International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

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Development and evaluation of anti-hemorrhoid alum suppositories

Sanskruti Vilas Pawshe and Bhavana Dnyandeo Tambe *

SMBT College of Pharmacy, Dhamangaon, Igatputi, Nashik, Maharashtra- 422403 India.

International Journal of Science and Research Archive, 2024, 12(01), 131–141

Publication history: Received on 20 March 2024; revised on 27 April 2024; accepted on 30 April 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.12.1.0760

Abstract

Rectal suppositories of Alum were prepared using different bases and polymers like Shea butter, and PEG-4000 and its effect on the In-vitro release of Alum was studied. The Agar-based suppositories were non-disintegrating, and non-dissolving, whereas PEG-4000 based were disintegrating and dissolving. The Fusion Method and Trituration Method were used for the formulation of the suppositories. In-vitro tests were carried out on the formulations. All the formulated suppositories were tested for several physical parameters namely weight variation, drug content of suppositories, disintegration test, and dissolution rate. The PEG-4000 and Shea butter suppositories were of macro melting range, disintegration, and liquefaction time.

Keywords: Alum; PEG-4000; Shea butter; Suppositories; Anti-hemorrhoid

1. Introduction

Hemorrhoids, which are also known as piles, are swollen veins that appear in the lower part of your rectum and anus. They look similar to the varicose veins you might see on your legs. These are of two types depending on its location that are internal hemorrhoids and external hemorrhoids where the former one occurs inside the rectum, while the latter one occurs under the skin around the anus. The inflammatory process of the hemorrhoid plexus is the cause of this disorder, which is relatively common. Swelling of the vein in the lower rectum and anus is a frequent symptom of hemorrhoids. The owner may not notice hemorrhoids which do not show any symptoms. However, symptoms may include: a mass around or inside the anus, bleeding and/or pain when passing stool, mucus discharge from the anus, and a feeling of incomplete bowel emptying[1-4].

Depending on where exactly they are present, hemorrhoidal diseases can be classified as external, internal, or interno-external hemorrhoids. Internal hemorrhoids are located higher up in the anal canal and are covered by a moist lining, while external hemorrhoids are located closer to the opening of the anus and are covered by regular skin. Characteristics of both types are found in Interno-external hemorrhoids

It is believed that venous dilation and prolapse, caused by growing older, heavy lifting or straining while urinating, and long periods of sitting are the causes of hemorrhoids. Occasional protrusion and painless bleeding during bowel movements are the distinctive qualities of internal hemorrhoids. It is essential to address the duration of symptoms and degree of severity, such as prolapse and bleeding, along with any problems related to peri-care. Moreover, determining the absence or presence of pain is crucial and should not be overlooked. Constipation exposes people to hemorrhoidal disease, so it is essential to carefully evaluate fiber intake and bowel habits, including consistency, regularity, and smooth evacuation[5-8].

* Corresponding author: Bhavana Dnyandeo Tambe

Objectives

- To reduce the swelling and inflammation of hemorrhoids
- To promote shrinking of hemorrhoidal tissue
- To offer soothing effect.

2. Suppositories

Suppositories are a type of medication that can be administered through the rectum or vagina to treat a wide range of health issues. They are specifically designed to provide a more convenient and efficient means of delivering medication compared to liquid enemas. The term "suppositorium" is derived from the Latin word "supponere," which means to "substitute"[9-12].

Suppositories are medicinal preparations that are intended to be administered via the rectum or vagina. They are solid dosage forms that can contain one or more active pharmaceutical ingredients (APIs) and are designed for either systemic absorption or local action of the API. Suppositories are generally intended to be used as a single dose, and they are inserted using appropriate applicators.

A suppository, upon administration, undergoes either melting or dissolution. This process is contingent upon whether the suppository is hydrophilic or lipophilic. The aqueous environment of the body facilitates the migration of water towards the rectum or vagina. By doing so, the drugs present in the suppository disseminate uniformly over the surface of the tissue. In the event that the drug is not soluble in water, it would require the aid of gravity or movement to liberate itself from the base of the suppository before dissolution. Suppositories that melt due to the heat of the body are employed in a similar manner.

2.1. Types of suppositories

- Rectal suppository
- Vaginal suppository
- Urethral suppositories

2.1.1. Advantages of Rectal suppository

- Many enzymes in the gastrointestinal tract are capable of breaking down the drug when administered orally, which decreases the bioavailability of the drug. However, this problem can be overcome by rectal administration of the medicinal product.
- The rectum receives blood from various rectal arteries and is drained by at least three veins, enabling drugs to be absorbed directly into the bloodstream, bypassing the liver's first-pass metabolism. This is a highly efficient system that allows medications to reach their intended targets quickly and effectively.
- Suppositories deliver medication through the rectum. They can deliver higher doses of medication than other methods.
- When it comes to absorbing drugs, administering them through the rectum provides a more consistent environment than taking them orally.

2.1.2. Disadvantages of Rectal suppositories

- In some parts of the world, giving medication through the rectum is not considered a common practice. This has caused drug companies to avoid creating medications that can be given this way, except in situations where it is necessary and recommended by a doctor.
- If drugs are administered rectally, there is a risk of loss of nonspecific drugs. This may be due to ineffective absorption due to interference of fecal matter with the active ingredient or excipient. This can decrease effectiveness and absorption.
- Because of the parameters such as melting, particle size, solubility, liquefaction, etc., formulation problems may occur.
- Rectal suppository is generally more expensive than tablets[13].

2.2. Methods for preparation of suppositories

- The method of rolling a hand
- The Compression Molding Method

- Melt molding method

2.2.1. Melt molding method

To prepare suppositories, a key step involves melting the suppository base. This melted base serves as the foundation for the medicine that will be added to it. The medicine is then either dissolved or dispersed in the melted suppository base, creating a uniform mixture. The next step involves pouring this mixture into molds that are specifically designed for suppositories. These molds are then allowed to cool and set, which means they become firm and take on the desired shape. Once the mixture has set, it is important to remove the suppositories from the molds as soon as possible. This ensures that they maintain their shape and don't stick to the mold. This process is effective for creating many different types of suppositories and is recommended for most of them[14].

Alum

The medical community has developed a novel treatment for hemorrhoids known as ALTA (Aluminium Potassium Sulphate and Tannic Acid. This treatment is highly effective in treating both bleeding and prolapse of internal hemorrhoids, replacing the need for invasive surgical procedures. It is a promising alternative that warrants further investigation and consideration in the medical field[15-17].

Alum is a chemical compound that comprises hydrated double sulfate salt of aluminum. It is naturally obtained from minerals such as kalanite, bauxite, leuconite, and alunite. It is widely recognized for its numerous advantages, including low cost, easily available, non-toxicity, reusability, and eco-friendliness.

The use of alum has been widespread in various industries, including water treatment, paper, textiles, and cosmetics, to name a few. Its ability to remove impurities and clarify water has made it an attractive option for water treatment plants. Moreover, its cost-effectiveness and easy availability make it a popular choice among paper manufacturers as a sizing agent.

Alum flour, alum meal, and cube alum are some of the common names for a highly refined substance that is often colorless, odorless and has a distinctively sweet taste. This material occurs as either transparent, large crystals or as a white powder. It finds many applications in various fields, such as dyeing and printing fabrics, producing lakes and paper, and in the manufacture of explosives. Additionally, it is employed in tanning, water purification, and sugar clarification. In the medical domain, it functions as an anti-inflammatory and astringent. Lastly, it is utilized as a hardening agent in microscopy and for strengthening plaster casts[18].

Figure 1 Alum

2.3. Rate of drug release

The selection of a suppository base is an important consideration in the delivery of medication. The rate of drug release is a crucial factor in determining the efficacy of the medication. Failure to release the drug in a timely manner may result in suboptimal therapeutic outcomes. Thus, it is essential to choose a base that is compatible with the drug and facilitates its optimal release.

To ensure maximum release of the drug from the base, the principle of opposite characteristics can be applied. This entails selecting a base with characteristics that are opposite to those of the drug. For instance, water-soluble drugs should be placed in oil-soluble bases, while oil-soluble drugs should be placed in water-soluble bases. The choice of base depends on the solubility of the drug, with some bases melting quickly in the rectum while others dissolve more slowly in mucosal fluids of particular note are PEG bases, which require dissolution in mucosal fluids to release the drug. The

use of PEGs with a higher molecular weight may lead to an extension of the dissolution time. It is also recommended to moisten the suppositories with warm water before insertion to facilitate their insertion and dissolution.

In conclusion, the choice of a suppository base is a critical consideration in optimizing drug release and therapeutic outcomes. The principle of opposite characteristics can be useful in selecting a base that is compatible with the drug, and careful consideration of factors such as solubility and dissolution time can help to ensure the effective delivery of medication [19]

3. Material and Method

Table 1 Ingredients and their Uses

Sr.No.	Name of Ingredients	Uses	Images
1.	Alum	Anti-inflammatory, Astringent, Antiseptic	
2.	Polyethylene glycol-4000	Suppository base, Osmotic Agent, Laxative	
3.	Shea butter	Suppository base, Anti-inflammatory	

3.1. Identification and authentication of alum sample: [20]

The physical properties of the alum were assessed based on its visual characteristics, color, scent, flavor, pH, and solubility. Furthermore, the existence of crucial elements such as aluminum ions (Al3+), potassium ions (K+), and sulfate ions (SO4 2−) was determined through qualitative chemical analyses.

3.1.1. Identification test of Aluminum Ion

- The identification of aluminum in a given sample can be achieved through a simple chemical test.
- A quantity of 1 gram of powdered alum is mixed with 10 milliliters of distilled water in a test tube.
- Subsequently, a solution of 0.1 M NaOH is gradually introduced; dropwise, to 1 milliliter of the above mixture.
- Finally, 1 milliliter of aqueous ammonia is added. The appearance of a white cloudiness would indicate the presence of aluminum in the sample.
- This method relies on the precipitation of aluminum hydroxide, which is an insoluble solid that forms when ammonium hydroxide reacts with aluminum ions.
- This test is a widely used technique in analytical chemistry for the detection of aluminum in various matrices

3.1.2. Test of Potassium Ion

- A cotton swab was immersed in distilled water and subsequently introduced to a container comprising alum powder.
- The treated cotton swab was then subjected to a non-luminous flame emanating from a burner. The resulting violet hue of the flame marked the presence of potassium ions within the alum sample

3.1.3. Identification Test of sulphate Ion

- The identification of the presence of sulphate ions in the chemical compound alum can be achieved through a simple test.
- A solution of the compound is mixed with dilute hydrochloric acid, following which a 0.2 M barium chloride solution is gradually added up to the subsequent mixture.
- The presence of sulphate ions in the alum is confirmed by the appearance of a white precipitate.
- This test is useful in the determination of the composition of the alum and its potential applications in various industries

3.2. Determination of pH of Solution

- Mix 1 gram of sample powder with 10 ml of water, filter the solution, and measure pH using a calibrated pH meter at room temperature.
- The pH value may vary based on the purity of the powder and accuracy of the measurement

3.3. Determination of Solubility of Alum in Water

- The water solubility of powdered alum was assessed by means of a rigorous experimental procedure. Specifically, 65 g of powder were accurately weighed using a weighing balance and was added to 100 ml of deionized water at 25 C ± 2°C. The solution was then agitated at regular intervals for the initial 30 minutes and left undisturbed for 2 hours at room temperature.
- After filtering the solution, dilute 7.3 ml of the filtrate up to 300 ml and subject it to complex metric back titration with ethylenediaminetetraacetic acid (EDTA).
- The aforementioned methodology involved the addition of 10 ml of the diluted filtrate to a conical flask, followed by the introduction of 50 ml of 0.01 M EDTA.
- The mixture was then boiled for approximately 5 minutes, cooled to room temperature, and treated with 5 drops of solo chrome black. Upon observation of a blue color change, 1 ml of 10% ammonia solution was poured to the above solution.
- The solution was then titrated against 0.01 M zinc sulphate solution until a pink color appeared as an endpoint, and the value of titer was recorded.
- The amount of alum was subsequently measured using the formula: EDTA volume (ml) – titer value of zinc sulphate (ml), by subtracting the titer value of zinc sulphate from the EDTA volume added.
- The presented methodology accurately estimates the solubility of powdered alum in water and can be utilized in various business or academic settings.
- Mass of alum = 23.73 mg × (EDTA vol (ml) − titer value of zinc sulphate) × dilution factor (DF)[21].

3.4. Evaluation Tests of Suppositories:[22]

3.4.1. Physical features of Formulated Suppositories

Sensory Analysis

To ensure consistent quality, manufacturers of suppositories conduct rigorous testing to ensure uniformity in appearance, texture, scent, and shape. Each individual suppository is carefully examined and evaluated for consistency of fragrance. This approach guarantees that every time a suppository is used, it is a reliable and standardized product

Surface Condition

The surfaces of suppositories have been thoroughly examined for parameters including dark areas, brightness, cracks, mottling, dullness, air bubbles, bursts, axial cavities and holes. Detailed observations have been meticulously recorded

Weight Uniformity of Suppositories

- The present study involved the assessment of suppositories to determine their weight consistency.
- A sample of 5 suppositories was randomly selected from each formulation and individually weighed. The average weight of the suppositories was calculated for each group (A and B) based on each suppository's respective weight.
- The individual weight of each suppository was then subtracted from its corresponding group's average weight (A-B), the percentage deviation from the average was calculated, for which the formula used was: |A − B| A × 100%, where A is the average weight of the suppositories and B is the weight of each one.

- The results indicated that no more than two suppositories deviated by more than 5% from the mean weight for each weight of suppositories, and no more than 10% from the mean weight overall.
- These findings suggest that the tested suppositories are consistent in weight, which is critical for ensuring the accurate delivery of medication

Disintegration Test of Suppositories: [23-25]

- The Disintegration apparatus [USP] for the tablet was utilized to conduct an assessment on 3 individual batches of suppositories. Each batch was composed of 3 suppositories, affixed with a plastic disc and placed within the basket rack of the disintegration apparatus.
- The machine facilitated the observation of the time it takes for all 3 suppositories to get dissolve or soften at a temperature of 37°C± 2°C in 1000 ml of deionized water.
- The noted data was subsequently used to determine the mean and standard deviation of the 3 determinations, providing a comprehensive overview of the sample's disintegration properties.

Content Uniformity of Suppositories

- The present study involved the selection of 3 individual suppositories from a group of formulations, to assess their drug content.
- Each suppository was subjected to a sequence of procedures, involving its placement in a beaker filled with 50 mL of distilled water, followed by its heating in a water bath at 50 °C and adjustment to 100 mL with additional distilled water.
- The solution underwent filtration using What man filter paper and a funnel and was subsequently subjected to analysis utilizing the complexometric back titration method, as delineated in the solubility test procedure.
- This protocol was systematically repeated for each of the ten arbitrarily chosen suppositories, culminating in the computation of the average content and standard deviation.

Dissolution test on Suppositories

- The present study aimed to investigate the dissolution behavior of suppositories utilizing the USP apparatus. The experiments were performed at a constant temperature of 37 °C± 0.5 °C, using 900 ml of deionized water with a basic pH of 6.8 and a basket speed of 50 rpm.
- 10 ml of the dissolution medium was extracted from the vessel at specified time intervals of 15, 30, 45, 60, 90, 120, 150, and 180 minutes and promptly passed through a filter into a test tube. The removed medium was subsequently replenished with an equivalent volume of fresh dissolution medium.
- The filtrate was diluted to 100 ml of distilled water and analyzed by a method known as complex metric titration, as mentioned in the solubility test.
- The amount of alum that was released, along with the percentage of alum released and the total amount released over time (cumulative percentage), was calculated.
- A graph illustrating the cumulative percentage of drug release over time was constructed.
- This study was designed to shed light on the dissolution characteristics of suppositories, which is critical to ensure their effectiveness.
- The USP apparatus is a widely accepted method for assessing the dissolution behavior of various pharmaceutical formulations.
- The experimental conditions were set to mimic the physiological environment, ensuring the reliability and relevance of the results. The data obtained from this study can aid in the development of optimized suppository formulations.

3.5. Authentication of Alum

Table 2 Authentication test of Alum

Sr. No.	Test	Result
1.	Aluminium ions	Present
2.	Sulfate ions	Present
3.	Potassium ions	Present
4.	pH	2.4
5.	ATR-FTIR Spectroscopy	Pass

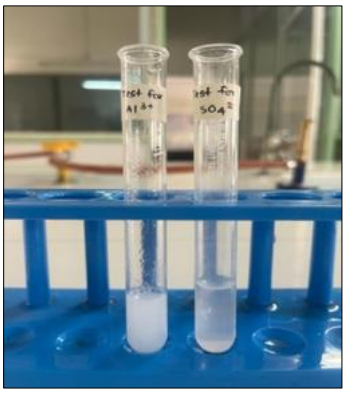

Figure 2 Test for Aluminium ions And Sulphate ions

Figure 3 Test for Potassium ions

Figure 4 pH of aqueous alum solution

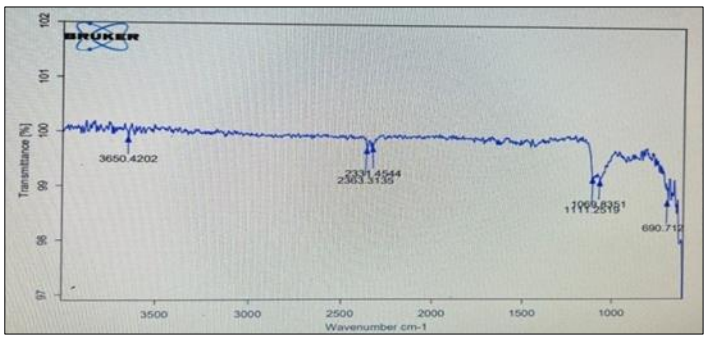

Figure 5 ATR-FTIR Spectroscopy of Alum

3.6. Determination of Displacement Value of Alum

Six suppositories of each base (shea butter with PEG 4000) were prepared and weighed (a mg) using a 2 g mold (method explained in detail these are referred to as blank suppositories. Six medicated suppositories containing 40% of the alum were also prepared for the above-stated bases and weighed (b mg). The amount of the bases (c mg) and alum (d mg) in the medicated suppository was determined the displacement value of the alum in a particular base was calculated using the following formula:

$$\text{Displacement Value} = d\ (mg)/a - c\ (mg)$$

Blank suppository using, for example, shea butter and PEG 4000 was prepared using the 2 g mold and weighed. For shea butter and PEG 4000 was used to calculate the total amount of base required for the formulation of the 20 suppositories by using the following equation.

$$\text{Amount of total base } (B) = (N \times y) - (N \times D/DV)$$

Where N is the number of suppositories to be formulated, y is the weight of a blank suppository (2.0317 g), D is the amount of drug in one suppository (0.5 g), and DV is the displacement value of base of the total base, 5% constituted the PEG 4000.

3.6.1. Formulation Table

Table 3 Formulation Table of Alum Suppositories

Name of Drugs	**Formulations and Quantity in gram**		
	F I	**F II**	**F III**
Alum	0.4 gm	0.4 gm	0.4 gm
PEG -4000	1.3 gm	1.4 gm	1.2 gm
Shea Butter	0.3 gm	0.2 gm	0.4 gm

3.7. Formulation of Alum Suppositories

3.7.1. Preparation of Suppositories

By Melt molding Method/Fusion Method:

- 1.2 grams of suppository mound were retrieved, subjected to a cleansing process, and subsequently dried using cotton. Following this, the mound was coated with liquid paraffin for lubrication.
- By using a weighing balance, alum was weighed. Then the PEG-4000 weighed was heated in a water bath using the Double boiling method at a temperature of 54-58 degrees Celsius. After melting the PEG-4000, Shea butter was added with continuous stirring to avoid overheating and finally weighed quantity of Alum was added.
- After the heating, the melted mass was poured into lubricated suppository molds.
- These suppository molds were then placed in the refrigerator for solidifying up to 30-40 minutes.
- After solidifying, the suppository's extra-base was scrapped out from the top of the molds.
- The suppositories were taken out of the molds, packed, and refrigerated.

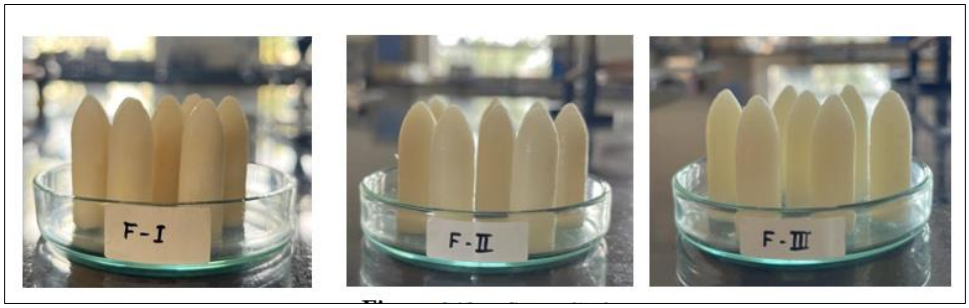

Figure 6 Alum Suppositories

Evaluation Parameter of Alum Suppositories

Table 4 Evaluation Test

Sr. No.	Evaluation Tests	Formulation		
		I	II	III
A	Physical Appearance			
1	Color	White	White	White
2	Odor	Odorless	Odorless	Odorless
3	Shape	Bullet shaped	Bullet shaped	Bullet shaped
B	Sensory Evaluation			
1	Feel	Smooth and Glossy	Smooth and Glossy	Smooth and Glossy
C	Weight uniformity	Pass I.P limit	Pass I.P limit	Pass I.P limit
D	Content uniformity	97.4%	96%	98.3%
E	Disintegration time	18 min	15min	22 min
F	Dissolution rate	80%	87%	84%

4. Result and Discussion

I prepared alum suppositories containing Alum, Shea butter, and PEG 4000 are well-known ingredients. Alum was authenticated by different tests like Aluminum ion, Sulphate ion, Pottasium ion, pH and FTIR are given in Table 2 and the prepared three formulations of Alum suppositories were evaluated by color, odor, shape, Feel, weight uniformity, content uniformity, disintegration time and dissolution rate obtained results are given in table 4.

The color of the formulation was shows White and off and white bullet-like shaped. The suppository feel is smooth and glossy. The weight of all formulation suppositories passes the I.P. limit. The disintegration time required for suppositories is between 15 to 25 minutes and the Dissolution rate is 80 to 90 %.

In three formulations F2 formulation shows less disintegration time and more dissolution rate.so F2 is better than F1 and F3.

5. Conclusion

The Alum Suppositories show a very good effect. Based on results and discussion, the formulation of F2 shows good results. And can be safely used in the rectal cavity. Alum shows anti-inflammatory, promotes the shrinkage of hemorrhoidal tissue, and provides soothing effects

Compliance with ethical standards

Acknowledgments

I would like to acknowledge and give my warmest thanks to my guide Prof. Bhavana Tambe, Who made this work possible, her guidance and advice carried me through all the stages of my project. I would also like to thank Dr.Y.V.Ushir Sir and SMBT Institute and SMBT College of Pharmacy for providing Me facilities.

Disclosure of conflict of interest

Authors declare that there is no competing conflict of interests

Author's Contributions

- Conception, design and writing of the work: Ms. Sanskruti V. Pawshe

- Drafting the article: Ms. Bhavana D.Tambe
- Critical revision of the article: Ms. Sanskruti V. Pawshe
- Final approval of the version to be submitted - All named authors should approve the
- Paper before submission: Ms. Sanskruti V. Pawshe, Ms. Bhavana D.Tambe

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