REVIEW OF LITERATURE

4.1 Introduction to Oral Cavity

4.1.1 Oral Cavity

Oral cavity is the foremost part of digestive system of human body because of its excellent accessibility and better patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and systemic therapy [88].

4.1.2 Overview of oral cavity

Oral cavity is the area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

1. Outer oral vestibule, bounded by cheeks, lips, teeth and gingiva (gums).

2. Oral cavity proper, which extends from teeth and gums back to the faces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

Figure 1: Structure of oral cavity
4.1.3 Anatomy of the Oral Mucosa

The oral mucosa consists of three distinctive layers i.e., epithelium, basement membrane and connective tissues. The outermost layer is the epithelium, below which lies the supporting basement membrane. The basement membrane is, in turn, supported by connective tissues.

![Figure 2: Structure of oral mucosa](image)

The epithelium forms a protective layer for the tissues beneath and is divided into (a) non-keratinized epithelium in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks, and (b) keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity [89]. The epithelial cells increase in size and become flatter from the basal...
layers to the superficial layers. The oral mucosal thickness varies depending on the site, the buccal mucosa measuring about 500-800 µm [90]. The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues, and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. The buccal epithelium is penetrated by tall and conical-shaped connective tissues. These tissues, which are also referred to as the lamina propria, consist of collagen fibers, a supporting layer of connective tissues, blood vessels, and smooth muscles [91]. Keratinized layers of the orals mucosa epithelia form a protective surface which is mechanically tough and resistant to physical insult and penetration by any foreign substances. Thus epithelia contain neutral lipids like ceramides and acrylceramides which are associated with barrier function. The non-keratinized mucosa is more mobile and found in regions of the oral cavity where a more flexible mucosa is required for functional purposes e.g. in the buccal and sublingual regions where mastication is predominant [92]. These epithelia do not contain acrylceramides and only have small amounts of ceramides. They also contain small amounts of neutral polar lipids mainly cholesterol sulfate and glucosyl ceramides [93].

4.1.4 Biochemistry of oral mucosa

All the layers of the oral mucosal membranes contain a large amount of protein in the form of tonofilaments, consisting at least seven proteins called ‘keratins’ with molecular sizes of 40-70 kilodaltons. Both keratinized and nonkeratinized tissues of varying thickness and composition are found in oral cavity. The difference between keratinized
and non-keratinized epithelia is merely the difference in the molecular size of existing keratins. Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular weight keratins. The lipid content of the cells varies between tissues [94].

4.1.5 Routes of drug transport across the oral mucosa

The epithelial cell membrane is lipophilic while the intercellular space is relatively hydrophilic. The entire epithelium therefore consists of hydrophilic and lipophilic regions, where the hydrophilic region is narrow and tortuous around the lipophilic cell membrane. Two pathways for passive diffusion of the drug across the buccal mucosa arise as a result of these regions i.e. paracellular and transcellular routes [95]. The hydrophilic compounds due to their low partition coefficient (low solubility) cannot penetrate the lipophilic cell membrane and hence paracellular route (intertcellular spaces) is preferred route for these compounds. The major limitation encountered by hydrophilic molecules is the limited surface area of the intercellular space and the tortuosity of this pathway. For lipophilic compounds, transcellular pathway is preferred due to their high partition coefficients. Also, since the surface area for this route is large and the path length is relatively short, they can easily penetrate through the lipophilic cell membrane. However, in general drugs preferentially move through the route that offers least resistance and can traverse both routes of transport simultaneously [96, 97]. Although majority of the compounds diffuse through the buccal mucosa by passive diffusion, a carrier mediated process has also been reported.
4.1.6 Barriers to drug transport across buccal mucosa

The rate and extent of absorption of drugs through the buccal mucosa is affected by the presence of barriers such as mucus, basement membrane, membrane coating granules and saliva. The major barrier exists in the outer one third of the epithelium.

Membrane Coating Granules: The permeability barrier in the oral mucosa is a result of intercellular material derived from membrane coating granules (MCG). As the cells undergo differentiation, MCG's start forming at the upper third of the epithelium and appear to fuse with the plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in nonkeratinizing epithelia are spherical in shape, membrane-bound and measure about 0.2 um in diameter. Permeation studies performed using the tracers such as horseradish peroxidase and lanthanum nitrate indicated that these tracers penetrated only through outermost layer or two of the cells when applied to the outer surface of the epithelium. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCG's could be seen adjacent to the superficial plasma membrane of the epithelial cells [98]. These results demonstrated that keratinization does not play a role in the barrier formation, while the MCGs serve as barriers to the transport of drug molecules through the epithelium.

Basement Membrane: Although the superficial layers of the oral epithelium represent the primary barrier to the permeation of drugs, the basement membrane may also present some resistance to the passage of materials across the junction between epithelium and the connective tissue. Permeation studies suggested that the basal region of pig buccal
epithelium may represent a barrier to small substances such as β-blocking agents [99]. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

*Mucus:* The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus. The mucus has a thickness range of 40-300 µm and consists principally of complexes made up of proteins and carbohydrates. In the oral mucosa, mucus is produced by major and minor salivary glands as a part of saliva. Minor salivary glands contribute approximately 70% of the total mucin found in saliva. Mucus serves as an effective delivery vehicle by acting as a lubricant, allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems [100]. At physiological salivary pH (5.8-7.4), mucus carries a negative charge and is capable of forming a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Substances such as ions, protein chains, and enzymes can modify the interaction of the mucus molecules with the active substances. Saliva is mainly produced by the three pairs of salivary glands and is composed of 99% water and 1% organic and inorganic materials. It moistens the oral cavity and functions to protect all of the tissues of the oral cavity from abrasion by rough materials and chemicals. There is considerable variation in the salivary flow between individuals, with time of day and during disease conditions. The amount of saliva produced throughout the day varies from 1-1.5 L, but can also be as low as 0.5-0.6 L [101]. Salivary secretion can be stimulated by mechanical (pressure), chemical (swell, taste) and/or psychic stimuli. Acid stimuli can increase saliva secretion up to 2 to 3 fold its normal rate. The pH of the saliva ranges from 5.8-7.4 depending on the flow rate. At higher flow rates, the higher
sodium and bicarbonate concentrations lead to an increase in pH of saliva. The presence of saliva may be considered as a positive or negative factor for oral transmucosal delivery of drugs. For oral mucosal delivery saliva serves as the dissolution medium. The continuous secretion of saliva into the oral cavity provides the ample supply of solvent to dissolve the drug prior to its absorption. The mucin found in saliva forms a thin film that lines the membranes of oral cavity and provides an opportunity to retain the dosage form in contact with the mucosa for prolonged periods by incorporating mucoadhesive compounds in the formulation. Such a system would be in close contact with the absorbing membrane thus optimizing the drug concentration gradient across the membrane and reducing the diffusional pathway. However, excessive salivary flow can result in dilution and or accidental swallowing of the dissolved drug resulting in a decreased absorption. Also, pathological conditions such as xerostomia or drugs that patient may be taking concomitantly may decrease the salivary flow and decrease the drug absorption.

4.2 Buccal as a site for drug delivery

The buccal route has been studied as a favorable site for the local and systemic delivery of drugs. Because of the rich blood supply and direct access to systemic circulation, the oral mucosa suitable for drugs, which are susceptible to acid hydrolysis in the stomach are extensively metabolized in the liver. The continuous secretions of saliva results in rapid removal of released drug and hence the oral cavity should be restricted to the delivery of drugs, which have a short systemic circulation. The buccal and gingival areas are associated with a smaller flow of saliva, thus the duration of adhesion of the delivery system would be longer at these areas than the sublingual region. The buccal or
gingival membrane, with their accessible, smooth surface offers a platform for prolong delivery of drugs.

4.2.1 Advantages of mucoadhesive buccal drug delivery [102]

Drug administration via the oral mucosa offers several advantages

1. Ease of administration and termination of therapy in emergency.
2. Permits localization of the drug to the oral cavity for a prolonged period of time.
3. Can be administered to unconscious and trauma patients.
4. Offers an excellent route for the systemic delivery of drug which bypasses first pass metabolism, thereby offering a greater bioavailability.
5. Significant reduction in dose can be achieved, thereby reducing dose, dose dependent side effects, and eliminates peak-valley profile.
6. Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.
7. It offers a passive system for drug absorption and does not require any activation.
8. It can be made unidirectional to ensure only buccal absorption.
9. Drugs which show poor bioavailability via the oral route can be administered conveniently.
10. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
11. Flexibility in physical state, shape, size and surface.
12. Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.

13. It satisfies several features of the controlled release system.

14. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than skin.

15. The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form.


4.2.2 Limitation of buccal drug administration [103]

1. Drugs which are unstable at buccal pH cannot be administered.

2. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.

3. Only drug with small dose requirement can be administered.

4. Only those drugs which are absorbed by passive diffusion can be administered by this route.

5. Eating and drinking may become restricted.

6. There is an ever present possibility of the patient swallowing the dosage form.

7. Over hydration may lead to slippery surface and structural integrity of the formulation may get disrupted. Swelling and hydration of the bioadhesive polymers may occur.

8. Drugs contained in the swallowed saliva follows the peroral route and the advantages of buccal route are lost.
4.3 FORMULATIONS: Buccal adhesive dosage forms are broadly classified in the following dosage forms:

- Solid buccal adhesive dosage forms
- Semi-solid buccal adhesive dosage forms
- Liquid buccal adhesive dosage forms.

4.3.1 Solid buccal adhesive dosage forms

Tablets: Buccal tablets are small, flat, and oval, with a diameter of approximately 5–8 mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Buccal tablets are designed to release the drug either unidirectionally targeting buccal mucosa or multidirectionally into the saliva. However, size is a limitation for tablets as they have to have intimate contact with the mucosal surface. Buccal tablets are usually prepared by direct compression, but wet granulation techniques can also be used. Multilayered tablet may be prepared by sequentially adding and compressing the ingredients layer by layer. Some newer approaches use tablets that melt at body temperature. Commercially available buccoadhesive buccal tablets are Buccastem (Prochlorperazine Maleate), Suscard (Nitroglycerine), Fentora (Fentanyl), Striant SR (30 mg testosterone), Oravig™ (miconazole), Corlan (2.5mg Hydrocortisone).

Buccal Patch/Film: Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner,
and a bioadhesive surface for mucosal attachment. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogenously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period.

4.3.2 Semi-solid buccal adhesive dosage forms

Buccal Gel/Ointment: Bioadhesive polymers include crosslinked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs. These are widely used in the delivery of drugs to the oral cavity. They have the ability to form intimate contact with the mucosal membrane and release rapidly the drug at the absorption site. One of the oral mucosal adhesive delivery systems-"Orabase R" consists of finely ground pectin, gelatin and sodium carboxymethylcellulose ("Orahesive" Powder) dispersed in a poly(ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 min. This has been used for the local application of steroids for the treatment of mucosal ulceration. Other commercially available bioadhesive gels are Daktarin oral gel (Miconazole), Pansoral gel buccal (Choline salicylate). Mucosal-adhesive ointment was a formulation containing polymethyl methacrylate in a base containing water, sodium hydroxide, glycerol and the active drug (tretinoin) which was used to treat lichen planus.
4.3.3 Liquid dosage forms

Liquid dosage forms like viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. Polymers were used to enhance the viscosity of products to aid their retention in the oral cavity. Eg. Buccolam® contains Midazolam Hydrochloride 5 mg in 1ml and Epistatus® contains Midazolam Maleate 10 mg in 1ml.

4.4 Introduction to Vagina

4.4.1 Anatomy and histology of vagina

Vagina is a fibromuscular tube that extends 6-12 cm from cervix of the uterus. The surface of the vagina is composed of numerous folds, often called rugae. These folds keep distensability, support and provide an increased surface area of the vaginal wall [104]. The vaginal wall is comprised of three layers: the epithelial layer, tunica adventia and the muscular coat. The epithelial layer creates the superficial layer, which is about 200 μm thick [105]. The smooth muscular fibres of the muscular coat are running along in both circular and longitudinal directions. This gives the vagina an excellent elastic character. Further, the connective tissue of the tunica adventia also increases the flexibility of the vagina. The vaginal wall compromises of a dense network of blood vessels and extends from internal iliac artery, uterine, middle rectal and internal pudental arteries [106]. The blood enters systemic circulation via rich venous plexus which empties primarily into internal iliac vein. The vagina lacks the direct release of mucus because it does not contain any goblet cells. But still it discharges a large amount of fluid. The fluid has its origin from transudates through the epithelium, cervical mucus, exfoliating cells, leukocytes, endometrial and tubal fluids [107]. The vagina’s nerve
supply comes from two sources. The peripheral, which primarily supplies the lower quarter of the vagina, makes it a highly sensitive area: the autonomic primarily supplies upper three quarters. Autonomic fibres respond to stretch and are not very sensitive to pain or temperature. The upper vagina is a very insensitive area because of few sensory fibres. This is why women rarely feel localized sensations or any discomfort when using vaginal rings, and are often unaware of the presence of such items in vagina [108]. The lactobacilli bacteria are an important component of the vaginal microflora. This bacteria converts glycogen from exfoliated epithelial cells into lactic acid, and as a result, maintains the pH around 4-5, with lowest being around the cervix. Body fluids such as menstrual blood, cervical and uterine secretions will all act as alkalizing agents and increase the vaginal pH.

Figure 3: Schematic representation of vaginal wall
4.4.2 Physiological changes and the influence on drug absorption

Women in post-menopausal stage experience many physiologically alterations. These changes manifests as reduction in production of estrogen through pre- and postmenopause. This leads to reduced glycogen content and elevated pH to 6.0 7.5 due to less conversion of lactic acid from glycogen by lactobacillus. The increased vaginal pH could often result in frequent vaginal infections. Furthermore, reduced vaginal discharges and thinning of epithelial layer occurs. The reduction is estimated to 50 % compared to those produced by women of reproductive age. Environmental changes in fertile women are associated with hormonal events in menstrual cycle. The epithelial layer thickness is changed approximately 200-300 μm during menstrual cycle. The pH is around 3.8-4.2 and tends to be lowest when estrogen is highest (ovulation). In this period, glycogen and epithelial desquamation is at its maximum which causes an increased viscosity. The physiological changes in vagina would affect the absorption of drugs and must be taken into consideration in the development of formulations. The thickness of epithelial layer could affect the permeability, where thin epithelium causes increased absorption. Amount of fluid is important because drugs must be in solution before absorption. For bioadhesive systems, wetting of the tablet is crucial for bioadhesion and increasing the residence time [109]. Viscosity may pose as a barrier for drug absorption and continuous secretion can result in removal of the dosage form. The influence of pH is important for absorption, where the unionized form is more readily absorbed.

4.4.3 Vaginal secretions

Vaginal discharge is a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, secretions of the Bartholin’s and
Skene’s glands, leukocytes, endometrial and tubal fluids. The cervical mucus contains inorganic and organic salts, mucins, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). Estrogens and sexual stimulation increase vaginal fluid secretion.

4.4.4 Vaginal pH

The vaginal pH of healthy women of reproductive age is acidic (pH 4–5); this value is maintained by lactobacilli that convert glycogen from exfoliated epithelial cells into lactic acid. The pH changes with age, stages of menstrual cycle, infections and sexual arousal. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase pH.

4.4.5 Microflora

The vaginal flora is a dynamic and closely interrelated system. The ecology of the vagina is influenced by factors such as the glycogen content of epithelial cells, glucose, pH, hormonal levels, and trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. Lactobacillus (Doderlein’s bacilli) is the most prevalent organism in the vaginal environment together with many other facultative and obligate aerobes and anaerobes.

4.4.6 Cyclic changes

The changes in hormone levels (especially estrogen) during the menstrual cycle lead to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions. The variations in enzyme activity (endopeptidases and amino peptidases) with hormonal changes further complicate the problem of achieving consistent drug delivery.
4.5 Vagina as Site for Drug Therapy

The effectiveness of the vagina as a site of drug administration for local effects has been well established [110]. It is an important route for local treatment of several gynecological conditions, such as infections and in hormonal therapy. This route provides advantages such as reducing or eliminating the incidence and severity of side effects, being easily and a non-invasive route of administration. These benefits could contribute to a better compliance, thus achieving improved therapeutic outcome [111]. Furthermore, the vagina possesses properties which include: large surface area of the vaginal wall, permeability, a rich blood supply and importantly, the ability to bypass first-pass liver metabolism [112]. These properties are considered to be advantageous in relation to drug absorption.

Currently, there are varieties of pharmaceutical products available on the market designed for intravaginal therapy (tablets, creams, suppositories, pessaries, foams, solutions, ointments and gels). However, their efficacy is often limited by a poor retention at the site of action due to the self-cleansing action of the vaginal tract [113]. Furthermore, the vagina has unique features in terms of microflora, pH and cyclic changes, and these factors influence the performance of the formulations. Therefore, a successful delivery of drugs through the vagina represents a pharmaceutical challenge.

4.5.1 Advantages of vaginal drug delivery

1. Vaginal route can be used for local as well as systemic effect, attaining sustained therapeutic levels compared to conventional oral route.
2. Vaginal administration permits use of prolonged dosing, with continuous release of medicaments, and hence, longer interval between doses, improving user compliance.

3. Avoiding the fluctuations resulting from daily intake may also lower the incidence of side effects. For example, vaginal delivery of bromocriptine reduces the incidence and severity of its gastrointestinal (GI) side-effects if administered orally.

4. Alleviating the inconvenience caused by pain, tissue damage and probable infection, it serves as a better alternative to parenteral route.

5. Some vaginal dosage forms allow self-insertion and removal of the dosage form like vaginal films, gel, pessaries, etc.

6. Unpredictable GI absorption consequent upon oral administration can be further complicated by vomiting, drug-drug interaction, or decreased intestinal absorption.

7. Avoiding metabolizing in liver and degradation in GI lumen for some compounds. For example, natural oestrogens are 95 percent metabolized by the liver when administered orally. Similarly, propranolol is more bioavailable when administered vaginally, compared to oral.

8. A number of compounds have been reported to exert greater effects when administered vaginally as against oral. For example, misoprostol, used for cervical ripening and labour induction, when administered vaginally has been shown to be more effective, having fewer side effects than when administered orally.
4.5.2 **Drawbacks of vaginal drug delivery**

1. Unawareness and gender-specificity
2. Genital hygiene issues
3. Menstrual cycle-associated vaginal changes
4. Coitus interference
5. Local side effects
6. Variable drug permeability

4.6. **Formulations**

The following types of dosage forms are available.

**4.6.1 Vaginal semisolids:** Vaginal semisolids dosage forms are vaginal creams, ointments and gels. These semisolid vaginal preparations are used mainly in conditions like infections, vaginitis, conditions of endometrial atrophy and for contraceptive purposes too. The vaginal topical preparations are mainly applied by special applicators. Anti-infective drugs (e.g. Nystatin, clotrimazole, miconazole, clindamycin, & sulfonamides); hormones (e.g. progesterone, dinetrol) and contraceptives etc are applied by these dosage forms. Commercially available vaginal creams are Mycelex (Clotrimazole), AVC (Sulfanilamide), Cleocin (Clindamycin phosphate) and Terazol-7 (Terconazole).

**4.6.2 Vaginal Suppositories:** Vaginal Suppositories are the most common dosage forms. Typically, these are torpedo-shaped dosage forms but in case of vagina, the oval shape is preferred. The composition is largely dictated by the physicochemical properties of the drug and the desired drug release profile. The most commonly used base for vaginal
suppositories consist of combination of the various molecular weight polyethylene glycols & surfactants & preservatives. They are buffered to acidic pH of about 4.5. Commercially available vaginal suppositories are AVC suppositories (sulfanilamide) MONISTAT-7 (miconazole nitrate).

4.6.3 Vaginal liquids: The vaginal douches and solutions are also available in market. They are used for irrigation cleansing of vagina. The unit dose douches are prepared which are mixed with warm water and applied by inserters in vagina.

4.6.4 Vaginal Aerosols: Aerosol foams containing estrogenic substances & contraceptive agents are available. The aerosol container has plunger which apply the foam in the vaginal cavity. Novel approach is use of bioadhesive foams. Marketed preparations like povidone-iodine vaginal foam and other contraceptive foams are available.

4.6.5 Vaginal rings: Medicated vaginal rings are fabricated from silastic 382 medical grade elastomer. Vaginal rings is revolution in contraceptive technology and hormone replacement therapy. This is due to their ease of administration, lack of gastrointestinal related symptoms, high efficacy and can be governed by the user. Marketed preparations like Estering vaginal ring (Estradiol) are available.

4.6.6 Vaginal inserts: These types of systems contains flat rectangular polymeric slab enclosed in a pouch of knitted polyester removal system. The buff colored semi transparent hydrogel slab contains drug. The retrieval system is in the shape of long knitted tape that is used to retrieve the slab. Marketed preparations like CERVIDIL are
available. CERVIDIL is a vaginal insert of dinoprostone. It contains 10 mg of drug and release the drug at the rate of 0.3 mg/hr. It can give continuous release for up to 12 hrs.

4.6.7 In situ gelling: These systems are prepared by using temperature-sensitive and mucoadhesive polymers. The water insoluble polymers swells in vagina and form bioadhesive gel on vaginal layer. This allows continuous release up to 25 to 50 hrs. Commercially available in situ gelling vaginal formulation is Crinone gel containing progesterone.

4.6.8 Medicated Vaginal Tampons: A medicated vaginal tampon, approved as a medical device by the Food and Drug Administration (FDA) is available (Ela Tampon, Rostam, Israel). This bifunctional tampon contains a polymeric delivery system (strips) that absorb menstrual fluid while gradually releasing lactic acid and citric acid. Ex. Brilliant pH tampons.

4.6.9 Vaginal Films: Vaginal films are polymeric drug delivery systems shaped as thin sheets, usually ranging from 220 to 240 μm in thickness. These systems are often square (approximately 5 cm × 5 cm) colorless and soft presenting a homogenous surface. Vaginal films are produced with polymers such as polyacrylates, polyethylene glycol, polyvinyl alcohol and cellulose derivatives. Ex. VCF vaginal contraceptive films.
4.7 Introduction to Rectum

4.7.1 Physiology and biopharmaceutical characteristics of rectum

The colon consists of the ascending, transverse and descending colons which encircle the small intestine; the sigmoid colon, which turns medially and downward; the rectum; and the anal canal. The rectum is about 15-20 cm long, and the anal canal is the last couple of centimetres of the colon that surrounds the anus. Clinically, the terminal end of the colon is usually referred to as the rectum [114].

The rectum has a good blood supply, and is characterized by absence of villi and a relatively small surface area (0.02-0.05 ml²). Rectum contains a small volume of viscous fluid (0.5-1.25 ml) which spread over the surface, and which has a clearly limited buffer capacity. Based on these factors, many drugs which are well absorbed orally are poorly absorbed rectally, even when administered in solution. Even if well absorbed, it is quite common that blood levels may vary after rectal absorption [115,116].

4.7.2. Permeability

The effective permeability of drugs across the intestinal epithelium is influenced by several physico-chemical and physiological properties and may differ in various intestinal regions [117]. Studies report that the absorption of water occurred at a lower degree in the rectum when compared with other parts of the gastrointestinal tract. They estimated that it might be explained by a smaller pore radius, tighter epithelium, less fluidity in the rectal membrane, lower number of pores in the rectal region, and a decreased mucosal surface area [118,119]. It has been proposed that the electrolytes and water are transported transcellularly in the colon/rectum, which is different in a high permeable
tissue in which the transport of electrolytes and water has been assumed to be by the paracellular route [120]. The tighter and less fluid rectal epithelium is probably due to a change in the lipid composition, such as increased cholesterol/phospholipid molar ratio and degree of saturation of fatty acid residues. Furthermore, Lennernas with his study group also suggest that an unstirred water layer is an essential factor since it might be thicker and more coherent in the colonic-rectal region [121] compared with what has been found in the jejunum in man [122].

The more pronounced effect of the absorption of drugs during an increased convective flow across the barrier is in agreement with indications that various absorption enhancers may be more effective in the colon/rectum compared with the small intestine [123]. Bile salts such as sodium glycocholate seem to bind with calcium ions and sodium caprate changes the pore size in the tight junctions of membranes. These promoters probably increase the permeability of membranes to hydrophilic macromolecules via the paracellular route. Sodium salicylate seems to increase transport by both paracellular and transcellular routes [124]. Nishihata [125] investigated the enhancement effect of salicylate on the rectal absorption of different types of drugs; theophylline as a neutral substance; lidocaine as a basic material; cefmetazole as acidic and levodopa which exists as a zwitterion in solution. Absorption of each drug was enhanced; particularly at pH values where the substances exist primarily in their ionic form. A requirement for the observed enhancement was that salicylate was present in the rectal membrane.
4.7.3 Effect of pH

The rectum as an absorption site has a higher pH (7-8) than that of the gastro-intestinal tract. It is not a favorable site for the absorption of most of the weak organic acids which have pKa values lower than the pH of the rectum, because most of the drug molecules exist in an ionized form in the rectum. If the pH of the drug absorption site in the rectum was temporarily lowered below the pKa value of the drug, increased rectal absorption of drug would be expected. Yagi and his study group [126] found that the mean areas under the plasma concentration-time curves (AUCs) following the administration of suppositories containing weak acids were larger than those of the suppositories containing bumetanide without weak acids (control) and those of an orally administered bumetanide suspension in rabbits. Moreover, the pH in the rectum decreased to between 2-4 for 30 minutes following the administration of the suppositories containing weak acids, like citric acid or tartaric acid.

The pH of the rectal fluid is determined by the contents of the rectum, because of the lack of buffering capacity [127]. Consequently, the absorption of the drug could be improved by adding acids or bases to a formulation until the balance of ionized and unionized forms of the drug is optimal. In this way, it could be possible to improve the solubility of the drug in the rectal fluid and at the same time ensure sufficient permeability. On the other hand, the study of Crommelin et al [128] showed that the rectum is able to secrete neutralizing agents when the luminal pH deviates from the physiological pH. The degree of the secretion depends on the magnitude of the deviation. In general, the dissociation reaction of a drug is an equilibrium reaction. Thus, if some of the undissociated form of a drug is eliminated from the system, new undissociated drug will be formed to compensate.
[129]. Consequently, if the proportion of the undissociated drug is 1-2 % then it would be absorbed.

4.8 Rectal drug delivery

4.8.1 Advantages of rectal drug delivery

- Useful in delivering drugs that cause nausea and vomiting.
- Irritation in stomach & small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drug may be avoided, also acidic & enzymatic degradation of the drug may be prevented.
- When oral intake is restricted, such as prior to x-ray studies or in patients with disease of upper GI tract or when the patient is unable to swallow.
- Useful in pediatric, geriatric & unconscious patients.
- Drug delivery can be stopped by removal of dosage form & drug absorption can be easily interrupted in case of accidental overdose or suicide attempts.

4.8.2 Disadvantages of rectal drug delivery

- Inconvenient for patients.
- The absorption of drugs is frequently irregular & difficult to predict.

4.9 Formulations

The following rectal formulations are available

4.9.1 Rectal semisolids: Rectal cream, gels and ointments are used for topical application to the perianal area for insertion within the anal canal. They largely are used to treat local conditions of anorectal pruritis, inflammation and pain and discomfort associated with hemorrhoids. The drugs include astringents (eg. Zinc oxide), protectants
and lubricants (eg. Cocoa butter, lanolin), local anaesthetics (eg. Pramoxine HCL), antipruritis and anti inflammatory agents (eg. Hydrocortisone).

The bases used in anorectal creams and ointments includes combinations of polyethylene glycol 300 & 3350, emulsion cream bases using cetyl alcohol & cetyl esters wax, and white petroleum and mineral oil. The preservatives like methylparaben, propylparaben, benzylacohol and butylated hydrocortisole (BHA) are also used. Several commercial rectal creams, ointments and gels available are - Anusol ointment (starch), Tronolane cream (pramoxine HCL), Analpram cream (Pramoxine), Diastat gel (Diazepam).

**4.9.2 Rectal suppositories:** Rectal suppositories are the most common dosage form used for rectal drug administration and represent greater than 98 % of all rectal dosage forms. Typically, these are torpedo-shaped dosage forms composed of fatty bases (low-melting) or water-soluble bases (dissolving) which vary in weight from 1 g (children) to 2.5 g (adult). Lipophilic drugs are usually incorporated into water-soluble bases while hydrophilic drugs are formulated into the fatty base suppositories. For suppositories made from fatty bases, melting should occur rapidly near body temperature (37 °C). Ideally the resultant melt would readily flow to provide thin, broad coverage of the rectal tissue, thereby minimizing lag time effects due to slow release of the drug from the suppository base. Water-soluble suppositories should likewise readily dissolve at 37 °C to facilitate drug release and subsequent absorption. Commercially available suppository products are Dulcolax (Bisacodyl), Canasa (Mesalamine) Numorphan (Oxymorphane), Anusol HC (Hydrocortisone) Panadol (Paracetamol).
4.9.3 Rectal liquids: Rectal suspensions, emulsions & solutions represent rectal dosage forms with very limited application, largely due to inconvenience of use and poor patient compliance. In many cases, these formulations are utilized to administer contrast media and imaging agents for lower GI roentgenography.

Enema: These are used for local and systemic action. The drugs like hydrocortisone (local effect) or aminophylline (systemic effect) etc are used in this dosage form.

Evacuation enema: These enemas are used for cleansing of bowel. The agents are sodium phosphate and sodium biphosphate, glycerin and docusate potassium and light mineral oil.

Rectal aerosols or foams: Rectal aerosol foam products are also accompanied by applicators to facilitate administration. The applicator is attached to the container and filled with a measured dose of product. Metered dose aerosols are available. The inserter is inserted in to the anus and the plunger is pushed to deliver the drug product. Marketed rectal aerosols are like Proctofoam HC, Cortifoam etc.

4.10 Bioadhesion

Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between polymer and / or co-polymer and a biological membrane. In case of polymer attached to the mucin layer of the mucosal tissue, the term ‘mucoadhesion’ is employed.

‘Bioadhesive’ is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time.
Bioadhesives are classified into three types based on phenomenological observation, rather than on the mechanism of bioadhesion [130].

**Type-I:** Bioadhesion is characterized by adhesion occurring between biological layers without involvement of artificial materials. Cell diffusion and cell aggregation are good examples.

**Type-II:** Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.

**Type-III:** Bioadhesion can be defined as an adhesion of artificial substances to biological substrate such as adhesion of polymer to skin or other soft tissue.

4.10.1 Mechanism of bioadhesion

Bioadhesion occur in 3 stages namely.

**Stage-1** Involves an intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.

**Stage-2:** After contact is established, penetration of the bio-adhesive into the surface of the tissue takes place.

**Stage-3:** Inter penetration of the chains of the bioadhesive with those of the mucous takes place and the low chemical bonds settles down.
The bond is established between the mucus and the biological substances mainly due to both physical and chemical interactions. Physical or mechanical bonds results from enlargement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

4.10.2 Theories of bioadhesion / mucoadhesion

Several theories have been proposed to explain the fundamental mechanism of adhesion. The surface characteristics, composition of the mucoadhesive materials as well as the substrate and the associated applied force to bring the adherence of substrate in contact, are important parameters to be considered in assessing mucoadhesion. The bonding occurs chiefly through both, physical and chemical interactions.

a. Wetting theory

Wetting theory is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behavior in terms of a liquid or a paste to spread over a biological system. The work of adhesion [expressed in terms of surface and interfacial tension (Y)] is defined as energy per cm² released when an interface is formed.

According to Dupres equation work of adhesion is given by:

$$W_a = Y_A + Y_B - Y_{AB}$$

Where A & B refer to the biological membranes and the bioadhesive formulation respectively. The work of cohesion is given by:

$$W_c = 2Y_A$$ or $$Y_B$$
For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by:

\[ S_{B/A} = Y_A - (Y_B + Y_{AB}) \]

\( S_{B/A} \) should be positive for a bioadhesive material to adhere to a biological membrane.

**b. Diffusion theory**

According to this theory, the polymer chains and the mucus mix to a sufficient depth, to create a semipermanent adhesive bond. The bioadhesive material and the glycoprotein are brought into close contact. The polymer chains penetrate the mucous; the exact depth of penetration depends on the diffusion co-efficient, time of contact and other experimental variables. The diffusion co-efficient depends on the molecular weight and decreases rapidly as the cross-linking density increases as shown by Peppas.

**c. Electronic theory**

According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucous glycoprotein network because of differences in their electronic structure. This result in the formation of an electronic double layer at the interface and adhesion occur due to attractive forces across the double layers.

**d. Fracture theory**

Fracture theory of adhesion is related to separation of two surfaces after adhesion.

The fracture strength is equivalent to adhesive strength as given by

\[ G = (E\varepsilon/L)^{1/2} \]
Where: E- Young's modules of elasticity

ε - Fracture energy

L - Critical crack length when two surfaces are separated

e. Absorption theory

According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished:

(I) Primary chemical bonds covalent in nature, which are undesirable in as their high strength may result in permanent bonds.

(II) Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Waals forces and hydrogen and hydrophobic bonds [131,132].

4.10.3 Factors affecting muco / bioadhesion

Structural and physicochemical properties of a potential bioadhesive material influence bioadhesion [133].

High molecular weight polymers are generally used for mucoadhesion and these polymers may be either natural or synthetic. Synthetic polymers are obtained by polymerization of monomers in presence or absence of cross-linking agents to give either a cross-linked water insoluble polymer or a linear polymer.
Hydrogen bonding due to presence of hydrophilic groups such as -COOH or -OH plays a significant role in mucoadhesion. Studies have shown that strongly anionic polyelectrolytes particularly those with high charge density of -COOH or –OH functionality are better candidates for bioadhesion than neutral molecules.

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also by the nature of the surrounding media. These factors are mainly divided in three classes:

a. Polymer related factors

b. Environment related factors

c. Physiological variables

4.10.4 Possible routes for drug transport across the oral mucosa

The majority of drugs move across the epithelial membrane including the oral epithelia by passive mechanisms which are governed primarily by the laws of diffusion. In case of single diffusion, two potential routes of material transport across the epithelium are:

1. The paracellular pathway and
2. The transcellular pathway

The paracellular route involves passage of molecules through the inter-cellular space, while transcellular route involving passage into and across the cell (intracellular). The most important property that determines whether a given non-electrolyte will pass rapidly across the oral mucosa seems to be its relative partition between lipid and water. Substances with a high solubility in lipid are expected to traverse the oral mucosa more
easily moving along or across the lipid rich plasma membranes of the epithelial cells while water soluble substances and ions probably move through the intercellular spaces. 

*Passive diffusion* is undoubtedly the major transport mechanism for drugs; the nutrients from the mouth are shown to be absorbed by carrier systems i.e. facilitated diffusion.

Transmucosal permeation of polar molecules, such as peptide based pharmaceuticals, may be by the way of paracellular route. However, several barriers exist during the course of paracellular permeation:

1. *Basal lamina* whose barrier function is dependent upon the molecular weight of the permeant molecules and its reactivity with the barrier as well as the structural and functional factors of the barrier.
2. *Membrane coating granules*, which extrude into the intercellular region of both keratinized and non-keratinized oral epithelium.
3. *The keratin layer whose* barrier function in oral mucosa is not as well defined as in the skin, although rate of permeation of water was shown to be greater in nonkeratinized than keratinized oral epithelium [134].

### 4.10.5 Permeation enhancers

Permeation enhancers are substances added to pharmaceutical formulation in order to increase the membrane permeation rate or absorption rate of a co-administered drug. They are used to *improve bioavailability* of drugs with normally poor membrane permeation properties. The permeation enhancer to be clinically accepted must increase bioavailability or increase membrane permeability without damaging the membrane and causing toxicity. Membrane permeation can be a limiting factor for many drugs
administered via the buccal or sublingual routes. For those compounds that penetrate the oral mucosal surface slowly or incompletely and for which effective systemic absorption cannot be attained, one strategy that can be used by those interested in their buccal or sublingual delivery is the co-administration of the permeation enhancing excipient. Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination. Differences in the cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions, are the structural and functional factors that vary the effectiveness of the enhancer from site to site [135].

4.10.6 Mechanism of Buccal Absorption Enhancer

The mechanism by which enhancers act are been poorly understood. Surfactants such as sodium lauryl sulphate interact at either the polar head groups or the hydrophilic tail regions of the molecules comprising the lipid bilayer. Interactions at these sites will probably have the effect of disrupting the packing of the lipid molecules, increasing the fluidity of the bilayer and facilitating drug diffusion. Interaction of an enhancer with the polar head groups may also cause or permit the hydrophilic regions of adjacent bilayers to take up more water and move apart, thus opening the paracellular pathway. Non-ionic Surfactants, long chain fatty acids and alcohols also increase membrane fluidity and have the capacity to solubilize and extract membrane components, thereby increasing the permeability. Agents such as DMSO, polyethylene glycol, and ethanol can, if present in sufficiently high concentrations in the delivery vehicle, enter the aqueous phase of the
stratum corneum and alter its solubilizing properties, thereby enhancing the partitioning of drugs from the vehicle into the skin.

All these agents produce varying degree of enhancement depending on the characteristics of the permeant, the composition of the delivery vehicle, whether the tissue was pretreated with enhancer and other factors. An important issue to be considered is toxicity of penetration enhancers [135].

Mechanisms by which permeation enhancers are thought to improve mucosal absorption include the following:

- Changing mucus rheology.
- Increasing fluidity of lipid bilayer membrane.
- Affecting the components involved in the formation of intracellular junctions.
- Overcoming the enzymatic barrier.
- Increasing the thermodynamic activity of drugs.
- Protein denaturation or extraction.
4.11 Review of Research Papers

Fergany Mohammed A, et al., Prepared slow-release buccal bioadhesive tablets of miconazole nitrate and carried out in vitro and in vivo evaluation. The tablets were prepared by using polymer mixtures of buccoadhesive materials such as hydroxypropyl methylcellulose, sodium carboxy methylcellulose, carbopol 934P, and sodium alginate. The dissolution of miconazole from all the prepared tablets into phosphate buffer (pH 6.8) was controlled and followed non-Fickian release mechanisms. All the prepared tablets gave reasonable buccoadhesion time (2.45–3.65 h). They concluded that the prepared slow-release buccoadhesive tablets of miconazole would markedly prolong the duration of the antifungal activity with more patient convenience [136].

Noha Nafee A, et al., prepared mucoadhesive buccal patches of miconazole nitrate and studied in vitro/in vivo performance and effect of ageing. The patches were prepared with ionic polymers, sodium carboxymethyl cellulose (SCMC) and chitosan, or non-ionic polymers, polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and hydroxypropylmethyl cellulose (HPMC). Patches containing 10% w/v PVA and 5% w/v PVP showed optimum drug release. Study of the in vivo release from this formulation revealed uniform and effective salivary levels with adequate comfort and compliance during at least 6 h. however, in vivo release of the commercial oral gel product resulted in a burst and transient release of miconazole, which diminished sharply after the first hour of application. They concluded that PVA patches exhibited uniform and effective miconazole levels in vitro and in vivo (>5 h) without being drastically being influenced by ageing [137].
Madgulkar, et al., developed buccal adhesive miconazole tablet with prolonged antifungal activity. The simplex centroid experimental design was used to arrive at optimum ratio of Carbopol 934P, hydroxypropylmethylcellulose K4M and polyvinylpyrrolidone. Swelling index, mucoadhesive strength and in vitro drug release of the prepared tablets were determined. The optimized formulation was subjected to in vitro antifungal activity, transmucosal permeation, drug deposition in mucosa, residence time and bioadhesion studies. Dissolution of miconazole from tablets was sustained for 6 h. The prepared slow release buccoadhesive tablets of miconazole would markedly prolong the duration of antifungal activity. Comparison of in vitro antifungal activity of tablet with marketed gel showed that drug concentration above the minimum inhibitory concentration were achieved immediately from both formulations, but release from tablet was sustained upto 6 h, while the gel showed initially fast drug release. Drug permeation across buccal mucosa was minimum from the tablet as well as marketed gel, whereas in vitro residence time and bioadhesive strength of tablet was higher than gel. Thus, they concluded that buccoadhesive tablets of miconazole nitrate may offer better control of antifungal activity as compared to gel formulation [138].

Tarun, et al., studied Swelling-controlled release system of Miconazole nitrate for vaginal delivery. An aqueous solution of 15 % w/w poly (vinyl alcohol) was mixed with a specific amount of miconazole powder and cross-linked by freeze thawing. They studied the effect of the number of freeze thawing cycles at four different levels. The effect of the presence of PEG was studied by mixing different concentrations of two different PEG grades (PEG1000, PEG1450). They demonstrated that the drug release was upto 10 h and was independent of number of freeze thaw cycles. The drug release was
lower from the batches containing PEG 1000 irrespective of concentrations when compared to PEG1450 [139].

**Libero Italo Giannola, et al.**, Formulated 5-fluorouracil (5-FU) buccal tablets for locoregional chemotherapy of oral squamous cell carcinoma. The drug release and histological effects on reconstituted human oral epithelium and porcine buccal mucosa were studied. The study reported that the development of buccal tablets suitable for direct application of low doses of 5-FU on cancer lesions. The topical administration could be effective on tumor area while systemic undesired side effects are avoided. Matrix buccal tablets, were designed for 5-FU local delivery, developed, prepared and release tests showed a highly reproducible Higuchian drug discharge. After tablet administration on buccal tissue specimens, the occurrence of histomorphological effects of 5-FU was highlighted. Apoptotic events were registered in all samples treated while only negligible amounts of 5-FU permeated the buccal membrane and reached the simulated plasma. They concluded that loaded matrix tablets containing 5 % of 5-FU could be a useful means in topical treatment of oral squamous cell carcinoma [140].

**Dhiman M, et al.**, formulated bioadhesive gels containing 5-fluorouracil (5-FU) for the treatment of oropharyngeal cancer. They investigated physicochemical interactions between FU and polymers by X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectrophotometry and differential scanning calorimetry (DSC). The gel formulations containing FU were prepared by using Poloxamer 407, HPMC K 15 M, and Gantrez S-97 (polymethylvinylether-co-maleic anhydride). They concluded that with increase in proportion of HPMC K 15 M and Gantrez S-97, bioadhesiveness of the gels is also
increased. *In vitro* release studies indicated that release could be sustained up to 8 h [141].

**Munish, et al.,** studied the effect of permeation enhancers on the transbuccal delivery of 5-fluorouracil. Sodium deoxycholate (SDC), sodium dodecyl sulphate (SDS), Sodium tauroglycocholate (STGC) and oleic acid were the permeation enhancers and *in vitro* buccal permeability was assessed. The order of permeation enhancement was STGC > SDS > SDC > oleic acid. Histological investigations were also performed on buccal mucosa and indicated no major morphological changes. They also evaluated the enhancing effect of STGC on the buccal absorption of FU from the mucoadhesive gels in rabbits. The authors concluded that, STGC emerged as the most efficient enhancer among the enhancers investigated for buccal absorption of FU and at 3 % of concentration, STGC showed the highest Kᵢ and EF across the buccal mucosa. From the histological investigations, they revealed that increase in intercellular space and swelling, especially inside the cells may be responsible for the permeation enhancement [142].

**Woolfson AD, et al.,** formulated bioadhesive cervical patch for the delivery of 5-fluorouracil for the treatment of cervical intraepithelial neoplasia (CIN). The patch was bilaminar design; with drug-loaded bioadhesive film cast from a gel containing 2 % (w/w) Carbopol® 981 plasticized with 1 % (w/w) glycerin. Release of 5-fluorouracil from the bioadhesive layer into an aqueous sink was rapid but was controlled down to an undetectable level through the backing layer. It was observed that 5-fluorouracil is substantially released through human cervical tissue samples over approximately 20 h. They concluded that bioadhesive and drug release characteristics of the 5-fluorouracil
cervical patch would be suitable for further clinical investigation as a drug treatment for CIN [143].

**Galandiuk S, et al.,** studied suppository delivery of 5-fluorouracil in rectal cancer. They compared suppository and intravenous 5-FU administration with respect to myelosuppression and tissue concentrations. White blood cell count, serum albumin, alkaline phosphatase, creatinine, and aspartate aminotransferase (AST) were determined before and serially after 5-FU administration in rats. Effect of 5-FU on portal and systemic blood, rectal, iliac lymph node, liver, and lung tissue was also studied at 30 min, 1, 3, 6, and 12 h after drug administration. They observed that no toxicity was observed in 5-FU suppository animals, whereas 63% of 5-FU i.v animals had diarrhea. Weight loss and myelosuppression occurred only in 5-FU i.v. animals. They concluded that 5-FU suppositories are associated with fewer systemic side effects and higher rectal 5-FU concentrations than with 5-FU i.v. administration [144].

**Marija Glavas Dodov, et al.,** formulated Liposome gels bearing 5-fluorouracil, intended for topical application and evaluated. Different formulations of liposomes were prepared by the film hydration method by varying the lipid phase composition (PL 90H/cholesterol mass ratio) and hydration conditions of dry lipid film (drug/aqueous phase mass ratio). Topical liposome gels were prepared by incorporation of lyophilized liposomes into a structured vehicle (1% m/m, chitosan gel base). Also, hydrogels containing different concentrations of 5-fluorouracil were prepared and drug release properties were investigated. The release rate of 5-FU from topical liposome gels was affected by the formulation variables. Comparing the liposome gels with hydrogel formulations, the release rate of liposome-entrapped drug was prolonged, while a steady-state release rate,
established after 1.5 hours, suggests that the liposomes function as a reservoir system for continuous delivery of the encapsulated drug substance. They concluded that, developed drug delivery showed the suitability for prolonged action of topically applied antineoplastic agents, with fewer side effects than conventional formulations [145].

Erem Bilensoy, et al., formulated thermosensitive mucoadhesive gel formulation loaded with 5-FU: cyclodextrin complex for HPV-induced cervical cancer. 5-fluorouracil has been formulated in a vaginal gel using the thermosensitive polymer Pluronic® F127 together with alternative mucoadhesive polymers e.g., hyaluronic acid, Carbopol 934 and hydroxypropylmethylcellulose. 5-fluorouracil was incorporated as its inclusion complex with 1:1 molar ratio with either β-cyclodextrin or hydroxypropyl-β-cyclodextrin. Following the characterization of drug: CD complexes, thermosensitive gel formulations containing different mucoadhesive polymers and the drug in free or complexed form were characterized. It was observed that complexation with cyclodextrin accelerated the release of 5-FU (except Carbopol containing formulation). They concluded that, formulation of an anticancer drug in free form or in complex with natural or synthetic cyclodextrins may exert favorable properties such as thermosensitive characteristics, controlled and prolonged release profile and high anticancer activity [146].

Shegokar Ranjita, et al., studied in-vitro release of paracetamol from suppcocire suppositories and also studied role of additives. Effect of various additives such as sodium lauryl sulfate (SLS), dioctyl sulfosuccinate (DOSS), Labrasol, lecithin, Miglyol 812, aerosil, Capryol PGMC (CPGMC) and span 80 were studied on drug release. White coloured suppositories were formulated and evaluated for various parameters like appearance, melting range, uniformity of weight, disintegration time, % drug content and
in vitro drug release. The Suppocire bases selected were evaluated for displacement value with respect to drug and noted to be 1.4, 1.46, 1.4 and 1.43 for Suppocire D, C, NCX and CP respectively. Paracetamol Suppocire suppository using amphiphilic base in combination with Labrasol showed optimal drug release as compared to other Suppocire bases. The developed paracetamol Suppocire suppositories gave controlled as well as fast release depending upon the additives added to the formulation and proved to be a good suppository base. Newly incorporated additives such as Labrasol and Capryol PGMC have promise to be used as adjuvants in suppository formulation [147].

Ofokansi KC, et al., formulated and evaluated microspheres based on gelatin-mucin admixtures for the rectal delivery of cefuroxime sodium. Cefuroxime sodium-loaded microspheres containing admixtures of gelatin and porcine mucin were prepared via an emulsification-crosslinking technique. The drug entrapment efficiency of the microspheres was evaluated in citrate/phosphate buffer (pH 7.4) while the swelling properties was evaluated in both simulated gastric fluid (SGF) without pepsin and simulated intestinal fluid (SIF) without pancreatin (pH 1.2). Release of cefuroxime sodium from the microspheres was evaluated in vitro in SIF and further evaluated in vivo after rectal administration to male Wistar rats. Microspheres formulated with equal portions of gelatin and mucin, showed high entrapment efficiency and led to a greater drug release (up to 85 %) and also a high bioavailability of the incorporated drug. Formulations based on varying portions of gelatin and mucin also showed high drug loading efficiency, resulted in high drug release in SIF within 3 h. Drug release from the different formulations was observed to be rapid and generally showed a biphasic pattern. They concluded that inclusion of S-mucin in the composition of the microspheres has an
enhancer effect on the release and rectal bioavailability of cefuroxime sodium that may be exploited in the design of a rectal delivery system of the drug [148].

**Singh S, et al.**, formulated buccal bioadhesive tablets containing clotrimazole and evaluated. Buccal bioadhesive tablets of clotrimazole (CTZ) and clotrimazole: hydroxypropyl-β-cyclodextrin (CTZ-HPβCD) complex were prepared by using polymer xanthan gum in combination with carbopol 974P. The prepared formulations were evaluated for physicochemical characteristics, swelling index, microenvironment pH, *in-vitro* drug release, bioadhesion strength, residence time and duration of antifungal activity (*in-vitro*). The dissolution of CTZ from the prepared tablets into phosphate buffer (pH 6.8) was controlled up to 8 h. All the prepared tablets gave reasonable *in-vitro* residence time. X-ray diffraction (XRD) studies of the CTZ-HPβCD complex, made by kneading and freeze-dried method, showed no CTZ crystal signals, demonstrating the inclusion of CTZ in the hydrophobic cavity of hydroxypropyl-β-cyclodextrin (HPβCD) and formation of amorphous inclusion complex. They concluded that the prepared buccal bioadhesive tablets of CTZ may increase the patient compliance by reducing the frequency of administration and improving overall therapy of oral candidiasis [149].

**Lei Wang, et al.**, formulated and evaluated novel ketoconazole bioadhesive effervescent tablet for vaginal delivery. Carbomer (Carbopol 974P, Carbopol 934P), hydroxypropylmethylcellulose (HPMC) and hydroxypropyl cellulose (HPC) were used as candidate bioadhesive polymers. Effervescent was incorporated into the formulations as a disintegration agent. The swelling behavior and bioadhesive strength of the drug-free tablets were investigated. The formulation containing 100 mg of effervescent, with the Carbopol 934P: HPC ratio of 1:9 was considered as optimized formulation. *In vivo* drug
residence tests were carried out by administering the formulation to female rats. They concluded that incorporation of effervescent into the bioadhesive tablets leads to the increase in the swellings and the rate of drug release and conversely decrease the tackiness. It is also observed that the KTZ release and bioadhesion properties of bioadhesive tablets can be controlled by changing the polymer type, polymer concentration and effervescent content [150].

**Rakesh Kumar Dev, et al.,** formulated novel microbially triggered colon specific delivery system of 5-Fluorouracil and **in vitro, in vivo** cytotoxic study was also carried out. A $3^2$ full factorial design was used for optimization. The independent variables employed were amount of pectin and amount of starch paste, each at three levels. The evaluated responses were hardness, percent cumulative drug release (% CDR) at 5$^{th}$ h and t90%. Drug release studies were carried out using change over media [pH 1.2, 7.4 and 6.5 in presence of 4 % (w/v) rat caecal contents]. It was observed that optimized formulation consisting of pectin (66.67 %w/w) and starch paste (15 %w/w) released negligible amount of drug at pH 1.2 and pH 7.4 whereas significant (p < 0.05) drug release was observed at pH 6.5 in presence of 4 % (w/v) rat caecal contents. The optimized formulation was subjected to **in vivo** roentgenographic studies in New Zealand white rabbits. Roentgenographic studies corroborated the **in vitro** observations. They concluded that pectin-based coated matrix tablet to be a promising system for the colon specific delivery of 5-FU for colon carcinoma [151].
4.12 Drugs profile [152]

Miconazole Nitrate

![Structure of Miconazole nitrate (MN)](image)

**Figure 4: Structure of Miconazole nitrate (MN)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>$C_{18}H_{14}Cl_4N_2O.HNO_3$</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>479.1 gm.</td>
</tr>
<tr>
<td>IUPAC name</td>
<td>1-[(2RS)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-Dichlorophenyl)ethyl]-1H-imidazole nitrate.</td>
</tr>
<tr>
<td>Description</td>
<td>A white or almost white powder.</td>
</tr>
<tr>
<td>Solubility</td>
<td>Miconazole nitrate is freely soluble in methanol, slightly soluble in ethanol (95%) and in chloroform, very slightly soluble in water and in ether.</td>
</tr>
<tr>
<td>Storage</td>
<td>Miconazole must be stored in an airtight container, protected from light.</td>
</tr>
<tr>
<td>Preparations</td>
<td>Miconazole nitrate cream, gels and pessaries.</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Miconazole is an imidazole antifungal agent and acts by interfering with permeability of fungal cell membrane. It has wide antifungal spectrum and also possesses some antibacterial activity.</td>
</tr>
</tbody>
</table>
Usual dose 100 mg per dose
Absorption Miconazole nitrate is incompletely absorbed from GI tract.
Elimination half life 24 hr.
Therapeutic uses It is used in the treatment of oral candidiasis, vaginal candidiasis, caused by Dermatophytes and candida species.

Fluorouracil

![Figure 5: Structure of 5-Fluorouracil (5-FU)](image)

Molecular formula C₄H₃FN₂O₂
Molecular weight 130.1
Melting point 282 to 283 °C
Description White to practically white, odourless, crystalline powder
Dissociation Constant 8.0
Solubility Sparingly soluble in water, slightly soluble in alcohol, practically insoluble in CHCl₃
Storage Stored in air tight containers protected from light.
Formulations Intravenous route, capsules.
**Identification**

Light absorption in the range 200-400 nm of a 10 µg/ml solution in 7.4 pH buffer exhibits absorption maximum at 267 nm

**pH**

4.5 to 5.0

**Mechanism of action**

The nucleotide of 5-FU, 5-Fluoro-2-deoxy-thymidylate synthase blocks the conversion of deoxyuridic acid to deoxy thymidylic acid

**Pharmacokinetic profile of 5-FU**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half life</strong></td>
<td>15 to 20 min</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>17.5 L/70kg</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>63 L/h</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>94%</td>
</tr>
<tr>
<td><strong>Therapeutic uses</strong></td>
<td>Anti neoplastic and immunosuppressive agent</td>
</tr>
</tbody>
</table>
4.13 Polymers profile [153]

Chitosan

![Structure of chitosan](image)

**Figure 6: Structure of chitosan**

**Nonproprietary Names**
BP: Chitosan Hydrochloride, PhEur: Chitosan Hydrochloride

**Synonyms**
2-Amino-2-deoxy-(1,4)-b-D-glucopyranan; chitosani hydrochloridum; deacetylated chitin; deacetylchitin; b-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-b-D-glucopyranosamine).

**Chemical Name**
Poly-β-(1,4)-2-Amino-2-deoxy-D-glucose

**Molecular Weight**
Chitosan is commercially available in several types and grades that vary in molecular weight by 10 000–1 000 000, and vary in degree of deacetylation and viscosity.

**Functional Category**
Coating agent, disintegrant, film-forming agent, mucoadhesive, tablet binder, viscosity increasing agent.

**Application**
Controlled drug delivery, mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and gene delivery. Chitosan has been processed into several pharmaceutical forms including gels, films, beads, microspheres, tablets and coatings for liposomes.

**Description**
Chitosan occurs as odorless, white or creamy-white powder or flakes.

**Safety**
Generally regarded as a nontoxic and nonirritant material biocompatible with both healthy and infected skin and biodegradable.
Carbopol 71G

**Synonyms**
Acritamer, acrylic acid polymer, Carbopol, carboxy Vinyl polymer.

**Chemical Name**
Carboxypolymethylene.

**Molecular weight**
3.5 billions.

**Appearance**
Fluffy, white, mildly acidic polymer.

**Description**
Carbopol is a white-colored, fluffy, acidic, and hygroscopic powder with a slightly characteristic odor. The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product benefits. Carbopol polymers have an average equivalent weight of 76 per carboxyl group.

**Bulk Density**
Approximately 208 kg/m$^3$ (13 lbs. ft$^3$)

**Viscosity**
4000-11000

**Specific gravity**
1.41

**Moisture content**
2.0 % maximum

**Equilibrium moisture content**
8-10 %

**pKa**
6.0 + 0.5

**pH of 1.0% dispersion**
2.5 - 3.0

**pH of 0.5% dispersion**
2.7 - 3.5

**Equivalent weight**
76 + 4

**Ash content**
0.009 ppm (average)

**Glass transition temp**
100-105 °C (212-221 °F)
### Carboxymethyl tamarind

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>yellowish powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>Cold water soluble</td>
</tr>
<tr>
<td>Ionic characteristic</td>
<td>Anionic</td>
</tr>
<tr>
<td>pH</td>
<td>9 - 11</td>
</tr>
<tr>
<td>Moisture</td>
<td>10 % max</td>
</tr>
<tr>
<td>Ash content</td>
<td>20 % max</td>
</tr>
<tr>
<td>Viscosity</td>
<td>60,000-65,000cps</td>
</tr>
<tr>
<td>Degree of substitution</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Noveon AA-1</strong></td>
<td><strong>Chemical nature</strong></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Polycarbophil occurs as fluffy, white to off-white, mildly acidic polymer powder with slightly acetic odor.</td>
</tr>
<tr>
<td><strong>Typical properties:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Acidity / alkalinity</strong></td>
<td>pH 2.5-3.0</td>
</tr>
<tr>
<td><strong>Ash content</strong></td>
<td>0.009 ppm</td>
</tr>
<tr>
<td><strong>Density (bulk)</strong></td>
<td>0.19-0.24 g/cm³</td>
</tr>
<tr>
<td><strong>Equilibrium moisture content</strong></td>
<td>8-10 %</td>
</tr>
<tr>
<td><strong>Dissociation constant</strong></td>
<td>6.0±0.5</td>
</tr>
<tr>
<td><strong>Glass transition temp</strong></td>
<td>100-105 °C</td>
</tr>
<tr>
<td><strong>Moisture content</strong></td>
<td>2.0 % max</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>1.41</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Thickening agent</td>
</tr>
<tr>
<td></td>
<td>Used in bioadhesive drug delivery system.</td>
</tr>
</tbody>
</table>
Sodium alginate

![Structure of sodium alginate](image)

**Figure 7: Structure of sodium alginate**

**Nonproprietary Names**
BP: Sodium Alginate, PhEur: Sodium Alginate, USP-NF: Sodium Alginate

**Synonyms**
Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; natrii alginas; Protanal; sodium polymannuronate.

**Functional Category**
Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent

**Applications**
Oral and topical pharmaceutical formulations, binder and disintegrant in tablets, diluents in capsule, sustained-release polymer in oral formulations, creams, gels and as a stabilizing agent for oil-in-water emulsions

**Acidity/alkalinity**
pH ~ 7.2 (1% w/v aqueous solution)

**Solubility**
Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures, slowly soluble in water, form a viscous colloidal solution.

**Viscosity**
Typically, a 1% w/v aqueous solution, at 20°C, will have a viscosity of 20–400 mPa s (20–400 cP).

**Safety**
It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.
4.14 Excipients profile [153]

Microcrystalline Cellulose (MCC)

**Figure 8: Structure of Microcrystalline Cellulose**

<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>BP: Microcrystalline cellulose Ph Eur: Cellulosum microcrystalline USP NF: Microcrystalline cellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonyms</td>
<td>Avicel, cellulose gel, E460, Emcocel, Fibrocel, Tabulose</td>
</tr>
<tr>
<td>Empirical Formula</td>
<td>((\text{C}<em>6\text{H}</em>{10}\text{O}_5)_n) Where (n \approx 220) Molecular weight (\approx 36000)</td>
</tr>
<tr>
<td>Functional Category</td>
<td>Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.</td>
</tr>
<tr>
<td>Applications</td>
<td>Used as a diluent in oral tablet and capsules, where it is used in wet granulation and direct compression process. It also has some lubricant and disintegrant properties that make it useful in tabletting.</td>
</tr>
<tr>
<td>Description</td>
<td>White colourless, odorless, tasteless, crystalline powder.</td>
</tr>
<tr>
<td>Safety</td>
<td>MCC is widely used in oral pharmaceutical formulations and food products and is generally regarded as non-toxic and non irritant material. It is not absorbed systemically followed by oral administration and thus has little toxic potential.</td>
</tr>
</tbody>
</table>
Magnesium Stearate

Nonproprietary Names  
BP: Magnesium stearate, JP: Magnesium stearate, PhEur: Magnesii stearas, USP: Magnesium stearate

Synonyms  
Magnesium octadecanoate; stearic acid magnesium salt; octadecanoic acid, magnesium salt.

Structural Formula  
\[\text{[CH}_3\text{(CH}_2\text{)}_{16}\text{COO]}_2\text{Mg}\]

Empirical Formula  
C\(_{36}\)H\(_{70}\)MgO\(_4\)

Molecular Weight  
591.34

Functional Category  
Tablet and capsule lubricant.

Applications  
Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%. It is also used in barrier creams.

Description  
Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Safety  
Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.
Talc

Non proprietary Name
BP: Purified talc JP: Talc PhEur: Talcum USP: Talc

Synonyms
Magsil Star; Powdered talc; Purified French chalk; Purtaclc; soapstone; steatite.

Empirical Formula
Mg₆(Si₂O₅)₄(OH)₄.

Functional Category
Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Description
Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Applications
Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations and in a novel powder coating for extended-release pellets and as an adsorbant.

Safety
Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas.
Sodium deoxycholate

![Structure of Sodium deoxycholate](image)  

**Figure 9: Structure of Sodium deoxycholate**

**Synonyms**  
7-Deoxycholic acidsodium salt; Desoxycholic acid sodium salt; 3α, 12α-Dihydroxy-5β-cholanic acid sodium salt

**Formula**  
C_{24}H_{39}NaO_{4}·H_{2}O

**Molecular Weight**  
432, 57 g/mol

**pH**  
7.5 – 9.5 at 43,3 g/l at 25 °C

**Detergent Class**  
Ionic (anionic)

**Purity (by HPLC)**  
≥98%

**Water solubility**  
ca.43. 3 g/l at 20 °C

**Functional Category**  
surfactant, permeation enhancer

**Carcinogenicity**  
No component of this product presents at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC

**Storage**  
Store in cool place. Keep container tightly closed in a dry and well-ventilated place.