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A REVIEW ON SUPPOSITORIES AND APPLICATION OF VAGINAL DRUG DELIVERY SYSTEM

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Abstract

Historically, medications that caused unconsciousness, haemorrhoidal, germicidal, and purgative effects were administered the rectal route as suppository injections. The majority of medicinal drugs on the market today are designed to be administered rectal in order to increase their bioavailability and achieve the necessary therapeutic blood concentration. Historically, only locally acting medications, such as steroids, prostaglandins, spermicidal, antifungal, antibacterial, and antiviral, were allowed during vaginal birth. The capacity to avoid first-pass hepatic processing, accessibility, a healthy blood supply, and permeability to big molecular weight medications, such as peptides and proteins, are the main benefits of this route. Vaginal medicine delivery devices that are frequently utilised include suppositories, creams, gels, pills, and vaginal rings. This message is intended to give the reader an overview of the developments in the area of vaginal medication delivery.

Introduction

A suppository is a dosage form used to deliver medications by insertion into a body orifice (any opening in the body), where it dissolves or melts to exert local or systemic effects. There are three types of suppositories, each to insert into a different section, rectal suppositories into the rectum, vaginal suppositories into the vagina, and urethral suppositories into the urethra of Suppositories are ideal for infants, elderly individuals and post-operative patients, who are unable to swallow oral medications, and for individuals experiencing severe nausea and/or vomiting. [1][2][3] Suppositories are specially shaped solid dosage form of medicament for insertion into body cavities other than mouth. They may be inserted into rectum, vagina or the urethra. These products are so formulated that after insertion, they will either melt or dissolve in the cavity fluids to release the medicament.

Suppositories are classified as

- Rectal suppositories.
- Vaginal Suppositories.
- Urethral Suppositories.
- Nasal Suppositories.
- Ear cones.

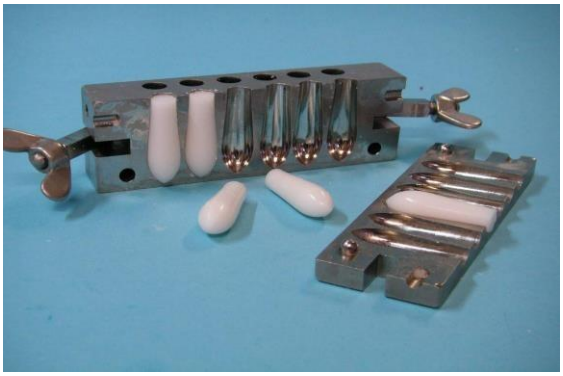

Fig:1-suppositories

the pharmaceutical literature, human vagina is often described as slightly S-shaped fibro muscular collapsible tubes between 6 and 10 cm long extending from cervix of the uterus. Hexagonal wall consists of three layers: the epithelial layer, the muscular coat and the tunica advent. During the menstrual cycle, the thickness of the vaginal epithelial cell layer changes by approximately 200– 300 Am. The surface of the vagina is composed of numerous folds, which are often called rugae. (3) The rugae provide distensibility, support and an increased surface area of the vaginal wall. The vagina

has an excellent elasticity because of the presence of smooth elastic fibers in the muscular coat. Loose connective tissue of tunica advent further increases the elasticity of this organ. The network of blood vessels that supply blood to the vagina include a plexus of arteries extending from the internaliliac artery, uterine, middle rectal and internal prudential arteries. In fact, arteries, blood vessels and lymphatic vessels are abundant in the walls of the vagina (5). Drugs absorbed from the vagina does notundergo first-pass metabolism because blood leaving the vagina enters the peripheral circulation via a rich venous plexus, which empties primarily into the internal iliac veins.

Factors affecting vaginal absorption of drugs:

a).The volume, viscosity and pH of vaginal fluid may have either negative or positive impact on vaginal drug absorption. The absorption of drug that is poorly water-soluble may be increased when the fluid volume is higher.

b). However, the presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from vaginal cavity and subsequently reduce absorption. The factors include physiological factors, physicochemical factors, pharmacological factors

Physiological factors:

As mentioned above, cyclic changes in thickness of vaginal epithelium, fluid volume and composition, pH and sexual arousal could potentially affect drug release from intravaginal delivery systems. For example, the vaginal absorption of steroids is affected by the thickness of the vaginal epithelium [6].Physicochemical properties such as molecular weight, lipophilicity, ionization,

surface charge, chemical nature can influence vaginal drug absorption.(7) For example, the vaginal permeability of straight chain aliphatic alcohols increases in a chain length dependent manner (8).

A). Since vaginal fluid contains a large amount of water, any drug intended for vaginal delivery require a certain degree of solubility in water.

B). In fact, data on the human vaginal permeability to drugs with different physicochemical properties is very limited; much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption.

Pharmacological factors:

However, the vaginal progesterone absorption in estrogen deficient women who were receiving vaginal estrogen was found to be increased, although the estradiol therapy should have caused increased thickness of the vaginal epithelium, so ultimately the drug absorption decreases.(9)

Drug absorption mechanism by Vagina Drug delivery routes drug transport across vaginal membrane may occur by a number of different mechanisms:

a) Diffusion through the cell due to a concentration gradient (trans cellular route)

b) Vesicular or receptor mediated transport mechanism or

c) Diffusion between cells through the tight junctions (intercellular route).

Novel Concepts in Vaginal Drug Delivery:

In development of vaginal dosage form, the following consideration should be addressed

a) Maintenance of an optimal pH for vaginal epithelium

b) Ease of application

c) Even distribution of drug

d) Retention in vagina

e) Compatibility of co-administered medicines

f) Traditionally, solutions, suppositories, gels, foams and tablets have been used as vaginaformulations. More recently, vaginal ring has been introduced for hormone replacement and contraceptive therapy.

g). Further, vaginal formulations may be designed to produce local effect such as spermicidal or antibacterial effect or to produce a systemic effect by continuous release of drugs such as

contraceptives.

Types of Suppositories:

Suppositories have a base made from substances like gelatin or cocoa butter that surrounds the drug. As the warmth of your body melts the outside, the drug slowly releases(10). Different types of suppositories go into the rectum, vagina, or the duct that empties your bladder, called the urethra. Sometimes they treat the area where you put them (11). Or the medicine absorbs into your blood and travels to other parts of your body.

Rectal suppositories go in your bottom. They are about an inch long and have a rounded or bullet- shaped tip. You might take them to treat:

- Allergies
- Anxiety
- Constipation
- Fever
- Hemorrhoids
- Motion sickness
- Nausea
- Pain and itching
- Seizures
- Mental health problems, such as schizophrenia or bipolar disorder

Vaginal Suppositories are oval-shaped. You can use them for:

- Bacterial or fungal infections
- Vaginal dryness
- Birth control

Urethral suppositories are rare. There's only one kind,

MUSE, which men with erection problems can use to take the drug alprostadil. The suppository is about the size of a grain of rice.:

Mechanism of action:

The rectal suppositories are extensively used as a mechanical aid to bowel evacuation which produce its action by either irritating the mucous membrane of the rectum (e.g. glycerol and bisacodyl) or by lubricating action or by mechanical lubrication.

Systemic treatment by the rectal route is of particular value for

(a). treating patients who are unconscious, mentally disturbed or unable to tolerate oral medication because of vomiting or pathological conditions of the alimentary tract.

(b). administering drugs, such as aminophylline, that cause gastric irritation, and

(c). treating infants.

Properties of ideal suppository base:

It should melt at rectal temperature (3600) or dissolve or disperse in body fluid. For eutectic mixturesand in tropical climate the melting range of the base should be higher.

1. Release medicaments easily.
2. Shape should remain intact while handling.
3. Non-toxic and non-irritant to sensitive and inflamed mucous membrane.
4. It should be stable on storage i.e. it does not change color, odor, or drug release pattern.
5. Compatible with broad variety of drug and adjuvants.
6. It should shrink so that it comes out easily from the mound without the use of any lubricants. For fatty bases the following additional specifications are required.
7. "Acid value" is below 0.2
8. "Saponification value" ranges from 200 to 245
9. "Iodine value" is less than 7
10. The interval points and solidification point are small.

Advantages, disadvantages and application of suppositories :(13-14)

Advantages:

Improved enzymatic drug stability: Many proteolytic and other enzymes in the GIT(Gastro Intestinal Tract) result in drug degradation, which prevents effective absorption following oral administration.

a) Partial avoidance of hepatic first pass: The rectum is extensively supplied with blood from the various rectal arteries. It is drained by at least three veins and drug absorption occurs through this venous network. It is usually reported that inferior and the inferior Venicia is connected tothe middle rectal veins. This allows bypassing the portal system and the associated first pass metabolism in the liver.

b) Higher drug load: Suppositories allow for two to three times higher drug loads to be administered, depending on the amounts of other excipients necessary in their formulation.

c) Lymphatic delivery: many researchers have studied and suggested that some of the drugs after rectal administration enters in to the lymphatic system thus bypassing the first pass effect.

d) Constant and static environment: Compared to the oral route of administration, the rectal route provides a much more constant environment for the drug as it is absorbed.

e) Patients with swallowing difficulty: Children, elderly people facing problems in swallowing can be largely obviated by the rectal administration.

f) Avoidance of overdosing: Certain drugs, viz., sedative oral administration may raise a concern with respect to the possibility of severe accidental or intentional overdosing. This danger is particularly eliminated by rectal administration.

Disadvantages:

a) Patient acceptance and compliance: In many cultures reluctance to consider rectal administration as dosage form has resulted in a tendency by pharmaceutical company to avoid rectal dosage forms, except for most obvious indications and situations.

b) Potential for non-specific drug loss: Ineffective absorption due to premature loss from rectum and interaction of fecal matter with the drug or excipient may reduce absorption and diminish effectiveness.

c) Limited fluid in rectum: Small volume (3 ml) may limit dissolution of drug particularly with low aqueous solubility.

d) Formulation: Melting, liquefaction, solubility, particle size, etc. can lead to formulation difficulties.

e) Expensive: These are more expensive as compared to tablets. (13-14).

Applications of Suppositories:

Suppositories are generally used for unconscious and pediatric patients and in geriatric persons. Suppositories are used for both systemic and local actions, where alternative is unavailable. A wide range of drugs have been incorporated into suppositories as shown in the following

Suppositories contains:

- Suppositories Containing Local Anesthetics agents
- Suppositories Containing Astringents
- Suppositories Containing Steroids
- Vasoconstrictors in Suppositories
- Protectants in Suppositories
- Use of Antiseptics in Suppositories
- Use of Keratolytic in Suppositories
- Suppositories Containing Polyresin
- Other Ingredients in Suppositories

1. Suppositories Containing Local Anesthetics agents:

The local anesthetics act by numbing the nerve endings and provide temporary relief from pain and itching. These act by causing a reversible block to conduction in the sensory nerves. These are well absorbed from the mucus membrane and used as surface anesthetics6. These provide good relief from discomfort encountered in cases of strangulated hemorrhoids, fissures and perianal hematomas. Some commonly used local anesthetics. Benzocaine 5 to 20%, Lidocaine 2 to 5%, Cinchocaine, Dibucaine 0.25% to 1%, Dyclonine 0.5% to 1%, Premixing 1% and Tetracaine 0.5 to 5%.

2. Suppositories Containing Astringents:

The astringent causes the cells of the anal skin to clump thereby drying the skin, which gives relieffrom burning and itching. Some common astringents that are used include Hamamelis water, which is a mild astringent prepared from twigs of Hamamelis virginiana. It helps in relief from the hemorrhoidal itch. Zinc oxide 5 to 25% prevents the irritation at the perianal area by forming a physical barrier on the skin that prevents the contact of the irritated skin with aggravating liquid or stool from the rectum.

3. Vasoconstrictors in Suppositories:

Hemorrhoidal cushions contain swollen blood vessels. The vasoconstricting agents can help in relieving symptoms of hemorrhoids. On application, these drugs cause the blood vessels to shrink, thereby reducing hemorrhoidal congestion. These products additionally contain mild form of anesthetic, which helps in relieving pain and itching. The commonly used vasoconstrictors are: Ephedrine sulfate 0.1 to 1.25%, Epinephrine 0.005 to 0.01% and Phenylephrine o.25%.

4. Protectants in Suppositories :

which ends in bleeding. Again, when this tender skin comes in contact with liquid or stool, it causes the skin to further itch and burn. Protectants, when applied in the form of suppositories, form a physical barrier on the skin and results in reducing the pain quotient and the pruritus. These also protect the broken skin from coming in contact with offending particles in the stool. While a variety of protectants are used in suppositories, a few commonly used are: Aluminum hydroxide gel11, Glycerin, Lanolin, Aloe vera, White petrolatum, Zinc oxide and Calamine.

5. Use of Antiseptics in Suppositories:Being a highly contaminated area, the anal and perianal skin are susceptible to variety of organisms, which can lodge there either from the adjoining area or from the contaminated stool. The chances of contamination further increase when the skin gets bruised during defecation. Antiseptics are used to keep the area clean and to prevent infection. The commonly incorporated antiseptics include: Benzalkonium chloride, Boric acid and FaceTime sulphate.

6. Use of Keratolytic in Suppositories:

Certain chemicals cause the outer layers of skin and other tissues to disintegrate when applied. They eventually help in better penetration in the tissues of other medications contained in the suppositories to bring quicker relief. The two commonly used keratolytic are: Aluminum Chlo hydroxy palatinate 0.2 to 2% and Resorcinol 1 to 3%. Use of Calcium Desolate in Suppositories Calcium desolate is a venom-tonic drug, which is widely prescribed for three main indications: chronic venous disease, diabetic retinopathy and the symptoms of hemorrhoidal attack. The drug acts on the endothelial layer and basement membrane of the blood capillaries.

7. Other Ingredients in Suppositories:

Imiquimod containing suppositories have been successfully used to prevent recurrence of anal condylomas. Trimebutine, an anal sphincter relaxant, has been used to relieve post hemorrhoidectomy pain(12). Ketoprofen suppositories were recommended in patients after anal surgery. A sedative cryotherapy was being used with the intention of producing tissue hypothermia, giving cool numbing effect over the hemorrhoids. Promethazine suppositories were proposed for hemorrhoidal complications while trichloroacetic acid was used for the treatment of anal fissure(13). A compound Arogenates suppositories has been shown to be useful in the treatment of mixed hemorrhoids. Few old references have described use of Ronal, Glucofuranose derivatives, Indacene, Parthenon, Rhubarb and Aloe, Phenylindanedione, Proctoglivenol in suppositories form.(14)

Insertion technique of suppositories:

It has been suggested that the suppositories should be inserted with the patient lying on the left lateral side with the right knee bent(15). The suppositories should be dipped in water before use, which facilitates the easy insertion of the suppositories. It should be kept in cold water or refrigerator for half an hour before use if the suppositories are too soft to be inserted, especially during warm weather(16). Emptying of bowel should be avoided for at least an hour after insertion ofthe suppositories to allow it to be fully absorbed.Method of preparation:

1. Hand Rolling
2. Compression Molding
3. Fusion Molding

These are the simplest and oldest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of

heating the cocoa butter(17).

Hand Rolling:

It is the simplest and oldest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base(18). It has the advantage of avoiding the necessity of heating the cocoa butter. By triturating grated cocoa butter and active ingredients in a mortar, a plastic-like mass is prepared(19). The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The cylinder is then cut into the appropriate number of pieces which are rolled ozone end to produce a conical shape. The suppository "pipe" or cylinder tends to crack or hollowing the center, especially when the mass is insufficiently kneaded and softened(20).

Compression Molding:

Compression molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mold using suppository making machines. The suppository base and the other ingredients are combined bythorough mixing. The base softens because of the friction in the process. A mortar and pestle can be used on small scale. On the other hand, large-scale manufacturing involves mechanically operated kneading mixers and a warmed mixing vessel(21). In the compression machine, the suppository mass is placed into a cylinder which is then closed. After that from one end pressure is applied to release the mass from the other end into the suppository mold or die. When the die is filled with the mass, a movable end plate at the back of the die is removed and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected[22]. The endplate is returned, and the process is repeated until all of the suppository mass has been used. When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.

1.Fusion Molding:

The fusion Molding process involves the following steps:

- Firstly, melting the suppository base.
- Then the drug is either dispersed or dissolved in the melted base.

The melt is allowed to congeal

Now the suppositories are removed from the mound.

2. Automatic molding machine:

Two types of molding machines are available:

(a) rotary molding machine and

(b) straight-line molding machine Manufacturing cycles in rotary molding machine:

1. Prepared mass is filled in an into a filling hopper where it is continuously mixed and maintained at constant temperature.
2. The suppository molds are lubricated by brushing or spraying lubricant solution. 3. The molten mass is filled in the molds to a slight excess.
4. The mass is cooled to solidify and the excess material is scrapped off and collected fore-use.
5. In the ejecting section the mold is opened and the suppositories are pushed out by steel rods.
6. The mold is closed and then moved to the first step of the cycle. The output of a typical rotary machine ranges from 3500 to 6000 suppositories an hour.

Stability studies:

Stability studies were carried out according to the ICH guidelines on the formulated suppositories at 4°C/ 60±5% RH (refrigerated temperature) as well as 27°C/ 65±5% RH (room temperature). Physical appearance tests, disintegration, drug content as well as dissolution tests were subsequently carried out on the formulated suppositories at three monthly intervals for a period of nine months.

Methods of structural, logical and systematic analysis of literary sources were used:

According to State Pharmacopoeia of Ukraine and the European Pharmacopoeia, suppository bases used for the manufacture of this dosage form are divided into hydrophobic, hydrophilic and diphasic. And according to USP, there are six main classes of suppository bases .(4-9)

1. Cocoa butter.
2. Cocoa butter substitutes.
3. Glycerin gelatin.
4. Polyethylene glycol.
5. Surfactant basis.
6. Tablet suppositories or inserts.

Medline (1950-2006) was searched for all published reports using the key words "Suppositories, anal, hemorrhoids, rectum and proctology". This study sums up various suppositories used in proctological practice, which either are in vogue and have been used with a proven degree of success, or suppositories which are described in the literature but are no more in use. The study attempts to highlight the advantages and drawbacks of each of them. The suppositories used for inflammatory and irritable bowel disease, malignancy and systemicinfection have been excluded .

But in some sources you can find the following classification of bases, which is based on their properties of melting or dissolution.

suppository base such as fat or oil, melts at body temperature;

- a glycerol-gelatin base that absorbs water

and dissolves to release API;

- water-soluble or water-miscible polymers or surfactants;
- a group of bases which contains disintegrating agents, natural resins, effervescent agents, collagen, fibrin, hydrogels, etc.

The requirements for suppository bases are the same all over the world and are listed in the State Pharmacopoeia of Ukraine and in other pharmacopoeias. They are as follows: (10-12)

- chemical and physical resistance during storage and use;
- no odor;
- aesthetically appealing appearance;
- non-toxicity, lack of sensitivity and irritation to sensitive tissues of the bod
- expansion-compression characteristics such that when cooled, suppositories must be
  compressed enough to be easily released from the molds;
- to melt and dissolve in the intended cavity of the body to release a medicinal substance;
- mixing and absorbing a small amount of water;
- the viscosity should be low enough in the melt for easy casting of the suppository mass into molds, but high enough for the suspending of the API solid particles.

Physiological factors:

As mentioned above, cyclic changes in thickness of vaginal epithelium, fluid volume and composition, pH and sexual arousal could potentially affect drug release from intravaginal
delivery systems. For example, the vaginal absorption of steroids is affected by the thickness of the vaginal epithelium. (18)

Physicochemical properties of drugs:

a) Physicochemical properties such as molecular weight, lipophilicity, ionization, surface charge,
b) chemical nature can influence vaginal drug absorption. For example, the vaginal permeability of straight chain aliphatic alcohols increases in a chain length dependent manner [19].
   a. Since vaginal fluid contains a large amount of water, any drug intended for vaginal delivery require a certain degree of solubility in water.
   b. In fact, data on the human vaginal permeability to drugs with different physicochemical properties is very limited; much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption.

Pharmacological factors:

However, the vaginal progesterone absorption in estrogen deficient women who were receiving vaginal estrogen was found to be increased, although the estradiol therapy should have caused increased thickness of the vaginal epithelium, so ultimately the drug absorption decreases.[20]

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d) Novel Concepts in Vaginal Drug Delivery:

In development of vaginal dosage form, the following consideration should be addressed

   a. Maintenance of an optimal pH for vaginal epithelium
   b. Ease of application
   c. Even distribution of drug
   d. Retention in vagina
   e. Compatibility of co-administered medicines
   f. Traditionally, solutions, suppositories, gels, foams and tablets have been used as vaginal formulations.

a) More recently, vaginal ring has been introduced for hormone replacement and contraceptive therapy.
b) Further, vaginal formulations may be designed to produce local effect such as spermicidal or antibacterial effect or to produce a systemic effect by continuous release of drugs such as
c) contraceptives.

Specific problems in formulating suppositories:

During the formulation of suppositories various problems arises which are as follows.

   a. Water in suppositories
   b. Hygroscopicity
   c. Incompatibilities
   d. Viscosity
   e. Brittleness
   f. Density
   g. Volume contraction
   h. Lubricant or mound release agent

Conclusion

The current focus of research is on drug delivery systems using nanoparticles via the vaginal canal. New vaginal

formulations for systemic and local distribution are probably going to come from bio adhesive vaginal formulations. It's still difficult to create suitable bio adhesive vaginal formulations because there are more and more new polymers discovered every year. The application of vaccination via the vagina is another topic that requires thorough investigation. In the female population, vaginal rings are widely accepted and have demonstrated great promise. In addition to treating pregnancy, chemotherapy, and allergy symptoms like emesis, the suppository may be helpful as a sustained-release, bi-layered, muco-adhesive, and many other formulation for the long-term management of chronic diseases like essential hypertension, asthma, diabetes, AIDS, anaemia, etc.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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