VAGINAL DRUG DELIVERY

The vagina, in addition to being a genital organ with functions related to conception it serves as a potential route for drug administration.

- **Mainly used for local action in the vaginal region.**
- **It has the potential of delivering drugs for systemic effects and uterine targeting.**

Advantages of vaginal delivery:

- Ease of access
- Reduced side effects

- Great permeation area
- High vascularization

- Relative low enzymatic activity
- Avoidance of first pass metabolism

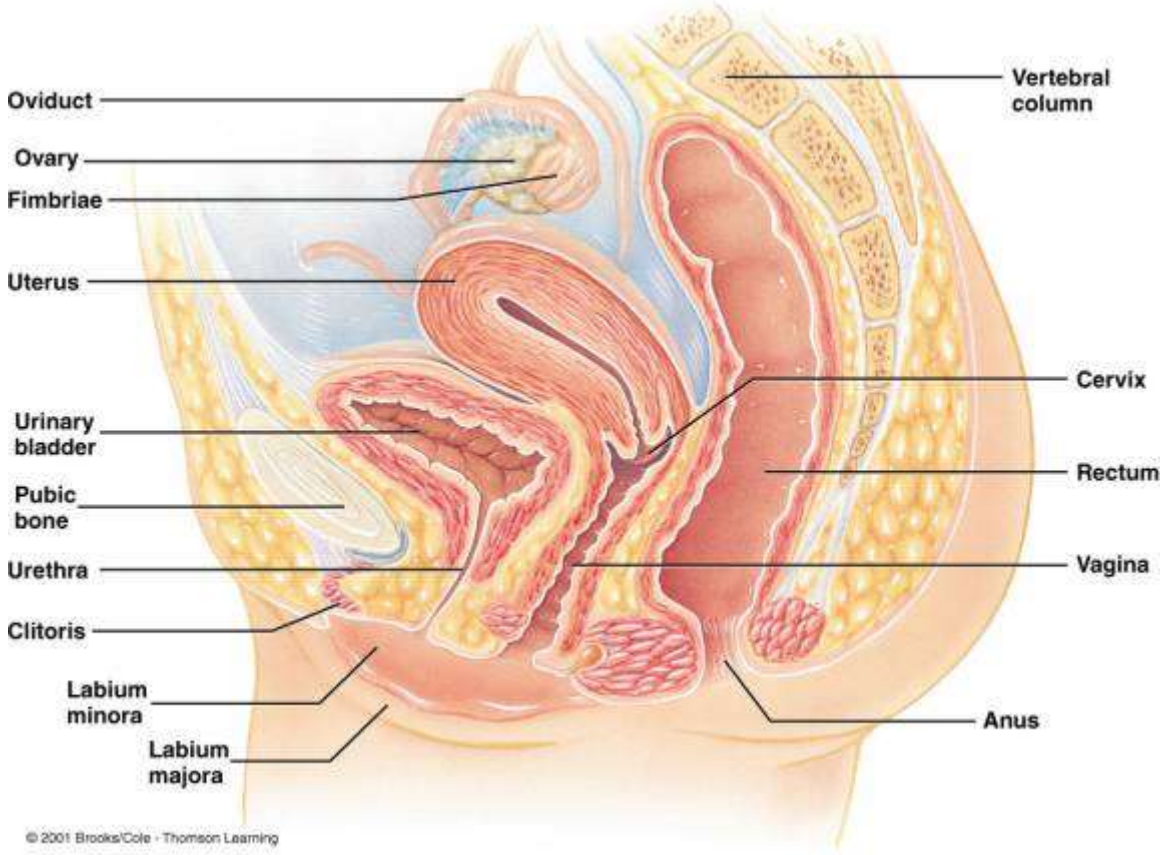
Drawbacks of vaginal delivery:

- Unawareness & gender-specificity
- Genital hygiene issues

- Menstrual cycle-associated vaginal changes
- Coitus interference

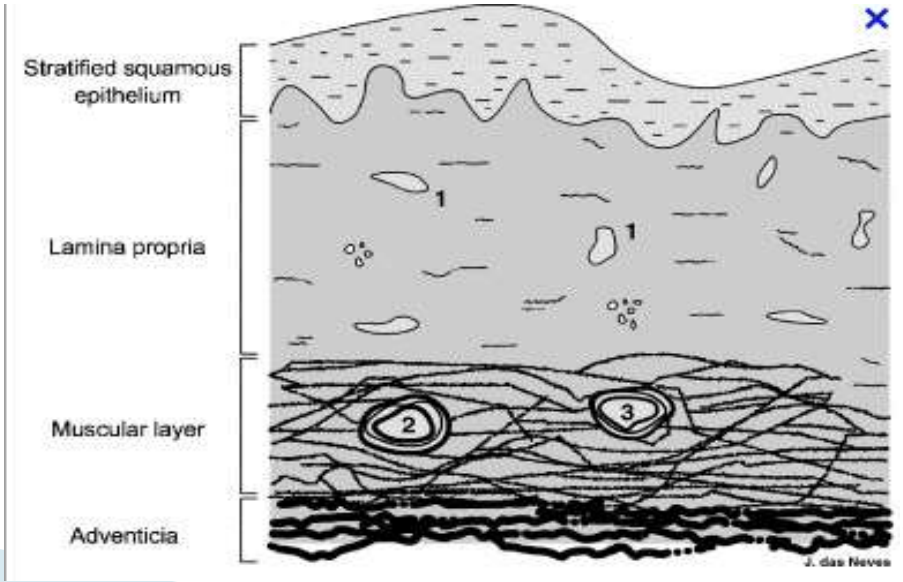
- Local side effects
- variable drug permeability

Vaginal anatomy and physiology:



Anatomy of vaginal mucosa:

- Outer covering of areolar tissue
- A middle layer of smooth muscle
- Inner lining of stratified squamous epithelium
  - Forms ridges and rugae
- No secreatory glands but kept moist by cervical secretions

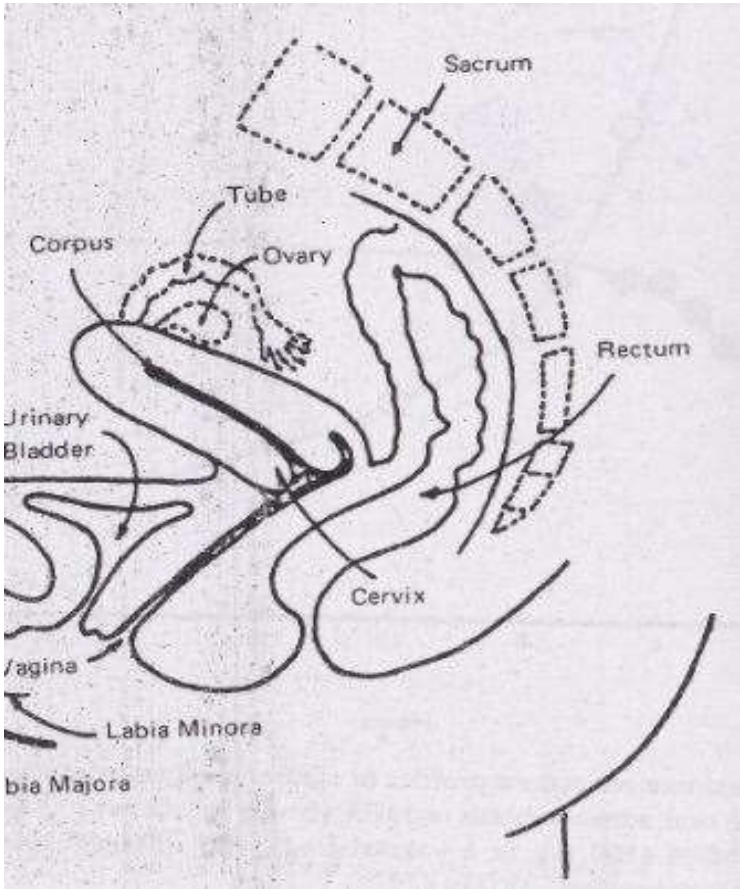


Physiology and Dynamics - Vagina

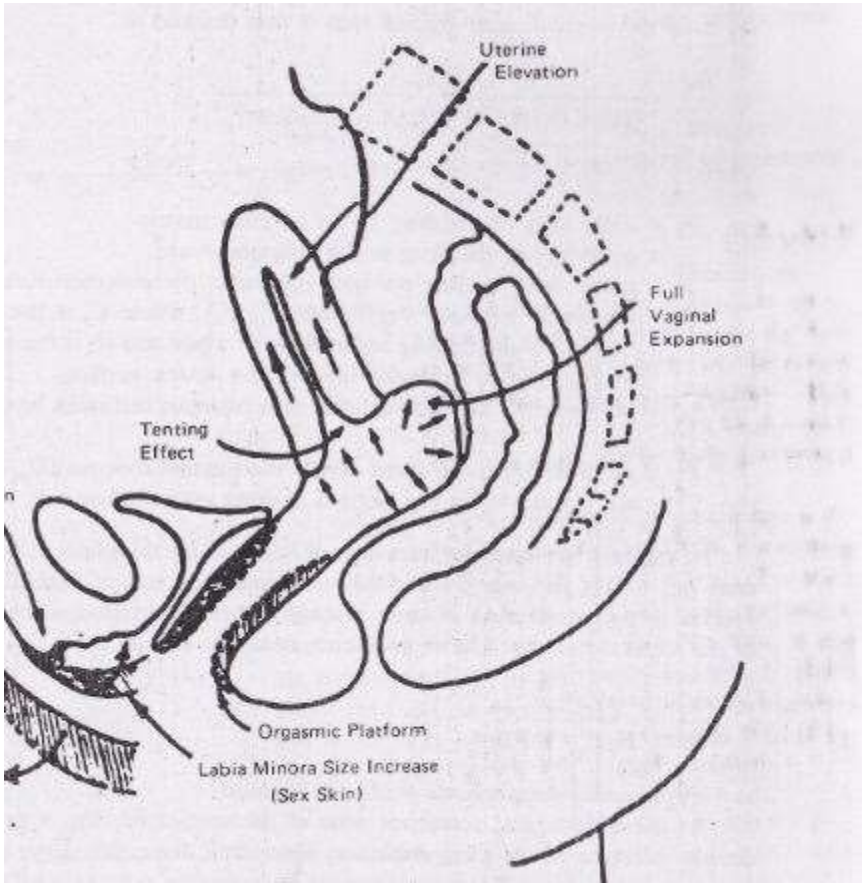
- S-shaped tubular canal of length 4-6 inch
- Lumen pH is about 4-5
  - Glycogen in the sloughed cells get metabolized to lactic acid ; hence the pH
  - pH also depended on the amount and duration of lumen secretion
- Micro organism and their metabolite have an effect of stability of drug delivery system

Cont…

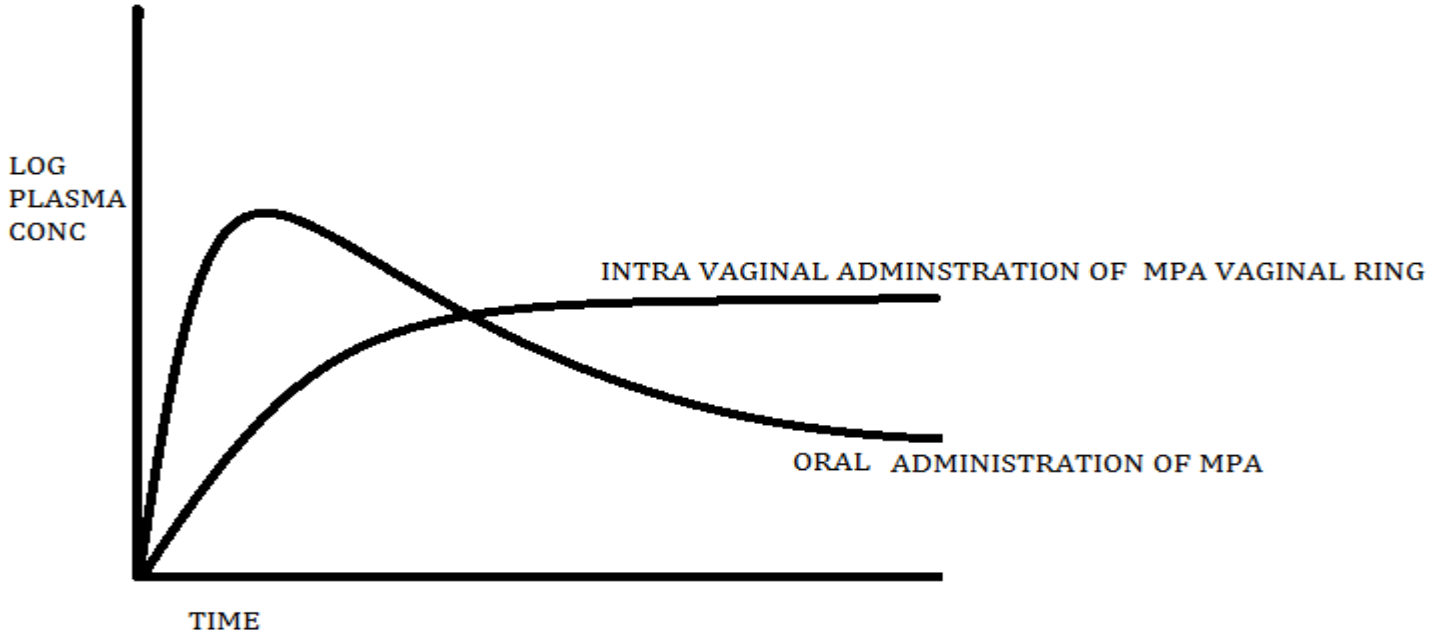
- Unstimulated vagina consisit of potential luminal space, but not physiologically
- On excitation tension induced anatomic variation takes place affect on long term intravaginal residence and controlled release profile
- According to masters and Johnson vaginal wall responses in four phases
  - Excitement phase
  - Plateau phase
  - Orgasmic phase
  - Resolution



Nonstimulated vaginal cross section



Stimulated vaginal cross section



Comparative plasma profile of medroxyprogestrone acetate (MPA) after oral and intravaginal administration

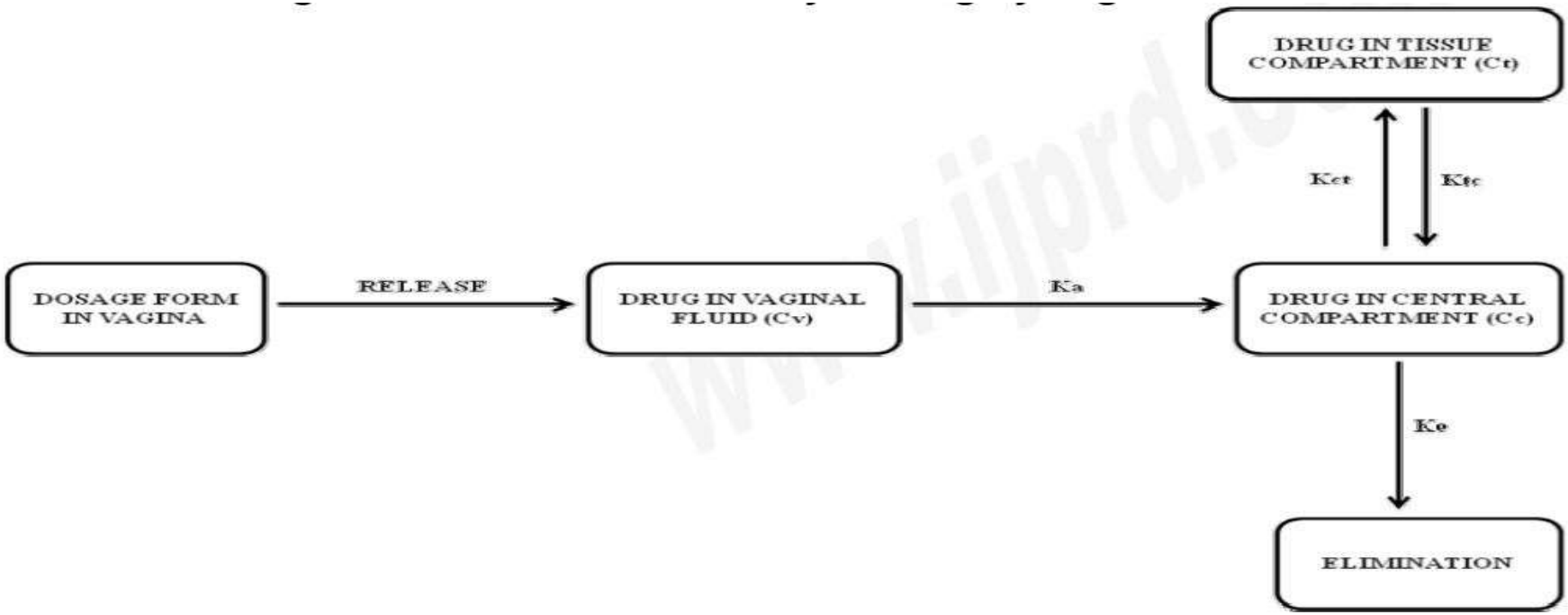
Oral

Peak conc α loading dose

Intravaginal

Peak conc α (loading dose)$^{1/2}$

Vaginal pharmaco kinetics



Vaginal absorption is described by simplified multi compartment open model with first order

ie, (dCb/ dt) = KaCv – KeCb

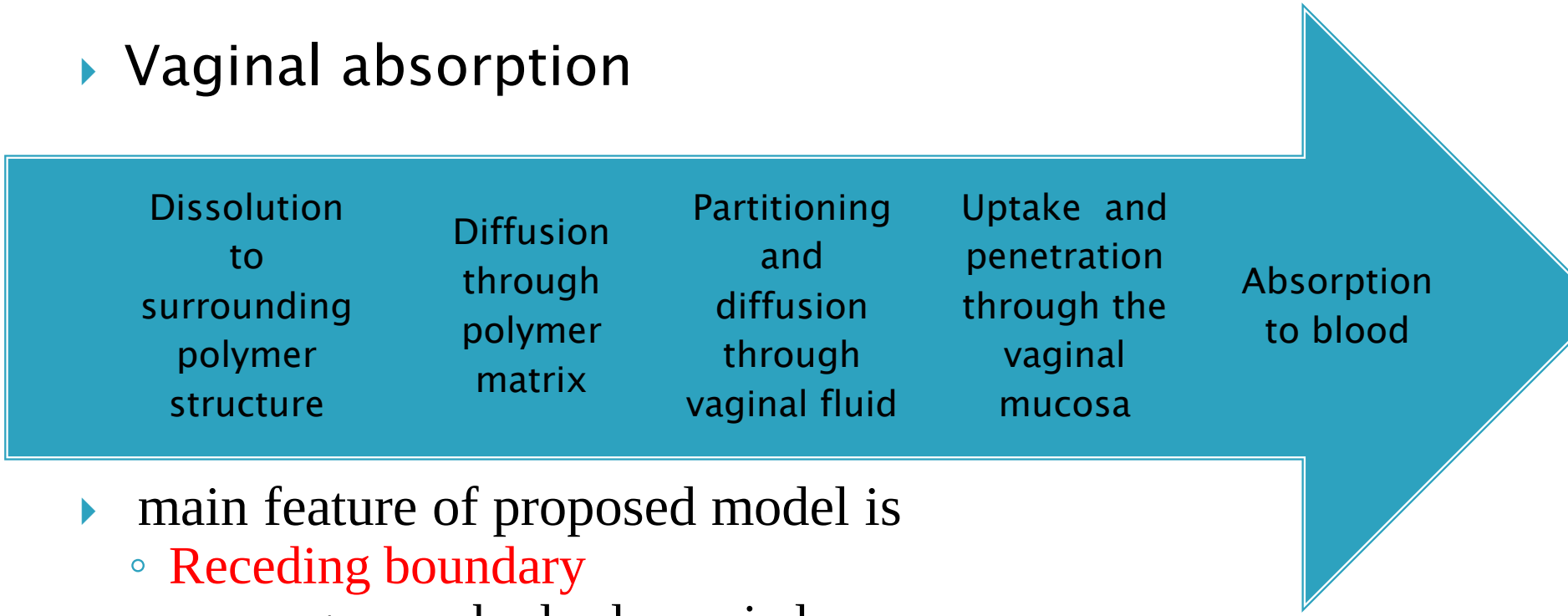
Cb = drug cocn in body

Cv = ,, ,, in vaginal lumen

Ka & Ke = rate constant

Theoretical model of drug release

- Vaginal absorption



- main feature of proposed model is
  - Receding boundary
    an aqueous hydrodynamic layer
  - Vaginal wall
    lipodal pathway and aquoeus pore pathway

Absorption of drugs:

Transcellular	Paracellular	Vesicular
• Concentration dependent diffusion	• Tight junctions mediated	• Receptor mediated transport

Factors affecting drug absorption:

1.*Physiological factors:*

1)Vaginal fluids: **Drug Dissolution**	Transudation, cervical fluid (mucus), endometrial fluids & leukocytes	Esterogen & sexual stimulation	Maximal at ovulation

Physiological factors (cont.):

2)Vaginal pH: **Drug Ionization** **e.g. PGE_2**	pH 4.0 - 5.0, (menstrual cycle; age, infections, sexual arousal)	Cellular glycogen or carbohydrates: Lactic acid	Menstrual, uterine secretions & semen: alkalizing agents

Physiological factors (cont.):

3)Cyclic changes:

Changes in hormone levels (estrogen)

The thickness of the epithelial cell layer, width of intercellular channels, pH, secretions and enzyme activity

2.Physicochemical properties of the drug:

- Molecular weight
- Lipophilicity
- Ionization
- Surface charge
- Chemical nature

Pharmaceutical and biological bioavailability

3.Factors associated with the dosage form:

- Drug release from the dosage form: Limited amount of fluid , type of dosage form
- Drug concentration: local irritation
- Effective area of contact (vaginal cavity: ~60 cm^2):
  Hydrophilicity; size of dosage form; viscosity
- Residence time : **bioadhesion and phase change polymers**

Classification of vaginal Drug Delivery System

- VAGINAL SEMISOLIDS: 1)CREAMS
  2)GELS
  3)OINTMENTS
  4)SUPPOSITORIES
- VAGINAL LIQUIDS: 1)SOLUTIONS
  2) SUSPENSIONS
- VAGINAL AEROSOLS
- VAGINAL CONTROLLED RELESE FORMULATIONS

VAGINAL SEMISOLIDS:

- ***VAGINAL CREAMS,OINTMENTS AND GELS***
  - Topical vaginal preparations are used for mainly conditions like infections,vaginitis,conditions of endometrial atrophy & for contraceptive purposes too.
  - The vaginal topical preparations are mainly applied by special applicators.
  - Drugs like ***anti-infectives***

    (eg Nystatin,clotrimazole,miconazole,clindamycin &sulfonamides);***hormones*** (eg progestron,dinesetrol) and ***contraceptives*** etc. Applied by this dosage form.

HOW TO APPLY??

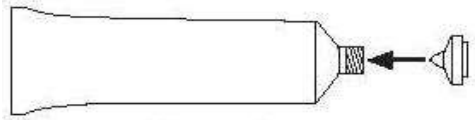


Figure 1

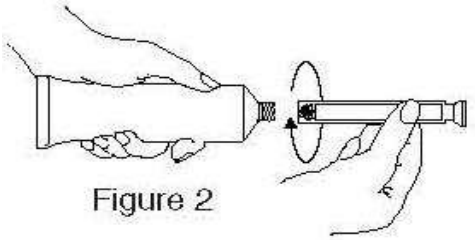


Figure 2

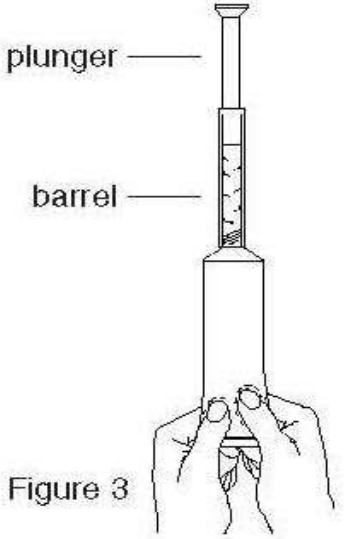
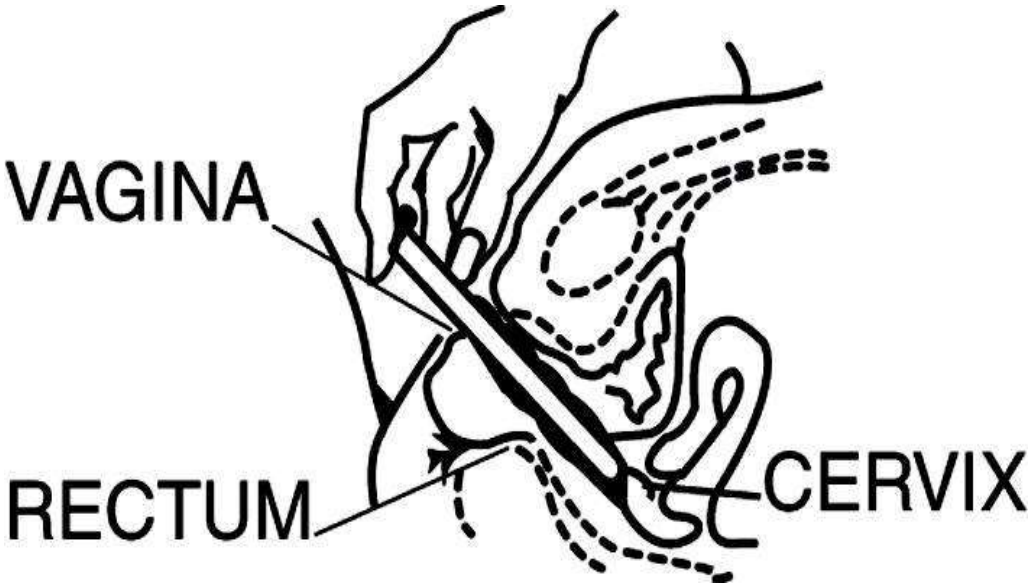


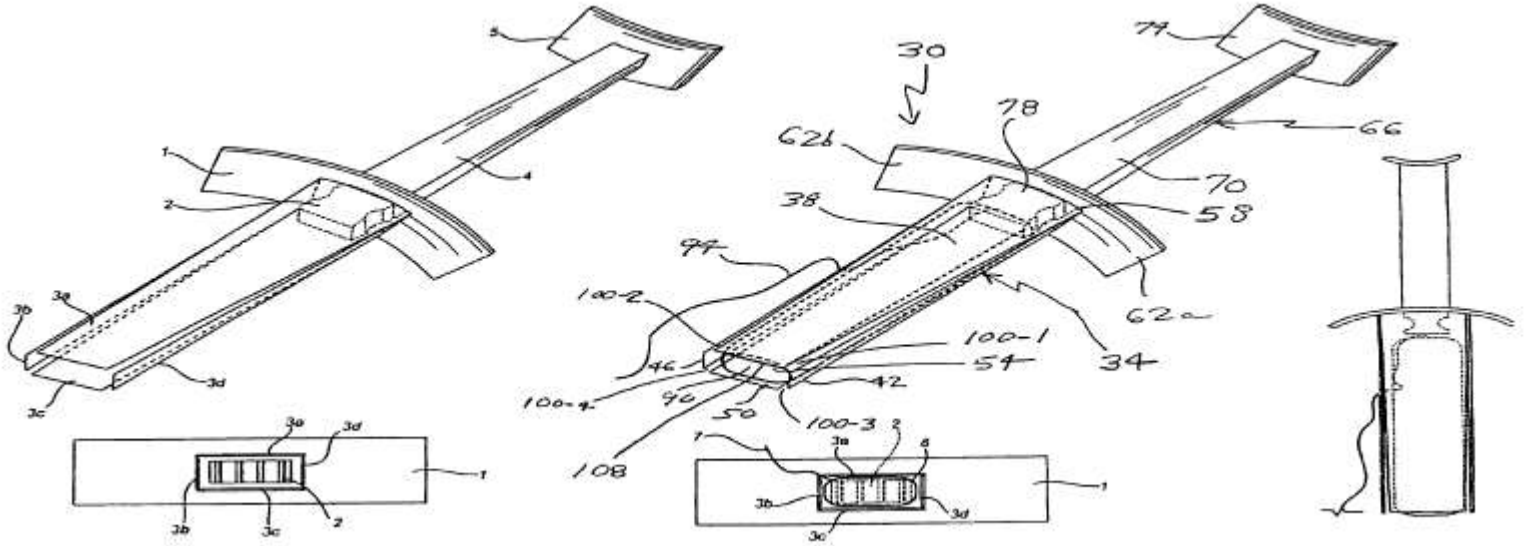
Figure 3



➢*VAGINAL SUPPOSITORIES*

- Solid suppositories are the most common dosage forms.
- Typically,these are torpedo-shaped dosage forms composed but in case of vagina the oval shape is more preferred.
- The composition is largely dicited by the physicochemical properties of the drug and the desired drug relese profile.
- The most commonly used base for vaginal suppositories consist of combination of the various molecular weight polyethyelene glycols, surfactants & preservatives.
- They are buffered to acidic pH about 4-5.

VAGINAL SUPPOSITORES INSERTANTS:



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 by mixing with water and applied by insertants into vagina.

VAGINAL AEROSOLS

- Aerosols foams containing estrogenic substances & contraceptive agents are available.
- The aerosol container has plunger which apply the foam in the vaginal cavity
- Novel approaches use bioadhesive foams.
- Marketed preparations are povidone –iodine vaginal foam etc.

VAGINAL ROUTE FOR SUSTAINED/CONTROLLED – RELEASE DRUG DELIVARY

- For the delivery of Sustained and controlled –release contraceptive steroid hormones most often selected route are vaginal and uterine areas.

Advantages of administration by this route

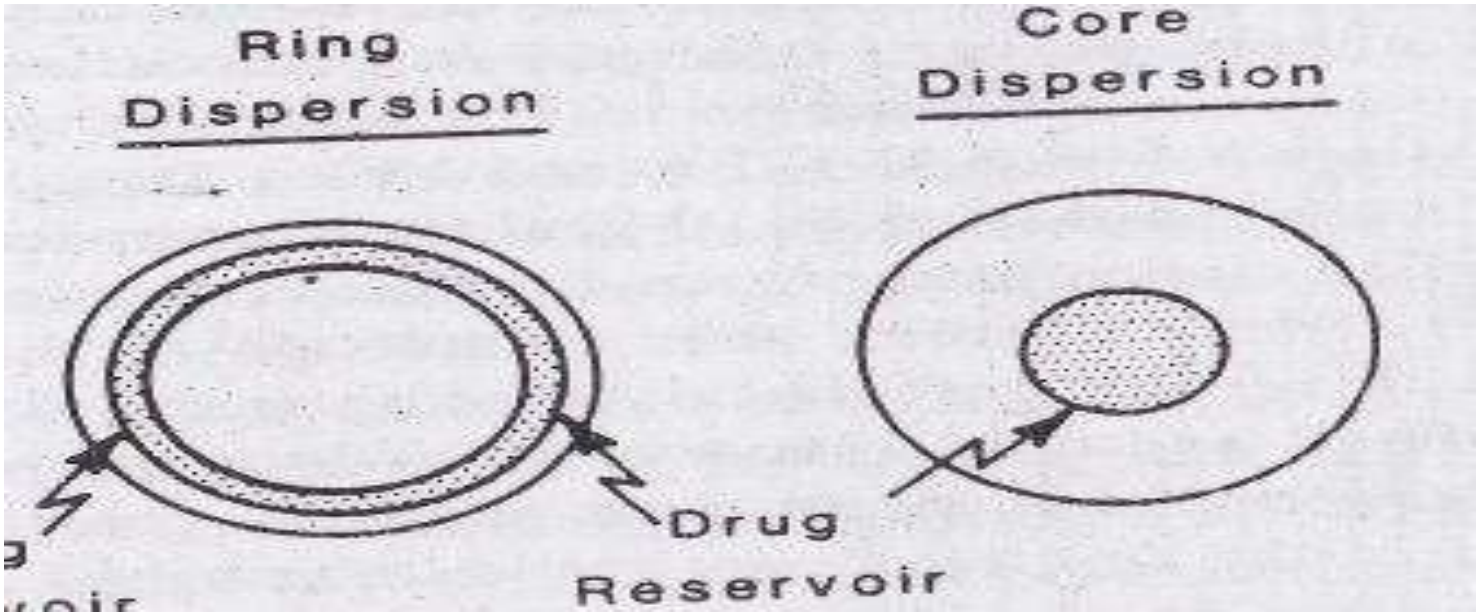
- Prolonged release
- Minimal systemic side effects
- An increase in bioavailability
- Use of less total drug than an oral dose
- First pass metabolism can be avoided.

1) Vaginal rings

- Vaginal rings are circular ring type drug delivery devices designed to release drug in a controlled release fashion after insertion in the vagina.
- Polymer generally used polydimethyl siloxane (silicone device)
- They are 5.5 cm in diameter with a circular cross section diameter of 4-9 mm, where drugs are homogeneously dispersed

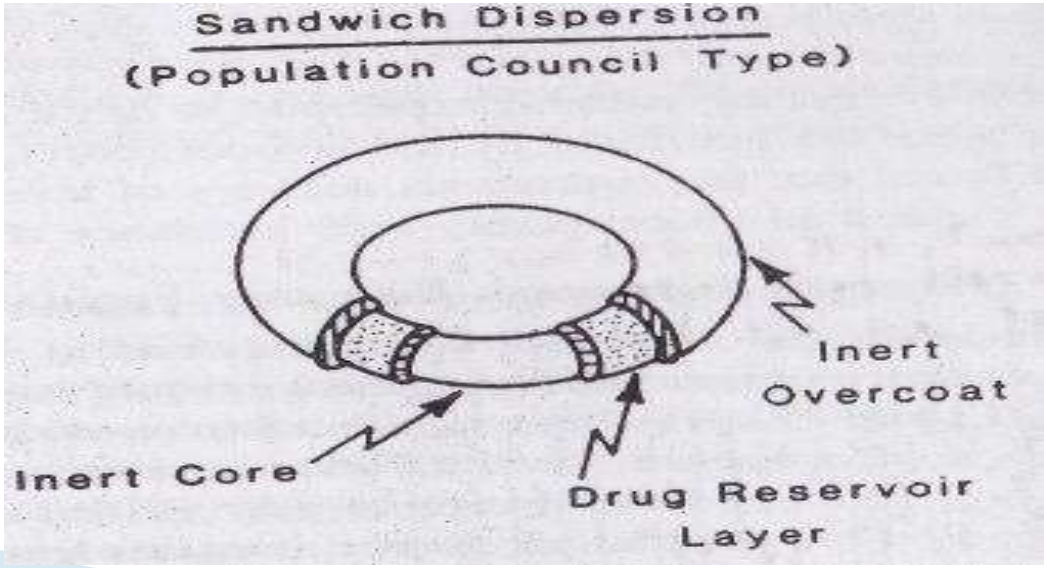
Cont...

- Reservoir type:
  - In reservoir type of rings, drugs are dispersed in a central core, which is than encapsulated by a drug free layer



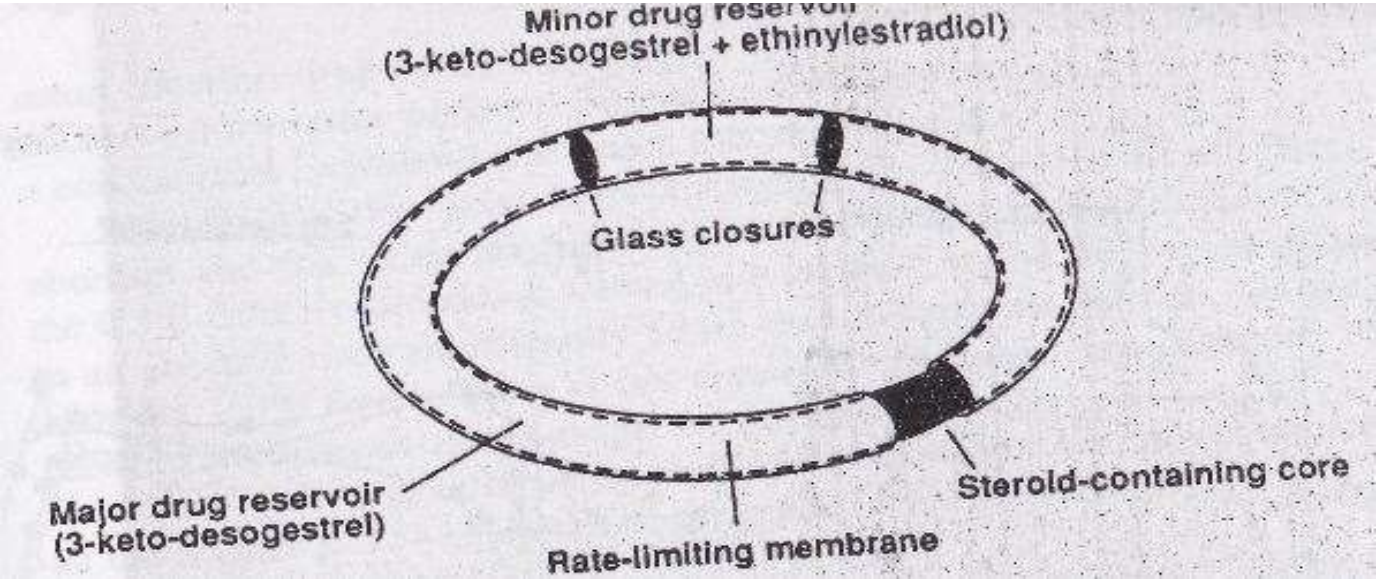
Cont..

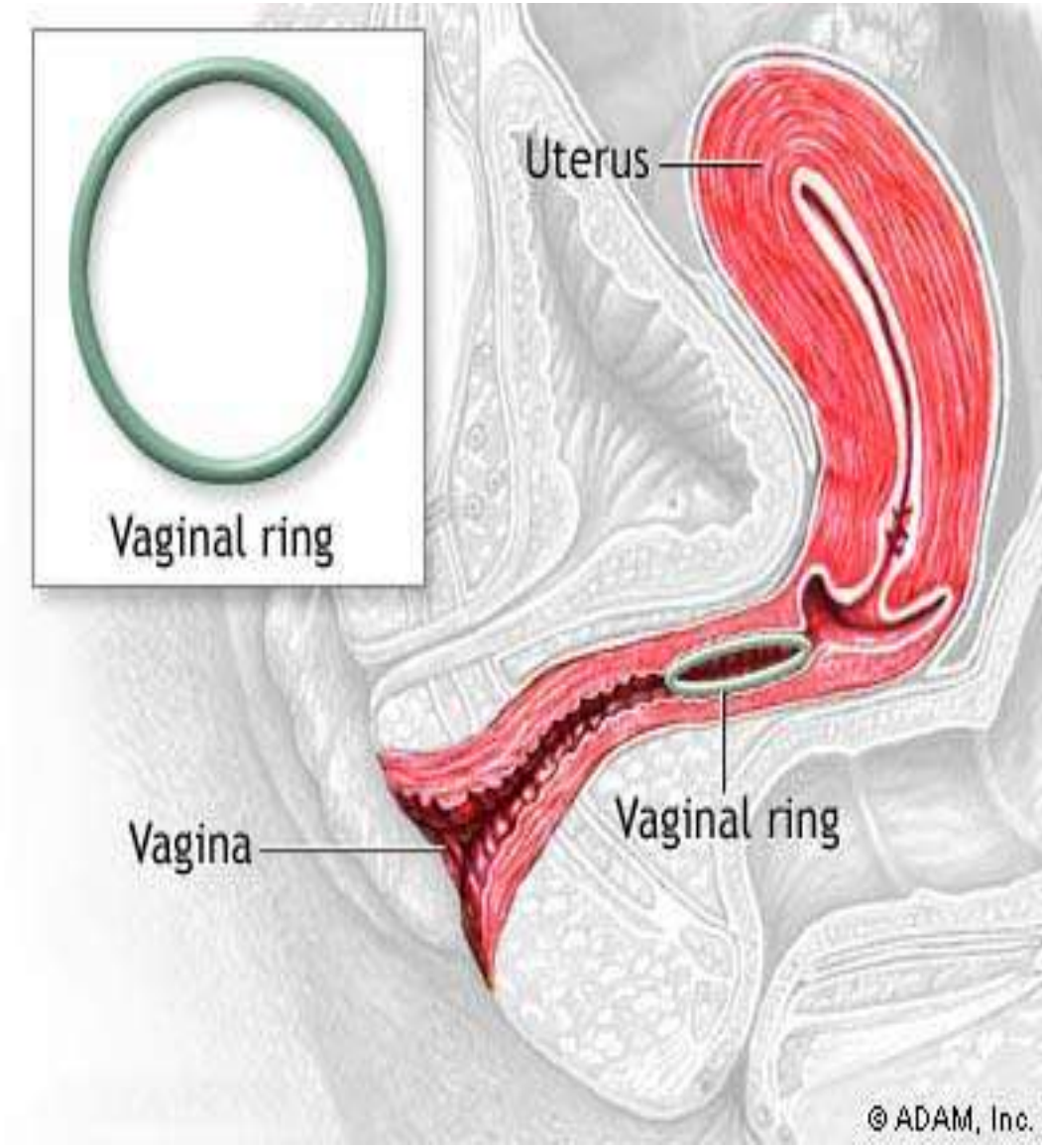
- Sandwich type
  - Sandwich type devices consist of a narrow drug containing layer located below the surface of the ring and positioned between a nonmedicated central core and a non-medicated outer band.



Cont..

- Combined contraceptive ring
  - To release combination of hormone simultaneously
  - Consist of major reservoir, minor reservoir and glass closures




Vaginal ring
Uterus
Vagina
Vaginal ring
© ADAM, Inc.

2)VAGINAL INSERTS

- These types of systems contains flat rectangular polymeric slab enclosed in a pouch of knitted polyester removal system.
- The buff coloured semi transparent hydrogel slab contains drug.
- The retrieval system is in the shape of long knitted tape thet is used to retrive the slab.
- Marketed preparations:CERVIDIL

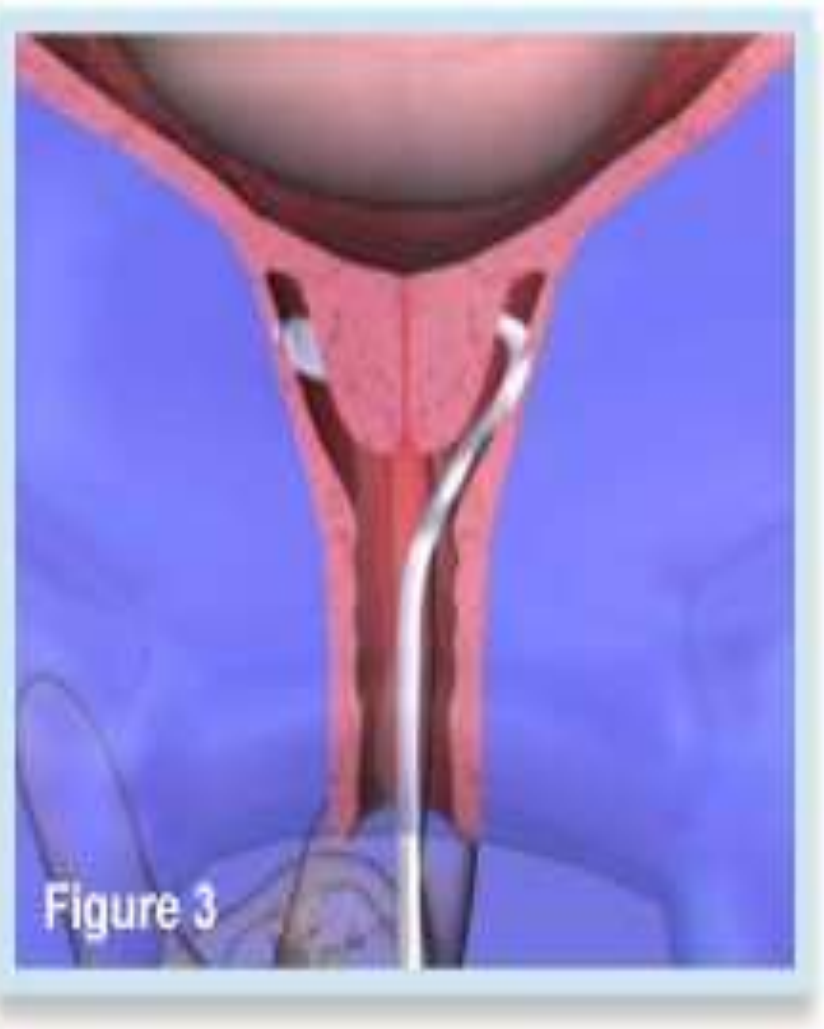


Figure 3

3) IN SITU GELLING

- Mucoadhesive formulations prepared using temperature-sensitive and mucoadhesie polymers,poloxamer and polycarbophil.
- The water insoluble polyemers swells in vagina and form bioadhesive gel on vaginal layer.
- This allows contionus relese up to 25 to 50 hrs.
- Liquid during immunization but gel inside the vagina.
- Example:CRIONE GEL

4) OTHER NOVEL APPROACHES:

- 1) ***medicated vaginal tampons-*** a medicated vaginal tampon, approved as a medical device by FDA.
- This bi-functional tampon contains a polymeric delivery system(strips) that absorb menstrual fluid while gradually releasing lactic acid and citric acid.

2)Vaginal films-

- Vaginal films are polymeric drug delivery systems shaped as thin sheets, usually ranging from 220 to 240 micro M in thickness.
- These systems are often square (approximately 5cm*5cm),colourless, and soft, presenting a homogenous surface.
- Vaginal films are produced with polymers such as polyacrylates,polyethylene glycol, polyvinyl alcohol and cellulose derivatives.


Vaginal
Contraceptive
Film

3) BIOADHESIVE FORMULATIONS

- Bioadhesive formulations can reduce the treatment time of fungal infections by at least 25% e.g. **Metronidazole** in starch–polyacrylic acid mixture.
- For systemic delivery, **Insulin** suspended in a polyacrylic acid gel base ⟶ ↑vaginal absorption in alloxan diabetic rats and rabbits.
- Bioadhesive polymer alone ⟶ **moisturizer** for dry vagina.

Prolonged release ⟷ Predictable rate

Mostly carbopol or polycarbophil has been used.

Crinone®: Polycarbophil-based progesterone vaginal gel for postmenopausal women

1)Microbicides:

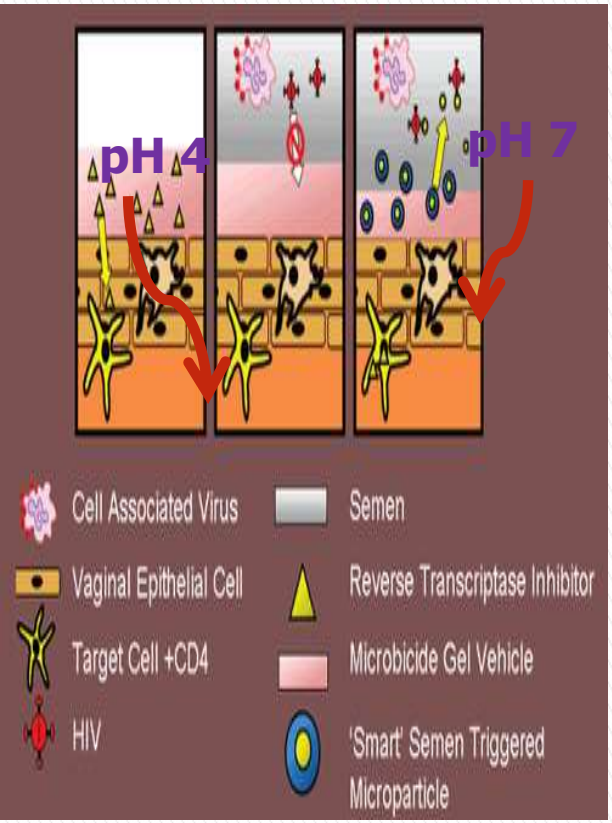
- Provide protection against microbial infections, including Acquired Immune Deficiency Syndrome (AIDS) and other sexually transmitted diseases (STD_s).
- Used in treatment of vulvovaginal infection, vaginitis, anti-infectives (**clotrimazole, miconazole, clindamycin, sulfonamide**), endometrial atrophy (**dienesterol, progesterone**) are used and contraceptive like **nonoxynol-9, octoxynol** are also used.

Microbicides (cont.):

The ideal microbicide would be:

- Active against a range of (STD)-causing pathogens;
- not irritate mucosal surfaces;
- be available in spermicidal and non-spermicidal formulations;
- coat and stick to mucosal surfaces;
- not be absorbed systemically;
- have long duration;
- be effective immediately;
- be stable at high climactic temperatures;
- and maintain normal vaginal ecology

Microbicides (cont.):Microbicide Drug Delivery:



1. Trans-vaginal epithelial delivery of HIV reverse transcriptase inhibitors (RTI) into genital tissue using RTI containing gels or vaginal rings.
2. Smart coating that responds to the vaginal environment and infectious biofluids to slow viral flux to the tissue.
3. Using pH changes and protease present in semen to trigger drug release when these components interact with semen containing HIV before reaching vagina.

Microbicides (cont.):

All these delivery systems include formulations that modify the genital environment:

- (e.g. polyacrylic acid gels and lactobacillus gels),
- surfactants (e.g. sodium lauryl sulfate),
- polyanionic therapeutic polymers (e.g. carageenan and carbomer/lactic acid gels),
- proteins (e.g. cyanovirin-N and monoclonal antibodies),
- protease inhibitors and other molecules (e.g. dendrimer based-gels and the molecular condom)

2)pH sensitive nanofiber gel microbicides:

Composed of peptide containing self-assembled nanofibers consisting of:

- hydrophobic tail (to load antiviral agents),
- hydrogen bonding domain and
- pH sensitive head group (hydrophilic head):

In vagina → viscoelastic semisolid gel.

In semen → becomes charged → disrupts the nanofiber construct → liquefies upon contact with semen and delivers drug directly into the infecting fluid: semen.

3)Bioadhesive vaginal foams:

Advantages of foams in intravaginal administration:

- Ready-to-use formulations with inexpensive disposable applicators.
- Excellent coverage of the intravaginal surface.
- Can incorporate bioadhesives to reduce dosing frequency.
- Easy intravaginal insertion.
- Accurate dosing (using metered dose valves).
- No dripping after treatment.
- Non-irritating excipients.

Bioadhesive vaginal foams (cont.):

They can be formulated as:

- Oil-in-water emulsion foam (cream-like).
- Water-in-oil emulsion foam (occlusive-cream-like).
- Petrolatum based foam (ointment-like).
- Waterless hydrophilic foam (hydrophilic-ointment like).
- Oily foam (ointment-like, with or without water).
- Suspension foam.

Bioadhesive vaginal foams (cont.):

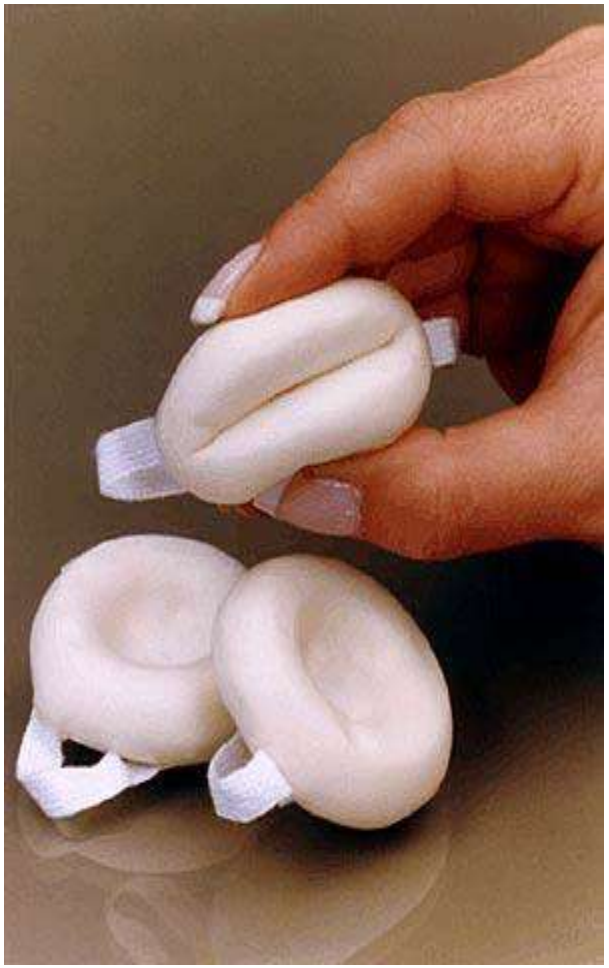
Vaginal foam adhesiveness:

Vaginal foams with:

(a) Mixture of hypromellose and carbopol;

(a) sodium carboxymethylcellulose; and

(b) hydroxyethylcellulose, were prepared and pressurized in aluminum monoblock containers.



4) Intravaginal liposomes:

They provide prolonged release but it is liquid in nature.

So, we can use viscosity increasing agents such as methylcellulose, as well as polymers derived from acrylic acid (Carbopol resins) as a vehicle to liposomes to deliver drugs e.g. Acyclovir.

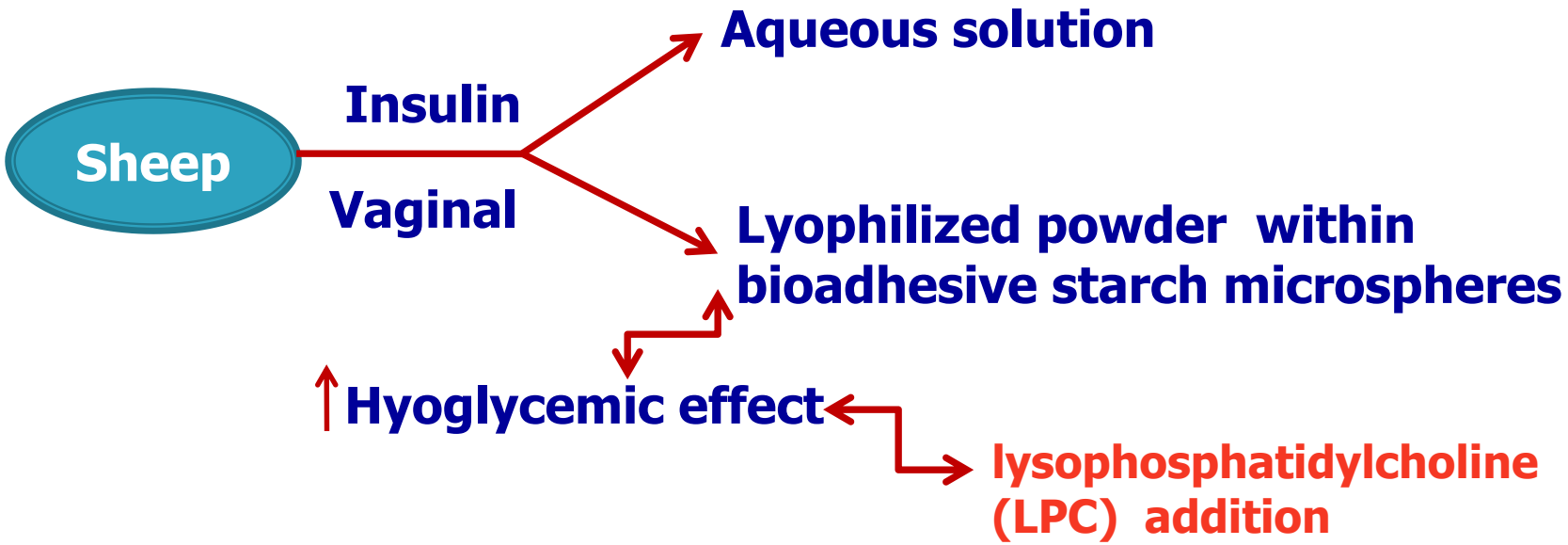
5) Microparticulate systems:

- ***Hyaluronic acid microspheres:***
  - Hyaluronic acid microspheres → calcitonin systemic delivery
  - Hyaluronan esters → salmon calcitonin
  - Hyaluronic acid+(HEC) → for vaginal dryness
- ***Microparticulate vaccine delivery system:***

Mucoadhesive polymer dispersed microspheres as delivery systems based on carboxyvinyl polymer.

Microparticulate systems(cont.):

- ***Insulin microspheres:***



6) Bioadhesive effervescent vaginal tablet:

Ketoconazole(KTZ) in effervescent vaginal formulation.

The KTZ release and bioadhesion properties of bioadhesive tablets can be controlled by:

- changing polymer type(Carbopol, HPMC or HPC),
- polymer concentration and
- effervescent content (act as disintegrating agent).

Vaginal delivery of prostaglandins:

Oxytocin, dinoprostone and misoprostol are commonly used prostaglandins for cervical ripening and induction of labor. A hydrogel of polyethylene glycol 600 providing constant release rates for prostaglandin E_2.

Vaginal delivery of peptides and polypeptides:

By use of polycarbophil hydrogels containing LH-RH the ovulation inducing activity was 3.3 times greater than the solutions.

The bioadhesive hydrogels as well as peptidase inhibition by (e.g. sodium laurate and disodium-EDTA) show significantly improved absorption of LH-RH.

Novel disposable intravaginal device:

For treating stress urinary incontinence (SUI).

- The core: flexible anchor and support poles made of resin to prevent the device from moving within the vagina.
- The cover: around the core made of soft, nylon mesh has large pores to allow for vaginal secretions.
- A cotton string is attached to the distal end of the cover for removal of the device. The core and cover are preassembled within a smooth, small-diameter applicator allowing for insertion directly into the vagina.

Evaluation of vaginal formulation

- Both invivo and invitro studies are necessary

Invitro studies:

- various physical, chemical, bio-adhesive, release characteristic etc ..
- Principle of tensile strength and shear stress – Bioadhesive property
- Release charecteristic
  - Membrane diffusion
  - Microbiological method
  - Vaginal dissolution tester
- Disintegration ,dissolution, melting, content uniformity – for pesseries

Invivo studies

- Assesment of efficacy, distribution, spreading, retention of formulation in vagina
- Models used include Sheep, Rat, Rabbit, Rhesus monkey, Dog, mice etc..
- The rate and extent of release is determined by
  - Monitoring quantities systemically absorbed
  - Measuring the pharmacological activity
  - Analysis of vaginal lavage
- Gamma scintigraphy: to asses distribution , spreading and retention of vaginal formulation
- Cycloscopy : used for direct in-vivo visualization