, 2002; 28: 621-630.
108. Ching, S.H.; Bansal, N.; Bhandari, B. Alginate gel particles- A review of production techniques and physical properties. *Crit. Rev. Food. Sci. Nutr.*, 2017; 57: 1133-1152.

109. Boyd, J.; Turvey, J.R. Structural studies of alginic acid, using a bacterial poly-a-L-guluronate lyase. *Carbohy. Res.*, 1978; 66: 187-194.
110. Ingar Draget, K.; Ostgaard, K.; Smidsrod, O. Homogenous alginate gels: A technical approach. *Carbohy. Polym*., 1990; 14: 159-178.
111. Sharma, R.; Ahuja, M. Thiolated pectin: Synthesis, characterization and evaluation as a mucoadhesive polymer. *Carbohy. Polym.*, 2011; 85(3): 658-63.
112. Mohnen, D. Pectin structure and biosynthesis. *Curr-opin. Plant Biol*., 2008; 11: 266-277.
113. Ralet-Renard, M.C.; Lerouge, P.; Quemener, B. Mass spectrometry for pectin structure analysis. *Carbohy. Res*., 2009; 344: 1798-1807.
114. Sriamornsak, P.; Wattanakorn, N.; Takeuchi, H. Study on the mucoadhesion mechanism of pectin by atomic force microscopy and mucin-particle method. *Carbohydr. Polym.*, 2010; 79(1): 54-9.
115. Russo, E.; Selmin, F.; Baldassari, S.; Gennari, C.G.M.; Caviglioli, G.; Cilurzo, F. A focus on mucoadhesive polymers and their application in buccal dosage forms. *J. Drug. Deliv. Sci. Technol*, 2016; 32: 113-25.
116. Joergensen, L.; Klosgen, B.; Simonsen, A.C.; Borch, J.; Hagesaether, E. New insights into the mucoadhesion of pectins by AFM roughness parameters in combination with SPR. *Int. J. Pharm.*, 2011; 411(1-2): 162-8.
117. Klemetsrud, T.; Jonassen, H.; Hiorth, M.; Kjoniksen. A.-L.; Smistad, G. Studies on pectin-coated liposomes and their interaction with mucin. *Colloids Surf. B. Biointerfaces., 2013;* 103: 158-165.
118. United States Pharmacopoeia 32- National Formulatory 27. Unites States Pharmacopeial Convention, 2008.
119. Lachamn, L.; Lieberman, H.A. The theory and practice of industrial pharmacy, CBS Publishers and Distributors pvt ltd. Fourth edition, 2013; 242-46.
120. Gandhi, J.; Patel, J.; Shah, P. Design and development of mucoadhesive vaginal drug delivery system of raloxifene hydrochloride. *Int. J. Chem. Tech. Res*., 2017; 10(10): 60-76.
121. Preetha, P.; Sreenivasarao, A.; Banutejanaik, B. Formulation and evaluation of stavudineas vaginal tablets. *Int. J. Pharm. Sci. Res.*, 2015; 6(2): 928-34.
122. Bhat, S.R.; Shivakumar, H.G. Bioadhesive controlled release clotrimazole vaginal tablets. *Trop. J. Pharm. Res.*, 2010; 9(4): 339-346.
123. Shaikh, A.A.; Pawar, Y.D.; Kumbhar, S.T. an in vitro study for mucoadhesion and control release properties of guar gum and chitosan in itraconazole mucoadhesive tablets. *Int. J. Pharm. Sci. Res.*, 2012; 3(5): 1411-14.
124. Agarwal, V. Design development and biopharmaceutical properties of bucoadhesive compacts of pentazocine. *Drug Deliv. Ind. Pharm.*, 1999; 25(6): 701-709.
125. Abidin, I.Z.; Rezoagli, E.; Paiva, B.S.; Fehrenbach, G.W.; Masterson, K.; Pogue, R.; Cao, Z.; Rowan, N.; Murphy, E.J.; Major, I. A bilayer vaginal tablet for the localized delivery of disulfiram and 5-fluorouracil to the cervix. *Pharmaceutics*, 2020; 12: 1185.
126. Hiorth, M.; Nilsen, S.; Tho, I. Bioadhesive mini tablets for vaginal drug delivery. *Pharmaceutics*, 2014; 6: 494-511.
127. Mc Conville, C.; Major, I.; Devlin, B.; Brimer, A. Development of multi-layered vaginal tablet containing dapivirine, levonorgestrel and acyclovir for use as a multi-purpose prevention technology. Eur. J. Pharm. Biopharm, 2016; 104: 171-179.
128. Notario-Perez, F.; Cazorla Luna, R.; Martin, Illana, A.; Ruiz-Caro, R.; Tamayo, A.; Rubio, J.; Veiga, M.D. Optimization of tenofovir release from mucoadhesive vaginal tablets by polymer combination to prevent sexual transmission of HIV. Published by Elsevier ltd., 2017.
129. Patel, A.; Patel, K.; Patel, J. Development and evaluation of mucoadhesive vaginal tablet of sertaconazole for vaginal candidiasis. Int. J. Pharm. Res., 2011; 3: 2175-2182.
130. Hassan, A.S.; Soliman, G.M.; Marwa, F.A.; Mona, M. Mucoadhesive tablets for the vaginal delivery of progesterone: in vitro evaluation and pharmacokinetics/pharmacodynamics in female rabbits., Drug. Dev. Indst. Pharm., 2018; 44: 224-232.