CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.17883109

https://www.iajps.com/volumes/volume12-december-2025/29-issue-12-december-25/

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON FORMULATION AND EVALUATION OF NEEM OIL SUPPOSITORIES

Mrs varsha, Mekala Arathi, Mididoddigambhir Himasree, Mohammad Malik, Nagandla Vaishnavi, Nalla Divyanjali

Malla Reddy College of Pharmacy, Secunderabad, Telangana

arathia6737@gmail.com

Mghimasree0@gmail.com

mohdmalikmohdmailk804@gmail.com

nallanjali2005@gmail.com

vaishuyadav3450@gmail.com

Abstract:

Neem oil (Azadirachta indica) is becoming increasingly popular as a phytotherapeutic agent due to its antibacterial, anti-inflammatory, and immunomodulatory characteristics. In recent years, neem oil-based suppositories have emerged as a viable delivery system for treating a variety of anorectal and gynecological disorders. This study highlights current understanding of their formulation methodologies, modes of action, therapeutic applications, and safety considerations. Neem oil suppositories are effective against bacterial, fungal, and viral infections, thanks to bioactive components such as azadirachtin, nimbidin, and gedunin. Their anti-inflammatory properties promote tissue repair, and the mucosal route increases localized drug availability while minimizing systemic exposure. Despite promising preclinical results and traditional medicinal use, high-quality clinical evidence is limited. Standardization, stability, and dose adjustment remain challenging. More study is needed to evaluate efficacy, develop safety profiles, and investigate innovative formulation methods. Neem oil suppositories constitute an important field of research in natural product-based therapies.

Keywords: *neem oil, Azadirachta indica, suppositories, phytotherapy, antimicrobial activity, anti-inflammatory agents, natural formulations, mucosal drug delivery, traditional medicine.*

Corresponding author:

Mrs varsha,

Malla Reddy College of Pharmacy,
Secunderabad, Telangana

QR CODE

Please cite this article in press ***Mrs varsha*** *et al.,* ***A Review On Formulation And Evaluation Of Neem Oil Suppositories****, Indo Am. J. P. Sci, 2025; 12(12).*

INTRODUCTION:

SEMI SOLID DOSAGE FORM:

Definition: Semisolid dosage forms are the topical dosage forms used for the therapeutic, protective, or cosmetic functions. It may be applied to the skin, nasal, vaginal, or rectal cavity.

Examples of semi-solid dosage forms: ointments, pastes, creams, plasters, gels, suppositories, and rigid foams.

Advantages of semisolid dosage form:

- Ease of application
- Flexible drug release
- Reduced systemic side effects
- High patient acceptability
- Cost-effective manufacturing

Disadvantages of semi solid dosage form:

- Poor dose accuracy
- Limited penetration
- Risk of contamination
- Stability issues
- Temperature sensitivity
- Potential for irritation
- Appearance and texture problems

Ideal properties of semisolid dosage forms:

- Smooth texture
- Elegant in appearance
- Non-dehydrating
- Non-gritty
- Non-greasy and non-staining
- Non-hygroscopic

Ingredients need for semi solid dosage forms:

- Bases
- Preservative
- Humectants
- Antioxidants
- Emulsifier
- Gelling agent
- Permeation enhancer
- Buffers

SUPPOSITORIES

Definition: Suppositories are semisolid dose forms of medications that are inserted into bodily cavities other than the mouth. They can be implanted in the rectum, vagina, or nasal cavity. The medication is combined into a suppository foundation, and the product is designed to melt or dissolve in the body cavity fluid, releasing the medication. Suppositories come in many shapes, sizes, and weights. Suppositories provide local, systemic, and mechanical action.

ADVANTAGES:

- Suitable for youngsters, the elderly, and those who are unable to swallow medications.
- Provide targeted medicine delivery directly into the body cavity.
- When taken rectally, it provides quick therapeutic results.
- Help to relieve constipation and prepare the bowel.
- Ensure precise and consistent dosing with a unit dose form.
- Useful for medications that irritate the gastrointestinal tract, cause vomiting, or disintegrate in stomach acid.
- Allow for a more lasting therapeutic effect by ensuring gradual and steady absorption.

DISADVANTAGES:

- Dose measurement during application may be inconsistent for some patients.
- Drug absorption from the rectal or vaginal tissues can be unpredictable.
- Some bases may feel oily, messy, or difficult to use.
- There is risk of contamination if the product is not handled appropriately.
- Certain formulations may melt or soften in warm temperatures, reducing stability.
- Certain substances may irritate sensitive mucosal tissues.
- Not suitable for drugs requiring rapid and complete systemic absorption.
- These cannot be prepared quickly.
- Suppositories should be stored at a low temperature of 10 ℃ to 20 ℃.
- They must be stored in a refrigerator, which is expensive for low-income patients.

Types of suppositories:

1) **Rectal suppository:** Rectal suppositories are intended to be inserted into the rectum for systemic action. These are typically manufactured from Theobroma oil and come in a variety of sizes to accommodate the needs of infants, children, and adults. Rectal suppositories typically weigh between one and two kg. They are either cone or torpedo shaped.
2) **Vaginal suppositories:** Vaginal suppositories are intended for insertion into the vagina. These suppositories, often called pessaries, are larger than rectal suppositories. Vaginal suppositories can be conical, rod-shaped, or wedge-shaped, and they typically weigh between 4 and 8 grams. Vaginal suppositories are mostly used to treat the vagina locally. Nowadays, vaginal tablets and capsules are available as an alternative for vaginal suppositories.

3) **Nasal suppositories:** Nasal suppositories, sometimes known as nasal bougies, are supposed to be inserted into the nasal cavity. They're similar to urethral suppositories. These are thin and cylindrical in shape and are always made using a glycero-gelatin base. Nasal suppositories are 9-10 cm long and weigh approximately 1.0 g.
4) **Urethral suppositories:** These are intended for insertion into the urethra and are also known as urethral bougies. These are thin, long, cylindrical cylinders with a rounded end for easy insertion. Their weight ranges from 2 to 4 g. These suppositories are extremely infrequently used.
5) **Ear cones:** These are intended for insertion into the ear and are also called as aurinaria. Nowadays, they are rarely utilized. These suppositories are thin, long, and cylindrical in shape, weighing around one gram. Ear cones are often produced with Theobroma oil.

Current trends of suppositories:
In recent years, a new concept for suppositories has emerged in terms of formulation and packaging. Several of these are described below:

1) **Tablet suppositories:** - Nowadays, rectal suppositories and pessaries are compressed in the same way that tablets are. The compressed pessaries are typically almond-shaped to facilitate insertion and give a broad surface area for breakdown and absorption. Rectal pills are typically coated with polyethylene glycol to provide protection and ease of entry into the rectum.
2) **Layered suppositories**: To avoid incompatibility, these suppositories include different medications in separate layers. Drugs with varying melting points or dissolution rates can be used to modulate the pace of drug release. These suppositories can be made by partially filling a mould with one type of material. When it has set, the additional materials are applied one at a time as distinct layers.
3) **Capsule suppositories**: Soft gelatin capsules of varying shapes and sizes are used to insert into the rectum or vagina. Soft gelatin capsules can contain liquids, semisolids, or solids. There is a high need for such capsules currently.
4) **Coated suppositories:** Suppositories are coated by dipping them in a solution containing coated materials such as polyethylene glycol and cetyl alcohol until the desired thickness is achieved. These are the dry ones. These suppositories have lubricating characteristics and provide protection during storage. They also help to regulate the release of medications.
5) **Disposable moulds**: Disposable moulds are constructed of plastic or tin foil. The suppository substance is placed into disposable molds and allowed to cool. The surplus material is trimmed away using a sharp razor or blade, and the molds are sealed. These are then put into boxes. The disposable moulds are both inexpensive and attractive. Their shapes can be modified for a reduced cost. Furthermore, if suppositories bulk melt during storage, they will remain in the mould and can be reconverted into suppositories once cooled.

SUPPOSITORY BASES:
According to the USP, there are six general classes of suppository bases (1):

1) Cocoa butter.

2) Possible replacements for cocoa butter

3) Glycerinated Gelatin

4) Polyethylene glycol basis.

5) Surfactant base.

6) Tableted suppositories and inserts. C.

Allen (2) classifies suppository bases into four types depending on their melting or dissolving qualities.

1. The first is a **fat- or oil-based base**, which must melt at body temperature to release the drug.

2. The **glycerin-gelatin** base suppository absorbs water and dissolves to release the drug.

3. The third category includes **water-soluble or water-miscible polymers,** as well as surface-active compounds.

4. The fourth class of bases includes **disintegration agents, natural gums, effervescent agents, collagen, fibrin, hydrogels, and so forth.**

Desirable properties of suppository bases:

- Chemically and physically stable under regular use and storage circumstances.
- Nonreactive and compatible with a large number of medicines and auxiliary agents.
- Free from unpleasant odor.
- An artistically pleasing appearance.
- Nontoxic, non-sensitizing, and non-irritant to delicate tissues.
- Expansion-contraction properties such that it shrinks just enough on cooling to release readily from suppository moulds.

- Melts or melts in the designated bodily orifice, releasing the medication.
- Nonbinding of medicines
- mixes with or absorbs some water.
- Viscosity low enough when melted to pour readily but high enough to suspend particles of solid drugs.
- Some wetting and/or emulsifying qualities so that the active ingredient(s) can spread, disperse, and be released at the administration site.

CLASSIFICATIONAND CHARACTERISTICS OF SUPPOSITORY BASES:

A. Cocoa Butter NF

1) Description
   a) Cocoa butter is the fat from the seeds of *Theobroma cacao* (chocolate beans). It can be extracted using a solvent or by expressing the oil from the seeds. Triglycerides of saturated and unsaturated fatty acids, mainly stearic, palmitic, oleic, lauric, and linoleic, make up its chemical composition.
   b) It is a mellow, whitish substance with a faint odor and bland flavor. It is solid at room temperature but melts at body temperature, with a melting point ranging from 31° to 34°C. The specific gravity of the melt ranges from 0.858 to 0.864. It is supplied as bars or grated.
   c) Cocoa butter does not include emulsifiers, so it does not absorb a lot of water. Tween 61, a tan, waxy, solid, non-ionic surfactant, can be added (5% to 10%) to boost cocoa butter's water absorption capabilities; however, the inclusion of non-ionic surfactants apparently results in suppositories with poor storage durability.

2) Solubility: It is insoluble in water but slightly soluble in alcohol and boiling pure alcohol.

3) Incompatibilities: The most noticeable compatibility issue with cocoa butter is a decrease in melting point with medications such as chloral hydrate, phenol, and thymol. This can be addressed by adding 4% to 6% white wax or 18% to 28% cetyl esters wax, although calculating the exact amount required to achieve an adequate melting temperature can be difficult and time-consuming. A collection of successful chloral hydrate suppository recipes has been published, including those using cocoa butter.

4) Advantages
   - **Non-irritant**
   - **Accessible**
   - **Pourable**
   - **Convenient**
   - **Gentle**
   - **Available**
   - **Fluidity**
   - **Ready to use**

5) Disadvantages
   - **Unstable.**
   - **Heat sensitive**
   - **Incompatible**
   - **Slow setting**
   - **Hydrophobic**
   - **Perishable**
   - **Costly**

B. Cocoa butter substitutes

1) Description
   a) The USP provides the following description of cocoa butter substitutes: Fat-type suppository bases can be made from a range of vegetable oils, such as coconut or palm kernel, which are changed through esterification, hydrogenation, and fractionation to yield products with different compositions and melting temperatures (for example, hydrogenated vegetable oil and Hard Fat). These products can be specifically formulated to decrease rancidity. At the same time, required properties such as short intervals between melting and solidification temperatures, as well as melting ranges to accommodate different formulations and meteorological circumstances, can be included.
   b) Chemically, this type of base is predominantly made up of triglyceride esters of saturated fatty acids in the C-12 to C-18 range, with smaller amounts of mono- and diglycerides. Other ingredients include beeswax, lecithin, polysorbates, ethoxylated fatty alcohols, and ethoxylated partial fatty glycerides. Some commercially available synthetic fatty bases include surfactants, self-emulsifying agents, and suspending agents, as described below.
   c) Because natural cocoa butter was scarce during WWII, substitutes were created throughout Europe. In recent years, compounding material suppliers in the United States have produced new items of this nature. A few of these are discussed below.
   d) Witepsol
      i) Witepsol is a whitish, waxy, brittle solid that melts to a clear to yellowish liquid. It is practically odorless and has a density of 0.95 to 0.98 at 20°C. It

contains emulsifying ingredients and can absorb small amounts of water.

ii) Although the Handbook of Pharmaceutical Excipients mentions 20 different grades of Witepsol, the H15 grade is the most widely available to pharmacists. It has a melting point range of 33.5°C to 35.5°C, which is very similar to its congealing range of 32°C to 34°C.

iii) Although some pharmacists recommend Witepsol bases, others report poor or inconsistent outcomes. Although suppositories created with this base firm quickly and should compress enough to easily release from the mould, there have been reports of suppositories shattering into pieces when withdrawn from the mould.

e) Fatty base

i) Fatty base is an opaque, white, waxy substance with no odor and a bland flavor. The specific gravity at 37°C is 0.89. It is composed of triglycerides derived from palm, palm kernel, and coconut oils, as well as self-emulsifying glyceryl monostearate and polyoxyl stearate, which act as emulsifiers and suspending agents.

ii) It has a melting point range of 32°C to 36.5°C, but the manufacturer, Paddock Labs, recommends that the base be heated gently and evenly to 49°C to 54°C before adding the active ingredients. The suppositories should be poured when the mixture reaches 43°C to 49°C. The base should not be heated above 60°C, and using microwave ovens to heat the base is not suggested.

iii) Fattibase provides the benefits of cocoa butter without the issues associated with cocoa butter's sensitive melting point range and polymorphism. Suppositories prepared with this base easily release from moulds; if necessary, lightly spray the moulds with vegetable oil.

f) Fatty blend

i) The suppository basis Fattyblend has the body-temperature melting property of cocoa butter without the polymorphism. When compared to cocoa butter, it provides homogeneity, a bland scent, little irritation, and great mould release capabilities.

ii) It includes triglycerides from palm, palm kernel, and coconut oils, as well as emulsifying and suspending agents.

iii) Due to its mild flavor, it has also been utilized in lip balms and lipsticks.

g) Supposiblend

i) This is a pellet form of a triglyceride (fatty acid blend) suppository base manufactured from vegetable oils, mostly palm kernel oil, which is resistant to oxidation and lacks the polymorphism found in cocoa butter.

ii) The melting point ranges from 34°C to 37°C. It compresses somewhat during cooling, providing excellent mould release properties.

iii) It contains emulsifiers to facilitate the absorption of small amounts of aqueous solutions.

h) Supposibase-F

i) Supposibase-F, like Supposiblend, is a pellet-form suppository base composed of refined, hydrogenated, and deodorized vegetable oils, predominantly palm kernel oil. It is believed to have strong chemical stability, a low tendency for oxidation, and physical stability with negligible polymorphism.

ii) The melting point ranges from 34°C to 37°C.

2) Solubility: Cocoa butter replacements are practically insoluble in water but marginally soluble in warm alcohol.

3) Incompatibilities: Cocoa butter replacements may experience similar temperature-lowering issues as cocoa butter.

4) Advantages

- **Non-irritant**
- **Stable**
- **Increased drug release**

5) Disadvantages

- **Temperature-sensitive**
- **Erratic-release**

C. <u>Glycerinated gelatin bases</u>

1) Description:
This base is composed of 70 parts glycerine, 20 parts gelatin, and 10 parts water. The process of preparation is like that of glycerinated gummy gel base.

2) These bases are rarely utilized since they are more complex to produce and provide limited benefits.

3) The basic substance has a soft, rubbery consistency (similar to candy, gummy worms), making it appropriate for vaginal administration but not solid enough for rectal application.

4) They do not melt but dissolve slowly in the mucous secretions of the vagina; they are advised for the long-term release of local antibacterial medications. Glycerinated gelatin suppositories should be moistened before insertion.

5) Glycerinated gelatin suppositories are hygroscopic; hence, they must be delivered in well-sealed containers.
6) Because they have been shown to foster mould or bacterial growth, they should be kept in the refrigerator and contain a preservative (e.g., methylparaben 0.18%, propylparaben 0.02%).

D. Polyethylene glycol bases

1) Description:
Polyethylene glycol (PEG) suppository bases are mixtures of polyethylene glycol polymers with varying molecular weights.
2) Some commercial polyethylene glycol suppository bases include extra ingredients, such as surfactants. Polybase and PEGblend are two of the most popular bases:
Both contain polyethylene glycols and the emulsifier polysorbate 80. Polybase is a white solid with an average molecular weight of 3,440 and a specific gravity of 1.177 at 24°C.
3) PEG suppository bases are designed to dissolve in human fluids rather than melting at body temperature. Before inserting suppositories manufactured from these bases, wet them with water.
4) Advantages
   a) Fusion allows for the easy creation of PEG suppositories.
   b) When made with the right PEG blend, they dissolve in body cavity fluids and release the active ingredient(s), which include both hydrophilic and hydrophobic medicines. Provided there are enough aqueous secretions in the human cavity, they allow more consistent drug release from the dose form than fatty bases.
   c) Because their melting points are easily regulated through suitable blending, these bases and suppositories do not necessitate carefully monitored storage temperatures.
5) Disadvantages
   a) PEG suppositories are irritating to body cavity tissues and so have lower patient acceptance than fatty-base suppositories.
   b) They are incompatible with a wide range of medications, particularly those that are susceptible to oxidation.
   c) They interact with polystyrene, a plastic commonly used in prescription vials; hence, they should not be delivered in these containers unless the suppositories are first wrapped in foil.

E. Surfactant or water-dispersible bases

1. Suppository bases are made using a variety of non-ionic surfactants, including polyoxyethylene sorbitan fatty-acid esters and polyoxyethylene stearates, either alone or in conjunction with other suppository vehicle ingredients.

2. This sort of base is less commonly employed in compounding since it is more difficult to manufacture.

3. If properly prepared, these bases have ideal melting points and consistency. Because they contain surfactants, they are easily distributed in body cavity fluids.

4. One easy-to-make drugstore combination contains 60% Tween 61 and 40% Tween 60. Both of these compounds are solid at normal temperature. They are available from merchants who compound medications and substances.

F. Tableted suppositories or inserts

1. Vaginal suppositories (now often known as vaginal inserts) are periodically made by compressing powdered ingredients into a suitable shape. They are also made by encapsulating them in soft gelatin.

2. The compression method is appropriate for suppositories that contain heat-labile medications or have a high proportion of insoluble components.

3. This method allows you to manufacture suppositories in a variety of shapes and sizes.

4. Lactose is commonly utilized as a filler in these suppositories, along with a dissolving agent, dispensing agent, and lubricant.

G. The release of drugs from suppository bases is a complex and unpredictable procedure. The rate-limiting stage in drug release is not just how quickly fatty bases melt or PEG bases dissolve, but also how long it takes for the drug to partition and diffuse out of the base into the rectal or vaginal lumen. In practice, because bioavailability studies are typically impractical, it is critical to monitor the efficiency of the drug delivery system through continuous monitoring of therapeutic results.

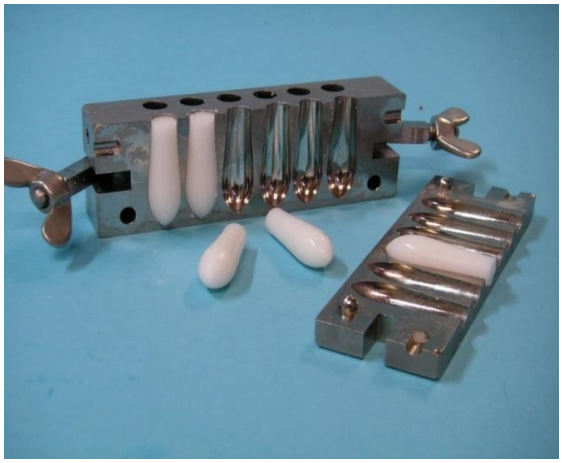
PREPARATION OF SUPPOSITORIES

The suppositories are made using any of the following ways.

- Rolling method
- Hot process or fusion method
- Cold compression method

A. **Rolling method:** It is an accident method of preparing the suppositories. The suppository base is rolled, and then the desired shape is given with the hand. The method is not used nowadays.
B. **Hot process or fusion method:** This method is commonly used in the preparation of suppositories for dispensing

purposes. The suppository base is melted; the medicament is incorporated in it and filled in a lubricated mould. On cooling, suppositories are formed, which are removed from the suppository mould.



C. **Cold compression method:** The method is useful for thermolabile and insoluble drugs because heating and stirring of the base with medicament is not required.

Packaging and storage

Suppositories are frequently stored in shallow partitioned cardboard boxes that can hold them upright and prevent them from coming into contact with one another. Many commercial suppositories are packaged individually in aluminum foil or PVC polythene strips. Glycero-gelatin suppositories are often packaged in tightly sealed screw-capped glass containers. Nowadays, suppositories are directly molded into basic packaging comprised of plastic or aluminum foil. The moulds are sealed. The surplus is cut and then put in cartons. The suppositories must be stored in a cool environment in order to maintain their shape at room temperature.

NEEM OIL

Introduction

It is a non-edible fixed oil derived from fully grown seeds of Azadirachta indica (family Meliaceae), gathered late in the summer. It is indigenous to the Indian Subcontinent.

Description: Neem oil is a golden to dark-brown liquid derived from the neem tree's fruits, seeds, and flowers. It has a profoundly unpleasant and repulsive odor. It is soluble in ether and chloroform.

Chemical constituents: Ingredients include fatty acids, limonoids, vitamin E, triglycerides, antioxidants, and calcium. It contains glycerides of both saturated and unsaturated fatty acids. The predominant fatty acids are oleic (50%) and stearic (20%) acids. The oil includes 2.0% of bitters, which are sulfur-containing chemicals called nimbidin, nimbin, nimbinin, and nimbidol. The unsaponifiable portion contains nimbosterol (0.03%).

Standards of quality:

Specific gravity: 0.913-0.918

Refractive index: 1.417-1.4627

Saponification value: 195-205

Iodine value: 68-75

Unsaponifiable matter: 0.7-1.0%

Acid value: not more than 2

Uses: This plant is particularly useful in various industries, including agriculture and medicine. Pusa Neem Golden Urea, an agrochemical composed of neem oil and urea, is used to suppress nitrification. Neem oil can be used as a green solvent because it is environmentally safe and the residues dissolve quickly. Neem seed contains up to 40% oil and has a strong potential for producing biodiesel. There are several methods for extracting neem oil; however, solvent extraction is the most often employed since it produces transparent oil with a higher yield than other methods. Given its importance, the United Nations designated the neem tree as the tree of the 21st century. Extensive research is being carried out around the world to reveal the benefits of this divine tree.

Medicinal uses:

Nimbin, nimbidin, and similar substances exhibit antiviral action. It is used as a non-edible oil to make soap as well as oleic and stearic acid. It is used in rheumatism, as a pesticide, and in medicinal soaps for skin ailments. It's also spermicidal.

The pharmacological properties of neem seed oil (NSO) have been extensively studied in literature. For instance, Naik et al. found a dose-dependent increase in anti-inflammatory effects in albino rats, suggesting that NSO may inhibit cyclooxygenase. Jagadeesh et al. found NSO to be more effective than indomethacin in terms of anti-inflammatory action. Furthermore, NSO demonstrated lesser ulcerogenic properties than indomethacin. Akihisa et al. isolated 17 limonoids from neem seeds and found them to have anti-inflammatory effects. There have been NSO dermatological dosage formulations published in the literature, such as creams and ointments, but there appear to be no rectal route dosage formulations, particularly those using the bases investigated in this study. As a result of NSO's outstanding anti-inflammatory properties, a rectal dose form was developed to treat inflammatory diseases in the rectal region and anus.

Neem Oil Extraction

The extraction procedure for neem oil varies depending on its intended application; however, there are four primary varieties.

Cold Pressing—It involves collecting the fruits and separating their kernels. The remaining seeds are then braided, dried, and passed through stainless steel presses to extract the oil. For the oil to be called cold pressed, the temperature must not climb above 120 degrees Fahrenheit throughout the extraction process. This process ensures that the oil retains its full flavor, aroma, and nutritional value.

Steam Pressure Extraction—The dried neem seeds are put into a steam boiler. The seeds are then inflated, and the growing pressure in the boiler extracts the oil from the seed without pressing.

Solvent Extraction—After weaving and drying the seeds, solvents such as hexane, acetone, and methanol are added. The resultant oil is stored in a silo, and pure neem oil is separated from the crude oil.

Aqueous Extraction – The simplest and most commonly used approach is water extraction. The extract is obtained by crushing or grinding the seed or neem leaves, immersing them in water, straining them through a thin cloth, and collecting them. This extract can be used as a spray for pest control without any modifications.

NEEM OIL SUPPOSITORIES

AIM:

The purpose of this study was to use the oil extracted from neem seeds as an active ingredient in an anti-inflammatory suppository formulation based on macrogol (MG).

MATERIALS AND METHODS:

Materials:

Azadirachta indica seeds were bought from the market. Other materials employed included n-hexane, aluminum foil, liquid paraffin, polyethylene glycol 1000 and 4000, sodium dihydrogen orthophosphate, sodium hydroxide, nutrient agar, ferric chloride, and distilled water.

Methods:

Extraction:

Neem seeds were harvested from the medicinal garden and validated at the herbarium. A quantity of 200 g of pulverized neem seeds using a blender was macerated with n-hexane at a ratio of 1:10; the mixture was stirred and allowed to stay still for eight days according to the previously used method. The supernatant was decanted, filtered using a Whatman no. 1 filter paper, and concentrated in a water bath at approximately 100°C. The subsequent extract was weighed, packed in a sterile container, and stored at room temperature.

PREPARATION OF NEEM SEED OIL SUPPOSITORIES:

MG was used as a water-soluble base. An oil-in-water emulsion of NSO using surfactants, such as Tween 80 and Span 20, was first made before incorporating it into the base. The pour molding method was used for the manufacture of the suppositories in pre-calibrated mould with different bases. Calculated displacement values were used in defining the various final quantities of the bases used. The suppository mould was thoroughly cleaned and lubricated with liquid paraffin. Appropriate quantities of base and NSO as presented in Table 1 were weighed differently into a beaker and positioned in a water bath (Karl Kobb) at approximately 60°C to melt. In the case of MG base, an emulsion was initially formed based on the required hydrophilic and lipophilic balance of NSO experimentally determined to be 12. The mixtures were vigorously stirred together with melted bases at approximately 50°C, using a magnetic stirrer to allow for a homogenous mixture. This procedure was repeated for the production of placebo suppositories as control formulations. This mixture was poured into the mould until it overflowed; the top was filled as the solidifying mixture was shrinking. The mould content was allowed to solidify, and the suppositories were thereafter removed and packaged in aluminum foil until further experiments were conducted.

TABLE -1: Composition of suppository formulation

Ingredients	composition
Neem seed oil	4.92
Tween 80	4.22
Span 20	0.78
PEG 1000 (80%) + PEG 4000 (20%)	98.40

EVALUATION OF SUPPOSITORIES:

Appearance

Six suppositories were randomly selected from each group, including the placebo, and evaluated both as a complete unit and after being separated longitudinally. Color, odor, shape, and the absence of fissuring, pitting, exudation, sedimentation, and migration of active substances were all evaluated.

Weight uniformity

The weight uniformity test followed the procedures outlined in the British Pharmacopoeia. Twenty suppositories were randomly selected from each batch of formulations, weighed independently on an analytical scale, and average weights and standard deviations were computed.

Determination of pH

The pH of each melted suppository was tested using a pH meter. Each measurement was an average of three and reported as mean ± standard deviation.

Hardness/crushing strength

The hardness tester was used to determine the suppository's crushing strength, which is a measure of its mechanical power or hardness. The measurement involved selecting six suppositories at random from each batch. The weight at which each suppository cracked was measured in kilogram force and converted to Newtons.

Liquefaction time:

Six suppositories were randomly selected from each lot. 60 mL of phosphate buffer with a pH of 7.4 was heated to 37°C ± 1°C and maintained. The suppository was dropped into the buffer, and the time taken for it to completely dissolve or melt was reported as the liquefaction time.

Melting point determination

The melting point of NSO suppositories was obtained using the Adebayo and Akala approach. A randomly selected suppository from each batch was placed in a beaker with a thermometer attached. The beaker was immersed in a water bath (Karl Kobb) at a depth of around 6 cm, with a continuous temperature rise of 1°C/2 min. The temperature at which the suppository sample began to melt was used as the melting point. The results were an average of five determinations. The melting point of bland suppository bases was found in a similar way.

In vitro release

The release of NSO from suppository bases was measured using the agar diffusion method. Measure 0.25 mL of melted suppository into a 25-mL volumetric flask, add 25 mL of phosphate buffer, and mix well. Sterilized nutritional agar was placed into a plate and allowed to settle before the surface of each plate was inundated with ferric chloride solution (5% w/v) and the excess solution was drained. Two holes were made in these plates with a 6-mm cork borer, and 0.5 mL of macrogol-formulated suppositories at 0%, 5%, and 10% w/w were put in each hole. The plates were then placed on a laboratory bench for 1 hour to allow diffusion before being transported to a Karl Kobb incubator

(37°C). The zones of color change for each sample were measured at time intervals of 1, 2, 3, and 12 hours.

pH determination

Three suppositories from each lot were used to determine pH. Each suppository was melted or dissolved in a 100-mL beaker, and the pH meter's electrode was dipped into it, and the results were reported.

RESULTS & DISCUSSION:

Neem seed kernels produce an unpleasant greenish yellow.

to brown fixed oil with a garlic aroma. The neem tree's widespread availability makes it essential for economic utilization. We believe that the oil supply can sustain industrial manufacture of a variety of therapeutic items, including suppositories, insect repellent, and dermatologicals.

Fatty acids are widely found in natural fats and dietary oils, and they serve an important function as nutritional elements and metabolites in living organisms. Many fatty acids are well known for their antibacterial and anti-inflammatory effects. Squalene, one of the chemicals found in the NSO GC-MS analysis, has been linked to immunomodulation and wound healing. Anti-inflammatory cytokines (IL-10, IL-13, and IL-14) increase, while pro-inflammatory cytokines (TNF-α) decrease.

Palmitic acid ethyl, one of the fatty acid esters found throughout the research, has anti-inflammatory properties. Stearic acid (20.22%) was one of the known chemicals in significant quantities. It reduces cholestasis-induced liver damage, which promotes inflammation in the liver. NSO's anti-inflammatory properties make it suitable for rectal use. The dissected suppositories were homogeneous in appearance and had no air bubbles. There were no holes or brittle fractures; therefore, the suppositories were not fragile and could resist transit and other mechanical stresses.

The weight variation experiment for all prepared suppositories yielded results within the permissible range of the British Pharmacopeia standard.

No suppository departed from the average by more than 5%, as seen in Table 2. The relative standard deviations of the average weight of the suppositories were less than 3.5%, showing that the mould had been accurately standardized. To guarantee correct dose administration at the location of action, dosage forms must have consistent weights or measures.

The suppositories were tested for hardness or crushing strength, which is a measure of their mechanical ability to endure handling and transit. Table 2 shows a considerable difference in crushing strength across bases without and with medicaments, with the latter being NSM1 (20.00 ± 1.92 N).

The presence of NSO often contributed to a reduced crushing strength when compared to blank bases.

Furthermore, higher flexibility (lower crushing strength) was seen primarily in suppositories produced with a macrogol basis. The more the flexibility of the materials, the less stress they can bear. Regardless, formulations with MG bases will be able to endure the demands of handling and transportation.

The pH values of medicated formulations were NSM1 (6.50 ± 0.01). NSO alone had a pH of 6.46-7.07. The pH levels of NSM1 appear to be comparable with those of the rectum (6-8). Products with low pH, when administered into the rectum, have the tendency to irritate the patient, which may lead to loss of compliance.

To avoid untimely and unwanted melting of suppositories before use, bases must have a softening or melting point that is higher than the normal room temperature in the tropics but lower than body temperature. Formulations with MG base showed mean temperatures of 36.80°C ± 0.62°C and 36.40°C ± 0.46°C for NSM1.

The lower melting point is due to the presence of NSO in the base, which weakens the intermolecular interactions of the various fatty acids in the network of both the oil and the fatty base. This weakening effect is not present in MG-based formulations, making it a better foundation in terms of melting point. The melting point is capable of withstanding storage temperatures while also dissolving at body temperatures.

Table 2: physicochemical and release properties of neem seed oil suppositories		
Physical and release parameters	**Macrogol base**	• **NSM1 (**neem seed oil macrogol base)
Shape	Torpedo	Torpedo
Colour	White	Off-white
Mean weight (g)	2.45 ± 0.04	2.38 ± 0.01
Melting point (°C)	37.20 ± 0.67	36.80 ± 0.62
Hardness (N)	25.00± 1.50	20.00 ± 1.92
Liquefaction time (min)	30.20 ± 0.45	30.60 ± 0.89
Displacement value	-	0.61
pH	6.086.08 ± 0.03	6.50 ± 0.01

The liquefaction time was also assessed to guarantee that the produced suppositories would dissolve or melt within the body temperature of 37°C, allowing the active pharmaceutical ingredient to be released and elicit the required pharmacological response. In general, the time required for liquefaction should not exceed 30 minutes. This is critical for improving patient acceptance and ensuring the drug's timely release.

Table 2 displays mean values of 30.60 ± 0.89 and 22.40 ± 0.55 min for MG-based formulations. The use of NSO reduced the melting point of the produced suppositories, shortening the liquefaction time. A difficult-to-liquefy suppository can irritate the rectal mucosa and cause delayed medication release.

Except for the control formulations (no NSO), the zone of color change of agar expanded over time in all samples. All formulations, including NSO, demonstrated release, with the MG base exhibiting a larger zone of color change. Lipophilic pharmacological compounds are known to have a lower affinity for hydrophilic vehicle bases and hence escape faster at the site of action.
Furthermore, it was shown that the rate of phytochemical release from the bases varies with time. The composition of the base and temperature were discovered to influence the rate of diffusion of active substances from various vehicles.

CONCLUSION:

In this research, NSO suppositories manufactured with a macrogol base demonstrated acceptable physicochemical properties. Therefore, further inquiry may reveal that MG can be employed as a base in the formulation of NSO as an anti-inflammatory treatment for the relief of painful hemorrhoids. The suppositories' anti-inflammatory efficacy is now being studied in our laboratory and will be reported separately.

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