

A Recent Advancements of Suppositories

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ABSTRACT

Suppositories are dosage form inserted into body cavity ties, most commonly rectum, to deliver drug to the systemic circulation and local tissue. Especially for patients unable to take drug orally due to nausea and vomiting advanced disease, or neurological defect.

In modern days most of the remedial medicines are prepared for rectal delivery to gain therapeutic blood concentration of the medicine and thereby enhancing the bio-availability

Interest of developing a combination of two or more drugs in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layered suppository is an attractive option to avoid chemical incompatibilities between drugs by physical separation, and to enable the development of different drug release profiles (immediate release with sustained release). Bi-layered suppository is a novel approach for the successful development of controlled release formulation along with various features to provide a way of the successful drug delivery system. Therapeutic strategies based on rectal, vaginal, urethral deliveries of bilayered suppositories are gaining more acceptance among researchers due to a confluence of factors, including advanced delivery strategies, patient compliance and combination therapy and increased bioavailability.

The analysis of current suppository bases is carried out depending on their physicochemical properties, classification of excipients from various pharmacopoeias. The advantages and disadvantages of suppository for the rational choice.

KEYWORDS: Suppositories, Rectal, Urethral, Vaginal, Suppository bases, Bi-layered

1. INTRODUCTION

Drugs or medications are administered through a variety of routes, the most common being the oral and parenteral route. While rectal route is less commonly used in routine practice, in proctological disorders it is being used effectively since long. [1]

Drugs mixed with various excipients and administered through the rectal route do provide satisfactory pharmacokinetics with acceptable local tolerance. [2]

Suppositories are a medicated solid dosage form intended for insertion into the body orifices where it dissolves or melts to exert local or systemic effects. The term suppositories have its origin in Latin and means, "to place under". It is comes under semi solid preparation because it is prepared by melting all ingredients (bases and other additives along with active ingredient). All types of suppositories are melt at normal body temperature after introducing in body cavity and produce their effects. [3]

It is comes under semi solid preparation because it is prepared by melting all ingredients (bases and other additives along with active ingredient). All types of suppositories are melt at normal body temperature after introducing in body cavity and produce there effects. Suppositories are ideal for infants, elderly individuals and post-operative patients, who are unable to swallow oral medications, and for individuals experiencing severe nausea and/or vomiting [4]

Administration of drug through the rectal route is responsive to both local and systemic drug delivery. It has been effectively used during the last centuries to treat local diseases of the anorectal area (for example hemorrhoids) as well as to deliver drugs systemically as an alternative to the oral route. [5]

There are three types of suppositories, each to insert into a different sections: rectal suppositories into the rectum, vaginal suppositories into the vagina, and urethral suppositories into the urethra of a male. [6]

1. Rectal Suppository (administered in rectum):

In 1991, a study on suppository insertion in *The Lancet* found that the "torpedo" shape helps the device to travel internally, increasing its efficacy [7]. The findings of this single study have been challenged as there is insufficient evidence on which to base clinical practice.[8]Rectal suppositories are intended for localized or systemic action to relieve pain, constipation, irritation, inflammation, nausea and vomiting, fever, migraines, allergies, and sedation.[9]

2. Urethral Suppository (administered in urethra):

Alprostadil pellets are urethral suppositories used for the treatment of severe erectile dysfunction (impotence). They are marketed under the name *Muse* in the United States. Its use has diminished since the development of oral impotence medications [10]

3. Vaginal Suppository (administered in vagina):

Vaginal suppositories are solid medications that are inserted into the vagina with a special applicator. The body absorbs drugs from vaginal suppositories quickly. They work faster than medications you take by mouth. This is because suppositories melt inside the body and absorb directly into the bloodstream. Vaginal suppositories are commonly used to handle urogenital infections and other local diseases. The vaginal route is efficacious in allowing the efficient transport of some drugs such as progesterone and azoles to the uterus while alleviating systemic side effects .[11]

4. Nasal Suppository (administered in nose)

5. Ear Cones (administered in ear)

2. HISTORY

Some archaeologists believe that pre-Columbus, Mesoamerican cultures were the first to invent suppositories in 1700 and some researchers have found evidence that the Ancient Babylonian culture were using **suppositories** as early as 2,000 B.C.

IN 1500's The Book "the Tale of the Dueling Neurosurgeons" records the story of King Henry.

He was wounded in an accident and his body was injured and he couldn't eat or swallow fluids. His doctors used a rectal **suppository** to keep the king alive; the procedure was a success.

IN 1763, Suppository was use in academic literature by Lemery in his work , "The Pharmacopoeia of Lemery, in which he used suppositories in Latin as "*suppositorium*" meaning a "substitute" for enemas. [12]

At this time, the medicines were enclosed in "solid forms" by adding honey and this form were replaced by **cocoa butter** in the late 18th century.

In 1841, active ingredients began being used inside the cocoa butter in solid forms by Henry and Guibourt. [13]A

In 1897, cocoa butter suppositories began to mixed with water, gelatin, and glycerin for more easily insertion .

IN 1963 The first literature reference on the use of paediatric rectal dosage form (for premedication before anaesthesia) was reported. [14]

3. ADVANTAGES:

1. Improved enzymatic drug stability:
2. Partial avoidance of hepatic first pass:
3. Higher drug load:
4. Lymphatic delivery
5. Constant and static environment.
6. Patients with swallowing difficulty:
7. Avoidance of overdosing.[15]

4. DISADVANTAGES :

1. A perceived lack of flexibility regarding dosage of commercially available suppositories resulting in underuse and a lack of availability.
2. If suppositories are made on demand, they may be expensive.
3. Suppositories as a dosage form are safe, but they exhibit variable effectiveness, depending upon many factors to be discussed later, including the pathology of the anorectal lesions.

4. Different formulations of a drug with a narrow therapeutic margin, such as aminophylline, cannot be interchanged without risk of toxicity.
5. The “bullet-shaped” suppository after insertion can leave the anorectal site and ascend to the rectosigmoid and descending colon. Hence, one may consider that suppositories with this shape possibly should not be used at bedtime. [16] [17]

5.1. Classification of suppository bases:

1.Fatty bases – they melt at body temperature

Example:- Theobroma Oil (Cocoa butter)

Synthetic fats : Example:- Hydrogenated edible oil

Arachis oil,

Coconut oil,

Palm kernel oil,

Stearic etc

2. Water-soluble or water miscible base – they dissolve or disperse in rectal secretions.

Example:- Glycero-Gelatin base

Polyethylene glycol bases

3 .Emulsifying bases – they emulsifies small amount of aqueous solution of drug.

Example :- Whitepol

Massa Esterium

Massuppol

5.2. Different categories of drugs incorporated into suppository Drug : [18]

1. **Antibiotics:** Eg. Ceftizoxime Amoxicyllin using Thiobroma Cefmetazol.
2. **Analgesics:** Eg. Indomethacin Paracetamol using PEG &glycero-gelatin Etodolac Ketoprofen using PEG.
3. **Bronchodilators/ anti-asthamatics:** Eg. Theophylline Terbutaline etc.

5.3. DRUGS USED IN RECTAL SUPPOSITORY

Table 1 Examples of rectal formulations for local absorption. [19]

S.No.	Drugs	Brand name	Indication
1	Bisacodyl	DULCOLAX,BISALAX	Constipation
2	Glycerol	Glycerol	constipation
3	Saline laxatives	Micolette Microlax	Constipation,Bowel preparation
4	Mesalazine	Pentasa salofalk	Inflammatory bowel disease
5	Budesonide	Budenofalk	Anti- inflammatory
6	Prednisolone	Colifoam	Anti- inflammatory
7	Hydrocortisone	Predsol colocort	Anti- inflammatory
8	Polystyrene sulfonate resins	Resonium A	Hyperkalemia

Table 2. Examples of rectal formulations clinically approved for systemic absorption. [20]

S.No	Drug	Brand name	Indication
1	Acetaminophen	Panadol,Acephen	Pain,fever
2	Oxycodone	Proladone	Pain
3	Ondansetron	Zofran	Nausea, Vomiting
4	Caffeine+ergotamine	Migergot	migraine
5	Prochlorperazine	Compro	Nausea, Vomiting
6	Promethazine	Phenergan	Antihistamine
7	Ibuprofen	nurofen	Pain, fever
8	Diclofenac	voltaren	Pain,fever
9	iIndomethacin	Indosin	Pain

5.4. ROUTE OF ADMINISTRATION : [21]

HOW TO INSERT SUPPOSITORIES :

1.GET PREPARED



Fig. 1

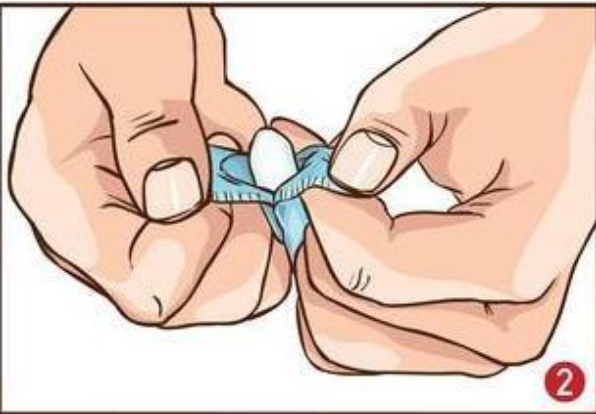


Fig. 2

2.INSERT THE SUPPOSITORY

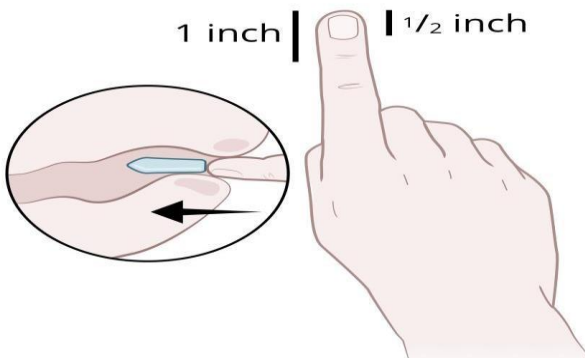


Fig. 3



Fig. 4

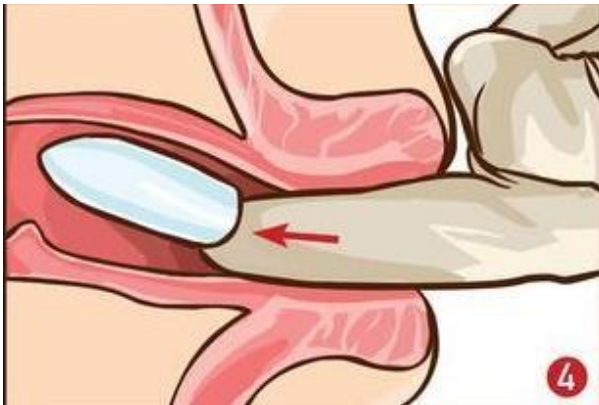


Fig. 5

3.CLEAN AND RELAX

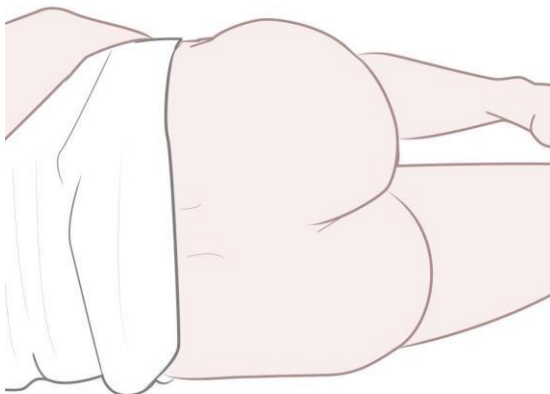


Fig. 6

Fig step by step procedure

6. RECENT ADVANCEMENT IN SUPPOSITORY:

6.1. NEWER CONCEPT OF SUPPOSITORY [22]

- 1 Tablet suppositories.
- 2 Layered suppositories.
- 3 Coated suppositories.
- 4 Capsule suppositories.

1 Tablet suppositories:

- This type of tablet prepared by compression like TABLET such type of suppository used for rectal and vaginal purposes.
- Pessaries tablet suppositories are present in almond like shape.
- Rectal tablets covered with thin layers of materials such as polyethylene glycol for protecting.



Fig 7 Marketed Products

2 Layered suppositories :

- In that type of suppositories are contains different drugs in different layers so that the compatibility drugs can be separated from each other.
- Similarly drugs having different melting points can be incorporated to control the absorption rate.

3 Coated suppositories:

- In that type of suppositories contains polyethylene glycol , acetyl alcohol etc.
- Those materials control their disintegration rate to impart lubricant properties and to provide protection action during storage.

4 Capsule suppositories:

- Soft gelatin capsule of different shapes and size are prepared in that type of suppositories.
- In that type of capsule suppositories are filled with liquids, semisolids or solid.
- This type of capsule is increasing in popularity.

6.2. THE MODERN RANGE OF SUPPOSITORY BASES

6.2.1 SUPPOSITORY BASES:

According to the USP, there are six general classes of suppository bases :

1 . Cocoa butter

Cocoa butter does not contain emulsifiers, so it does not absorb water. But, Tween-61 containing a tan, waxy, solid, nonionic surfactant [5% to 10%] can be added which can provide an increase in the water-absorbing ability of cocoa butter, although the addition of nonionic surfactants leads to instability of suppositories during storage .[23]

- Cocoa butter containing chloral hydrate, phenol or thymol in suppositories may decrease its melting point , this can be overcome by eliminated by adding 4% to 6% white wax or 18% to 28% cetyl ester wax. [24]
- cocoa butter suppositories may have an incomplete or somewhat less release of certain APIs, this release of the body cavity depends on the water / base distribution coefficient in the medicine, because many organic molecules of the medicinal substance are insoluble in water and are lipophilic. So in order to increase the bioavailability of APIs, it is advisable to use them in the form of water-soluble ionized (salt) forms, because they have high water / base distribution coefficients. [25]

2. Cocoa butter substitutes [26]

- Witepsol
- Fattibase
- Fattyblend
- Supposiblend
- Supposibase F

3. Glycerinated gelatin : [27]

- Glycerin [70 parts]
- Gelatin[14 parts]
- Water [16 parts]

4. Polyethylene glycol base. PEG 4000- 33 parts

PEG 6000- 47 parts

PURIFIED WATER- 20 parts

5. Surfactant base.

6. Tablet suppositories or insert.

According to Allen, four classifications of suppository bases are usually described, based on their melting or dissolution properties; [28]

- 1) The first is the fat- or oil-type base, which must melt at body temperature to release its medication.
- 2) The second is the glycerin-gelatin base suppository, which absorbs water and dissolves to release its medication.
- 3) The third is the water-soluble or water-miscible polymers and surface-active agents.
- 4) The fourth is a group of bases containing disintegrating agents, natural gums, Effervescent agents, collagen, fibrin, hydrogels, etc

6.2.2 CHARACTERISTICS OF MODERN SUPPOSITORIES;[29,30]

- Chemical and physical resistance during storage and use;
- Compatibility with a wide range of active pharmaceutical ingredients and excipients;
- Aesthetically appealing appearance;
- Non-toxicity, lack of sensitivity and irritation to sensitive tissues of the body
- Expansion-compression characteristics such that when cooled, suppositories must be compressed enough to be easily released from the molds;
- To melt and dissolve in the intended cavity of the body to release a medicinal substance;
- Mixing and absorbing a small amount of water;
- The viscosity should be low enough in the melt for easy casting of the suppository mass into molds, but high enough for the suspending of the API solid particles.

7. HOLLOW TYPE SUPPOSITORY

Hollow type suppositories came into existence in the 1980s. It contains a hollow cavity that can accommodate either solid, liquid or gel. [31]

A special kind of mould (rod like adaptor) is used to make a hollow cavity. It consists of two phases which prevents:

- The interaction between drug molecule and suppository base by eliminating the co-heating step and thus can accommodate thermolabile.
- The drug can be incorporated in the shell as well as in the hollow cavity, which can provide rapid drug release from the core followed by sustained release from the shell. [32] Also HT suppositories have been found to be more advantageous over conventional suppositories for the treatment of some chronic diseases such as asthma. [33]

Sustained release hollow-type (SR-HT) suppositories have offered more controlled release of API from the suppository bases aided by muco-adhesive polymers and natural gums including xanthan gum and alginate derivatives alter the viscosity of the rectal fluid, while mucoadhesion increases mean residence time (MRT) and prevents spreading of the formulation towards the colorectal area. [34]

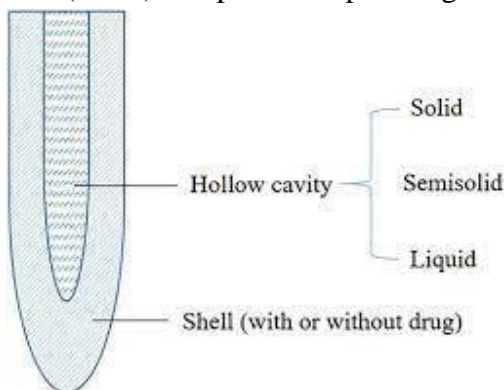
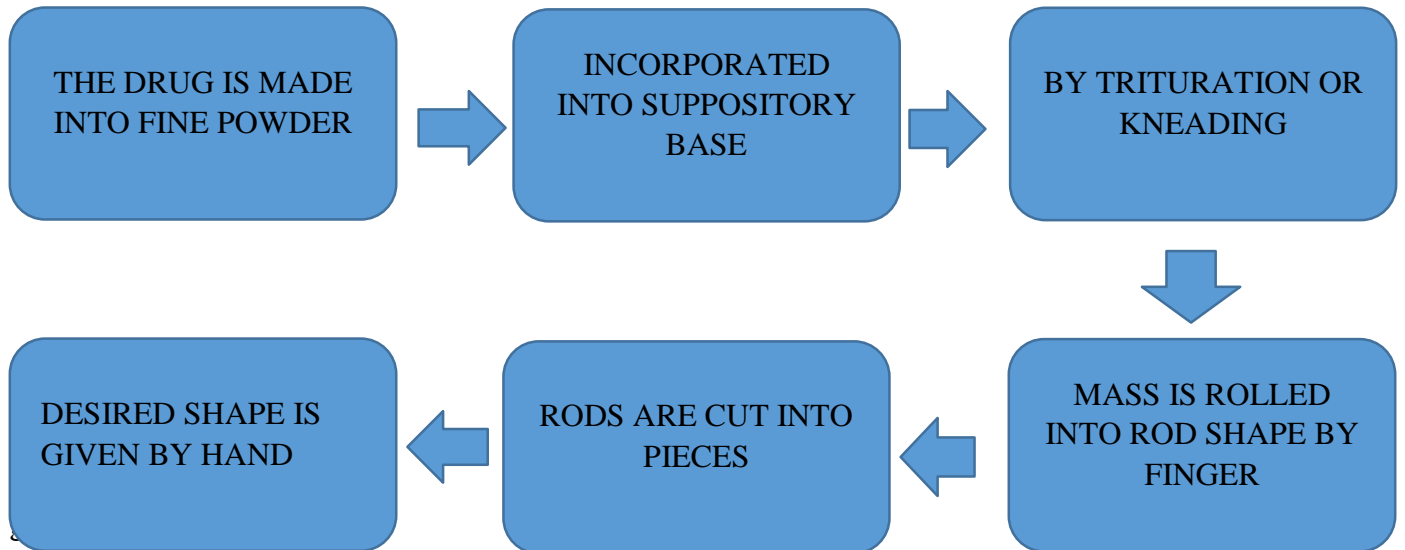


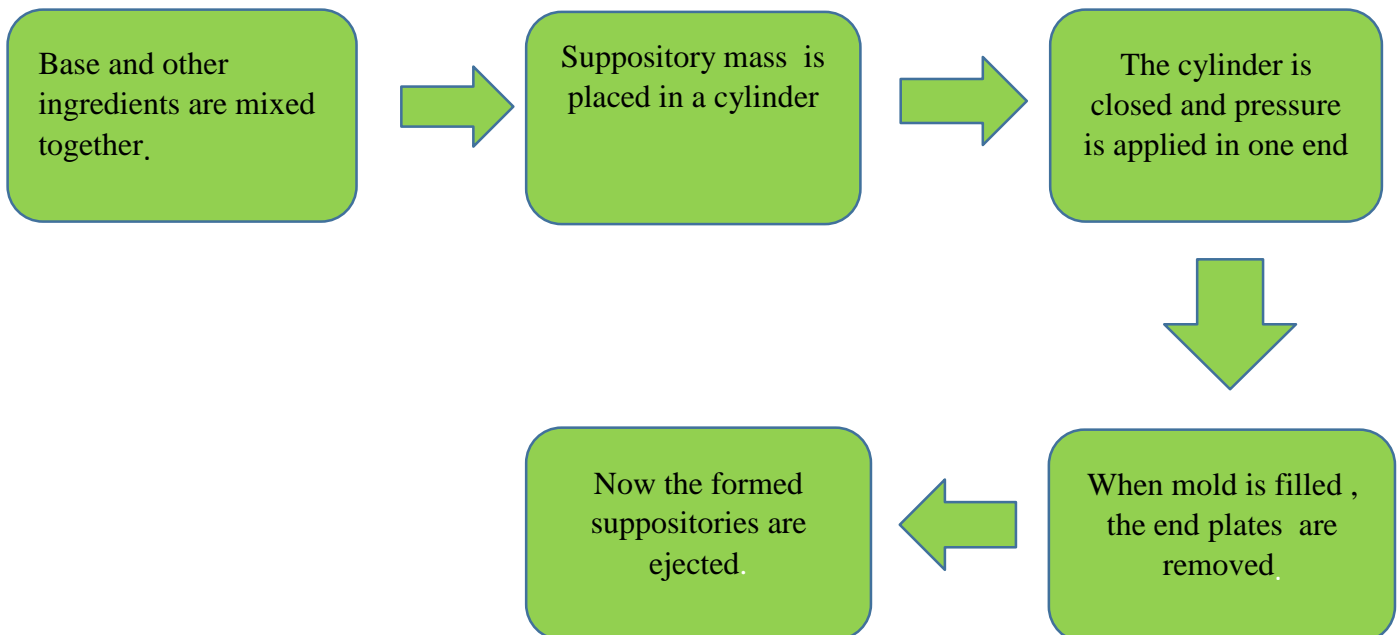
Fig 8 Structure of Suppositories

8. METHODS OF PREPARATION OF SUPPOSITORIES [35]

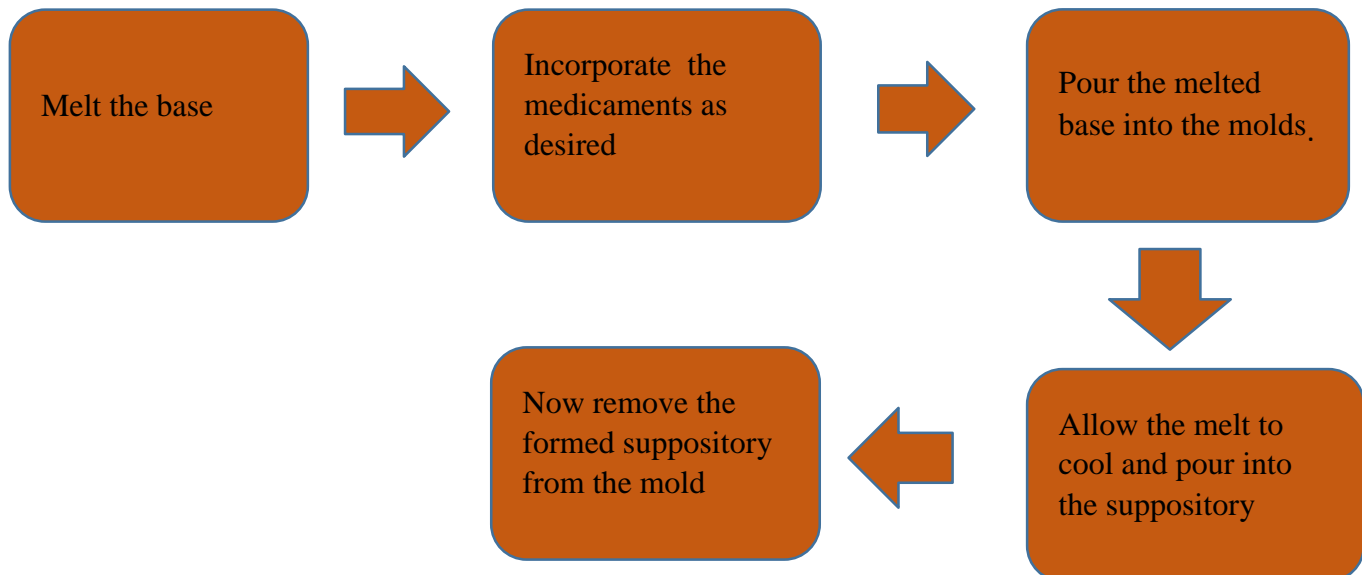
1. HAND MOLDING METHOD



2. COMPRESSION METHOD



3. MOLDING



9. USES OF SUPPOSITORIES: [36]

Allergies, Anxiety, Constipation, Fever, Hemorrhoids Motion sickness, Nausea Pain, and itching. Seizures Mental health problems, such as schizophrenia or bipolar disorder Bacterial or fungal infections dryness Birth control etc .

10. BILAYERED SUPPOSITORY

Bi-layered suppository is a novel technology for the development of a combination of two or more active ingredients in a single dosage form for proper release of incorporated drugs and to avoid incompatibility between them .

It has been developed for dual release of a drug from a single dosage, combination of the two drugs to maximize the therapeutic effect and reduce side effects and also for better patients compliance (37)

Bilayered Suppository is made by combining layers of different drugs with various release patterns, or by combining slow release with immediate-release layers of incorporated drugs. The release characteristic of active ingredients can be modulated as prolonged release by using a different - different base in each layer of the suppository to enable the development of different drug release profiles. (38)

10.1. Objectives for Designing of Bi-layered Suppositories

To administer fixed dose combinations of different drugs, to separate the incompatible drugs from each other, and to control the delivery rate of either single or two different drugs.

10.2. ADVANTAGES: [39]

1. Avoidance of repetitive dosing and incompatibility between two or more drugs.
2. Sequential release of two drugs
3. Controlled delivery of active pharmaceutical ingredients by combining layers with various release patterns, or by combining slow release with immediate-release layers in a single dosage form
4. Different active ingredient or same active ingredient can be delivered at differing rates in a single suppository.

10.3. DISADVANTAGES: [40]

1. Bilayered suppository involves multiple layered, incorporation of incompatible drugs, additional equipments for manufacturing and many formulations methods and operational challenges .
2. Development of two layers implies additional time spent on formulation, analysis and validation.
3. Bi-layered suppositories are much expensive.
4. Bioavailability problems occur with drugs of poor wetting and slow dissolution properties.

10.4. ADVANCEMENT IN BILAYERED SUPPOSITORIES :

Factors like solubility of drugs , particle size, and excipient such as melting point , fusion rate, viscosity, hydrophilic-lipophilic characteristics have a vital role in release rate and absorption of a drug from suppositories . (41)

It has been concluded that higher solubility of drug in solvent, lower the drug release and drug absorption from the dosage form. The same drug dose is therefore able to produce a different therapeutic response when included in excipients with different properties.[42]

Table 3. Various advances in bi-layered suppository

Active ingredient(s)	Rational	Year	Ref no
Paracetamol and Metoclopramide HCl	Combination therapy	2017	43
Paracetamol and Licorice Extract	Combination therapy	2015	44
Propranolol HCl	Sustained release	2013	45
Probiotic (lactobacillus sp.) and prebiotic(organic acid)	Combination therapy (vaginal route)	2012	46
Diclofenac sodium	Bioavailability improvement	2012	47
Lactobacilli and antibacterial herbal extracts	Combination therapy (vaginal route)	2011	48

10.6. CHARACTERISTICS OF BILAYERED SUPPOSITORY : [49]

- Bi-layered suppository should be elegant and free of defects like chips, cracks, discoloration, and contamination.
- It should have the required chemical and physical stability to maintain its physical attributes over time and must be able to release the medicinal agents in a desired, predictable and reproducible manner.
- In addition, bi-layered suppositories should have sufficient mechanical strength to withstand mechanical shock during its production, packaging, shipping and dispensing.

10.7. Preparation of Bi-layered Suppositories :

The simple bi-layered suppository is prepared with one layer of drug for immediate release with the second layer designed to release the same or different drug, either as a conventional release of a second dose or in an extended release form.

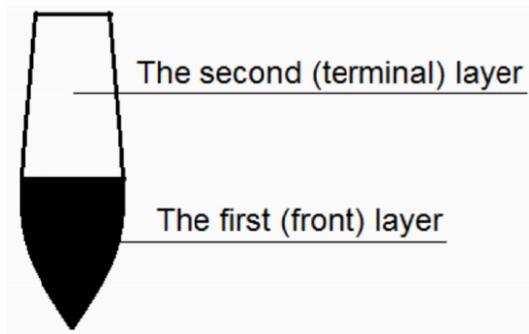


Fig 9 The general structure of bi-layered suppositories.

To obtain these bi-layered suppositories, two distinct masses with each of selected excipients containing the same or different drug are prepared by melting the excipients of each layer separately at a suitable temperature to obtain two fractions. Then, the drug is uniformly dispersed. The first layer is prepared by partially filling the mould with a first fraction of the mass in a predetermined volume. When it gets solidified, the second fraction is added into the same mould to get a second layer and A Review on Bi-layered Suppositories cooling them again to room temperature. An additional intermediate layer of inert base may also be included into separate two incompatible drugs to minimize the area of contact between the two layers (50).

Another structure of bi-layered suppository, which consist of core and outer layers was developed as seen in figure 2. There are two methods to prepare such suppositories. In the first method, bilayered suppositories are prepared using two metal molds with different hole size. The core bases have higher temperature of melting than the bases of the outer layer. The core layer is prepared by melting suppository base over the water bath. Then, drug and other additives are added into the melted base with gentle stirring until a homogeneous mass was obtained. The mixture is poured into the mold with small holes at a temperature just above the congealing point of the suppository base and cooled. The melted base of the outer layer is prepared and homogenized. Then, the cores are fixed on the needles in the centre of the larger mold, the outer layer mixture is added and then cooled. [51]

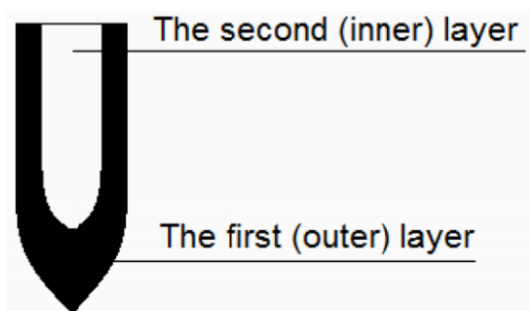


Fig 10 The general structure of bi-layered suppositories

In the second method, the suppository base is melted on a water bath and then mixed with drug and the mixture is filled into the stainless steel suppository mold to form an outer layer. This mold composed of the stainless steel rods to place into the outer layer component during setting to form mold cavity and

then the rods are removed before the inner layer component is subsequently filled into the created cavity. [52]

TABLE 4: Recent Patents of suppositories

S.N O.	Applicants Number	Suppositories	Patent No.	Inventors	Assignees	References
1	09/899,5677	SUPPOSITORY AND COMPOSITION COMPRISING AT LEAST ONE POLYETHYLENE GLYCOL	US 6,740,333 B2	Christian Westy Beckett, Aalsgaarde (DK); Per Robert Topp Eliassen, Koersouer (DK)	Anestic ApS, Aalsgaarde (DK)	53
2	301,966	VIRACDAL, BACTERICDAL AND SPERMICDAL WAGINAL SUPPOSITORY	5,466,463	Larry C. Ford, Irvine, Calif.	Lafor Laboratories Limited, Newport Beach, Calif.	54
3	15 / 787 , 978/ AXIM Biotechnologies , Inc . , New York , NY (US)	SUPPOSITORIES COMPRISING CANNABINOIDS	US 10 , 092 , 538 B2	Lekhram Changoer , Ridderkerk (NL) ; George Anastassov , New York , NY or (US	Axim Biotechnologies , Inc . , New York , NY (US)	55

4	: 758,883	CONTROLLED RELEASE MATRIX References	56 Cite	5,215,75 8	Thinnayam N. Krishnamu rthy , 5,110. 5/1992	Thinnayam N. Krishnamurt hy,	56
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Conclusion: Bi-layered suppository is improved beneficial technology when compared to single layered suppository. It provides one of the important design approaches where two or more incompatible drugs can be incorporated into a single unit. Bi-layered suppository is suitable for sequential release of two drugs, with different indication, in combination and also for sustained release suppository in which one layer is immediate release as initial dose and second layer is maintenance dose. The objective of the dosage form is to ensure that the drugs available to the people are not only safe and effective, but should be properly manufactured and packaged in a convenient to meet the quality target product profile over its shelf life. Therefore, to develop a robust bi-layered suppository a complete understanding must be developed through the application of scientific tools to produce suppositories with desired characteristics such as sufficient mechanical strength, optimum release profiles, stability and shelf life.

The results shows that prepared Double –layered suppositories may be more acceptable than conventional because of the sequential release of the two drug ,enhancing the release of drug administered rectally and improving bioavailability of drug with significant first -pass effect to get a rapid pharmacological effect.

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