SUPPOSITORIES

Why is rectal-vaginal drug delivery preferred?

- General condition of the patient
- Properties of the active substance
- Application and removal of the dosage form is painless and safe
- The duration of drug action can be extended and designed with appropriate formulations

Disadvantages:

- Slow and sometimes insufficient absorption of active agents
- Absorption differs among individuals
- Proctis development
- Cultural and traditional beliefs
- Problems with the large scale production of suppositories and obtaining appropriate shelf life

Rectal-Vaginal Dosage Forms

- Suppositories
- Rectal capsules
- Rectal solutions
- Emulsions and suspensions
- Tablets and powders for rectal solutions and suspensions
- Semi-solid rectal preparations
- Foams

Suppository

- Differently shaped (conical, cylindrical, globular) and sized (usually from 1-4 g) solid or semi-solid preparations that contain one or more active agents dispersed or dissolved in a suitable base (water-soluble or dispersible or soluble in body temperature). Usually medicated, for insertion into the rectum, vagina, or urethra.

- The content of the active agent ranges from 0.1% to 40%.

Suppositories based on the application area- USP

Rectal suppositories
~ 2 g for adults
~ 1 g for children

Vaginal suppositories - "pessaries"
drop or oval shaped
~ 3-5 g

Urethral suppositories "bougie"
125 mm length, 4 g for men,
50 mm length, 2 g for women

Rectal route

Local effect

It is mostly used for the treatment of local pain and itching caused by hemorrhoids.

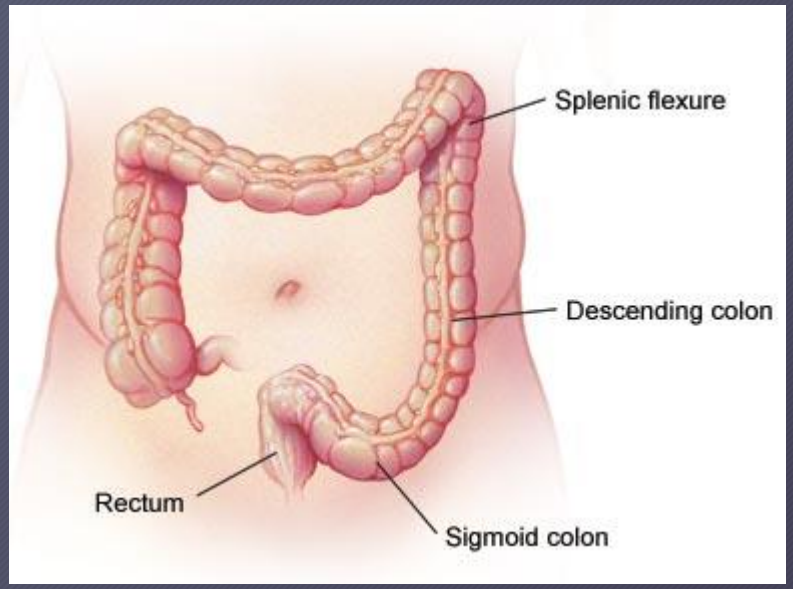
Astringent, antiseptics, local anesthetics, vasoconstrictors, anti-inflammatory compounds and sedative and protective agents, laxatives

Systemic effect

Anti-asthmatic, anti-inflammatory and analgesic drugs are commonly administered rectally. Rectal preparations can also be used for diagnostic purposes.

Peptide drugs

Structure of rectum



Total volume of mucus: 3 mL (in a total surface area of about 300 cm 2)
pH: approximately 7.5 in adults (ie close to neutral)

Rectal Absorption

- Absorption of active substances from the rectum is mainly by passive diffusion. The bioavailability of drugs after rectal administration is very uncertain due to individual differences between patients and rectal venous drainage of the rectum. In general, the rate and amount of absorption of the active ingredients is lower than the oral route due to the small surface area for absorption.

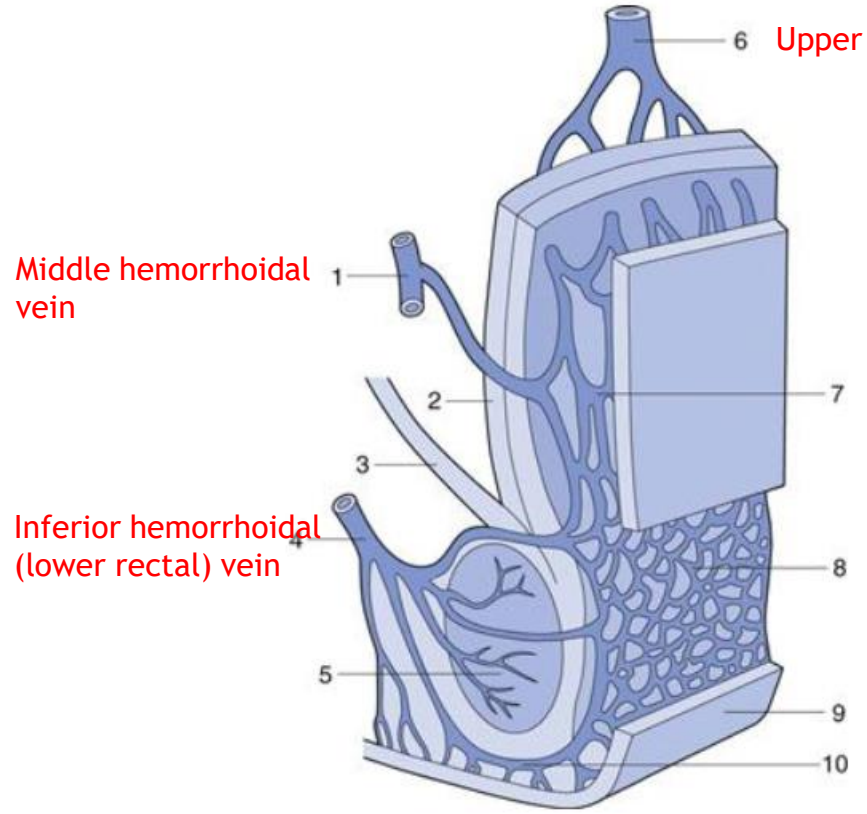


FIG. 42.1 Venous drainage of the human rectum: **1** middle haemorrhoidal (middle rectal) vein; **2** tunica muscularis; stratum longitudinale; **3** muscularis levator ani; **4** inferior haemorrhoidal (lower rectal) vein; **5** muscularis sphincter ani externus; **6** superior haemorrhoidal (upper rectal) vein; **7** and **8** plexus venosus rectalis (submucosus); **9** skin; **10** venosus marginalis. (Adapted from Tondury, 1981, with permission.)

- Applying a suppository to the rectum results in a chain of events leading to absorption of the active agent. Depending on the character of the suppository base, the suppository dissolves in the rectal fluid or melts in the mucus layer.

- Soluble active substance molecules diffuse from the mucus layer and then from the epithelium forming the rectal wall.
- Absorption occurs by passive diffusion.
- The active transport mechanism in the upper regions of the gastrointestinal tract is not present in the rectal region.

Physiological factors affecting absorption from rectum

- The amount of fluid present in the rectal region
- Properties of rectal mucus
- Rectum content
- Mobility of rectal wall
- Absorption zone
- Rectum temperature

Factors of suppository base affecting absorption from the rectum

- Melting point of base,
- The solubility of the base in the fluids of the application area
- The solubility of the active agent in base,
- Characteristics of the release of the active agent from the base
- Spreading property of the base.
- Viscosity of the base (etc.).

Factors of active agent affecting absorption from rectum

- Solubility of active agent in water
- The degree of ionization and pKa of the active agent
- Solubility of the active agent in lipids / partition coefficient
- Particle size of active agent

BASE	ACTIVE AGENT	DRUG RELEASE
FATTY(Oleaginous)	OIL SOLUBLE	SLOW
FATTY(Oleaginous)	WATER SOLUBLE	FAST
WATER MISCIBLE	OIL SOLUBLE	MEDIUM
WATER MISCIBLE	WATER MISCIBLE	MEDIUM

Suppository Bases

- 1- Fatty (Oleaginous) bases
- 2- Synthetic or semi-synthetic fatty bases
- 3- Non-ionic surfactants
- 4- Water-soluble, water-miscible bases

Suppository Bases
1-Fatty bases:

- Theobroma oil

- polymorphism →→ Due to fatty acids in its structure

- Theobroma oil can exist in 4 different polymorphic forms of which only one is Stabile

1. Unstable gamma form melting at 18°C
2. Alpha form melting at 22°C
3. Beta prime form melting at 28°C
4. Stable beta form melting at 34.5°C

Suppository Bases
1-Fatty bases:

- Hydrogenated oils:

- For the preparation of hydrogenated oils, vegetable oils are hydrogenated by special reactions and catalyst and obtained as solids. Hydrogenated peanut oil, soybean oil, sunflower oil and hazelnut oil are the most commonly used. They have commercial samples such as Suppolanol, Suppositol.

Suppository bases
2-Synthetic or semi-synthetic fatty bases

- These are mixtures of natural or synthetic vegetable oils consisting of a mixture of 12-18 carbons, saturated fatty acid triglycerides, waxes and fatty alcohols. Bases with desired melting point can be prepared using the appropriate combination of components.

- Commercial examples:
- Cotmar, Dehydag, Fattibase, Suppocire and Witepsol.

Suppository bases
2-Synthetic or semi-synthetic fatty bases

- Saturated fatty acid glycerides:
  - Witepsol
    - Fatty acid (palmitic, lauric (etc.) triglycerides with 12-18 carbon
    - Water retention capabilities
    - Ex. Witepsol has different types with melting points ranging from 29 to 44 ° C.
    - Whitepsol H, Whitepsol S, Whitepsol W, Whitepsol E etc
  - Massa Estarinum
    - Mixture of mono, di and triglycerides of fatty acids with 11-17 carbons
  - Adeps solidus, Massuprol, Lasuprol, Suppository Base G, Rectonal and Hexenol

Suppository bases
3-Non ionic surfactants

- Polyoxyethylene fatty acid esters
- Polyoxyethylene stearate
    - Tween 61
    - Tween 61 + Tween 60
    - Tween 61 + glyceryl laurate

Suppository bases
4- Water soluble-water miscible bases

Polyethylene glycol derivates (Carbowax, Suppogen, Postonal, Polywachs):

- They are stable for a long time, do not get hydrolyzed and decomposed by oxidation.
- Their structure is not suitable for microorganism growth.
- Suitable bases for antiseptic substances.
- They can easily release the active agent in the rectum due to their water soluble nature.
- Composed of PEGs with different MW.

Suppository bases
4- Water soluble-water miscible bases

- Glycerin-Gelatin-Water Bases:

The suppositories prepared with this base do not melt at body temperature but dissolve in the mucosal fluid and release the active agent.

Gelatin	20 g
Glycerol	70 g
Purified water	10 g

- Glycerin-Soap Base:

It consists of glycerin and sodium stearate soap.

Excipients added to suppository bases:

- ▫ Emulsifying agents
- ▫ Viscosity enhancers
- ▫ Materials that have water holding and liquid binding properties
- ▫ Solvents
- ▫ Agents to improve mechanical resistance
- ▫ Others (dyes, antioxidants, stabilizers, etc.)

Calculation of required amount of bases

In order to prepare the suppository:

- it is necessary to know the space that the active agent comprise in suppository base.
- This depends on the densities of each active substance.
- If the density of the active agent is equal to that of the base; the active agent in the suppository will hold the same volume.
- If the density of the active agent is different from the density of the liquid, then the volume for the active substance must be calculated.

The displacement value (or replacement factor)

- The displacement value (or replacement factor) of a drug (f) is the number of parts by weight of drug which displaces (occupies the same volume of) 1 part by weight of the base. The displacement value is applied to insoluble materials and is listed in practice for various substances.

Calculation of the amount of bases required by the displacement value:

Calculation of the base required for the prescription is made with the value of the displacement value.

M = S – [(f1.g1)+(f2.g2)+.....+(fn.gn)]

M : Amount of bases (g)

S : Weight of unmedicated suppository (g)

f : displacement value (replacement factor)

g : Amount of active substance (g)

An ideal suppository base should have the following properties:

1-It should not be toxic and irritant for mucosal membranes,

2- Must be compatible with the active substance,

3- Base should melt at the rectum temperature or dissolve in the rectum fluid,

4- The difference between degree of freezing and degree of melting be suitable for preparation,

5- Can be easily removed from the mold,

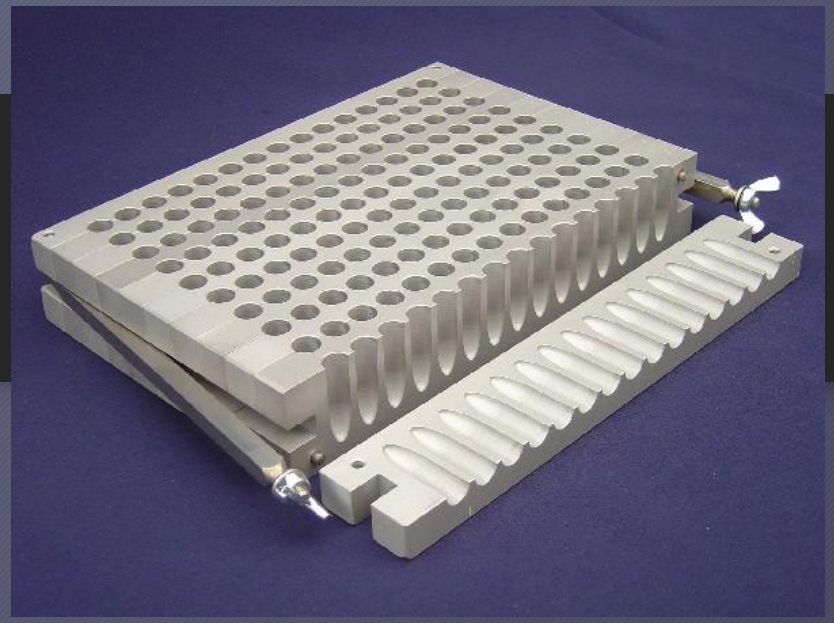
6- It should be stable.

- Diluents
- Adsorbents
- Surfactants
- Lubricants
- Antimicrobial preservatives
- Excipients such as coloring agents may be added.

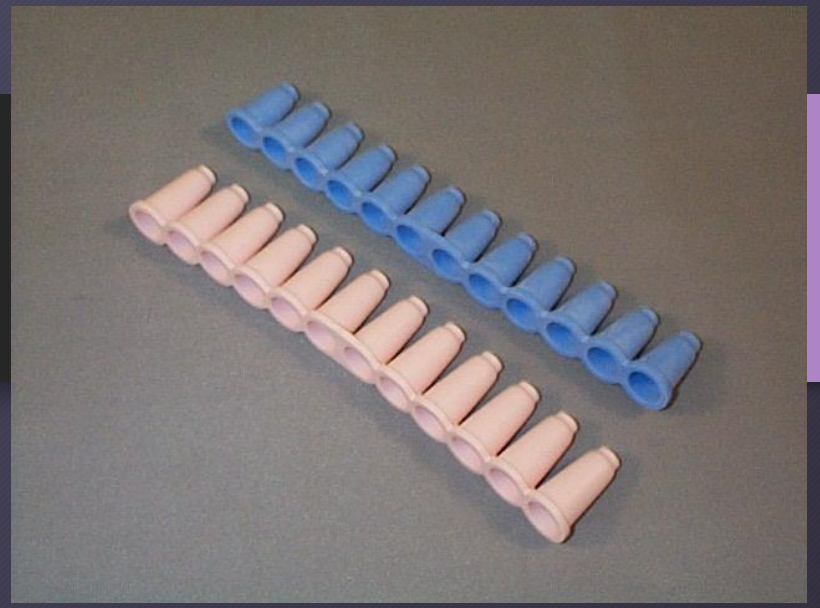
Preparation of Suppository

1) Pour moulding (hot preparation)

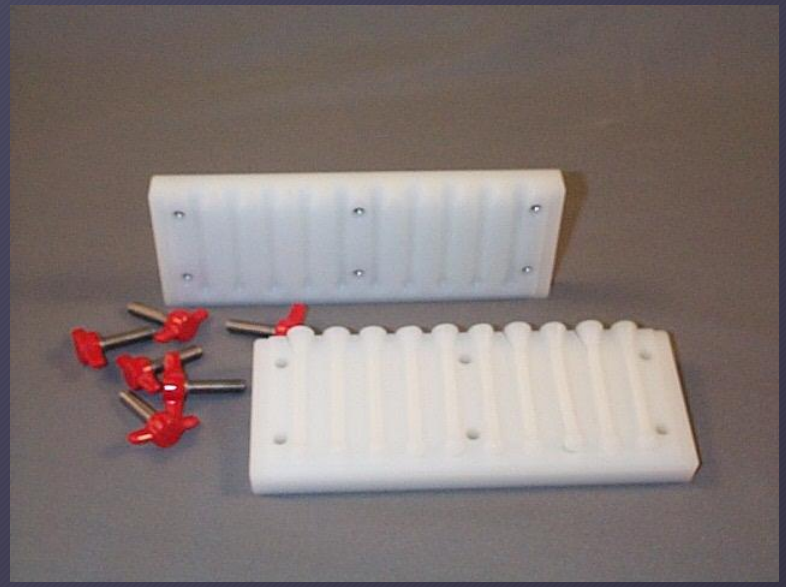
Melting the bases → Drug+base mixing → Pouring into Molds



Aluminum Metal Molds



Flexible Plastic Molds

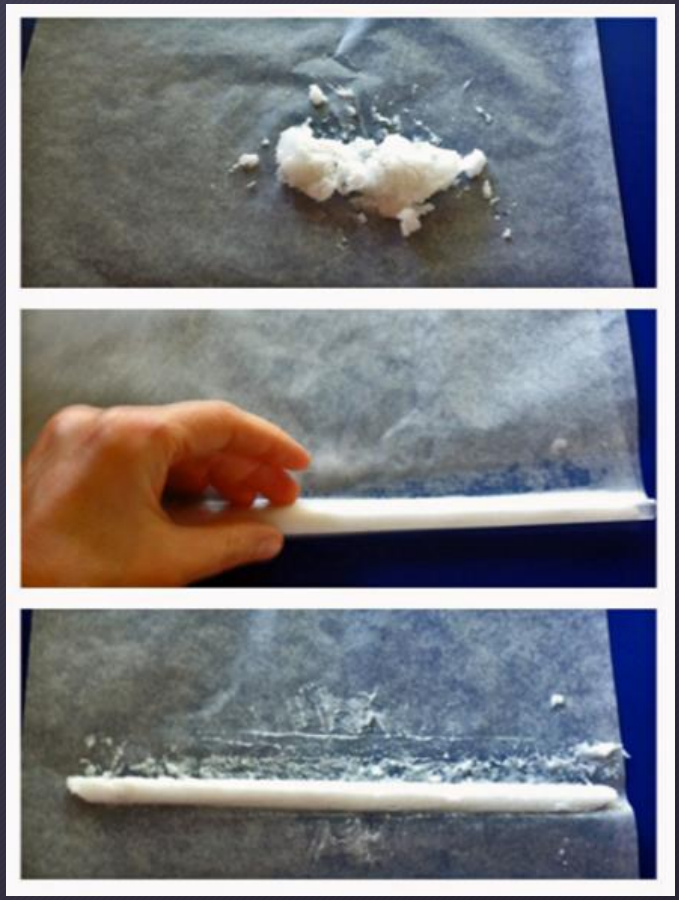


Hard Plastic Molds

Preparation of Suppository

2) Hand moulding (cold preparation)

Mixing of powders in mortar → Drug+base mixing to form a homogenous mass → Cutting to a certain length after rolling into a stick of appropriate thickness



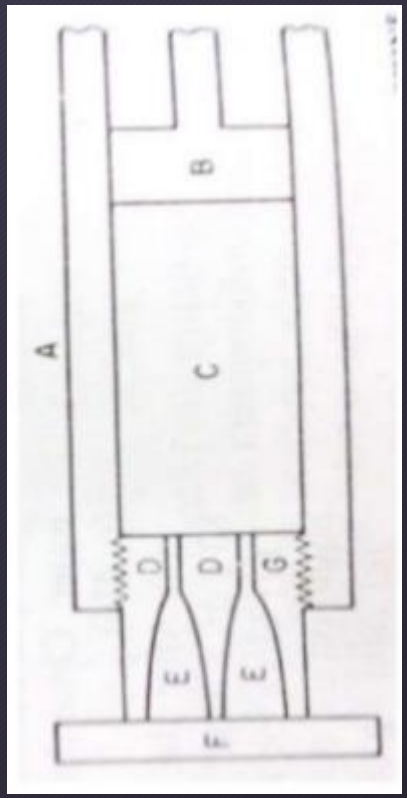
Preparation of Suppository

3) Compression moulding

Mixing of powders in mortar

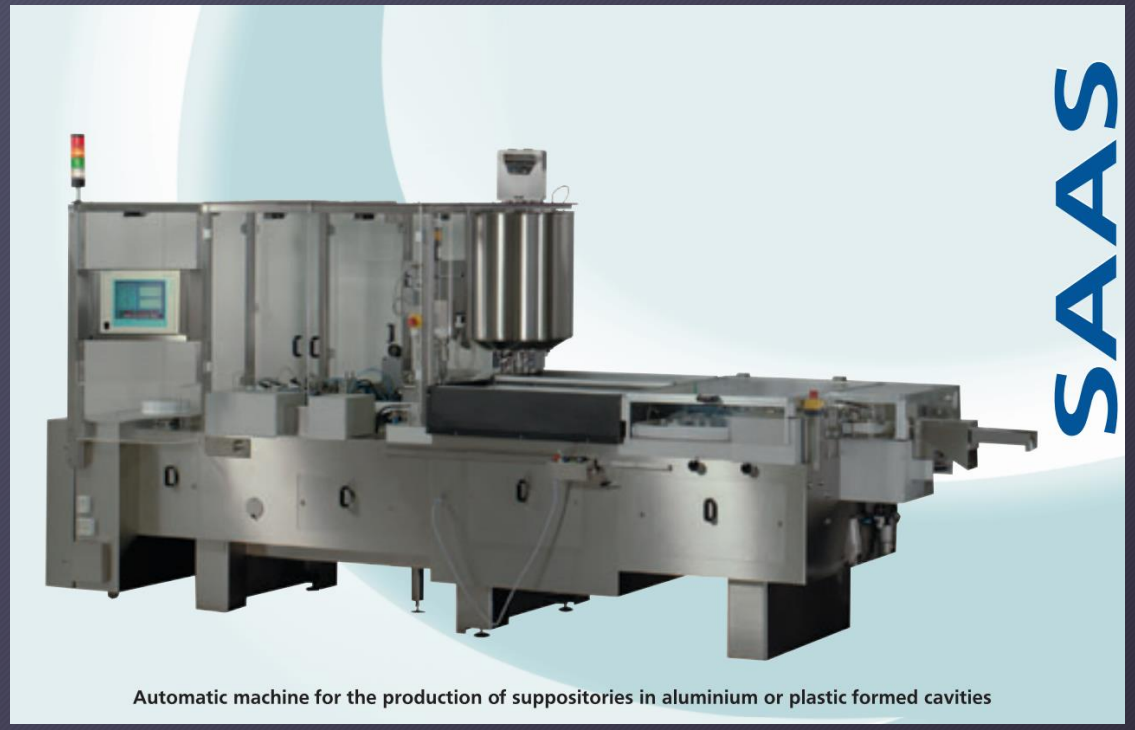
Drug+base mixing to form a homogenous mass

Poured/pushed into cylinder and close the cylinder. The screw is pushed into the mold by bending or pressing from the top



Preparation of Suppository

4) Preparation with automatic machines



QUALITY CONTROL TESTS

1) Determination of melting point
2) Determination of Melting Time
3) Hardness and Mechanical strength
4) Disintegration test
5) In vitro drug release test
6) Penetration test