CHAPTER-1

INTRODUCTION

In ancient era, drugs inducing unconsciousness, haemorrhoidal, vermicidal and purgative actions was inserted through rectal route in the form of suppository. 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. By inserting the drug through rectal route the presystemic effect in hepatic region and in GIT can be prohibited.

Anal drug delivery systems, used as controlled release dosage form for treating the ailments like arthritis, increase blood pressure, asthma, AIDS and diabetes.

Moreover, there is a rising interest that the suppositories can be used in the treatment of post operative pain and pain related with malignancy.

Rectal drug delivery system is the area of enthusiasm for many researcher’s to evaluate consumption of drug from the rectal region for drug which are currently inserted through parental route. Viz., antibiotic and polypeptides.

The absorption of antibiotic and polypeptides is more effectivet from the small intestine than form the rectum and hence can be formulated using different absorption enhancers\(^1\).

ADVANTAGES, DISADVANTAGES AND APPLICATION OF SUPPOSITORIES\(^2\):

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

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

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

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

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

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

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

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

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

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

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

e) **Expensive:** These are more expensive as compared to tablets.

**Applications of Suppository:**

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

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Researchers</th>
<th>Example</th>
<th>Suppository base</th>
</tr>
</thead>
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<tr>
<td>Antibiotics</td>
<td>Askura et al³</td>
<td>Ceftizoxime</td>
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<tr>
<td></td>
<td>Webster JA et al⁴</td>
<td>Amoxicilln</td>
<td>Thiobroma oil</td>
</tr>
<tr>
<td>Section</td>
<td>Authors</td>
<td>Drug(s)</td>
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<td>---------------------------------</td>
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<tr>
<td>Analgesics</td>
<td>Kim YA, Young KS</td>
<td>Indomethacin</td>
<td></td>
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<tr>
<td></td>
<td>Basvaraj BV and Nanjunda Swamy NG</td>
<td>Paracetamol</td>
<td>PEG &amp; glycero-gelatin</td>
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<tr>
<td></td>
<td>Martinez MT, Herrero R, Gutierrez JA, Iglesia SJM, Fabregass JC</td>
<td>Etodolac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Babar A, Bellete T and Plagkogiannis FM</td>
<td>Ketoprofen</td>
<td>PEG</td>
</tr>
<tr>
<td>Bronchodilators/anti-asthamatics</td>
<td>Ahmed MN and Bandopadhyia</td>
<td>Theophylline</td>
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<tr>
<td></td>
<td>Maity S et al</td>
<td>Terbutaline</td>
<td>--</td>
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<tr>
<td>Anti-histamines</td>
<td>Laura et al</td>
<td>Promethazine hydrochloride</td>
<td>--</td>
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<tr>
<td>Steroids</td>
<td>Arunya Usayapant &amp; Bragodeesh R.Iyer</td>
<td>Prednisolone dexamethasone hydrocortisone</td>
<td>Witepsol PEG</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Pinaar EW et al</td>
<td>Phenytoin</td>
<td>--</td>
</tr>
<tr>
<td>Anti-gout agent</td>
<td>Samy EM et al</td>
<td>Allupurinol</td>
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</tbody>
</table>
Human alimentary canal consists of small and large intestines which is about 7.5 meters long beginning at caecum in right iliac fossa and terminating at the rectum and anal canal deeply in pelvis. Rectum of the human body is like a sac like structure through which various
medicaments can be inserted and holds for some time in the rectum, thus absorbing the drug form the mucous membrane.

Rectum is final, straight and dilated section of colon about 13 cm long. It leads from sigmoid colon and ends in anal canal 16,17

The mucosal lining of rectum consists of large number of goblet cells, forming tubular glands which secrete mucus. The total mucus in absence of fecal matter is about 3 ml, and is spread over total surface area of 300 cm². The pH of total mucosal layer is reported as approximately 7 to 7.5. Furthermore there seems to be little buffer capacity 18

Inferior mesentric artery is continued as superior rectal artery into renal pelvis, in the sigmoid colon where it divides into two branches, which descends each side of rectum. The distal section of rectum is attached by middle rectal artery as a part of internal iliac arteries.

Venous drainage from proximal part is by inferior rectal vein, which finally drains into inferior mesenteric vein. Middle rectal vein drains blood from distal part of rectum and anus, joins internal iliac veins. Hence, this drainage into the inferior vena cava of inferior and middle rectal vein bypasses first pass metabolism 19

Normal rectal temperature ranges from 97.6°F to 100.4°F, which is roughly 1°F above oral and 2°F above armpit on an average rectal temperature is 0.7°C higher than oral temperature 20

**FACTORS AFFECTING RECTAL ABSORPTION:**

**Physiological Factors** 21:
A number of drugs cannot be administered orally, because either the drugs are affected by the digestive juices, or their therapeutic activity is modified by the liver after absorption. More than half (50 to 70%) of rectally administered drugs are absorbed directly into the general circulation. The lymphatic circulation also helps in absorbing a rectally administered drug and in diverting the absorbed drug from the liver.

The pH of rectal mucosa is a vital parameter for controlling the rectal absorption of. The absorption of a drug would be enhanced most likely by a change in the pH of the rectal mucosa that would increase the proportion of unionized drug.

This diffusivity is influenced not only by the nature of the medicament, such as the presence of the surfactant or the water-lipoidal solubility of the drug, physiological conditions of colon such as the state of anorectal membrane also play a role in drug absorption. This membranous wall acts as a barrier for the transportation of medicament from the porous membrane.

**Physiochemical Characteristics of the Drug**

In order for the drug to be available for absorption, the drug release form the formulation is essential for the distribution of the drug in the surrounding fluids.

If the drug has a lipid-water coefficient favoring fat solubility, the drug is released slowly from its suppository excipient. Therefore hydrophilic and the salts insoluble in oil are preferred in fatty base.
The rate-determining process in absorption of drug from rectal delivery system is the drug partition from the base. Solution of the drugs in solid-polyethylene glycol and oleaginous bases results in delayed absorption times, because the drug is slowly eluted into the surrounding fluids. As would be expected, the larger the particle size, the slower the rate of solution and as a result, the rate of drug absorption may be increased or decreased with increasing drug particle size. Surfactants can enhance or reduce the drug absorption rate.

Once the drug is released from the suppository base and reaches the site of absorption on the lumen wall, the lipid-soluble undissociated drug is the most freely absorbed. Highly ionized compounds are poorly absorbed.

**Physicochemical Characteristics of Bases and Adjuvants**

Various properties of the suppository base can affect drug absorption. The absorption rate is faster from fatty bases having a narrow melting range than from those which have broader melting ranges, absorption rate increases along with hydroxyl values. The drug absorption from the base is affected by the presence of adjuvants in the formula, varying the rheology of the base at normal temperature i.e., 37°C and also on the amount of dissolution of the active ingredient in the dissolution medium of the dosage form. E.g., the bioavailability of certain hydrophilic antibiotics in lipophilic bases was found to enhance by using salicylates, the release of salbutamol from rectal preparations was enhanced by the utilization of tween 80 (2 percent weight/weight), Sodium lauryl sulphate (0.75 percent weight/weight). Surfactants like tween-20, tween-80, Brij-35 were used to enhance release of chloroquine suppository. The impact of the various polymers on the amount of drug released form the suppositories depend upon the nature of the suppositories base such as the
hydrophilicity and hydrophobicity of the bases. The flow chart of the release of drug from various bases as shown below.

**RELEASE MECHANISM:**
FORMULATION:

Suppositories require three main ingredients.

1. Drug
2. Base
3. Additives
4. Packaging

Drug:

Any pharmacological agent that is either disadvantageously administered using other routes or that treat disorders of lowest bowel (vagina) should be considered via suppository. For suppository formulation active agents can be either solid, liquid or pasty in nature. The dimensions of the particle play an substantial role in the preparation of suppository. Specific gravity plays an important role in formulation consideration. If there is significant difference in the density of the active medicament and excipient, maintaining product homogeneity will require special effort. The problem can be overcome by reducing size, or by increasing product viscosity. Solubility of the drug in the excipient also influences manufacture in several ways. Increased solubility increases the homogeneity but also decreases the release if there is too great propensity of medicament to remain in the excipient.

SUPPOSITORY BASES:

Different substances are being used as a material for the suppository base. Depending on their availability they are utilized as suppositories bases. Various physical and chemical measurement has provided the basis for setting standards for suppository bases.

The standards and specification of suppository bases involves the following.

1) Origin and chemical composition
2) Melting range
3) Solid fat index
4) Hydroxyl value
5) Solidification
6) Saponification value
7) Iodine value
8) Water number
9) Acid value

**Origin and Chemical Composition:**

The composition of base indicates the source of origin like the base is either completely natural or synthetic or semi synthetic products. Tangible or chemical interaction of the base with other constituents may be predicted if the nature and exact composition is known.

**Melting Range:**

As the fatty suppository bases are composite mixture of triglycerides they do not have sharp melting points, therefore it is difficult to conclude the melting point hence melting nature are asserted in terms of range i.e., the minimum point at which the base initiates to soften and maximum temperature at which the base melts entirely. The melting range is determined by utilizing various apparatus such a willey melting point capillary melting point apparatus.

**Solid Fat Index (SFI):**

By the SFI we can illustrate the solidification and melting ranges of fatty base as well as the molding characteristics surface feel and hardness of the base. A base with a sharp drop in solids over a short temperature proves to be fragile if molded instantly. This type of bases requires a reduced differential between mold temperature and mass temperature for easy
molding. Solid fat index determines the suppository hardness at room temperature depending upon the contents of suppository.

**Hydroxyl Value:**

Hydroxyl value represents the amount of potassium hydroxide that would neutralize the acetic acid used to aceylate 1 gm of fat.

**Solidification Point:**

The time required for congealing the base when it is freezed in the mold is called solidification point. If the temperature differences within the melting range and solidification point is 10 °C the time essential for solidification may be decreased by refrigerating to produce a more efficient manufacturing process.

**Saponification value:**

The amount of potassium hydroxide essential to nullify the free acids and saponifying the esters present in the 1gm of fat is an indicator of glycosides and amount of glycosides present.

**Iodine value:**

The volume of iodine reacts with 100gm of fat or alternative unsaturated materials is called as iodine value. The decomposition of materials increases with high iodine value.

**Water Number:**

The volume of water in grams that can be included in 100 gm of fat is exhibited by this value. The water number may be enhanced by incorporation of surface active agent, monoglycosides and other emulsification.

**Acid value:**
The number of milligram of potassium hydroxide essential to nullify the free acid in 1gm of substrate is exhibited by this value. The suppository bases are considered to be best when the acid value are low or absent.

**THE IDEAL PROPERTIES OF A SUPPOSITORY BASE**

The ideal properties of a suppository base may be described as follows.

1) Having reached equilibrium crystallinity, the majority of component melts at rectal temperature but bases with higher melting ranges may be employed for eutectic mixtures.

2) The base must be completely nontoxic and nonirritant to sensitive and inflamed tissues.

3) Suppository base should be adaptable with broad variety of drugs.

4) Bases should not have meta stable forms

5) Suppository bases should shrink sufficiently on cooling to release itself from the mold without the need of mold lubricant

6) It must be nonsensitizing

7) Suppository base should have good wetting and emulsifying effects

8) It must have water number so that high percentage of water can be incorporated in the suppository

9) Selected suppository base should be durable when stores for a long span of time and should not change colour, odour and drug release forms.

**Types of Suppository Bases:**

Suppositories bases on the basis of composition fall in three categories.

1. Natural bases e.g., theobroma oil (cocoa butter), agar, mango seed fat, gelatin.
2. Synthetic bases e.g., polyethylene glycol, hydrogels (HPMC, PVP)

3. Semisynthetic bases e.g., Novatta, suppocire, wecobee, etc.

**Natural Bases**

- Theobroma oil (cocoa butter) 23 Theobroma oil is the solid fat obtained from roasted seeds of theobroma cocoa.
- Appearance: Yellowish white, solid fat, odour agreeable and resembling that of cocoa.
- Solubility: Freely soluble in chloroform, in ether and in petrol (boiling range 40 to 60ºC), slightly soluble in ethanol.
- Melting point: 31ºC to 34ºC.
- Saponification value: 188 to 196.
- Acid value: Not more than 4.0
- Applications: As suppository base.

**b) Hydrogenated Vegetable oils**

- Hydrogenated vegetable oil is derived from palm, palmkernel and various other oil producing plant, which is composed of triglycerides, glyceryl monostearate and polyoxy stearate
- Needs no special storage conditions
- The lubrication of the mould is not necessary as it posses good mould release characteristics.
- Melting point 35-37ºC
- Specific gravity 0.890 at 37ºC
• Water insoluble
• Application as Suppository base

**Polyethylene glycols** \(^{24,25}\)

Synonyms: PEG, carbowax, borox PEG, macrogols.

Polyethylene glycol is a derivative of ethylene oxide in water, chemically represented as \(H(O-C-H_2 C-H_2)_n -OH\) where ‘n’ is the mean number of oxy-ethylene.

<table>
<thead>
<tr>
<th>Type of macrogel</th>
<th>Viscosity(cps) ((100^\circ C))</th>
<th>Freezing point (\left({}^\circ C\right))</th>
<th>Hydroxyl value</th>
<th>Density ((g/cc))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 1000</td>
<td>20.4 – 27.7</td>
<td>35 – 40</td>
<td>107 – 118</td>
<td>1.080</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>102 – 158</td>
<td>53 – 59</td>
<td>25 – 32</td>
<td>1.080</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>185 – 250</td>
<td>55 – 61</td>
<td>16 – 22</td>
<td>1.080</td>
</tr>
</tbody>
</table>

**Agar** \(^{26}\)

• Agar consists of polysaccharides from various species of rhodophycae family belonging to the genus Geladium.

• Appearance: Odourless, colourless to pale yellow translucent strips, flakes and powder is tough when damp and becomes brittle when dried.

• Solubility: Insoluble in cold water and soluble in hot water.

• Swelling index: The swelling index should not be less than 10 and is within 10% of value stated.

• pH: It is stable from pH 3 to 11.
• It is commonly used in enteral and topical pharmaceutical preparations

Glycerin (Glycerol) $^{27}$

• Glycerin is a achromic, syrupy and odor free liquid
• It gives initially a Sweet taste latter produces the sensation of warmth.
• Completely dissolves in aqueous medium and in alcohol but completely insoluble in solvent chloroform and in di ethyl ether and in fixed oils.
• used as a pharmaceutical aid.

Gelatin $^{27}$

• Description: achromic or pale yellowish translucent sheets/ flakes.
• Odor and taste: Very slight.
• Gelatin is insoluble in cold water but swells and softness when immersed in it gradually absorbing from 5 to 10 times its own weight,
• Soluble in hot water, insoluble in ethanol, chlorofrom and in solvent ether.
• Incorporated as encapsulating agent, diffusing agent, binding and coating agent.

Additives

The rheological characteristics of the suppository bases at normal temperature can be affected by presence of adjuvant in formulae or by affecting the dissolution of the active ingredient in media of the dosage form. Some of the additives which can be used in suppository are:

Polyvinyl pyroldine (PVP) $^{28}$:

• Molecular weight: 10,000 to 700,000.
• PVP is odorless, tasteless, white colored fibrous or granular particles.

• completely dissolved in solvents like water, ethanol, chloroform and propanol.

• It is used in the preparation of solid dispersions, binder in tablet coating agent, dispersing and suspending agent

**Hydroxypropyl Methyl Cellulose (HPMC)**

• Chemical Name: Cellulose-2-hydroxypropyl methyl ether.

• Description: HPMC is an odor free and flavor less white or creamy white colored stringy or coarse powder.

• Molecular Weight: Approximately 10000 – 1500000.

• Application: Pharmaceutical aid.

**Sodium-carboxymethylcellulose (Na-CMC):**

Na-CMC is the sodium salt of a moderately displaced poly (carboxy-methyl) ether of cellulose.

• It is almost white, granular, odourless and hygroscopic in nature.

• Sodium CMC is insoluble in acetone, ethanol, solvent ether and in toluene.

• It is as suspending agent, viscosity increasing agent.

**ABSORPTION PROMOTING AGENTS (ADJUVANTS):**

Drug with low bioavailability like antibiotic and having high molecular weights are well administered through rectal route and or by various sophisticated drug delivery systems. Most of the ionic surfactants such as sodium lauryl sulphate, and chelating agents like sodium-ethylene diamine tetra acetic acid are harmful to the rectal mucosa. Hence nutrients like lipids are employed safely as a promoting agent. Lipids are water insoluble in nature; un harmful adjuvants are
employed for making the lipids soluble. Aminoglycoside such as streptomycin and cephalosporins like cefazoline are selected as drugs with low water sorption along with soluble adjuvant.

The mono olein taurocholate mixed micelles concentration is necessary to enhance the sorption of heparin from the colon.

The rectal bioavailability of sodium cefmetazol, cefoxitine, penicillin-K may be improved by the addition adjuvants like sodium 5-methoxy salicylate

Now-a-days polypeptide hormone such as erythropoietin is delivered by parenteral route due their poor diffusivity through a membrane without an promoting agent, erythropoietin developed by recombinant technology is not absorbed from the rectal mucosa. Therefore glycolates and salicylates of sodium is used to enhance the absorption rate of erythropeoitin from rectal mucosa, The bioavailability of erythropoietin after rectal administration was more by 1.2 percent by utilizing five percent sodium salicylate as compared to intravenous administration.

**METHOD OF FORMULATION**:31

The following methods are used for the preparation of suppositories

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

1. **Hand Molding:**

One of the most premier and easiest method for preparing suppository is hand rolling method and is commonly used for preparing suppositories containing cocoa butter as base. In this the base is first minced and then blended with active ingredient in a mortar, until the resultant product is plastic and thoroughly blended. The active ingredient are usually finely
powdered, or dissolved in water, or sometimes blended with little quantity of wool fat to help incorporation with suppository base. The blended mixture is then rolled into a cylindrical rod of desired length and diameter of intend weight. The rod is sliced into portions, and then one end is pointed. This method is practical and economical for the manufacture of small number of suppositories.

2. **Compression Moulding:**

A more uniform and pharmaceutically elegant suppository can be made by compressing the cold grated mass into a desired shape. A hand turned wheel pushes a piston against the suppository mass contained in a cylinder, so that the mass is extruded into moulds. The cold compression method is simple and results in more elegant appearance than does hand molding. It avoids the possibilities of sedimentation of the insoluble solids in suppository base, but is too slow for large scale production. One of the major disadvantages in the use of cold compression technique for molding fat type base suppositories is air entrapment.

3. **Fusion molding or Pour Molding**

The most frequently used method for the developing suppositories in both laboratory and industry is the molding technology. First the base material is melted, preferably on a water bath to avoid overheating, and then the active ingredients are either emulsified or suspended in it. Finally, the mass is poured into cooled metal moulds, which are usually chrome or nickel plated.

**PACKAGING OF MOLDED SUPPOSITORIES:**

The most important aspect of the suppositories are the storage and packaging. Suppositories must be packaged so that each suppository is over wrapped or suppositories should
be kept in container in such a way that they should not come in contact with each other. Staining, brakage or deformation by melting caused by jostling or adhesion can result from poor wrapping and incomplete or improper packaging. As the direct contact of suppositories with each other impaires by fussion resulting from change in ambient temperature, due to this the suppositories are partially melted and stain the outer package. Thus to prevent staining suppositories are to be over wrapped or wrapped with other materials, which avoids the contact of suppository with the outer container. Therefore usually suppositories are packed in tin or aluminium foil in some instances plastic and papers are also used. Various methods are employed for over wrapping of the suppositories, the commonly used methods are by hand and by machine. The later process is slow and yields a integrant product. By using the modern packaging machine the above problems can be overcome. Most of packaging machine are capable of packaging/wrapping uniformly about 8000 suppositories per hour. Many suppository are not individually wrapped, in such cases they are placed into cardboard boxes or plastic containers. That have been molded to provide compartments for 6 to 12 suppositories, individually suppositories are usually packed in slide and folding boxes. The hygroscopic and volatile ingredient of suppositories requires glass or plastic containers. The glycerinated gelatin suppositories are packed in a well sealed container.

**IN PACKAGE MOULDING:**

In this era of advance technology automated suppository manufacturing machines are gaining importance for packaging of suppositories directly in their wrapping material. Machines utilizing thermoform the mould and fill the mass into previously thermoform moulds. Machine using aluminium foil/propelling/lacquer laminate emboss to alongside strips of foil so that when they are packed together, moulds are formed. Disposable mould have the additional advantage of
being suitable for suppositories, intened for tropical climates. If the mass should melt at the high storage temperature, the mould still retains in its proper shade. So that upon cooling it can be dispenced without distortion.

**APPROACHES TOWARDS FORMULATING SUPPOSITORY BASES:**

As a formulator one has to consider the following approaches.

1) Is the medication intended for local or systemic use.

2) Desired site of application such as rectal, vaginal or urethral.

3) What kind of effect is intended, ie quick/slow and prolonged.

**PRIMARILY THE SUPPOSITORY BASES ARE EVALUATED FOR THE FOLLOWING.**

1) Determination of availability of drug from the suppository in water.

2) Should be evaluated in for the stability of both the base containing drug and the ingredient, at 4°C and room temperature.

3) Selection of suppository bases depending upon the stability, ease of moulding and release from the manufacturing equipment.

After all the above parameters are established, toxicity and drug availability are determined in animals.

Suppositories are classified into two, depending upon the desired effects such as.

1) Suppository for systemic effect

2) Suppository for local effect.

**Suppository for systemic effect:**

In the formulation of suppository the selection of base is very important. The selection of base should be such that in which the drug should be homogeneously dispersed and should
be able to liberate the drug at the predetermined rate to the aqueous body fluid surrounding the suppository. The solubility of the active ingredient should be well known depending upon the solubility of drug, the base is selected i.e. if the drug favors water a faulty base with low water number is desirable on the contrary, if the active ingredient is highly fat soluble a water – type base is desireable. In addition to enhance the solubility the surfactants are used. Most of the suppository formulation are moulded in laboratory and stored at room temperature (25±3 °C) for at least 3 days before undergoing in vitro testing.

Suppositories for local effect:

The suppository formulations intended for local effect. It usually contains non absorbable drugs such as haemorrhoidal, local anaesthetic and antiseptics. For these kind of suppository formulation non absorbable base are preferred, which are slow in melting and slow in drug release. Local effects are generally delivered within a half hours and last at least 4 to 6 hours. The suppository that does not release within 6 hours test period will not release the drug completely and cause discomfort to the patient.

SPECIFIC PROBLEMS IN FORMULATING SUPPOSITORIES:

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

1) Water in suppositories
2) Hygroscopicity
3) Incompatibilities
4) Viscosity
5) Brittleness
6) Density
7) Volume contraction
8) Lubricant or mould release agent
9) Weight and volume control
10) Rancidity and antioxidant.

**Water in suppositories:**

The use of water should be avoided as a solvent for incorporating substances in suppository bases for the following apprehensions.

1) Water accelerate the oxidation of fats.
2) Evaporation of water causes the crystallization of dissolved substances.
3) If water is present at a higher concentration than that require for dissolving the drug, the water has little effect on drug absorption. The rate of absorption from suppositories containing water increases only if an oil in water emulsion exist.
4) The presence of water in suppository result in the possible interaction between the ingredient contained in the suppository to avoid these problems anhydrous bases are used.
5) Bacteriostatic agents such as parabens are incorporated in the formulation to avoid the fungal growth and contamination.

**Hygroscopicity:**

The use of hygroscopic ingredients such as glycerine and gelatin. In suppository formulation it loses moisture by evaporation in dry atmosphere and absorb moisture under condition of high humidity. Polyethylene glycols are also hygroscopic in nature but the rate of moisture change in PEG depends not only on the humidity but also chain length of the molecule, as the chain length increases the hygroscopicity decreases.

**Incompatibilities:**
PEG bases are found to be incompatible with silver salts, tannic acids and sulfonamides. Most of the chemical have the tendency to crystallize out of PEG. Higher concentration of salicylic acid softens PEG to an ointment like consistency and aspirin complexes it.

**Viscosity:**

In the manufacture of suppository and its behaviour in the rectal region after melting depends upon the viscosity of the suppository mass. Therefore for suppositories made with low viscosity bases extra care should be taken to avoid sedimentation of suspended particles. To avoid the segregation of particles suspended in the molten base the well mixed molten mass must be handled at the lowest temperature necessary to maintain fluidity, constantly stirred without entrapping air and quickly solidified in the mold. The given below approaches may be taken to overcome the problems caused by low viscosity base.

a) Narrow melting range bases should be used.

b) 2% aluminium, monosterate used in the formulation increases the viscosity of the fatty base, and also aids in maintaining a homogenous suspension of insoluble material.

**Brittleness:**

Synthetic fatty bases which have a high degree of hydrogenation and stearate contents are brittle when compared to the cocoa butter suppositories, which are elastic in nature and do not fracture readily. Fracturing of the suppositories prepared with such bases is often induced by rapid chilling of the melted base in an extremely cold mould. To overcome the problems of fracturing and brittleness. The temperature difference among the melted base and mould should
be as low as possible. The brittleness of suppositories can be avoided by using the small amount of tweens, castor oil, propylene glycol etc.

**Density:**

The volume of mould cavity is fixed depending on the density of the mass. The knowledge of suppository wt can be obtained from a given mould, and density of the chosen base, the active ingredients can then be added to the bulk base, in such an amount that exact quantity of drug is present in each moulded suppositories. Density alone cannot be the criterion for the calculating suppository weight per fixed volume mould. Therefore volume contraction must be considered.

**Volume contraction:**

This phenomenon occurs in many melted suppository bases after cooling in the mould. The results are described in following ways.

1) Good mould release:- This is caused by the mass pulling apart from the sides of the mould. This shrinkage facilitates the removal of suppositories from the mould eliminating the need for mould release agents.

2) Contraction hole formation at the open end of the mould. This unwanted effects results in lowered suppository weight and imperfect appearance of the suppository. This type of volume shrinkage can be avoided by draining a mass slightly over its congealing temperature into a mould heated to about same temperature. In volume production using standard mould were adequate control of temperature may not be feasible, the mould is over filled so that the excess mass containing the contraction hole can be scrapped off.

**Lubricants or mold release agents:**
The suppositories from cocoa butter have a tendency to adhere to the suppository molds because of low volume contraction and is difficult to remove from the mold. Therefore various mold release as mold lubricants are used to rectify the problems of cocoa butter suppositories. The agents used are mineral oil, aqueous solution of sodium lauryl sulphate and various silicons, alcohol and tincture of green

**Weight and volume control:**

The amount of active ingredients or drug in each suppository depend on the following.

1. The amount of drug in the bulk
2. The capacity of the mold volume
3. The specific gravity of the base
4. The volume difference among the molds
5. Weight difference among suppositories due to improper manufacturing process.

**Rancidity and antioxidants:**

Rancidity results from the anti oxidation and subsequent decomposition of unsaturated fats into low and medium molecular weight saturated and unsaturated aldehydes, ketones and acid which have stable disagreeable odors the lower content of unsaturated fatty acid constituent in the suppository base the greater the resistance to rancidity.

**EVALUATION**

**Physical Parameters:**

- **Visual Evaluation:** Surface appearance and color can be verified visually to assess the absence of fissure, pit, blooming, exudates and transfer of drug.
a) **Melting Range**: Melting range test are performed to check the physical and absorption characteristics of each manufactured batch.

b) **Liquefaction Time**: It determines the period required for a suppository to liquefy under simulated conditions of rectal mucosa in presence of water at body temperature. This signifies the physical nature of suppository subjected to highest degree of temperature (37°C). Liquefaction time should be no longer than 30 minutes.

c) **Mechanical Strength**: This is the determination of the mechanical force necessary to break a suppository and indicates whether a suppository is brittle or elastic. The Erweka method is used for this test. The mechanical strength in no case should be less than 1.8 to 2 Kg as measured by Erweka method. The tensile strength of suppositories is determined by hardness or breaking test. The tensile strength of suppository asses the ability of suppository to withstand hazards of packaging and transportation.

**Chemical testing:**

**Analytical Testing:**

Investigation of the determination of assay, content uniformity and dissolution parameters of suppository formulation.

a) **Assay**: Four steps are involved in the analysis of active ingredients in a unit dose formulation.

- Preparation of uniform composite.
- Extraction of the drug from the excipients.
- Separation of excipients from the mixture.
- Analysis that selectively quantitates the active components.

b) **Content Uniformity:**
The dose to dose variation can be accomplished by content uniformity in which suppository are randomly chosen to check drug content uniformity as per USP/BP specification.

c) Dissolution Testing\(^{33}\):

The in vitro assessment of product efficacy can be determined by dissolution studies. Under FDA guidelines, dissolution testing is also a requirement for suppository to test for hardness and polymorphic changes of drug substance and base in both control and stability testing. The following methods are used in dissolution testing of suppositories:

- Basket method
- Paddle method
- Beaker method
- Diffusion method
- Dialysis method
- Continuous flow method.

RELEASE MECHANISM:

The liquefaction and softening time of suppository, dispersion of active ingredient and diffusion of drug through rectal mucosa determines the rate release and initiation of therapeutic effect.

The below mentioned relationship gives a broad understanding of the relationship of how the drug is released by utilizing various suppository bases.
**Relationship between drug release-drug-suppository Base**

<table>
<thead>
<tr>
<th>Active ingredient (Drug)- Base</th>
<th>Release Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil soluble active ingredient-Oily vehicle</td>
<td>Retarded rate of release and minimum escaping efficiency</td>
</tr>
<tr>
<td>Hydrophilic active ingredient - Oily base</td>
<td>Faster dissolution rate</td>
</tr>
<tr>
<td>Oil soluble active ingredient – hydrophilic base</td>
<td>optimal dissolution rate</td>
</tr>
<tr>
<td>Hydrophilic active ingredient - Hydrophilic base</td>
<td>slow dissolution rate</td>
</tr>
</tbody>
</table>

For hydrophilic suppositories made from PEG etc., the drug release is by dissolution and for those suppositories made from hydrogels like agar, CMC, etc, the drug release is by diffusion mechanism. For lipophilic suppositories made from cocoa butter etc., the drug release is by melting of the suppository.

The release rate form the rectal suppositories can be considered as mass transport phenomenon involving diffusion of drug from a region of higher concentration in the dosage form to a region of lower concentration in the surrounding environment.

Attempts to drug release from the suppositories have been reported that the mechanism follows in accordance with Higuchi’s equation:\(^{34}\):

\[
Q = Kt^{\frac{1}{2}}
\]

Where

\[
\begin{align*}
Q & = \text{Weight in gm of drug release} \\
 t & = \text{time}
\end{align*}
\]
Thus for diffusion controlled mechanism, a graph of cumulative percent drug released against the $\sqrt{T}$ should be straight line (linearity). The drug release can also be confined to any other order viz., zero or first order process.

**Preformulation Studies:**

As the physical and chemical properties changes with internal structure of the solid drug, including melting point, density, hardness, crystal shape, optical characteristics and vapour pressure, characterization of polymorphic forms and solvated forms involves quantitative analysis of these varying physical land chemical properties. Different methods for studying the solid forms are as follows.

1) Microscopy
2) Fusion Method( Hot stage Microscopy)
3) Differential Scanning Colorimetry (D.S.C)
4) I.R spectroscopy
5) X-Ray powder difraction
6) Scaning Electron Microscopy
7) Thermogravimetry
8) Dissolution or solubility evaluation

**Differential Scanning Calorimetry:**

Differential scanning calorimetry analyze the heat lost or gained occurring due to physical or chemical changes within a sample as part of temperature. DSC involves two types of heat process

1) Heat absorbing process (Endothermic)
Example: Fusion, Boiling, Sublimation, Vaporization, Desolvation, Solid-Solid transition and chemical degradation

2) Heat liberating process (Exothermic)

Example: Crystallization and Degradation

Quantitatively the above process have many application in the pharmaceutical preformulation studies which includes purity, polymorphism, Solvation, Degradation and excipient compatibility.

In order to characterize crystal forms the heat of fusion is obtained from the area under the curve for melting endotherm. The sharp peaks of melting endotherm indicates the relative purity while the broader peaks or curves suggests impurities. The apparent temperature of solid transitions are affected by the heating rates. The most common variable in DSC is the atmospheric temperature which is in contact with the sample. To avoid the variation in DSC caused to atmospheric temperature, continuous nitrogen flow is maintained within the heating chamber. The desolvation of dehydrate species releases water vapour which if not released can cause degradation prior to the melting of the anhydrous form. Initially various atmospheres are tried until the desired thermal process becomes fully understood.

Differential scanning analysis can also be used to quantitate the presence of a solvated species within the a bulk drug sample. DSC is micro technique which depends on thermal process. The considerable variable in DSC includes

1) Sample homgenity
2) Smample size
3) Particle size
4) Heating rate
5) Sample atmosphere

6) Sample preparation

**INFRARED SPECTROSCOPY**

The infrared part of the electromagnetic spectrum is branched the near, mid & far IR regions, as per their relativity to the visible spectrum. The far IR, regions lies between 400-10 cm\(^{-1}\), lying beside the microwave portion, has less frequency therefore can be used for rotational spectroscopy. The mid IR, regions ranges between 4000-400 cm\(^{-1}\) which may utilized to examine the basic vibrations and mixed rotational - vibrational structure. The more frequency near IR, equal to 14000-4000 cm\(^{-1}\) can initiate overtone or harmonic fluctuations.

IR spectroscopy utilizes the fact that molecules have specific energy at which they oscillate or fluctuate analogous to discrete frequencies. These resonant frequencies are analyzed by the shape of the molecular potential energy surfaces, the weight of the atoms and, by the mixed rotating coupling. In order for a vibrational mode in a molecule to be IR active, it must be accompanied with variation in the everlasting dipole. In specific, in the Born - oppenhimer and harmonic examinations, i.e. when the molecular hamiltonan relating to the electronic base state can be related by a harmonic oscillator in the neighborhood of the equilibrium molecular geometry, the resonant frequencies are analyzed by the normal modes relating to the molecular electronic base state potential energy surface. Nevertheless, the resonant frequency can be in a first approach corresponding to the strength of the bond, and the amount of the atoms at either end of it. The frequency of the vibrations can be associated with a specific bond type. Diatomic molecules have only single bond, which may elongate. Complex ingredients have several bonds, and oscillations can be combines, resulting to infrared absorption at particular frequencies that may be related to chemical bands. The atoms in a CH\(_2\) group, commonly found in organic
compounds can oscillate in six different ways: symmetric and anti-symmetric stretching, scissoring, rocking, wagging and twisting.

The IR spectra of a molecule are collected by rendering a beam of IR-light through the molecule. Analyses of the transmitted light depicts how much energy was consumed at each wavelength, which may be done with a monochromatic beam, which varies in wavelength over time, or by employing a FT-IR instrument to determine all wavelengths at once. From this, a transmittance or absorbance spectrum can be developed, indicating at which IR wavelengths the sample absorbs. Analysis of these typical absorption reveals details about the molecular structure of the sample.

This technique works almost exclusively on samples with covalent bonds. Simple spectra are obtained from samples with few IR active bonds and high levels of purity. More complex molecular structures lead to more absorption bands and more complex spectra. The technique has been used for the characterization of very complex mixtures.

**SAMPLE PREPARATION**

- Gaseous samples require little preparation beyond purification, but a sample cell with a long pathlength (typically 5-10 cm) is normally needed, as gases show relatively weak absorbances.
- Liquid samples can be sandwiched between two plates of a high purity salt (commonly sodium chloride, or common salt, although a number of other salts such as potassium bromide or calcium fluoride are also used). The plates are transparent to the infrared light and will not introduce any lines onto the spectra. Some salt plates are highly soluble in water, so the sample and washing reagents must be anhydrous (without water).
Solid samples can be prepared in two major ways. The first is to crush the sample with a mulling agent (usually nujol) in a marble or agate mortar, with a pestle. A thin film of the mull is applied onto salt plates and measured. The second method is to grind a quantity of the sample with a specially purified salt (usually potassium bromide) finely (to remove scattering effects from large crystals). This powder mixture is then crushed in a mechanical die press to form a translucent pellet through which the beam of the spectrometer can pass.

**FOURIER-TRANSFORM INFRARED SPECTROMETERS**

Fourier-transform infrared (FTIR) spectroscopy is based on the idea of the interference of radiation between two beams to yield an interferogram. The latter is a signal produced as a function of the change of path length between the two beams. The two domains of distance and frequency are interconvertible by the mathematical method of Fourier-transformation. The basic components of an FTIR spectrometer. The radiation emerging from the source is passed through an interferometer to the sample before reaching a detector. Upon amplification of the signal, in which high-frequency contributions have been eliminated by a filter, the data are converted to digital form by an analog-to-digital converter and transferred to the computer for Fourier-transformation.

**ADVANTAGES**

FTIR instruments have several significant advantages over older dispersive instruments. The Fellgett advantage is because to an improvement in the SNR per unit time, proportional to the square root of the number of resolution elements being examined. This results from the large
number of resolution elements being examined simultaneously. In addition, because FTIR spectrometry does not need the use of a slit or other restricting device, the total source output can be passed through the sample continuously. This results in a substantial gain in energy at the detector, hence translating to higher signals and improved SNRs. This is known as Jacquinot’s advantage. Strength of FTIR spectrometry is its speed advantage. The mirror is capable to move minute distances quickly, and this, together with the SNR improvements due to the Fellgett and Jacquinot advantages, make it possible to gain spectra on a millisecond timescale. In interferometry, the factor which determines the precision of the position of an infrared band is the precision with which the scanning mirror position is known. By using a helium–neon laser as a reference, the mirror position is known with high precision.