General information on Pharm. Tech. theory

- Midterm tests:
  - Written test on Unipoll next week from the 1-6 week's theory
  - The first test is only practice, but if it's above 60%, you can accept it as a sharp test

- Two questions:

  1. During the COVID period, short tests will be constructed (5 questions/lecture) on each week or at the end of the semester one big test?

  2. Time of tests should be on a fix date, fix time or we give you on a fix date 4 hours and you can start the test anytime during these 4 hours, but from starting you'll get limited time!

Rectal, vaginal and intrauterine drug delivery systems

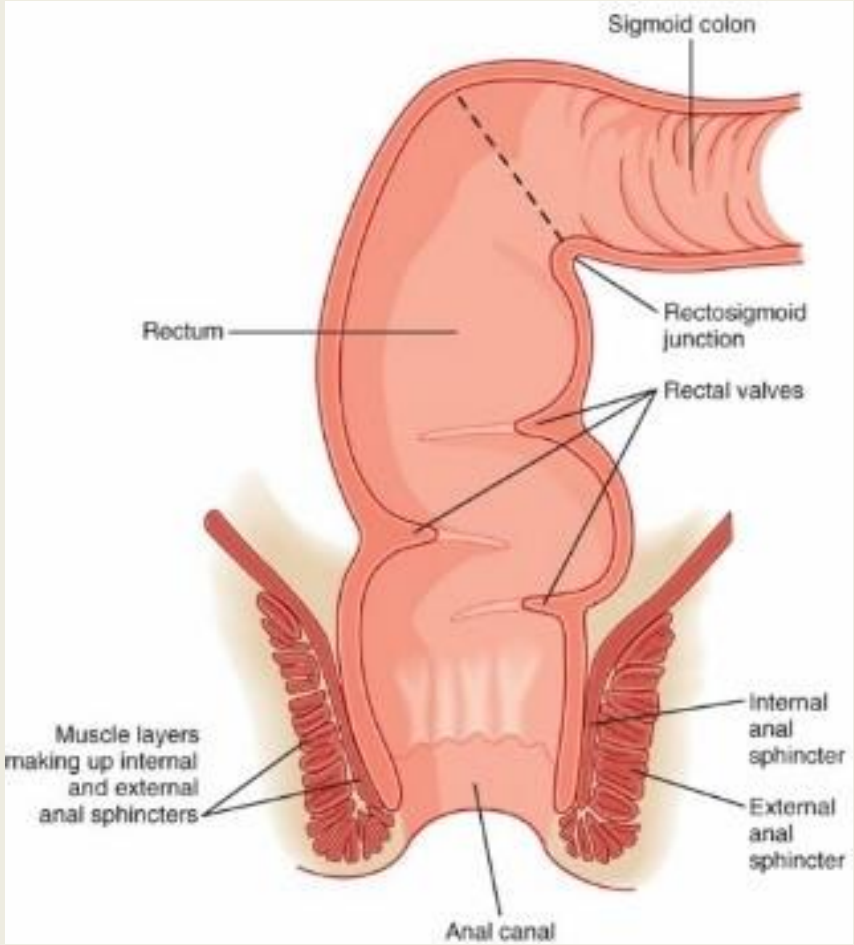
Institute of Pharmaceutical Technology and Biopharmacy

RECTALIA

The anatomy and physiology of the rectum

Main data

No peristaltic movement, and the rectal juice is only 2-5 ml.
It has a smooth surface richly vascularized.
These vessels are the part of the veins. The proper blood flow can ensure the rapid (im) absorption.

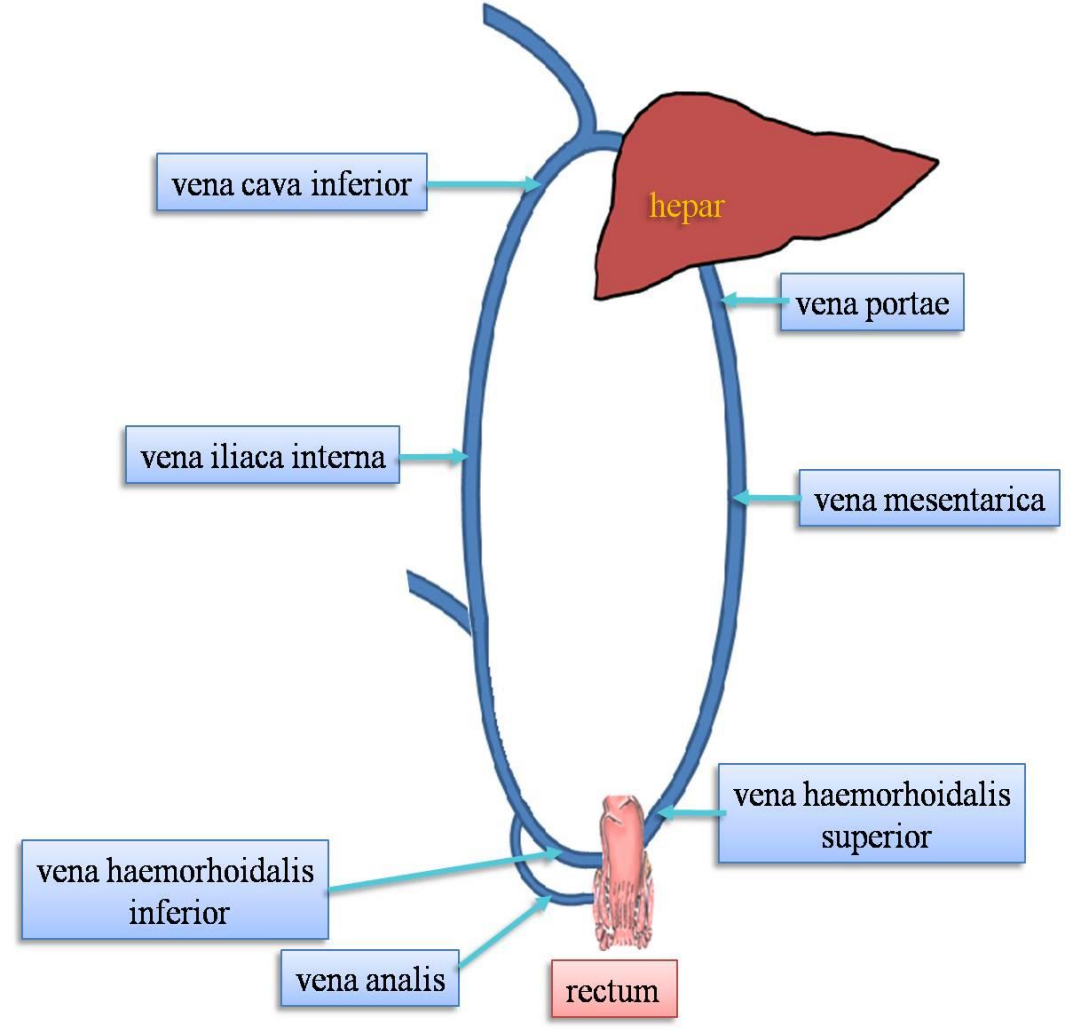


length (m)	surface area (m^2)	pH	residance time	number of microorganisms
0,15-0,18	0,30	7,3-7,7	10-30 min	~10^{10}

The anatomy and physiology of the rectum

The most reliable method of the measurement of the body temperature is when thermometer is placed into the rectum.

The normal temperature of the rectum is 36.2 -37.7 °C.
This is higher than the temperature measured in the armpit or in the mouth (the temperature of the mouth is less at least 0,5 C°, and the temperature of the armpit is less at least 1 C°)



Biopharmacy of rectal preparations

Absorption

- Rapid absorption
- No „first-pass effect”
- This is a possible route of administration if the patient is a child or unconscious
- A potential solution for the avoidance of stomach irritative APIs.
- Suppositories or enemas

Biopharmacy of rectal preparations

Advantage	***Disadvantage***
• ***for unconscious person too***	***•inconvenient***
• ***for children too***	***•bad patient compliance***
• ***in case of vomiting***	***•little amount of dissolution medium (2-5ml)***
• ***relatively quick absorption (im)***	***•(More expensive than the normal tablets)***
• ***no first pass effect***	
•swallowing difficulty	
•high amount of API	
•(not easy to overdose)	

Rectal preparation

The most common indications of rectal preparations:

- analeptics
- analgetics, antipyretics
- anorganic ions
- antidiabetics
- antiepileptics
- antiemetics
- antibiotics
- diuretics
- hormons
- anti-migrain preparations
- vitamins
- sedatohypnotics

Rectally used medications and preparations

Rectal preparation

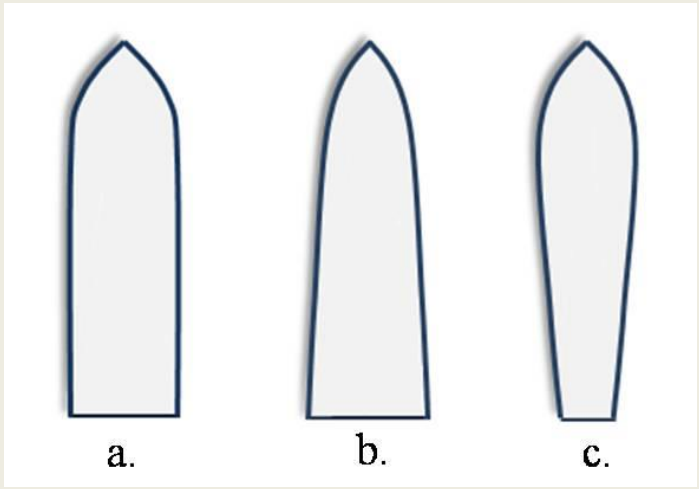
Rectalia (Ph.Hg.VIII.)

„Rectal preparations are intended for rectal use in order to obtain a systemic or local effect, or they may be intended for diagnostic purposes.”

Several categories of rectal preparations may be distinguished:
— suppositories,
— rectal capsules,
— rectal solutions, emulsions and suspensions,
— powders and tablets for rectal solutions and suspensions,
— semi-solid rectal preparations,
— rectal foams,
— rectal tampons.

Rectal preparation

Suppository



The suppositories can be molten or dissolved at body temperature or in body fluids.

The spreading ability of different types of base materials is different.

a. cylindrical
b. conical
c. torpedo

aminophenazone, phenobarbitale

treatment for flu with vomiting

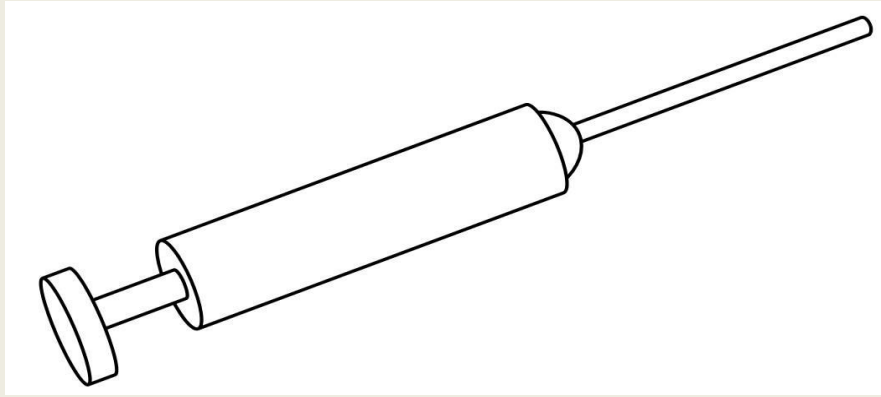
dimenhydrinate, chlorobutanol

travel sickness preparation

Rectal preparation

Enemas

Salofalk 4g/60ml rectal suspension
Mesalazine
Rectal suspension. It is applied for the acute treatment of **colitis ulcerosa** and other diseases of the colon with acute inflammation.



Gels or in situ gel forming systems can be administered with the proper devices.

The onset of action is delayed by applied emulsions (Diazemuls®). A rapid absorption can be achieved by applied gel systems. (DIASTAT®)

(API: diazepam, it is appropriate for the treatment of epilepsy, when the patient is incapable to swallow any oral tablets. Physician's assistance is not needed.)

Rectal foams:

The spreading and local effect is good.
Applied for hemorrhoids.

Budenofalk 2mg rectal foam

(budesonid➔ Applied for ulcerative colitis that localized in the rectum and the colon)

Rectal gels:

They cannot cause foreign body sensation, the pH is easily set.

DIASTAT®

(diazepam➔*epilepsy, seizure*)

Rectal preparation

Rectal capsules and tablets

Rectal capsules (shell suppositories) are

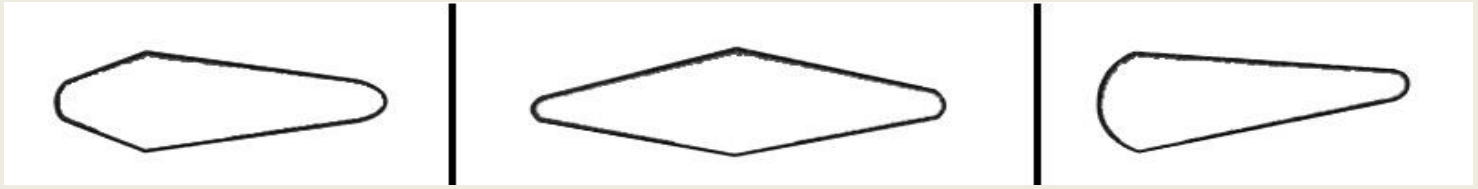
solid, single-dose preparations generally similar to soft capsules.

They are of elongated shape, are smooth and have a uniform external appearance.
Length: 20-45 mm, diameter 8-12 mm, volume 0,6-1,8 ml.

They may have lubricating coatings.

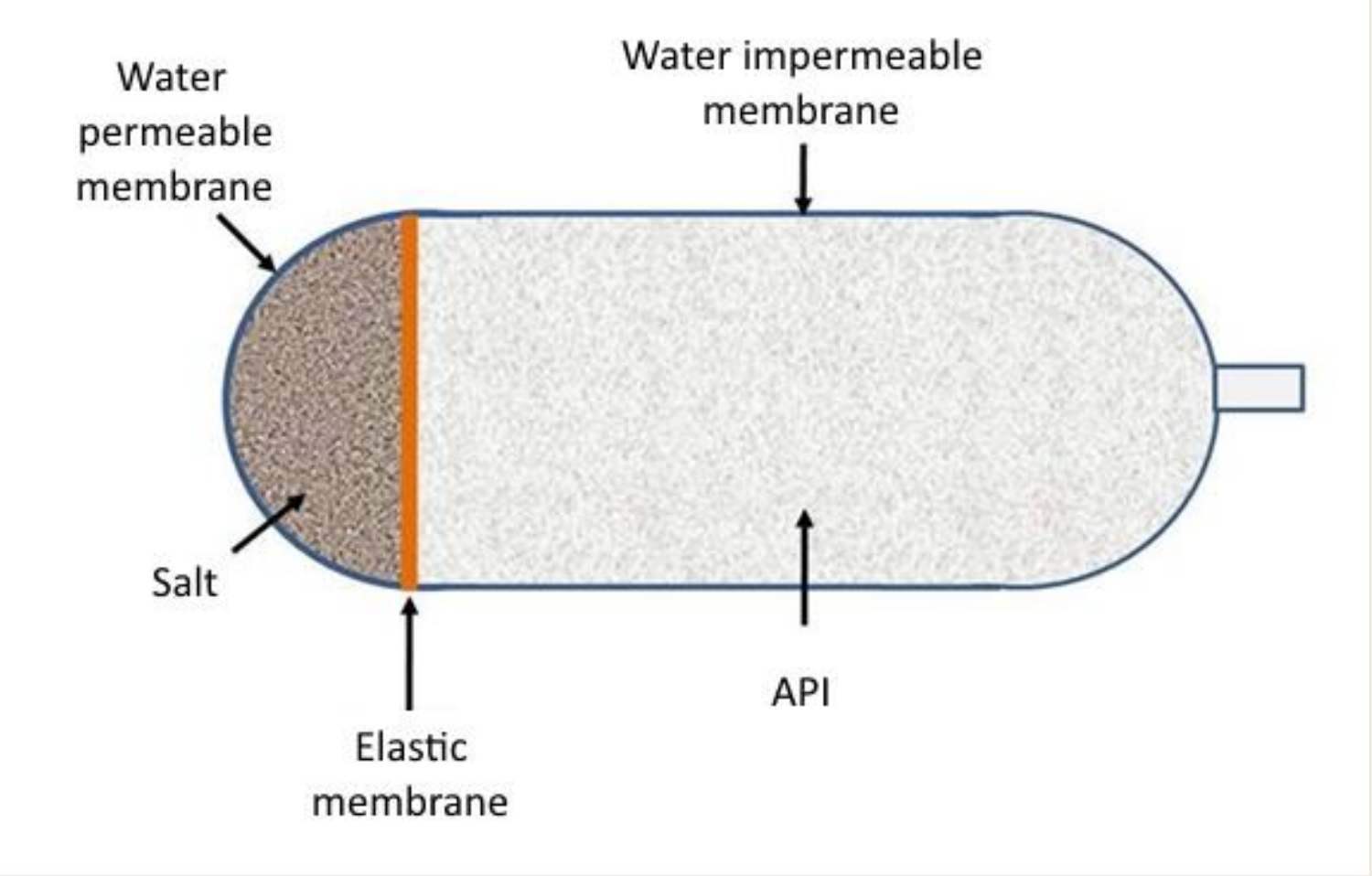
- Advantages:
  - Accurate dosing
  - They can contain heat sensitive ingredients
  - The coating technology can protect the preparation from the external impacts.
  - Tropical protection (not melt)

- Voluminizing ingredients:
  - Vehicle, solvent: lipophilic-fatty oils, semi synthesized triglycerides
  - surfactants: Tween 80
  - Stabilizing agent (beeswax, hydrogenated herbal oils, Aerosil, glycerine-monostearate)
  - Flow behavior regulators: lecithin
- Particle size: <100 μm, optimal absorption: 50 μm



Rectal preparation

Osmotic pumps



Preparation and examination of rectal preparations

Magistral practice

Latin (singular)	Latin (plural)	English
suppositorium	suppositoria	suppository
ovulum	ovula	pessary
globulus (vaginalis)	globuli (vaginales)	ball for vaginal use
globulus vaginalis longiformis	globuli vaginales longiformes	cylinder for vaginal use
bacillus urethralis	bacilli urethrales	urethral stick
pertica	perticae	medical rod

Magistral practice

The prescription can be prescribed in a **dispensed** or **divided** form.
In the first case, the prescription contains the amount needed for **one suppository** of the ingredients.
In the second case, the prescription contains the amount needed for **two or more** suppositories of the ingredients.

Dispensed form of the prescription	**Divided form of the prescription**
Rp. **Metamizoli natrici** **gramma semis (0,50 g)** **Vehiculi** **quantum satis (qu.s.)** ***Misce fiat suppositorium*** ***Dentur tales doses numero sex (No. VI)*** **Signetur: Anti-febrile suppository**	**Rp.** **Metamizoli natrici** **grammata tria (3,00 g)** **Vehiculi** **quantum satis (qu.s.)** ***Misce fiant suppositoria*** ***Divide in doses aequales numero sex (No. VI)*** **Signetur: Anti-febrile suppository**

Magistral practice

Suppository (1,0-1,5 g): A rectally used semi-solid medical preparation which has a torpedo shape.

Pessary (3,0-4,0 g): A vaginally used semi-solid medical preparation which has an almond shape.

Ball for vaginal use (2,0-3,0 g): A vaginally used semi-solid medical preparation which has a ball shape.

Cylinder for vaginal use (6,0-10,0 g): A vaginally used semi-solid medical preparation which has a long form.

Urethral stick (1,0-2,0 g): This is a thin medical stick, its thickness is not more than 3 mm. It should be placed into the urethra to affect a local effect.

Medical rod (6,0-10,0 g): Its shape as the 'cylinder for vaginal use', but it is applied on the skin surface for rubbing.

Magistral practice

The suppositories can be prepared by **molding** and **compression** method, too.

In the case of molding, we can use different type of ‚**base materials**'.

These base materials can be divided into three basic groups:

Lipophilic

- **Butyrum cacao** (cocoa butter)
- **Adeps solidus 50** (hard fat)
- **Adeps solidus 3**

Lipohydrophilic

- **Adeps solidus compositus**

Adeps solidus 50 (95%)
Polisorbatum 20 (2.5%)
Polisorbatum 61 (2.5%)

Hydrophilic

- **Massa macrogoli**

Macrogolum 1540 (95%)
Sorbitanum laurinicum (5%)

Preparation and examination of rectal preparations

Additional excipients for preparation of suppositories:

- **Fillers**: If the amount of dispersed material **does not reach 10%**, **lactose** addition should be applied in the proper amount.
  - lactose (qu.s.)

- **Viscosity enhancers**: They can inhibit the velocity (speed) of the sedimentation during the pouring process, thus ensuring the homogenous distribution of the API.
  - glycerinum monostearinicum (1-5%)
  - silica colloidalis anhydrica (1-2%)

Preparation and examination of rectal preparations

Additional excipients for preparation of suppositories:

- **Dispersing agents**: They can assist the homogenous distribution of the API with their surface active properties or because they are the proper solvent of the API.
  - Aqua destillata (for Extractum belladonnae siccum)
  - Polysorbatum 20/61
  - Sorbitanum laurinicum

- **Consistency softening agents**: They can **decrease the melting point**, and so the time needed for the liberation of the API from the suppository.
  - Paraffinum liquidum (2-10%)
  - Oleum neutrale (2-10%)

Preparation and examination of rectal preparations

Additional excipients for preparation of suppositories:

- **Consistency hardening agents**: They can **increase the melting** point, and so the time needed for the liberation of the API from the suppository.
  - Cera alba (1-2%)
  - Cetaceum (1-2%)
  - Lanalcolum (1-2%)
  - Alcoholum cetylstearylicum (1-2%)
  - Alcoholum cetylicus (1-2%)

Preparation and examination of rectal preparations

Additional excipients for preparation of suppositories:

- **Liquid absorbent**: If the preparation contains too much liquid components, which do not dissolve in the external phase.
  If we do not want to prepare an emulsion, than the fluid components should be absorbed with a solid material, and this should be suspended into the external phase.
  - Silica colloidalis anhydrica (qu.s.)

Preparation and examination of rectal preparations

General rules of the choice of excipients:

- Try to choose materials with **opposite solubility**, because the absorption will be better if the API cannot dissolve well in the base material. In this case, the solubility is a drawback, because it causes a distribution between the body fluids and the base material. For this reason, most suppositories contain the APIs in dispersed (suspended) form.

- The suppositories containing the API in dissolved form have to prepared with molding method.

- If we choose the molding technique, the suspended or emulsified ingredients have to reach the 10% of the weight of the suppository, because this can ensure the inhibited sedimentation.

- If we choose the molding technique, than we have to calculate with the **displacement factor** of the API.
  The displacement factor can prescribe that amount (weight) of the base material, what is displaced (excluded) by the API.

Preparation and examination of rectal preparations

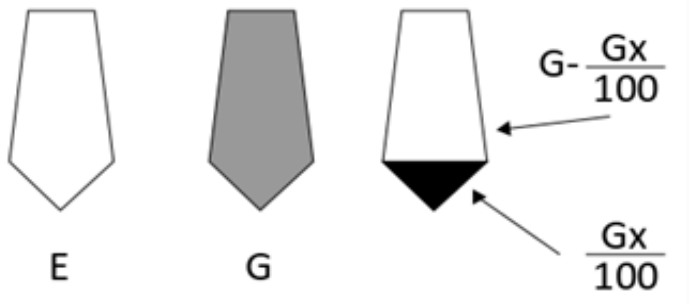
Displacement factors

	In case of **cocoa butter**	In case of **hard fat**
Acidum acetylsalicylicum	0.93	0.85
Barbitalum	0.81	0.72
Balsamum peruvianum	0.83	0.61
Bismuthum subgallicum	0.37	0.35
Camphora	1.49	0.98
Chloralum hydratum	0.67	0.40
Morphin. chlorat.	1.00	0.85
Phenobarbital. natr.	0.84	0.62
Theophyllinum	0.60	0.63
Zincum oxydatum	0,20	0.15
Metamizolum	0,88	0,75

Preparation and examination of rectal preparations

Displacement factor determination

Determination of displacement factor (f)



$$f = \frac{E - (G - \frac{Gx}{100})}{\frac{Gx}{100}} = \frac{100\,(E - G)}{Gx}$$

if $\rho < 1$ than $f > 1$
if $\rho > 1$ than $f < 1$

Where:
E = mass of 1 suppository prepared from the base material only
G = mass of 1 suppository prepared with API
x = the percentage of the API in the suppository
r = density of the API
f = displacement factor

Calculating of suppository base amount (T_m)

$$T_m = E - (f * s)$$

$$T_m = E - (f_1 * s_1 + f_2 * s_2 + \ldots f_n * s_n)$$

Where:
T_m = the necessary amount of the base
E = the mass of 1 suppository prepared from the base only
f_1 = displacement factor of API_1
s_1 = mass of the API in 1 suppository
f_2 = displacement factor of API_2
s_2 = mass of the API in 1 suppository
….
f_n = displacement factor of API_n
s_n = mass of the API_n in 1 suppository

Preparation and examination of rectal preparations

Requirements of the base material:

- It should be melt at most 37°C or dissolved in body fluids
- congeal fast
- should be stable, with no polymorphism
- viscosity, consistency should be appropriate
- own HLB value
- compatible with APIs

Preparation and examination of rectal preparations

Requirements of the base material:

- Preparation method with:
  - moulding and
  - compression technique
- non-irritant, and non-toxic
- fast disintegration
- good bioavailability
- stability during storage
- cheap and available

Preparation and examination of rectal preparations

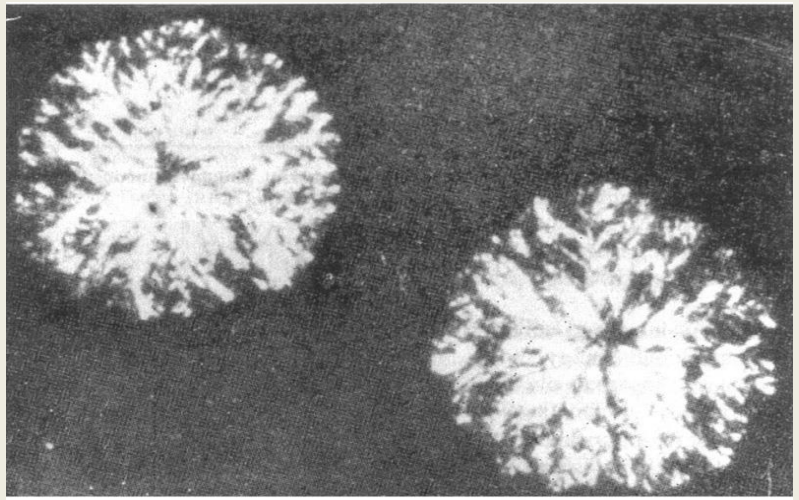
Butyrum cacao:

- (cocoa butter, Oleum cacao, Oleum theobromatis)
- Theobroma cacao (Sterculiaceae) it is prepared by the seeds of Theobroma cacao with applied pressure. The extracted mixture of triglycerides can easy become rancid.
- It can be dissolved in ether, chloroform, carbon-tertrachlororide
- Storage: close container, protected from light.
- Incompatible: alkalic pH.

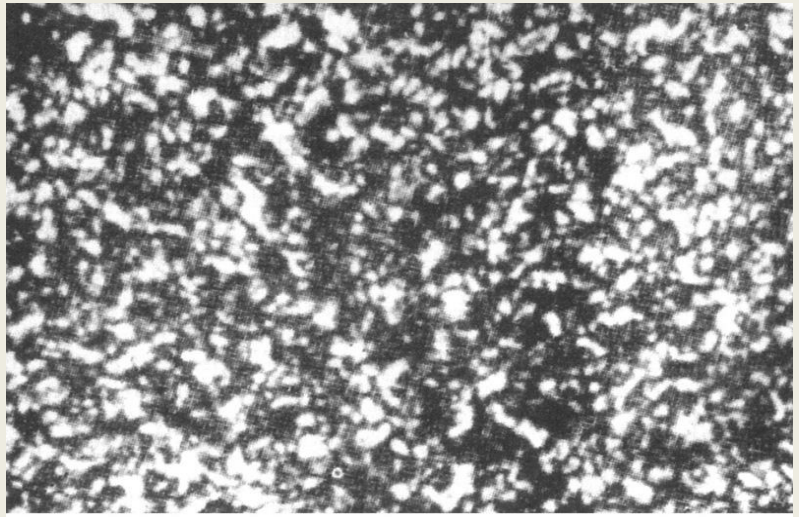
Preparation and examination of rectal preparations

- Mixture of triglycerides:
  - Palmitic acid 24%
  - Stearic acid 35%
  - Oleic acid
  - Linoleic acid 2%

- Disadvantage:
  - polymorphism!!!
  - rancidity (especially in field form)



A stabil (β) módosulatú kakaóvaj mikroszkópos képe

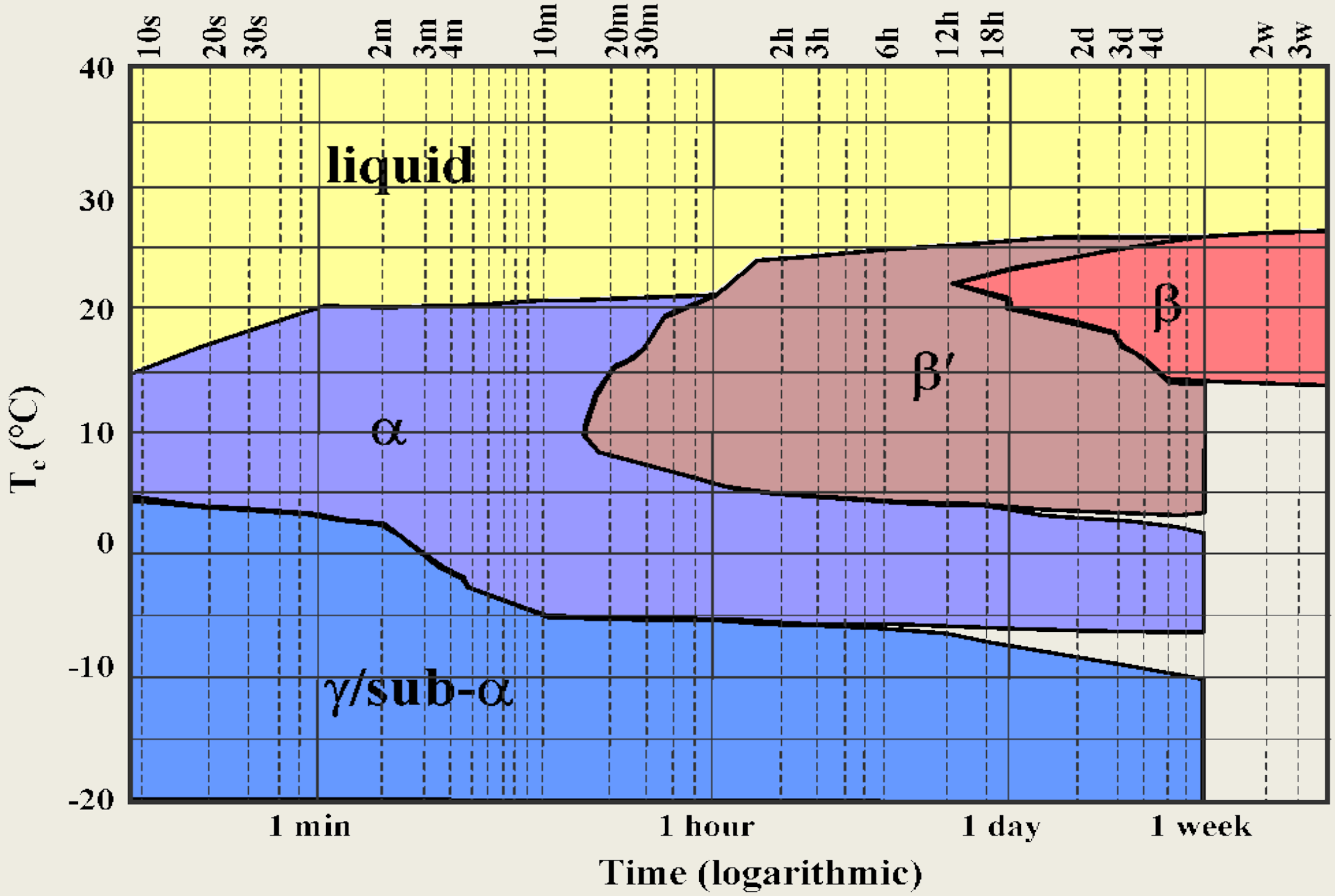


Az instabil (α) módosulatú kakaóvaj mikroszkópos képe

Butyrum cacao polymorphy

Melting points of polymorph forms of cocoa butter		
The nomination form of cocoa butter-species		Melting point °C
Wille and Lutton	Vaeck	
I.	γ	17.3
II.	α	22.3
III.	-	25.5
IV.	β˘	27.5
V.	β	33.8
VI.	-	36.3

Butyrum cacao polymorphy



Preparation and examination of rectal preparations

Adeps solidus:

- This is a mixture of **tri-**,**di-** and **monoglycerides**.
- Production:
  - Starting materials: palm oil, palm kernel oil, coconut oil (plant materials rich with lauryl acid)
  - *Saponification*, then
  - Separation by vacuum-distillation
  - Esterification
  - This process can ensure the proper ratio of the oleic acid.

Preparation and examination of rectal preparations

The numbers behind the name mark the **number of free hydroxyl groups**. The more amount of hydroxyl groups the higher is the probability of the hydrolysis of the sensitive ingredients (acetylsalicylic acid) in this type of base material. It cannot close any water in itself.

Base material	Melting point °C	Congealing point °C	Acid number	Saponification number	Hydroxyl-number
Witepsol W 35 (Adeps solidus 50, Ph. Hg. VII.)	33.5-35.5	27.0-32.0	max. 0.3	225-235	40-50
Witepsol H 32	31.0-33.0	30.0-32.5	max. 0.2	240-250	max. 3
Witepsol S 58	32.0-33.5	27.0-29.0	max. 1.0	215-225	60-70

Preparation and examination of rectal preparations

- No polymorphism
- It can close a little amount of water due to the free hydroxyl groups
- The melting point is near to the congealing point
- Well soluble in apolar solvents
- Equal with Butyrum cacao

Adeps solidus 3

- Saturated fatty acids (C12- C18) , no any free hydroxyl group (mixture of triglycerides)
- Use in case of **acetylsalicylic acid**

Preparation and examination of rectal preparations

Adeps solidus compositus:

- The disintegration can be facilitated by the used surfactants, which are responsible for the faster absorption of the API, and can enhance the solubility, too. This type of base material is commonly used, if fast absorption is the aim (a rapid onset of action is the purpose), or the API can dissolve poorly in the intestinal fluids (Theophillinum can dissolve poorly in water, and pain-killers are recommended to use with this base material).

- **Adeps solidus compositus** (FoNo VII.)

Adeps solidus 50	95 %
Polysorbatum 20	2.5 %
Polysorbatum 61	2.5 %

- In closed container, protected from light

Preparation and examination of rectal preparations

Massa macrogoli:

Its melting point is above 50 °C, and it is a **hydrophilic base** material.
Consequently, ***it cannot melt at body temperature, but it can dissolve*** in water (rectal or vaginal juice).
It is very useful in **vaginal preparations**, because it does not cause unpleasant feeling, and cannot form thin waxy rests.

- **Massa macrogoli** (FoNo VII.)
  - Sorbitanum laurinicum (Span 20) 5%
  - Macrogolum 1540 95%

Well closed container, protected from light, until at most 1 year.

Preparation and examination of rectal preparations

Non-official base materials in Hungary:

PEG mixture of macrogols with different molecular weight:

	1.base	2.base	MP.
• PEG 1000	96%	75%	~30
• PEG 4000	4%	25%	>50

- 1. base: -low melting point
  -fast drug delivery

- 2. base: -high melting point
  -slow drug delivery

Preparation and examination of rectal preparations

Glycerinated gelatine

- USP 24:

  10 g H_2O,
  70 g glycerol,
  20 g gelatin

- It is commonly used for vaginal preparations

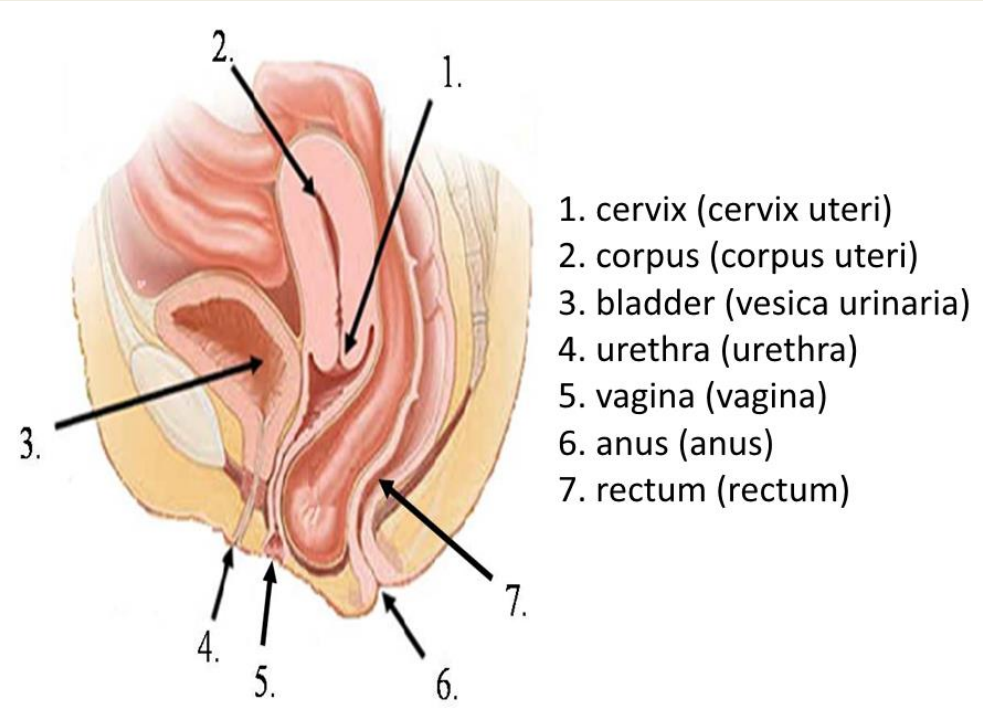
(local antibiotics, progesterone)

Vaginal and intrauterine drug delivery systems

Anatomy and physiology of the vagina

Main data

The vagina is a 7-9 cm long organ, what is covered by non-keratonized stratified squamous cells.
Beneath this surface layer, the connective tissue, vessels and smooth muscle cells are placed.



The proper pH of the vagina is ensured by *Döderlein-fluor* (*Lactobacillus acidophylus*).

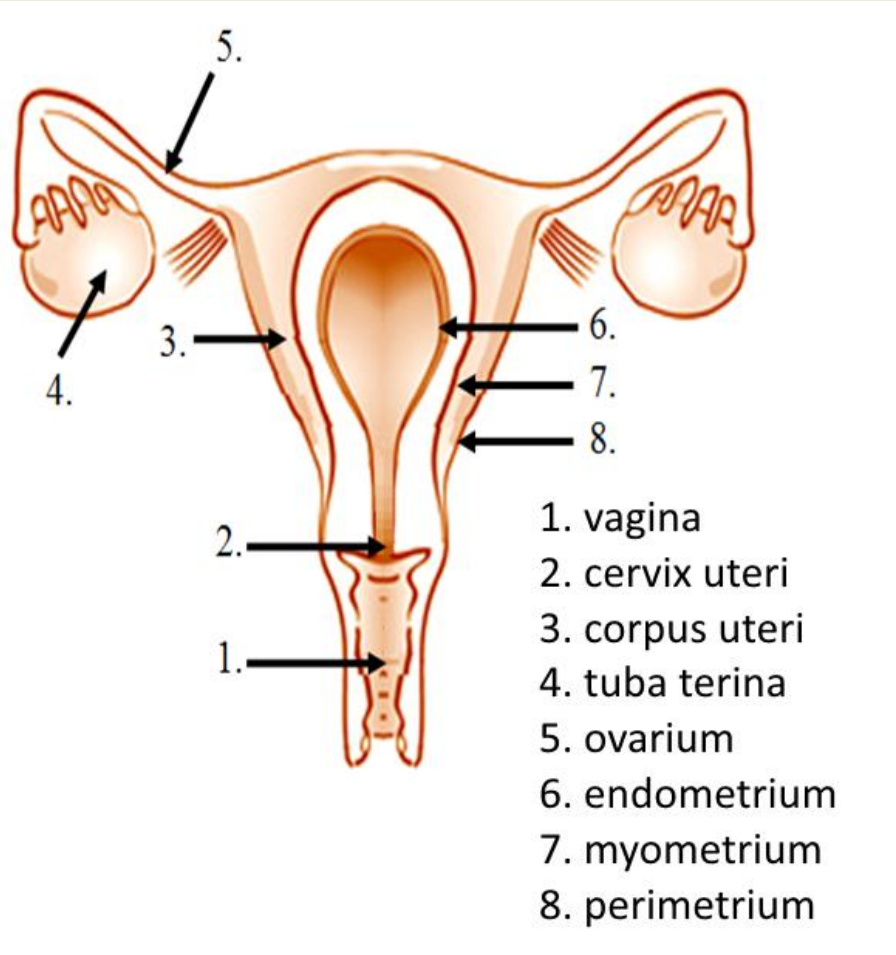
Length (m)	Surface area (m^2)	pH
0,07-0,09	0,01	4-5 (7,0)

Anatomy and physiology of the uterus

Main data

The uterus is a hollow organ which wall is thick from the numerous smooth muscle cells.
Its form is like a pear.

Length is 9 cm,
widht is 5 cm,
thickness 3 cm.



Length (m)	Surface area (m^2)	pH
0,09	0,13	7,2

Biopharmacy of vaginal and intrauterine preparations

„The vagina is impermeable for exogen materials” , but this is not exacly true, because some ingredients can absorb from the vagina.

(alkaloids, inorganic salts, disinficients, steroids, prostaglandins, iodine, a few antibiotics)

The absorption may be happen through the epithelium and so can reach the vein vessels (*plexus venosus vaginalis*).
These little veins flow into the veins of the pudenda (*vena cava inferior).*

The three possible routes of absorption:

- **transcellular** diffusion (lipophilic),
- **intercellular** diffusion (hydrophilic)
- **vesicular** or **receptor mediated trasport**

The different enzymes and microorganisms can influence the stability of the preparation (*Streptococcus, Corynebacterium, Escherichia, Mycobacterium*).

Medications and preparations applied vaginally and intrauterineally

Vaginalia (Ph.Eur. 6)

„Vaginal preparations are liquid, semi-solid or solid preparations intended for administration to the vagina usually in order to obtain a local effect. They contain one or more active substances in a suitable basis."

Several categories of vaginal preparations may be distinguished:

— pessaries,
— vaginal tablets,
— vaginal capsules,
— vaginal solutions, emulsions and suspensions,
— tablets for vaginal solutions and suspensions,
— semi-solid vaginal preparations,
— vaginal foams,
— medicated vaginal tampons.

Medications and preparations

Vaginal tablets

- different forms, and sizes (round, oval, elliptical, almond)
- it must not have sharp edges
- dissolves layer by layer

Foam forming tablets

CANESTEN KOMBI 200 mg vaginal tablet and cream

clotrimazole

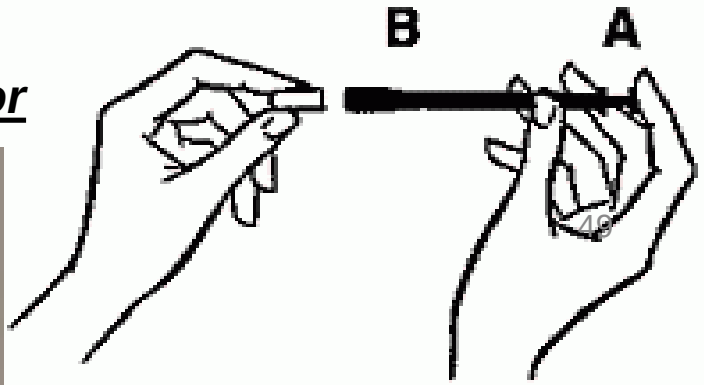
It is applied for the treatment of conditions caused by Candida albicans

Use of the applicator

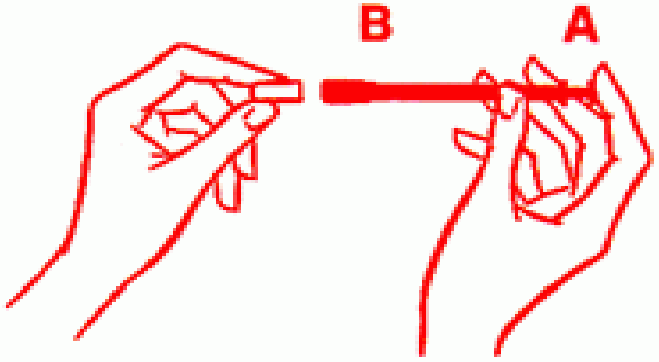
CANESTEN 100 mg vaginal tablet with applicator

clotrimazole

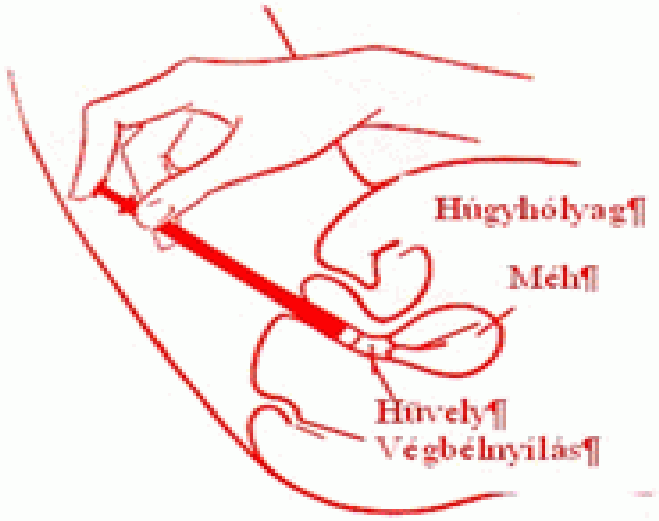
It is applied for the treatment of infections caused by Candida albicans



-Pull the end of the applicator into right position.
-Place the tablet into the end of the applicator. The rounded end of the tablet should be placed outside. Fix the tablet with gently pushing the applicator.



-Insert the applicator with tablet into the vagina. Place it deep. (for this reason, lie down on your back)
-Push the end of the applicator firmly. The tablet is placed in the vagina.
-Clean the applicator with warm but not hot water.



Medications and preparations

Vaginal capsules

- soft capsules
- form like an egg
- smooth surface
- Advantages: liquid and solid APIs

Medicated vaginal tampons

- fixed-dose
- absorb the abnormal secretions
- inhibit the leakage

Medications and preparations

Vaginal solutions

- powders, tablets
- contraceptive, antiseptic, acid
- irrigation (II. microbial group.)
- it can cause the rinse of the physiological flour
- viscosity enhancers

Vaginal aerosols

- foam forming preparations (contraceptives)
- with appropriate applicator
- Absorption surface, good distribution, prolonged

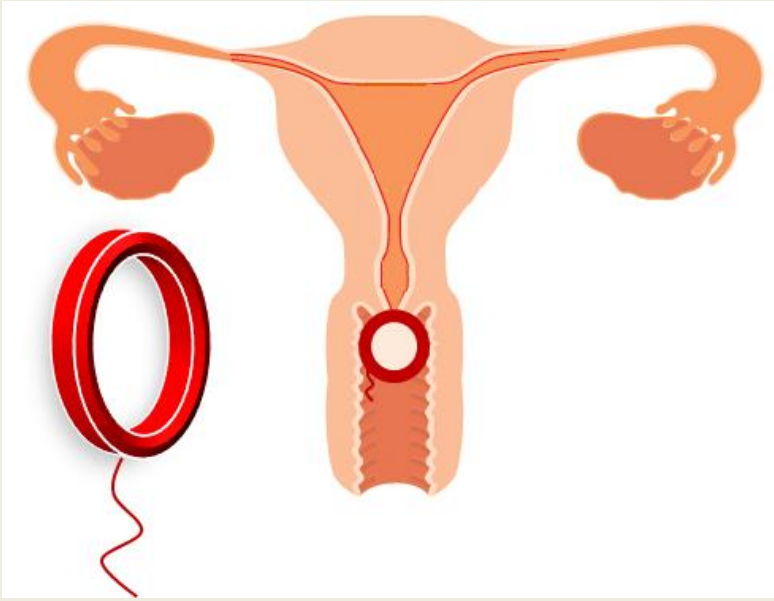
Vaginal ointments

- Mild acidic gels
- O/W

Medications and preparations

Intravaginal drug delivery systems

Estrace VR® is a intravaginal estrogen ring. It can reduce the non desired systemic side effects. It is well applied in the case of night sweatening and some urogenital disorder.



Estring® is an elastic vaginal ring, that contains the API in a silicone media.
It can remain active for 3 months.

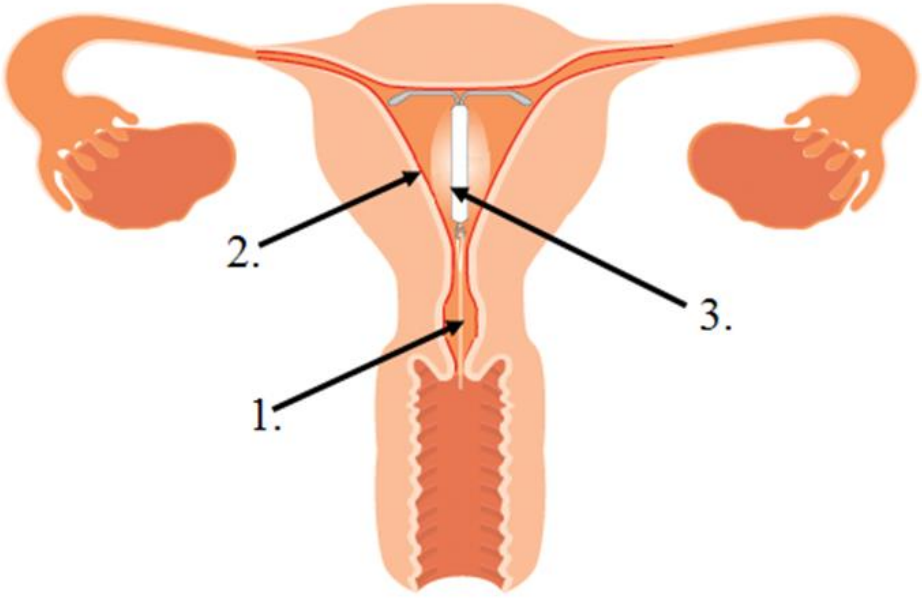
Medications and preparations

Intra Uterine Devices (IUD)

The Intra Uterine Devices may be prepared in different forms. (diaphragm, ring, spiral).

The APIs (hormones) can leave the device and cause local effects. It can ***inhibit the implantation of the oocyte***.

The gynaecologist is allowed to place the device into the uterus. The spiral may be placed ***at most 5 years.***



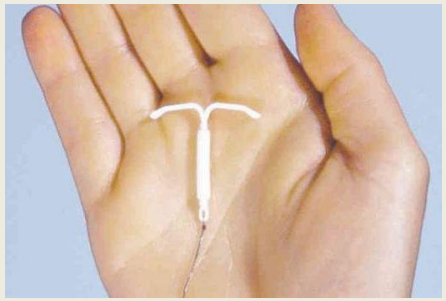
1. Thickening of the cervical mucosa
2. Inhibition of the proliferation
3. Stimulation of leukicytes and prostaglandines release

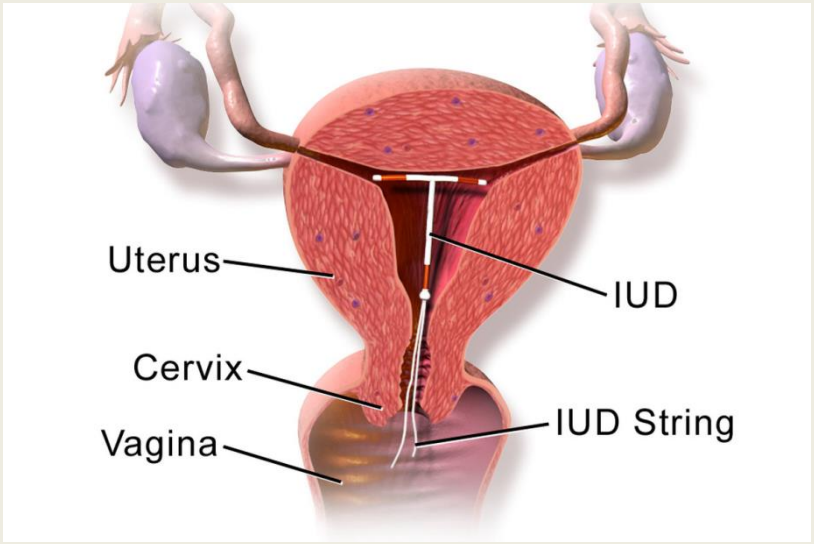
The causal relationship between a spiral and an infection is controversial, because no enough evidence is to prove the connection.

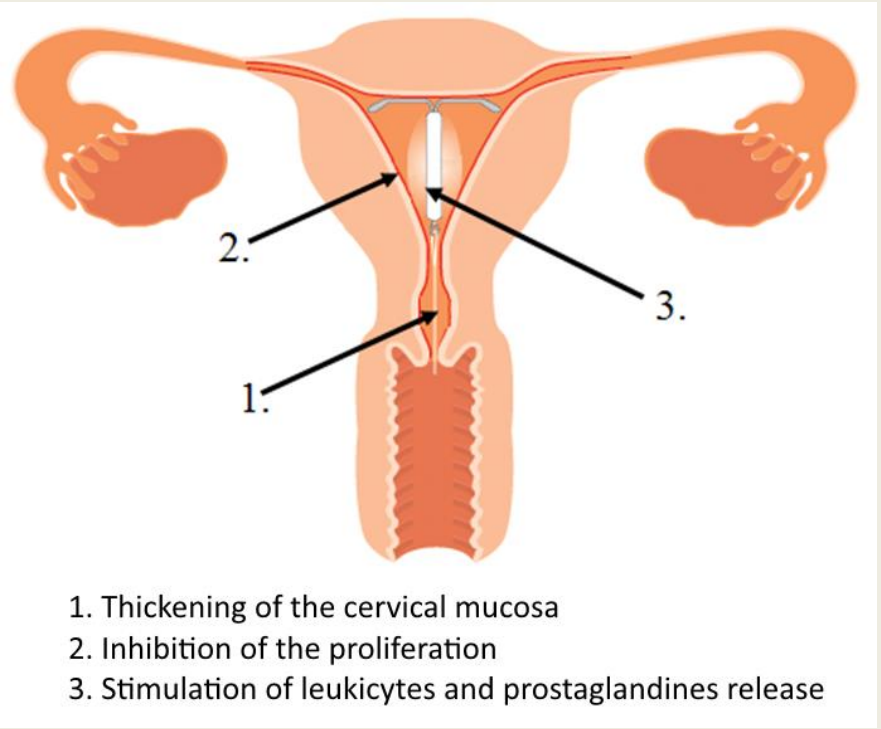
It has a T-like shape.

The Pearl index is 0,2% in the first year, and 0,7% in 5 years period.

Medications and preparations

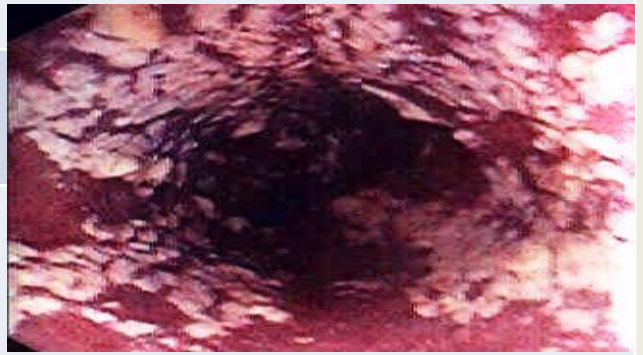






The devices containing contraceptive APIs (hormones) are prepared by plastics. It has a T-like shape. The Mirena® does not contain estrogene, but it contains ***levonogestrel*** (progestagene component) that can decrease the sensitivity of the estrogen receptors. In the beginning, it can release levonogestrel (20 µg/day), The Pearl index is 0,2% in the first year, and 0,7% in 5 years period.
Indications: contraception, menorrhagia, hyperplasy of the endometrium, HRT

Vaginal preparations for common diseases

pathogen	disease	
Chlamydia trachomatis	Inflammation of the uterus and tubes	
Neisseria gonorrhoeae	Tripper, Inflammation of the uterus and tubes →	
Mycopasms	Inflammation of the uterus ans tubes	
Candida species	Inflammation of the vagina →	
Trichomonas vaginalis	Inflammation of the vagina and urethra	
HPVs →	Genital warts and cervical cancer	
Herpes simplex	Genital herpes →	

Other preparations

Medications and preparations

Medical rod (pertica)

- It is intended for the treatment of skin
- Pertica dithranoli FoNo VII.
- Moulded into the mold of the cylinder for vaginal use
- (lip salve)

Urethral stick (bacillus urethralis)

- It can melt or dissolve in the urethra
- Diameter 3-5 mm, length 5.0 cm
- compression or moulding

Thank you for your attention