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Review Article

Advances and Challenges in Suppository Formulation: A Comprehensive Review of Suppository Drug Delivery and Design.

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ABSTRACT

In modern pharmaceutical development, suppositories remain an important but understudied dosage form, giving an alternative way of drug delivery, particularly for patients with swallowing or gastrointestinal difficulties. To address the complexities of pharmaceutical delivery via the vaginal and rectal routes, this study investigates the newest breakthroughs and ongoing challenges in suppository formulation. enhanced manufacturing procedures, enhanced medication release strategies, and new excipients are all significant advances. The review also discusses important formulation aspects that influence medicine absorption and therapeutic mechanism of action findings, such as preparation procedures, evaluation tests, classifications, and applications. The analysis also looks at patient-centered and regulatory aspects, underlining the importance of personalized strategies in suppository design. The review offers perspectives on potential future developments and ways to enhance suppository-based drug delivery systems by assessing the advancements and ongoing challenges in this area.

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Introduction

The rectum lasts 12–19 cm of the human colon. The rectal epithelium comprises a single layer of columnar or cuboidal cells and goblet cells, with a surface area of approximately 200-400 cm2. [1]
Suppositories have excellent chemical and microbiological stability, do not require sterile manufacturing, are less expensive, and are easier to administer, resulting in higher patient compliance. Suppositories can help mask rectally administered medications' unpleasant smell and bitter taste. When bilayered suppositories are compared to traditional monolayer suppositories, some significant advantages become apparent. Typical dosage formsrequire repeated dosing, which can be avoided. [2], [3]
Suppositories and ointments are the two most common medication delivery methods in the rectum. They are used to deliver drugs that have systemic and local effects. The main premise is that the suppository is delivered as a solid and dissolves or melts inside the body, providing the drug via the numerous blood arteries. [4]

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Despite an extensive history of medicine administration via rectal and vaginal suppositories, the globally active suppository industry is now limited due to patient difficulties. As a result, new medications in this dosage form were not developed in significant quantities. Suppositories, on the other hand, have various advantages over other dosage forms and are one of the most commonly used for treatinggynecological and proctological illnesses. [5], [6]
Suppositories and pessaries as medication delivery systems are not novel dosage forms. Rectal medication delivery is one of the worldwide oldest drug dosage techniques, with rectally applied medicinal products extending back hundreds of years. Suppositories have been mentioned in the Hebrew Scriptures. Even vaginally administered pessaries are ancient, with documentation found in Egyptian papyruses. Hippocrates described many acorn-based remedies used rectally and vaginally for local therapeutic effects [7].

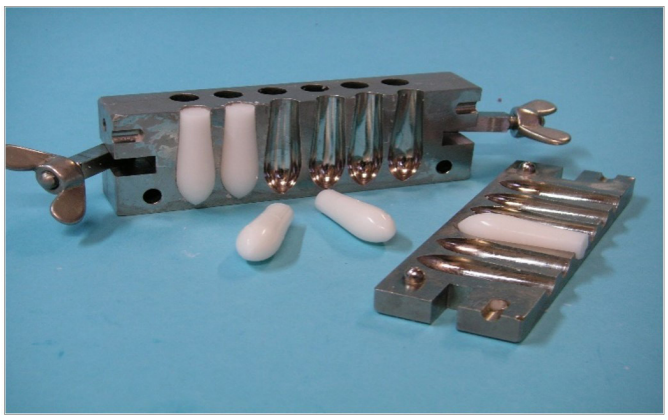


Figure. No.1: suppositories and casting mold

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Definition

The Latin root of the word "suppositories" is "to place under." Suppositories are solid dosage forms of medication meant to be put into body orifices. Suppositories are solid dosage forms inserted into a bodily orifice to melt, soften, or dissolve, causing local or systemic effects. Suppositories are intended to be put into body cavities or orifices, where they dissolve and melt at body temperature, causing a local impact on the body. The effects of suppositories are determined by the drug's content, concentration, and rate of absorption in the body [8].

Composition

They typically comprise a stiff or semi-rigid foundation, an inert framework, and an active component. No chemical interactions occur between the active and inactive components during this dispersion. This is done to prevent changes caused by the active ingredient or the suppositories. The dispersion phase can be added to suppositories in the form of a liquid or a solid (powder) (aqueous, alcoholic, glycolic solution, or oil and extracts). Base materials can be obtained naturally or artificially, depending on their ability to melt or dissolve at the temperature of the body. Various bases are available, which are employed depending on the chemical composition requirements. These can be either fatty bases, PEG, or suppository mixtures. [9], [10].

Shape and size

Suppositories are available in a variety of sizes and forms, making them easier to insert and retain in the cavity. Adult rectal suppositories weighed about 2 g, whereas children's suppositories weighed roughly half that much. Suppositories have traditionally been cylindrical, longer than wide, with the most frequent shapes being 'bullets' or 'torpedos'. Other popular shapes for suppositories include round and elongated ovals, tampons, and 'teardrop' or 'cones. [11]

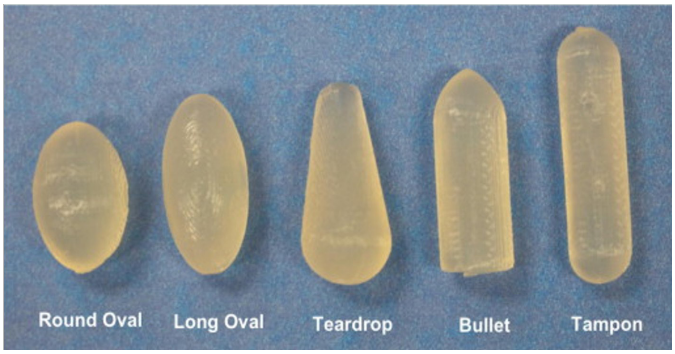


Figure. No.2: Typical suppository shapes. round oval, long oval, teardrop, bullet, and tampon.

Advantages

- •The suppository can be utilized with unconscious patients.
- •Suppositories are compact dose forms.
- •They have a lower risk of side effects.
- •It can be administered to people who are experiencing acute nausea and vomiting.
- •Suppositories are appropriate for children and elderly individuals who are unable to swallow tablets.
- •They can be used to prevent rectal and vaginal infections.

Disadvantages

- •Patients have difficulty accepting suppositories.
- •It's inappropriate for patients with diarrhea.
- •Suppositories are not suitable for irritating medications.
- •Incomplete absorption may occur.
- •Store them at low temperatures to prevent melting.
- •Patient compliance.
- •Inconsistent and unwanted absorption.
- •Placement too high in the rectum may cause first-pass metabolism.
- •Instillation may cause a defecation reaction.[12], [13]

Ideal properties of suppository

- •The ideal suppository basis is neither poisonous nor irritating.
- •It should also dissolve or disintegrate in the presence of mucous secretions, or melt at body temperature, to allow medication to be released.
- •It must retain the right form and size.
- •It should maintain its stability throughout storage.
- •It should not interfere with the drug's release or absorption.
- •should be attractive and devoid of flaws such as chips, cracks, discoloration, and contamination.
- •It should have the chemical and physical stability to retain its physical properties over time, as well as the ability to release therapeutic substances.
- •Should have enough mechanical strength to endure mechanical shock during production, packaging, shipping, and dispensing. [14], [15]

Manufacturing of suppository

Suppositories are made in four steps: raw ingredients are prepared, the medicine is mixed with the melted substance, suppositories are molded into blisters, and the formulation is crystallized.

Methods of preparations of suppositories

- •Moulding
- •Compression
- •Heat molding/fusion
- •Hand rolling & shaping
- •Double casting technique

Preparation by Moulding

It is a method of making suppositories from a mixture of grated suppository bases and medicaments that is pushed into a specialized compression mold. To determine the capacity of the molds, compress a tiny amount of the base into the dies and weigh the final suppositories. When active substances are introduced, a portion of the suppository base must be omitted due to their density.[16]

Lubrication is seldom necessary when the base is

- •Cocoa butter
- •Polyethylene glycol
- •Glycerinated gelatine

Preparation by compression method

This approach is appropriate for thermolabile and insoluble medicines because heating the base with the medicament is not required. The cold mass of the drug-containing base is squeezed into suppositories using a hand- or power-operated compression machine. A wheel-operated press is used to press the suppository material, which is often a mixture of grated theobroma oil and medication, into a mold. the mass is pushed into the mold openings, pressure is relieved, and the mold is removed, opened, and replaced.Cold-compression machines are typically hydraulically powered, water-jacketed for cooling, and screw fed. A piston is used to provide pressure to the mass and compress it into mold holes. [17]

Heat molding/ fusion method

The suppository base is first melted, and the medicine is then dispersed or dissolved in it. The mixture is taken off the heat and placed into a suppository mold. Once the mixture has congealed, the suppositories are taken from the mold. The fusion process is compatible with all types of suppositories and should be used with the majority of them. When they are mixed, melted, and placed into suppository mold cavities, they take up a volume equal to that of the mold cavity. Mold calibrations are essential to produce correct doses since the components are measured by weight and then multiplied by volume density calculations. [18]

Hand rolling and shaping method

This is the earliest and most basic way of producing suppositories. The manipulation demands significant talent while avoiding the problems

of heat and mold preparation. A suppository foundation containing medicament is rolled with the hand until the appropriate form is obtained. Take the prescribed amount of medicinal medicines and an adequate amount of theobroma oil/suppository base.

The appropriate amount of grated theobroma oil is then added, and the components are completely incorporated with a pestle to form a mass resembling a pill. When the mass has become plastic as a result of the pestle's strong kneading, it is rapidly freed from the mortar using a spatula and transferred to a sheet of filter paper held between the mass and the hands during the kneading and rolling process.

The mass is rolled into a ball with fast, rotating movements of the hands and placed instantly on a pill tile. The kneaded substance is rolled between fingers to form rod-shaped units. The rods are split into pieces, and one end is pointed with a spatula. The suppository "pipe" or cylinder is prone to cracking or hollowing in the center, particularly when the mass is not thoroughly kneaded and softened. [19]

Double casting technology

The total amount of medication is mixed with insufficient base to fill the gaps. The liquid is poured into a mold, partially filling each hole before filling the rest with the molten parison base. The cold suppository is then removed, redissolved, mixed, and poured again to ensure that the active component is evenly distributed. The pharmacist can compute the density factor by documenting the necessary information, which includes the weight of the base displaced by the drug. [20]

Evaluation test of suppository

Visual examination test

The suppository's entire design, visual identity, and elegance are essential for client approval. The suppositories are checked with naked eyes (subjective to evaluation) to determine the uniformity of the surface appearance and colour, as well as the absence or presence of smoothness or gritty conditions, fissuring, pitting, fat blooming, exudation, and active ingredient motion.

Shape and size

Suppositories come in a variety of sizes and forms, making them easier to insert and retain in the cavity. Adult rectal suppositories weigh about 2 g, whereas children's suppositories weigh about half that much. The suppository's size and shape can be characterized dimensionally by measuring and controlling its width and length.

Color

The color's intensity, nature, and uniformity should be checked.

Odor

Odor verification can help to avoid confusion while processing comparable suppositories. A change in scent could also be indicative of a deterioration process.

Uniformity of Weight

Twenty suppositories are chosen at random. Weight and average weight are determined. No more than two suppositories must depart from the average weight by more than 5%, and no suppository may differ by more than 10%. [21]

Melting range and melting point determination

The melting point should be at or below 37 ◦ C. A non-destructive approach must be employed since melting the suppository before taking a measurement may cause the suppository ingredients to become metastable. [22]

The use of a U-shaped capillary tube to assess melting point provides precise information for excipient management and consistency in the fabrication of suppositories containing soluble active principles.

To establish the melting point, insert a small-diameter wire into the mold containing the suppository melt before it solidifies. To determine the melting point of a suppository, submerge it in water and gradually raise the temperature (approximately 1 ◦ C every 2-3 minutes) until it falls off the wire. [23]

Liquefaction time

Another effective test for manufactured suppositories is a modified version of the Krowcynski approach. It consists of a U-tube that is partially submerged in a constant-temperature water bath. A structure on one side secures the suppository in the tube.

The softening time is calculated by placing a glass rod on top of the suppository and recording the time it takes for the rod to pass through the constriction. This can be done at temperatures ranging from 35.5 to 370 degrees Celsius as a quality control check, as well as to study physical stability over time. [24]

Suppository penetration test

The SPT6 Suppository Penetration Tester is used to determine the softening time of 6 samples at the same time. It is made in strict compliance with the monograph of the EP Apparatus A. The Apparatus needs to be placed into a suitable Plexiglas water bath. It is possible to use the SPT6 in a Pharma Test Tablet Disintegration Tester of the type series PTZS, DIST3, or PTZ AUTO. Using it within the PTZ AUTOEZ instruments the softening time can be detected automatically.

Mechanical strength/crushing test

This identifies the mechanical force required to break a suppository and whether it is brittle or elastic. The Erweka technique has been used in this exam. The mechanical strength should not be less than 1.8 to 2 Kg, as determined by the Erweka method. The suppositories' tensile strength is assessed using a hardness or breaking test. The suppository's tensile strength determines its capacity to survive packaging and transportation dangers.[25]

Disintegration test

The disintegration test for lactobacillus vaginal suppositories was modified from the method published by BP to use a tablet disintegrator. To test the suppository, it was placed in a cylindrical glass container with perforated ends and immersed in 1,000 cc of citric acid/phosphate buffer solution pH 4.4 at 37±0.5°C.

The cylindrical glass container was slid up and down in the buffer. The time for disintegration was measured when the suppository had entirely melted (Witepsol) or dissolved (PEG) in the medium. The mean results were derived using six parallel measurements. [26], [27]

Content uniformity test

Take ten suppositories and use an appropriate analytical method to determine the active components in each one. If not more than one of the obtained individual values is outside the limit, i.e., a percentage of the average value, and none of them is beyond the limit, i.e. 25% of the average value.[28]

Content uniformity can be used to reduce dose-to-dose variation by randomly selecting suppositories to assess drug content uniformity according to USP/BP specifications.[29]

Table. No.1: Suppositories for various ana-rectal pathologies.[30], [31], [32]

Pathology	Ingredients in suppositories
Bleeding hemorrhoids	Local anesthetics, vasoconstrictors, and Calcium dobiselate
Hemorrhoidal thrombosis	Local anesthetics, vasoconstrictors, and Calcium dobiselate
Anal fissure	Local anesthetics, steroids, protectants, antiseptics, keratolytic and Policresulen
Pruritus ani	Steroids, astringents, and protectants
Anal cryptitis and proctitis	Local anesthetics, astringents and antiseptics
Anal rhagades	Keratolytic, antiseptics, and policresulen
Post anal surgery	Local anesthetics, vasoconstrictors, antiseptics, and Calcium dobiselate

Mechanism of action

The suppository will either dissolve in the liquid or melt on the mucous layer, depending on whether it is hydrophilic or lipophilic. The osmotic characteristics of the dissolving vehicle bring water to the rectum or vagina, and as the suppository melt dissolves, the medications it contains distribute out toward the mucosal epithelial surfaces.

If the medicine is water-immiscible, it must first be released from the suppository's base through gravity or ambulation before it may dissolve in liquid. Lipophilic melting suppositories soften and disperse without the presence of fluid. Suppositories dissolve when heated and employ the same method of pharmaceutical administration.[33]

Suppositories can operate as both local tissue defenders and carriers of therapeutic agents, as the local or systemic effects of the base suppositories utilized have a significant impact on therapeutic agent release. Hemorrhoids are classified into two types: internal and external hemorrhoids. Internal hemorrhoids are located along the lines of palatinea and are covered by the mucosa's epithelial layer, which is a collection of internal hemorrhoidal veins.

Meanwhile, external hemorrhoids develop from swelling of the external hemorrhoidal plensus, which is positioned distal to the linea pactinea and is covered by tissue beneath the anal epithelium. [34]

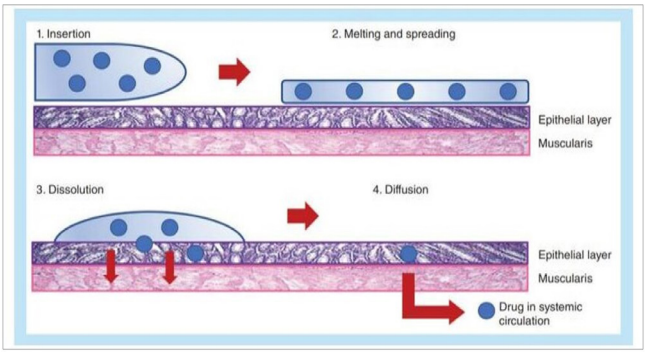


Figure. No.3: mechanism of action of suppositories

Table. No.2: Relationship between drug release-drug-suppository Base.

Active ingredient (Drug)	Base Release Rate
Oil soluble active ingredient-Oily vehicle	Retarded rate of release and minimum escaping efficiency
Hydrophilic active ingredient - Oily base	Faster dissolution rate
Oil soluble active ingredient – hydrophilic Base	optimal dissolution rate
Hydrophilic active ingredient - Hydrophilic Base	slow dissolution rate

Classification of suppositories

Suppositories are classified as

- Rectal suppository
- Vaginal suppository
- Urethral suppository
- Nasal suppository
- Ear cone suppository

Rectal suppositories

The rectal route is a viable alternative to the oral route for children and adolescents because it does not require swallowing or taste masking. Rectal forms can also be used in an emergency to treat unconscious or vomiting youngsters. [35]

In humans, the rectum is the last 12-19 cm of the colon, and the rectal epithelium is made up of a single layer of columnar or cuboidal cells and goblets cells with a surface area of approximately 200-400 cm2. [36]

The rectal route allows for both local and systemic medication administration. It has been used successfully for decades to treat local anorectal disorders (for example, hemorrhoids) as well as to deliver medications systemically as an alternative to the oral route (including antipyretic and analgesic pharmaceuticals like Paracetamol or Diclofenac.[37]

The latter instance may be beneficial for medications that

- Limited upper gastrointestinal absorption.
- Proteolytic enzymes are unstable.
- Demonstrate strong hepatic first-pass impact.
- May irritate the stomach mucosa.
- Require high doses that are difficult to convert into oral solid dosage forms.

However, similarities and differences between adults and children of various ages have not been systematically reported for the rectal route, despite this route being considered from preferred acceptability to best/ preferred applicability in children under 6 years of age (preschool). [38]

They treat conditions, such as

- constipation
- fever
- hemorrhoids
- mental health issues such as anxiety, schizophrenia, or bipolar disorder
- nausea, including motion sickness
- pain

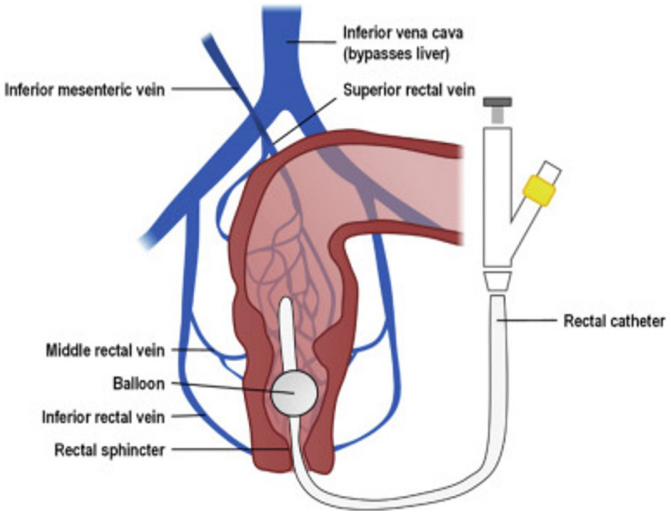


Figure. No.4: Schematic diagram of the rectum with a rectal catheter inserted. The major veins of venous return. [39]

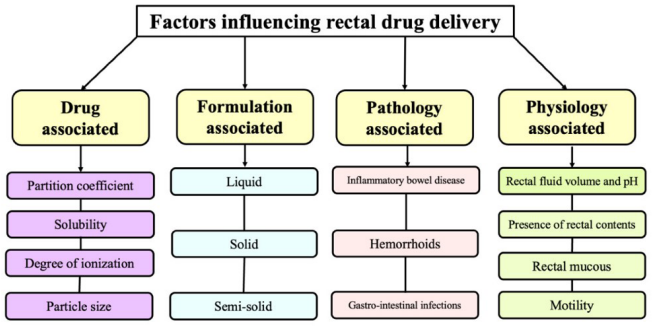


Figure. No.5: Factors affecting rectal suppositories drug delivery. [40]

Vaginal Suppositories

Vaginal suppositories are powerful or semi-strong medicines that are inserted into the vagina. They are commonly used to treat certain vaginal disorders, such as yeast infections or bacterial vaginosis. [41].
The suppositories frequently contain dynamic fixes that assist kill or regulate the population of specific germs. [42]

People may insert vaginal suppositories into the vagina to treat:
•bacterial or fungal infections
•vaginal dryness
A vaginal suppository gives specific relief for vaginal ailments. They are also known to be fast-acting due to their quick absorption.

Vaginal suppositories can help cure fungal infections and vaginal dryness. Contraceptive suppositories are another type of vaginal suppository used for birth control. Suppositories will take varied amounts of time to act depending on their intended use. The rate at which a suppository dissolves is also determined by its size and composition. [43]

Urethral Suppositories

Urethral suppositories, known as bougies, are pencil-shaped. Those meant for guys weigh 4 g and measure 100-150 mm long. Females' versions weigh 2 grams and measure 60-75 millimeters in length. [44]

A therapeutic urethral suppository for erections originated in the 1990s. An applicator inserts a tiny medicinal pellet containing alprostadil into the urethra. Alprostadil is a prostaglandin E1 (PGE1) that causes vasodilation in the blood arteries of the penis. When the pellet is dissolved, it increases blood flow to the penis, causing an erection. Previously, this was thought to be the second-best therapy choice for ED patients. However, many patients are put off by side effects like as penile and urethral pain or burning, and overall efficacy is low (about 30%). It is used to treat erectile dysfunction (sexual impotence) in men. [45]

Nasal Suppositories

There are 4 types of suppositories in other dosageforms

•Tablet Suppositories
•Layered Suppositories
•Coated Suppositories
•Capsule Suppositorie

The suppository bases used to make this dosage form are classed as hydrophobic, hydrophilic, or diphilic according to the State Pharmacopoeia of Ukraine and the European Pharmacopoeia. Furthermore, the USP categorizes suppository bases into the following 6 categories, which include bases that melt at body temperature and are utilized as suppository bases. [46]

1.Cocoa butter.
2.Alternatives to cocoa butter.
3.Glycerin-based gelatine.
4.Glycerin-based gelatin Polyethylene glycol.
5.Basis of surfactants.
6.Tablet inserts or suppositories. [47], [48]

Ear cone suppositories

Aurinaria is intended for introduction into the ear. Theobroma oil, which is rarely utilized, serves as a basis. Prepared in urethral bougies mold and cut to size.

Type of suppository bases

There are mainly 3 types of suppository bases

•Oily/fatty bases.
•Water soluble bases.
•Emulsifying bases.

Cooling and Finishing

The mold can be left to set at room temperature for 15-30 minutes before being refrigerated for another 30 minutes. If necessary, extra material is removed from the top of the mold (the back of the suppository); this can be done easily by dipping the blade of a stainless-steel spatula in a beaker of warm water and cutting off the excess material.

This will also help to provide a flat surface for the suppository; alternatively, a razor blade works nicely. If the suppository mold is still chilly, it should be somewhat contracted, making it simpler to remove from the mold. Individual suppositories can be wrapped in foil, but this is not necessary. This presents an excellent product to the patient. [49]

Packing

Aluminum metal molds have a variety of cavity diameters and several cavities per mold. Common sizes range from 1 g to 2.5 g, with cavities ranging from 6 to 100. The mold's two pieces are connected by nuts or, in certain cases, a single-centered screw. [50]

Plastic suppository shells come in long strips that can be torn into a variety of cavities. The suppository mixture is put directly into the shell, up to the mark. These disposable molds do not require lubrication, regardless of the suppository composition. [51]

Once the mixture has solidified, the plastic mold is heat-sealed. When a patient is ready to use a suppository, they choose one shell and peel the

edges off to reveal the suppository. One advantage of this sort of mold is that if the suppository melts, it will not spill out of the mold. If the material can be placed on the geals again, it will maintain its suppository shape. This sort of mold is available in 1 g to 5 g sizes and many different colours.

Application

Suppositories are commonly utilized for unconscious, children, and elderly patients. They are employed for systemic and local acts when other avenues are unavailable. Suppositories contain a wide range of medications. [52]

- •Suppositories can be used for either local or systemic effects.
- •Babies or elderly adults who are unable to swallow oral medications.
- •People who are unable to move.
- •Post-operative patients who are experiencing extreme nausea or vomiting.
- •helpful for patients who have severe nausea or vomiting.
- •Utilized to treat intestinal obstruction.

Conclusion

Ultimately, suppositories have a long history as an efficient medicine delivery mechanism, particularly for rectal and vaginal applications. They provide various benefits, such as increased stability, easy access to administration, and suitability for individuals who are unable to take oral prescriptions. The versatility of their composition and preparation procedures allows for a wide range of therapeutic applications.

However, challenges such as patient compliance, absorption variability, and the need for adequate storage conditions remain critical. Despite these drawbacks, suppositories continue to play an important role in treating local and systemic disorders, particularly in gynaecology and proctology. The development of innovative approaches, such as bilayered suppositories, improves their efficacy while addressing certain limitations.

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Authors Contributions

Mr. Abdallah Abdalmalk Mohamed was responsible for the article's planning, design, drafting, typing, manuscript framing, and literature search. Mr. Sarfaraj Ahamad Khan contributed by supervising the final editing and conducting a critical assessment of the work to identify any significant intellectual material.

Conflict Of Interests

The authors have declared no conflicts of interest.

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