1.0 INTRODUCTION

1.1 Introduction to novel delivery systems

For many years the treatment of an acute disease or a chronic disease has been mostly accomplished by the delivery of drugs using various dosage forms such as tablet, capsules, pills, suppositories, ointments, liquids, aerosols, and injectables. All these are the conventional drug delivery systems. These systems are the primary pharmaceutical products commonly seen in the prescriptions and they will be available as over the counter. The release of these drug delivery system shows significant fluctuation in drug levels in the body. To avoid these several technical advancements have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and the most important one targeting the delivery of drug to a tissue. These are known as novel drug delivery systems and they have revolutionized the method of medication which provides a number of therapeutic benefits.¹

1.1.1 Advantages of novel drug delivery systems

These systems

1. Improves the therapy by increasing the duration of action and reducing the side effects.

2. Increases the patient compliance and provides convenient route of administration.

3. Achieve the targeting of drugs to a specific site which reduces the unwanted side effects and obtain maximum efficacy.

4. Reduces the dose and thus reduces the side effects of drugs.
1.1.2 Types of novel drug delivery systems

There are number of novel drug delivery systems are available\(^2\). They are

1. **Hydrogels**

2. **Colloidal drug carrier systems**
   a) Micelles
   b) Microspheres
   c) Nanoparticles
   c) Liposomes and neosomes

3. **Mucoadhesives**

4. **Transdermal drug delivery**

5. **Ocular drug delivery**

6. **Nasal drug delivery**

1. **Hydrogels**

   Hydrogels are three dimensional hydrophilic polymeric networks capable of absorbing large amount of water or biological fluids. These networks are composed of homopolymers or copolymers and are insoluble because of the presence of chemical or physical crosslinks like entanglements or crystallites. The hydrogels exhibit thermodynamic compatibility with water which allows them to swell in aqueous medium. They are used to control the drug release in reservoir based controlled release system or as carriers in swellable and swelling control release devices\(^3\).

2. **Colloidal drug carrier systems**

   Colloidal drug carrier systems like micellar solutions, vesicle and liquid crystal dispersions, microspheres, nanoparticles, consisting of small particles, ranging from
10nm to 400nm diameter. They show great promise as drug delivery systems. When developing these formulations the aim is to obtain systems with optimized drug loading and release properties, long shelf life and low toxicity.

a) Micelles

Micelles formed by the self assemble of amphiphilc block copolymers in aqueous solutions. The size ranges from 5 to 50 nm. They will provide grate interest in drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelle and transported at concentration that can exceed their intrinsic water solubility.

b) Microspheres

Microspheres are the delivery systems that contain a matrix of the polymer in which the drug in micron size is uniformly dispersed. Microcapsules are those where the drug is coated with the polymer. The microcapsules and microspheres prolong drug release where as microspheres are used for drug targeting.

c) Liposomes and niosomes

Liposomes are a form of vesicles that consists of many or one phospholipid bi layer the polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphillic and lipophilic molecules are solubilised with in the phospholipid bi layer according to their affinity towards phospholipids. Presence of non ionic surfactant instead of phospholipids in the formation of bilayers results in the formation of niosomes.
d) Nanoparticles

The size ranges from 10 to 1000nm. They can absorb and encapsulate a drug thus protecting it from chemical and enzymatic degradation. The nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. Nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers will be formed from both biodegradable and non biodegradable polymers. They will provide massive advantages regarding drug targeting, delivery, and release\(^6\).

3. Mucoadhesive systems

Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and mucin molecules. They can adhere to the gastric mucosa or the buccal mucosa. This concept has altered the possibility that these polymers can be used to overcome physiological barriers in long term drug delivery. This mucoadhesive drug delivery system gives more effective and safe treatment not only for topical disorders but also for systemic problems\(^7\).

4. Transdermal drug delivery

Transdermal drug delivery is the administration of drugs across the skin. If the skin is the site of action then high concentration of drugs can be localized at the skin, which results in reducing the systemic drug levels and also reducing the systemic side effects. It is an alternative route for the delivery of systemically acting drugs. This route has several advantages when compared with oral drug administration. It bypasses the lever there by the dose is reduced and the side effects are minimized\(^8\).
Chapter 1

Introduction

5. Ocular drug delivery

Ocular drug delivery is one of the most challenging drug delivery systems. This field has improved significantly over the past 20 years. The improvements have largely focused on maintaining the drug in eyes for an extended period of time unlike conventional eye drops.

6. Nasal drug delivery

The nasal route appears to be an alternative to parenterals for administering drugs intended for systemic effects. The nasal route provides rich vascularity high permeable structure for absorption. It avoids hepatic first pass metabolism. Proteins such as insulin are reported to have fast and sustained action when administered through the nasal route.

1.2 Targeted drug delivery systems

The word drug targeting was put forward by Dr. Paul ehrlich. Most of the drugs introduced to clinical medicine produce their effects by interacting with cell and cell membrane related structures and function through concentration dependent, reversible interactions at specific receptor sites. To obtain a desirable therapeutic response the correct amount of the drug should be transported to the site of action with the control of drug input rate. The efficacy of many drugs is limited by their potential to reach the therapeutic site of action. In most cases only a small amount of the administered dose of the drug reaches to the site. While most of the drug is distributed to the rest of the body.

Most of the drugs when administered in conventional or controlled release dosage forms, they will travel freely throughout the body leading to uptake by cells tissues or organs. This distribution of the drug to other tissues is unnecessary, wasteful and causes
severe toxicity. This lack of target specificity can be attributed to the barriers that the body presents to a drug.

When the drug is administered by the parenteral route the problems associated with the gastro intestinal tract are avoided. However deactivation and metabolization of the drug and dose related toxicity is observed. Along with these drawbacks there is no certainty that the drug will reach its desired destination in adequate concentrations.

The site specific drug delivery would not only increase the amount of drug reaching the site but also decreases the amount being distributed to the other parts of the body. Thus a target oriented drug delivery system supplies the drug selectively to its site of action or sites of actions in manner that provides maximum therapeutic activity. For drugs that have a low therapeutic index targeted drug delivery provides effective treatment at a relatively low drug concentrations

**1.2.1 Requirements for targeted drug delivery systems**

1. The delivery system should be biochemically inert, non-immunogenic, physically and chemically stable *in vivo* and *in vitro*.

2. The carrier must be biodegradable or readily eliminated without any problems.

3. The delivery system must be reproducible, cost effective and simple.

**1.3 Approaches to drug targeting**

There are three approaches to drug targeting. The first approach involves the use of biologically active agents that are both potent and selective to a particular site in the body. The second approach involves the preparation of pharmacologically inert forms of active drugs that on reaching the active sites become activated by a chemical or enzymatic reaction. This approach is also called as prodrug approach. The third approach
involves the delivery of the original drug by specially designed drug delivery system this approach utilizes a biologically inert macromolecular carrier system that directs a drug to a specific site in the body where it accumulates and produces a response.

1.3.1 Drug-carrier delivery system for drug targeting

The basic rationale behind using carriers in intravenous application is that the drugs included in the system gets distributed according to the properties of the carrier therefore the carrier is expected to seek out the preferred site and the drug is directed to the site of action for this action the particulate carrier must have access to the site of drug action and be able to avoid interactions with other sites within the body.

Some ideal properties should be present for a particulate carrier.

1. Prolong the drug effect by giving a longer circulation time.
2. Increase the drug concentration at the required site of action.
3. Reduce the drug toxicity in the tissue.
4. Protect the drug from metabolism and immune system until it reaches the target site.
5. Confine the drug delivery system to the anatomical compartment by selecting an appropriate particle size.
6. Interact selectively with the cells of the target site.
7. Retain the drug within the particle while in transit and release the drug at the target site at the appropriate rate.
8. Delivery the drugs to the appropriate phagocytic cells by participating in adsorptive endocytosis.
Various mechanisms are present for the drug carrier delivery system to transport the drug only to the target site.

They are

1. **Passive targeting.**

2. **Inverse targeting.**

3. **Active targeting.**

4. **Double targeting.**

1. **Passive targeting.**

   The targeting occurs because of the body’s natural response to physicochemical characteristics of the drug or drug carrier system. It is a passive process that utilizes the natural course of biodistribution of the carrier system through which it eventually accumulates in the organs of the body. The ability of some colloids to be taken up by the reticuloendothelial system especially in the liver and spleen has made them ideal vectors for passive targeting of drugs.

2. **Inverse targeting.**

   It is the reversion of the biodistribution of the carrier. The method essentially avoids passive uptake of carriers by reticuloendothelial system. This effectively leads to the reversion of the biodistribution of carriers and hence the process is referred to as inverse targeting. One strategy used to achieve inverse targeting is to suppress the function of reticuloendothelial system by pre injecting a large amount of blank, colloidal carriers such as dextron sulphate. This approach leads to reticuloendothelial system blockade and results in impairment of the host defensive system.
3. Active targeting

Active targeting exploits the modification or manipulation of drug carriers of drug carriers to redefine their bio fate. The natural distribution pattern of the drug carrier composite is enhanced using chemical, biological and physical means so that it approaches and is identified by particular bio sites. Facilitation of the binding of the drug carrier to target cells by using ligands or engineered homing devices to increase receptor mediated localization and target specific delivery of the drug is referred to as active targeting.

Active targeting is of two types a) Ligand mediated

b) Physical targeting

a) Ligand mediated

The targeting components are bioconjugates which are called as ligands. Ligand mediated active targeting can be achieved by using specific up take mechanism such as receptor dependent up take of natural, low density lipoprotein particles and synthetic microemulsions of partially reconstituted lipoprotein particles coated with apoproteins. The apoprotein coat serves as a ligand for the lipoprotein receptors expressed in the body.

b) Physical targeting

Selective drug delivery that is programmed and monitored at the external level with the help of physical means is referred to as physical targeting. In this targeting some characteristics of the bio-environment are used either to direct the carrier to a particular location or to pass the selective release of its content. The release of the drug from temperature sensitive liposomes in the vicinity of a tumor is brought about by serum components mostly lipoproteins which at phase transition induce the release of the
entrapped drug. Alternatively the application of and external magnetic field has been suggested for localization of liposomes and microspheres with in a preselected capillary bed.

4. Double targeting

It is a combination of spatial control and temporal control of drug delivery. The temporal control of drug delivery has been developed in terms of controlled drug release. Spatial control has been developed in terms of drug targeting. This approach may bring about improvement to the therapeutic index by a combination of a spatially selective delivery and a preferable release pattern for a drug like zero order release. When these two methodologies are combined it is called as double targeting.

1.4. Introduction to nanoparticles

The most challenging goal in recent times, in the research of delivery of drugs is the formulation of nano systems which reaches to the specific sites of the body at right amount in right time\textsuperscript{12-17}.

Nanoparticles have gained a very important role in novel drug delivery systems. They have a immense role in targeted drug delivery with long shelf life and able to entrap plenty of drugs which can cross the intestinal epithelium more better than the other types of dosage forms. According to Desai et al, more number of nanoparticles were crossed the intestinal epithelium than microspheres. Nanoparticles with polymers especially biodegradable and biocompatible polymers are widely used as carriers for drug delivery which will adsorb as such in the gastrointestinal tract after administration by oral route.
As these are having unique particle size and surface characteristics, they became a platform for carrying the low molecular and macromolecular drugs for the treatment of different diseases.

These particles of nano size are having desirable size distribution, drug carrying capacity and all tunable characteristics, they became an upcoming treatment option for cancer. Some of the nano structures will give response to biological properties, called as intelligent nano particle, which encourages the release of drug in control manner at targeted site. Generally the site where the tumor develops is having abnormal pH profiles and pathophysiology. Such type of sites requires localized release of drug. In this regard the above type of nano structures will play an important role in targeting the infected site. The colloidal structures like NPs are able to penetrate the Blood Brain Barrier (BBB) which is formed by tight junctions (TJ) of endothelial cells. Due to these TJs many drugs like anticancer, antibiotic and peptide drugs are unable to penetrate the BBB. Not only the penetration, the NPs modify the drug distribution in the body. According to Karsten Ulbrich et al Drugs like loperamide, dalargin, kyotorphin, tubocurarine, and doxorubicin crossed the BBB.

So, all these excellent properties of nano structures are possible by biodegradable polymers. The polymeric materials created its own importance in medical field like medical device and artificial organ implantation, in optholmology, dentistry and bone repair and most importantly in designing of drug delivery systems. Nanoparticles with these polymers can be prepared from natural or synthetic macromolecules like polycyanoacrylates, gelatin, serum albumin, poly acids, and most recently introduced and widely used one is chitosan.
The polymer chitosan is not harmful toxicologically because it is degraded by the bacteria present in the colon. Along with this advantage it is having less cost, so it gained its widespread usage in most of the pharmaceutical formulations.

1.4.1 Chitosan a biocompatible polymer

Chitosan is a linear polyaminosaccharide which is polycationic biopolymer, degraded by lysozyme a human enzyme. It is vividly available next to cellulose. It is obtained from a component from chitin by a chemical process called alkyl deacetylation. Chitin is the important component of protective layers (cuticle) of crustaceans like crabs, prawns, shrimps, lobsters. It is also available in the cell walls of Aspergillus, a fungus. It consists of a single polymer with β-(1, 4)-linked N-acetyl-glucosamine units. But the polymer chitosan has one primary amino acid with two free hydroxyl groups for each homopolymer. This biologically degradable polymer has many more applications and can be used in the formulation of powders, gels films, sponges, gastro retentive tablets and colloidal systems like nanoparticles\textsuperscript{18-20}.

Reasons for the wide spread usage of chitosan:

- The first and foremost reason is, it is a biocompatible and biodegradable polymer
- Metabolized by enzymes available in the human body, which decreases the risk of toxicity
- It opens the tight junctions of the epithelial cells, so acts as penetration enhancer.
- Increases the retention time of the drug in the GIT at physiological pH as it acts as bioadhesive
- Having the characteristic of wound healing and also stops the growth of the bacteria (bacteriostatic).
- Its availability is rich and low cost
- \( \text{CO}_2 \) removal (Dilute HCL, washing)
- Hydrogels contains chitosan as one of the main component

1.4.2 Chitosan production

**Chitin** (Major source e.g. cuticles of crustaceans, especially shells of shrimp and crab and other byproducts of the food industry, and the exoskeletons of cephalopods)

- **Co\(_2\) removal (Dilute HCL, washing)**
- Demineralization and deproteinization of crustacean shells using highly concentrated solutions of sodium hydroxide
  - (Under high temperature)
  - Washing (NaOH, Washing)
  - Organic solvent treatment, repetitive washing
  - (Pigment removal)
  - NaoH treatment for De acetylation

**Chitosan**
1. Chitin mainly separated from cuticles of crustaceans, especially shells of shrimp and crab and other byproducts of the food industry, and the exoskeletons of cephalopods by N-deacetylation of chitin.

2. N-Deacetylation of chitin was prepared utilizing high concentrated aqueous or an alkali of alcohols, alkalis includes sodium or potassium hydroxide.

3. The temperature was set at 100 to 150°C for a period of 1 to 5 h under heterogeneous condition.

4. This process results in 70% deacetylation.

5. To increase the degree of deacetylation the procedure of deacetylation was repeated.

6. But due the repeated deacetylation there is decrease in molecular weight appears due to decrease in polymer chain was observed.

7. Sodium thiophenolate will be used widely in order to avoid catalysis as a replacement of NaOH.

Chitosan is a weak base insoluble in water and organic solvents\textsuperscript{21-30}. Chitosan is a weak base and is insoluble in water and organic solvents, however, it is soluble in dilute aqueous acidic solution (pH < 6.5), which can convert the glucosamine units into a soluble form (R–NH\textsuperscript{3+})
In the medical field majorly it has application in gene delivery, tissue engineering, enzyme immobilization. Chitin is the most attainable compound in the universe after cellulose, containing nitrogen.

1.4.4 Chitosan has many benefits for developing nano and microparticulates as a drug delivery system.

1. It can be used in preparing platform for gene drug delivery

2. Chitosan solubility in slightly aqueous acidic solutions avoids use of organic solvents during the fabrication of particulate systems.
3. At low pH value the amino group is protonated which permits ionic crosslinking with multivalent anions e.g: Sodium tripoly phosphate, Calcium chloride e.t.c.

4. Mucoadhesive properties also grants the ability to provide the release of active agent such as convert growth factor - β1.

1.4.5 Chitosan as a drug delivery tool:

Initially chitosan was tested for its efficiency for the delivery of drugs. Yaowalak Boonsongrit et al., used three model drugs (Diclofenac sodium, Insulin, Salicylic acid) developed microparticles and nanoparticles based on ionicgelation technique using sodium tripoly phosphate as crosslinking agent.

Eve Ruel-Garie´py et al., developed thermo sensitive gels developed using paclitaxel for the local delivery for the treatment of breast cancer. The prepared injectable controlled gel forming paclitaxel hydrogels is proven to quite efficient in preclinical studies.

a. Methods of preparation of nanoparticles

Several methods are used to manufacture the nanoparticles. All these methods allow extensive modulation of their structure, composition and physicochemical properties. The selection of the suitable method depends on materials used and the solubility properties of the drug.  

The first and foremost method is polymerization method which is a traditional one. But the polymerization based methods are having more number of drawbacks and limitations.
They are

1) Nanoparticles formulated by polymerization have less biodegradability properties.

2) It is not easy to find out the molecular weight of the resulting polymerized materials because of multicomponent nature of the polymerization media.

3) Drug activity will be inhibited. This was due to interactions with activated monomers or H\(^+\) ions present in the polymerization process.

4) Toxic residues will be formed and the elimination of these residues is a time consuming process.

To avoid these limitations which are resulted from natural polymers, synthetic preformed polymers are used.

The preparation methods using synthetic preformed polymers includes

1. Solvent emulsification evaporation method

2. Salting out method

3. Emulsification diffusion method

4. Spontaneous emulsification, Solvent diffusion method

5. Solvent displacement method

1. Solvent emulsification evaporation method

This method was patented by wanderhaff et al., in this technique the preformed polymer and the drug are dissolved in water immiscible organic solvent. This is emulsified in an aqueous solution containing a stabilizer. This crude emulsion is then exposed to a high energy source such as an ultra sonic sonicator or passed through homogenizer, colloidal mill or micro fluidizer to reduce the globule size. The subsequent
removal of the organic solvent by heat and vacuum results in the formation of a fine aqueous dispersion of nanoparticles\textsuperscript{35-36}.

**Mechanism**

The homogenization step is the key factor in obtaining nanoparticles the emulsification of oil and water by mechanical shear produces a droplet of size 2 µm to 5 µm on the other hand the diffusional motion of water immiscible solvents in to the aqueous phase is slow and once the limiting concentration for polymer precipitation is reached, phase separation occurs from the interface. Thus each emulsion droplets forms one polymer nanoparticles when the solvent is removed.

**Schematic representation**

![Schematic representation of the process](image-url)
2. Salting out

This was patented by Bindschadler et al. This method was subsequently adapted and optimized by allemann and leroux. It is based on the separation of water miscible solvents from aqueous solution through a phenomenon called salting out. Generally acetone is selected as the water miscible solvent because of its solubilising property and its well known separation from aqueous solutions by salting out method. The polymer and the drug are dissolved in acetone and it is emulsified under magnetic stirring in an aqueous gel containing the salting out agent (Magnesium acetate or Magnesium chloride) and stabilizer. The emulsion which is obtained from above process is diluted with a sufficient volume of water. This will improves the diffusion of acetone in to the aqueous phase. This diffusion process indicates the formation of nanoparticles.

Mechanism

Diffusion of acetone in to aqueous solution is the key step. This diffusion takes place due to dilution with excess water. It creates interfacial turbulence leading to polymer aggregation in the form of nanoparticles.

Schematic representation
3. Emulsification diffusion

It is a modification of salting out method which avoids the use of salts and hence the more purification occurs. In this method a partially water soluble solvent is used which is previously saturated in water. This saturation provides the initial thermodynamic equilibrium of both liquids\textsuperscript{38-39}. The polymer is dissolved in water saturated solvent to form a organic phase. This organic phase is emulsified under vigorous agitation in aqueous solution containing the stabilizer. The addition of water to the system results in the diffusion of solvent in to the external phase followed by the formation of nanoparticles.

**Mechanism**

Each emulsion droplet reduces numerous numbers of nanoparticles which are formed by interfacial phenomenon during diffusion. It is also suggested that nanoparticles also formed because of physicochemical instability given by solvent transport.

**Schematic representation**

```
Organic and Aqueous solution
(Polymer + drug in partially water miscible solvent)

↓

Homogenization

↓

Diffusion of organic solvents

↓

Submicron particles

↓

Purification

↓

Purified nanoparticles
```
4. Spontaneous emulsification, Solvent diffusion method

This method was reported by Niwaa et al., The submicron particles are obtained by mixing the polymeric organic solution in to an aqueous phase with moderate stirring. In this method binary mixture of water miscible organic solvent and water immiscible solvent are used for the preparation of polymeric solution. Nanoparticles are formed by emulsification followed by solvent evaporation\textsuperscript{40-42}.

**Mechanism**

The polymer is dissolved in an organic solvent mixture containing dichloromethane and acetone. These solvents are water immiscible and water miscible solvents respectively. This solution is slowly added to the aqueous solution containing a stabilizer and it is agitated with a magnetic stirrer. Emulsion droplets are formed in the aqueous phase, the acetone quickly diffuses out from each emulsion droplet which reduces the size the solvent evaporation removes dichloromethane and the droplets are solidified to form polymeric nanoparticles.

**Schematic representation**

```
Organic and Aqueous solution
(Polymer + drug in mixture of acetone and dichloromethane) ↓
Diffusion of acetone ↓
Removal of dichloromethane by evaporation ↓
Solidification of droplets ↓
Purification ↓
Purified nanoparticles
```
5. Solvent displacement method

This method was patented by Fessi et al. In this process the polymer and the drug along with a lipophilic stabilizer (Optional) are dissolved in a semipolar water miscible solvents like acetone, ethanol. This solution is injected in to an aqueous solution containing a stabilizer like poloxamers 188 under magnetic stirring. Solvent diffusion occurs fallowed by the formation of nanoparticles these formed nanoparticles are removed from the suspension by heating under reduced pressure\textsuperscript{43-46}.

Mechanism

The interfacial turbulence created during the solvent displacement is the key step in the formation of nanoparticles in this method. Droplets of solvent which is in nanometric size or migrated from the interface in to the solution. The migrated droplets are rapidly stabilized by stabilizing agent until diffusion of the solvent is completed. Simultaneously along with the diffusion polymer aggregation has occurred. In the later stages the formed aggregates will be solidified in to nanoparticles. This process is also called as nanoprecipitation.
Schematic representation

6. Ionic gelation mechanism.

The novel mechanism which involved in the formation of nanoparticles first explained by Calvo et al. As the complexation between positively charged chitosan or macromolecules (polysaccharides) which is a (β-1, 4)-linked D-glucosamine, N- deacetylated derivative of chitin, the most abundant natural polymer after cellulose, constituting the exoskeleton of arthropods and cell walls of fungi and yeast, which is generally represented as a homopolymer. However, the deacetylation process is rarely complete, and most commercial products tend to be a copolymer of N-acetylglucosamine (NAG) and N-glucosamine repeat units and poly anionic molecules such as sodium tripolyphosphate (STPP) or calcium chloride.

Mechanism

Anionic behavior of STPP, molecular weight of chitosan and pH plays important role in the ionically crosslink with chitosan amide group. Due to their sub-
cellular and sub-micron size, can penetrate deep into tissues through fine capillaries, cross the fenestration present in the epithelial lining (e.g., liver and lungs).

**Table: 1.1 Representation of various methods involved in nanoparticles synthesis their advantages and disadvantages**

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent emulsification</td>
<td>Convenient homogenization</td>
<td>1. Induction of chemical reaction occurs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Degradation of nanoparticles occurs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Difficult in scaling up</td>
</tr>
<tr>
<td>Salting out</td>
<td>1. High amounts of polymer and drug can be incorporated</td>
<td>Limited to lipophilic drugs only</td>
</tr>
<tr>
<td></td>
<td>2. Easy to scale up</td>
<td></td>
</tr>
<tr>
<td>Emulsification diffusion</td>
<td>1. Absence of homogenization step</td>
<td>High volume of water to be evaporated</td>
</tr>
<tr>
<td></td>
<td>2. High yield and high batch to batch reproducibility</td>
<td></td>
</tr>
<tr>
<td>Spontaneous emulsification</td>
<td>Easy to scale up in industrial setup</td>
<td>-------no----</td>
</tr>
<tr>
<td>Solvent displacement</td>
<td>1. Simple process</td>
<td>Difficult to choose the drug /Polymer/solvent system</td>
</tr>
<tr>
<td></td>
<td>2. Does not involve homogenization</td>
<td></td>
</tr>
<tr>
<td>Ionicgelation</td>
<td>Easy and simple process.</td>
<td>Limited number of polymers and crosslinking agent</td>
</tr>
<tr>
<td></td>
<td>Does not involve extensive homogenization</td>
<td>Polymers e.g: Chitosan, Sodium alginate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crosslinking agents e.g: Calcium chloride, Sodium Tripolyphosphate (STPP)</td>
</tr>
</tbody>
</table>

**1.5 Suppositories**

Suppositories are solid dosage form of medicament intended for putting into body cavities other than mouth.
They are usually planned for use in the rectum, vagina, and to lesser extent, the urethra. Rectal and urethral suppositories usually operate vehicles that soften at body temperature, whereas vaginal suppositories, sometimes also called pessaries, are also made as compressed tablets that disintegrate in the body fluids. Suppositories vary in their sizes, shapes and weights. Generally suppositories weighing 1 to 2 grams are prepared. Coca butter or glycerol gelatin are commonly used as bases.\textsuperscript{47-49}

Oleum Theobromae was first recommended to American pharmacists by A.B. Taylor in 1852 and it soon grew in popularity as the suppository base of choice. Glycerinated gelatin mixtures did not appear as suppository vehicles until about 1875. In 1913, Bruno Solomon published a critical study of suppository bases, in which he classified them into three broad types.

1) **Cocoa butter**

2) **Fat and wax combinations with cocoa butter, and**

3) **Glycerinated gelatin bases.**

---

**Figure: 1.1. Rectal insertion of suppository**
In the 1930s, several unwanted side effects and disadvantages inherent to oral therapy focused attention, principally in Europe, on the rectal route for administering drugs. Industrial concerns, principally in Germany and France, synthesized special lipid excipients, which were designed to replace cocoa butter. Water-soluble polyethylene glycol type bases were introduced as an improvement on glycerinated gelatin and lipid type suppository bases.

For the combined prescription and over-the-counter market, suppositories represent about 1% of all medication in Europe and South America than in the United States.

1.5.1 Shapes and Sizes of suppository

The suppositories are marked in varying sizes for use in the different body cavities. The common types are:

1. **Rectal suppositories:**
   They are meant for introduction into the rectum and generally weigh 1 or 2 grams. Rectal suppositories are either cone or torpedo shaped.

2. **Vaginal suppositories:** Pessaries are meant for introduction into vagina are either 4 gm or 8 gm size. they are generally cone or wedged shaped.

3. **Urethral bougies:** They are intended for introduction into the urethra and are thin and cylindrical. Their weight is usually 1 gm and length regarding 8 cms.

4. **Nasal bougies:** They are intended for insertion into nasal cavity and are about 9 to 10 cms long and about 1 gm in weight. These bougies are always made with gelato-glycerin base.
1.5.2 Therapeutic Uses

Drugs may be administered in suppository form for either local or systemic effects. Such action depends on the type of the drug, its concentration, and the rate of absorption. Emollients, astringents, antibacterial agent, hormones, steroids, and local anesthetics are dispensed in suppository form for treating local conditions of the vagina, rectum, or urethra.

Many articles have been published recently on the use of prostaglandin containing vaginal suppositories for interruption of early pregnancy. Rectal suppositories are primarily intended for the treatment of constipation and haemorrhoids. Suppositories are also used rectally for systemic use. Rectal suppositories are also utilized for systemic actions in conditions where oral medication would not be retained or absorbed properly, such as during severe nausea and vomiting or in paralytic illness.

1.5.3 Medicaments are prescribed in suppositories for three reasons:

a) To Exert a Direct Action on the Rectum

Most suppositories in this group are used to relieve the pain and irritation of haemorrhoids. They contain local anaesthetics such as cinchocaine and benzocaine, astringents such as bismuth subgallate, hamamelis extract and tannic acis, and anti inflammatory agents such as hydrocortisone and its acetate, which are of powder in some products.

Eg: Hamamelis and Zinc Oxide suppositories B.P.C.

Compound Bismuth Subgallate suppositories B.P.C.
These provide protection to inflamed areas.

b) **To Promote Evacuation of the Bowel**

Some laxative drugs like glycerol and bisacodyl exert their effect by irritating the rectum. They produce mechanical action on the lower bowel and facilitate evacuation in the treatment of anal irritation, constipation etc. They cause irritation to the mucous membrane of the rectum or by lubrication cause evacuation. The glycerin suppositories are a representative example of evacuant suppositories.

c) **To Provide a Systemic Effect**

In the U.K., rectal systemic therapy is used for comparatively few drugs. The official examples are amilophylline, which by relaxing involuntary muscles gives relief to asthmatics and chronic bronchitis, morphine, a powerful analgesic and anti-inflammatory actions of which are helpful in relieving the pain of arthritis, rheumatism, gout and skeletal diseases. They are often administered at bed time to give relief during the night. On the European mainland, and particularly in France and Italy, suppositories are much popular than in the U.K. and antibiotics, antihistamines, hormones and tranquilisers are among the additional drugs prescribed in this form.

**Systemic therapy by the rectal route is of special value for:**

a) Therapy to patients who are involuntary, mentally interrupted or not capable to indulge oral medication because of vomiting or pathological requirement of the alimentary tract

b) Managing drugs, of similar kind aminophylline, that causes gastric irritation and

c) Treating infants.
Pessaries are used mainly for vaginitis (inflammation of vagina) and leucorrhoea (unpleasant discharge of vagina). Vaginitis may be happened by a variety of microorganisms or by the old age. The medicaments in the official pessaries are:

**The Acetarsol** : an antiprotozoal agent.

**Di-iodohydroxyquinine** : for yeast and protozoal infections.

**Lacticacid** : useful in leucorrhoea.

**Nystatin** : for yeast infections.

**Crystal violet** : for number of microbial infections.

**The Hydragaphen** : for number of microbial infections.

Suppositories are comfortable mode of management of drugs which bother the gastro-intestinal tract, happen vomiting, are damaged by the hepatic circulation, or are damaged in the stomach by pH replace, enzymes, etc. The rectal suppositories are used for lubricating and soothing effect. The lower part of the rectum offers a large absorption surface area from which the dissolvable substances quickly can pass and reach the venous circulation directly and rapid action of the drug is produced. However the rate and extent of absorption of the drugs depends upon the nature of the base in which they have been incorporated. The maximum therapeutic effect is produce if the drug incorporated is in a readily absorbable form. The rectal suppositories act as mechanical aid to bowel evacuation which produces its action by irritating the mucous membrane of the rectum or by lubricating action\(^49\).
1.5.4 Suppositories Classification

1. Rectal suppositories:

These are intended for into the rectum for their systemic use. They are tapered at one or both ends and usually weigh about 2gm. The rectal suppositories intended for children are in smaller size and weight than the adult suppositories. They usually weigh about 1gm.

2. Vaginal suppositories:

They are also known as pessaries and are meant for introduced into vagina. They are larger than rectal suppositories and weight ranges from 3 to 6 gm. The vaginal suppositories may be conical, rod shaped or wedged shaped. They are exclusively used for their local action on the vagina. Special shaped suppositories are manufactured and are supplied with application to facilitate insertion into the vagina. Now a days a few special tablets and capsules, oval or suppository shaped are prepared for use in the vagina and are known as vaginal tablets and vaginal capsules respectively.  

3. Urethral suppositories:

They are also known as urethral bougies and are meant for introduction into the urethra. They are long, thin and cylindrical forms rounded on one end. Their weight varies from 2 to 5 cm. Suppositories of Urethral are used rarely.

4. Nasal suppositories:

They are also known as nasal bougies or buginaria and are intended for introduced into the nasal cavity. They are comparable shape to urethral bougies. Their
weight is regarding 1 gm and length 9-10 cm. They are constantly prepared with glycerol-geltin base.

5. Ear cones:

They are also known as aurinaria and are meant for introduction into the ear. They are very rarely used. Mostly theobroma oil is used as a base, made ready in an urethral bougies mould and cut as required size.

1.6 Newer Concept of Suppositories

Recently some newer concepts of suppositories regarding their formulation and packaging has been introduced which are given below:

1. Tablet suppositories:

Suppositories such as rectal suppositories and pessaries are formulated and prepared by compression like tablets. They contain disintegrating agents like effervescent combinations or starch. Pessaries are generally prepared as almond shape for ease in insertion and to provide a large surface area for disintegration and absorption. Rectal tablets are generally covered with thin layers of materials such as polyethylene glycol for protection and to facilitate insertion into the rectum.

2. Layered suppositories:

These types of suppositories contain different drugs in different layers. Thus the incompatible drugs can be separated from each other. Similarly drugs having different melting points or dissolution characteristics can be incorporated to control the absorption rates. These types of suppositories can be prepared by partially filling the mould with one
type of material, when it congeals then the other materials are added ASA separate layer and allowed to cool\(^49\).

3. Coated suppositories

Suppositories are given coating with materials such as polyethylene glycols, cetyl alcohol, etc., to control their disintegration rate, to impart lubricant properties or to provide protective action during storage, for coating the suppositories are dipped in solutions of coating materials until coats of desired thickness have been obtained and then dried\(^52\).

4. Capsule suppositories:

Soft gelatin capsules of different shapes and sizes are prepared for insertion into the rectum or the vagina. These types of capsules are increasing in popularity. Liquids, semisolids or solids can be filled in such capsules.

5. Packing in disposable moulds:

Previously the suppositories prepared in metallic moulds or by compression method were individually wrapped and supplied in boxes but in recent method the suppositories are directly made in disposable moulds made up of plastic materials or tin foils. The suppository mass is poured into the disposable moulds and cooled, the excess is trimmed off and the moulds are sealed. Then they are packed in cartons. These types of moulds have the advantage that if due to any reason the mass melts it will remain in the mould itself which can be used after cooling.
1.6.1 Suppository Bases

Since suppositories are spherical dosage form of medicament they must retain its shape, solidity and firmness during storage and administration but melt or dissolve in the cavity fluids when inserted into the body cavity. Therefore the materials used as suppository bases must impart these properties and also fulfill other formulation requirements. There are a large number of bases used but the theobroma oil, glycerogelatin base and polyethylene glycols fulfill the requirements.

An ideal suppository base should have the following properties:

- The base should be completely non toxic non irritating to sensitive and inflamed tissue.
- It should be suitable with broad variety of drugs.
- It should not have metastable form.
- It should shrinks sufficiently on cooling to release itself from the mould without the need for mould lubricants.
- It should be non sensitising.
- It should have wetting and emulsifying properties.
• The water number should be high i.e. a high percentage of water can be incorporated in it.

• It is should be stable on storage i.e. does not change color, odor or drug release model.

• It can be manufactured by molding by either hand machine compression or extrusion.

If the base is the fatty it has the following extra necessity

• Acid value should be less than 0.2

• Saponification value should be in the range of 200 to 245

• Iodine value should be less than 7

• The interval between melting point and solidification point must be small or the SFI curve must be sharp.

A suppository base containing all of these properties has not been found. Indeed some of the properties are mutually exclusive and non ideal in all situations, often the addition of the base. Judicious formulation requires the use of the physical values described for they help in the choice of the base for the drug.

1.6.2 Classification of Suppository Bases

There are three types of suppository bases.

1) Oily bases
2) Water soluble and water miscible bases

3) Emulsifying bases

Oily Bases

a) Emulsified theobroma oil

Emulsified theobroma oil may be used as a base when large quantities of aqueous solutions are to be incorporated. Several agents have been used to form emulsified theobroma oil suppositories. The use of 5% glyceryl monostearate, 10% lanette wax, 2-3% cetyl alcohol, 4% bees wax and spermaceti up to 12% is recommended for emulsified theobroma oil suppositories.

b) Hydrogenated oils

As a replace of theobroma oil a number of hydrogenated oils like hydrogenated edible oil, palm kernel oil, hydrogenated pea oil, stearin and a mixture of oleic and stearic acids are suggested.

Advantages

(a) Over heating does not affect the solidifying point.

(b) They are resistant to oxidation.

(c) Their emulsifying and water fascinating capacities are pleasant.

(d) Mould lubrication is not required.

(e) They produce colorless, odorless and elegant suppositories.
Disadvantages

(a) On rapid cooling in the refrigerator they become brittle

(b) When melted they are more fluid than theobroma oil and result in greater sedimentation of the added substances.

This difficulty may be overcome by the addition of some thickening agents such as bentonite, magnesium stearate and colloidal silicon dioxide etc.

Macrogols

In addition to their applications in the formulation of ointments, macrogols are suitable as suppository or pessary bases. Commonly mixtures of two or more grades are used.

Advantages

(a) The mixtures usually have a melting point higher than 40°C. Hence, cool storage is not required, they are satisfactory for use in hot climates, and administration is easy because they are not slippery to handle.

(b) Because of this higher melting point they do not melt in the body but gradually dissolve and disperse, freeing their medication slowly and providing longer action than fatty bases.

(c) Their physical properties can be varied by suitable admixture of high and low polymers. High polymers give hard products that disintegrate and release their drug slowly, softer, less brittle preparations that disperse and liberate the drug more
quickly are obtained by mixing high with either medium or medium and low polymers, or by adding plasticers.

(d) Unlike glycerol–gelatin bases, macrogols do not stick to the mould and since they contract significantly on cooling, no lubricant is required.

(e) They absorb water well and have excellent solvent properties.

(f) Products have a clean smooth appearance.

**Disadvantages**

(a) They are hygroscopic and have the consequent disadvantages mentioned under glycerol gelatin. Irritancy is particularly undesirable in a product for soothing inflamed tissues and although discomfort can be reduced by incorporating about 20% of water in the mass or by instructing the patient to dip the preparation in water just before insertion this type of base is more satisfactory for systematically active drugs.

(b) Its good solvent properties can result in retention of the drug in the liquefied base in the body, with consequent reduction in therapeutic activity.

(c) Products sometimes fracture on storage particularly if they contain water. One cause is the high solubility of macrogols which can lead to a super saturated solution in the water and subsequent crystallization, this in turn, makes the mass granular and brittle.

(d) Crystal growth of certain medicaments may occur, particularly if they are partly in solution an partly in suspension in the base, in addition to making the product brittle, the crystals may be irritating and because they are large, take longer to dissolve.
(e) They are incompatible with bismuth salts, tannins and phenol, and liquefaction often occurs in the last two instances. They lower the activity of some antibacterial agents necessitating care in choosing containers.

1.6.3 Manufacture of Suppositories

Manufacture of suppositories is done by following methods:

1) Hand Molding
2) Hot process or Fusion method
3) Cold Compression method

1) Hand Molding

The simplest oldest method of preparing a suppository by hand, i.e. by rolling the well blended suppository base containing the active ingredients into the desired shape. The base is first grated and then kneaded with the active ingredients by use of a mortar and pestle, until the resultant mass is plastic and thoroughly blended. The active ingredients are usually finely powdered, or dissolved in water, or sometimes mixed with a small amount of wool fat to help incorporation with the suppository base. The mass is then rolled into a cylindrical rod of desired length and diameter or into vaginal balls of the intended weight. Starch of talcum powder on the rolling surface and hands prevent the mass from adhering. The rod is cut into portions, and then one is pointed. This method is practical and economical for the manufacture of small numbers of suppositories.
2) Hot Process of Fusion Method

Different types and sizes of suppository moulds were for commercial use. In the dispensary suppository moulds with six or twelve cavities with required size and shape may be utilize. They are prepared up of stainless steel to 500 cavities may be used. They are prepared up of nickel-copper alloy, stainless steel, aluminum or plastic, brass.

Cleaning, lubrication and elimination of suppositories the mould can be unsealed longitudinally by unsealing the screw in the center of the plates. For cleaning, the opened plates are immersed in hot water containing detergent, and then they are washed with water and dried thoroughly. Care must be taken that the inner surfaces of the cavities do not have any scratch otherwise suppositories with uneven surface will be produced.

a) Lubrication of Moulds

Whenever cocoa butter or glycerol-gelatin as a base for the preparation of suppositories it is necessary to lubrication the mould otherwise suppositories with smooth surface will not be obtained because of the sticky nature of these bases which stick to the sides of the mould. The lubrication applied must be of different nature than the base, otherwise it will be absorbed and failure to furnish a buffer film between the suppositories is and the metal of the mould. Therefore an oily lubricant for cocoa butter suppositories and aqueous lubricant for glycerol gelatin suppositories is useless. So a lubricant contain soft soap 10gm, glycerol 10gm and alcohol (90%) 50ml is most suitable for oily bases and liquid paraffin or arachis oil for glycerol gelatin suppositories respectively.
Wherever emulsifying bases or macrogol bases are used there is no need to lubricate the moulds. Products with better surface are obtained if the mould is kept dry.

For lubricating the moulds the lubricant should be with the help of a brush or a swab made of gauze. Cotton wool should not be used because it detaches the fibers too easily. Excessive lubrication of the mould should be avoided, if it happens so, the mould should be closed and inverted on a white tile to drain the excessive lubricant out.

b) Calibration of the Mould

Unless otherwise stated a standard mould of 15 grains or 1 gram capacity is used, but it is not wise to assume that capacity of the mould is correct. Though the size remains same but the weight varies with is change of basses and medicaments. This is due to the change in densities of different basses and medicaments. Therefore the mould must be calibrated for individual base and medicament. This done by preparing a set of suppositories using the base alone, weighing the product and average mean is considered the true capacity of the mould. These values may be recorded for future use.

c) Replacement Dosage Factor

The quantity of base that is displaced by active ingredients in the suppository formulation can be calculated. The replacement factor (F), is derived from the following equation:
\[
F = \frac{100 (E - G)}{(G)(X)} + 1
\]

**Where** \( E \) = Pure base suppositories weight

\( G \) = Suppositories weight \( X \% \) active ingredient

Most commonly used drugs are tabulated by replacement factor, using cocoa butter arbitrarily assigned the value 1 as the standard base:

**Table: 1.2 List of drugs and their replacement factor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boric acid</td>
<td>0.67</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.81</td>
</tr>
<tr>
<td>Mild silver protein</td>
<td>0.61</td>
</tr>
<tr>
<td>Balsam peru</td>
<td>0.83</td>
</tr>
<tr>
<td>Bismuth sub nitrate</td>
<td>0.33</td>
</tr>
<tr>
<td>Camphor</td>
<td>0.49</td>
</tr>
<tr>
<td>White or yellow wax</td>
<td>1.0</td>
</tr>
<tr>
<td>Spermaceti</td>
<td>1.0</td>
</tr>
<tr>
<td>Castor oil</td>
<td>1.0</td>
</tr>
<tr>
<td>Phenol</td>
<td>0.9</td>
</tr>
<tr>
<td>Procaine hydrochloride</td>
<td>0.8</td>
</tr>
<tr>
<td>Resorcin</td>
<td>0.71</td>
</tr>
<tr>
<td>Sulfanilamide</td>
<td>0.6</td>
</tr>
</tbody>
</table>
General method of Preparation

Thoroughly clean and lubricant the mould with a suitable lubricant, keep it on ice the inverted position to cool add drain any excess of the lubricant. The lubrication of the mould is unnecessary with synthetic bases\textsuperscript{57-60}.

Taking into account the displacement value of the medicament place the calculated quantities of powdered or shredded cocoa butter in a dish. (Execs must be calculated because of unavoidable wastage during preparation. For this the amount for two extra suppositories is sufficient, that means if eight suppositories are to be dispensed then calculate for ten suppositories instead of eight) Heat the dish over water bath and when two-third of the base melts remove the dish form the bath and stir thoroughly until whole of the mass melts. This process prevents overheating o the base.

Place the weighed quantity of powdered medicament to be incorporated on a warmed ointment slab, over it put about half the melted base, rub it thoroughly with flexible spatula, care must be take to prevent the formation of lumps. Transfer the mixed mass to the dish ad mix thoroughly so that a uniform mass is formed.

Warm the dish over water bath for few seconds with constant stirring until the mass becomes pour able. Transfer this melted mass rapidly into the cavities of the mould kept over ice. Fill each cavity to overflowing. This is done to prevent the formation of hollows in the tops of the finished suppositories because cocoa butter contracts on cooling and hollows are formed at the top of the suppositories. While pouring the mass into the cavities it must be continuously stirred to ensure even distribution of the medicament in all the suppositories.
When the mass has just set remove the excess of the mass with the help of a sharp knife or razor blade or a slightly warmed spatula. Keep the mould in cool place or over ice for 10 to 15 minutes. Then open the mould and remove the suppositories. If any lubricant is there, wipe it off lightly with a clean cloth.

3) Cold Compression Method

This method has the advantage that it avoids heat and stirring therefore it is suitable for thermo labile and insoluble drugs. It is not suitable for suppositories in which glycerol gelatin is used as base and other bases in which melting is necessary. In this method first mixing the powdered drug with an equal amount of grated cocoa butter and then incorporating prepare the mass or the remaining amount of grated cocoa butter. Allowance is made or unavoidable wastage during preparation by calculating for sufficient extra suppositories.

The prepared mass is placed in a cylinder of the machine which is forced to the cavities of the mould through the narrow opening by applying pressure to the piston or handle of the machine thus forming suppositories. The pressure is further applied. And then the finished suppositories are taken out.

d) Packing and Storage

Suppositories ate usually packed in shallow, partitioned cardboard boxes, which hold the suppositories in upright position ad do not allow them to come on contact with each other. If plain boxes are used suppositories should be separately wrapped in waxed paper or tin foil. Glycerol gelatin suppositories should be packed in a well closed glass or plastic containers.
1.7 Rectal Absorption

a) Anatomical and physiological features

The Human rectum comprises the last 12-19 cm of large intestine and the rectal epithelium containing a single layer of columnar or cuboidal cells and goblet cells, its surface area is around 200-400 cm square. The absorbing surface area of the rectum is considerably smaller than that of the small intestine, as the former lacks villi and microvilli. However, the epithelia in the rectum and the upper intestinal tract are histological similar, giving them comparable abilities to absorb drugs. The rectal mucosa is richly vascularized, prominent blood supply containing the inferior and middle veins, which are directly joined to the systemic circulation and the superior rectal vein, which is joined to the portal system. This ensures that drugs in suppository form which are absorbed in the upper rectum will not by-pass the hepatic first-pass elimination, dependable for the metabolism and rapid removal of number of orally administered drugs, such as the macrolides.

Since many experimental studies of rectal drug administration are performed in animals, it is necessary to note the differences in the structure between human and animal rectums. In most animal species, histological analysis reveals more goblet cells in rectal mucosa than in the colon; in rats and rabbits there are many lymph nodes in the lamina propria and sub mucosa. The mucosa is also thrown into several longitudinal folds containing large veins; this structure seems favorable to local absorption of drugs. A rapid colorectal cell turnover has also been described, potentially stimulated by chemicals
such as ethanol or iso energetic carbohydrates but such response has not always been discussed in studies of antibiotic administration in rats and rabbits.

b) Drug absorption in the rectum

The method of rectal absorption of drugs are not prominently different from those in the upper part of the gastro intestinal tract. The rectal absorption of sulphonamides with perfusion techniques has been studied in rats; by Debore et al and have concluded that, subsequent rectal insertion, passive moment is the main method of drug absorption, that the absorption is principally dependents on the lipid solubility, molecular weight and degree of ionization of molecules, and that basic drugs are absorbed faster in the presence of anions like sodium lauryl sulphate. Therefore rectal absorption of drugs is controlled greatly by the general principles of moment of antibiotics. Depending on their chemical structures, drugs may cross the rectal wall either by absorption across the epithelial cells or from the tight junctions inter join the mucosal cells. Several local host factors may influence absorption in the rectum, mucosal layer, the variable volume of rectal fluid, the basal cell membrane, the tight junctions and the intracellular compartments may each constitute local barriers to drug absorption, depending on histological factors and on the molecular structure of the administered drug. The pharmaceutical formulation, therefore, may play a prominent role in the rectal absorption and as result in the systemic distribution and pharmacokinetics of antibiotics given through suppository.

Absorption of systematically active drugs from suppositories involves release in the rectum, diffusion through the rectal mucosa, absorption by the tissues and transport into the general circulation.
Depending on the height at which absorption occurs in the rectum, the drug passes into the inferior, middle or superior hemorrhoid veins, of which the inferior vein is nearest the anus. Drug carried by the inferior or middle veins goes directly into the circulation and bypasses the liver, to which the drug in the superior vein is first transported.

It was once believed that medicaments from suppositories were largely transported by the inferior and middle hemorrhoid veins and, consequently, that rectal administration of a drug provided a means of avoiding degradation of the drug by the liver and damage of the liver by the drug. However, it appears that a suppository may travel far enough into the rectum for much of its medicament to be transported by the superior vein and therefore, it is unwise to rely on these advantages.

Among the factors influencing rectal absorption are as follows:

c) **Partition coefficient of drug**

Drugs with a high fat to water partition coefficient are liberated relatively slowly from fatty bases. Partitioning between base and rectal fluid is also affected by the extremely variable volume of water in the rectum at different individuals; this volume is often very small. Formulation of a medicament in a different base may significantly alter release and absorption rates.

d) **pH of Rectal secretions**

The principal method of drug absorption is diffusion through lipid region of cell membranes and therefore, unionized drugs, which are more soluble in lipids than the ionized forms, are absorbed more readily.
The state of ionization of a drug depends on the pH of the environment, acidic and basic drugs being most ionized and hence, least well absorbed at high and low pH\(^8\) respectively. Consequently, absorption of a rectally administered drug is influenced by the rectal pH and if as is claimed by some workers, this is alkaline, then basic drugs will be poorly ionized and well absorbed.

e) Physical state of medicament:

The absorption of a medicament in suspension is limited by its dissolution rate and, therefore, when a drug is formulated as a suspension in a suppository it is advantageous to use a fine powder to increase surface area and enhance dissolution and absorption. This precaution is particularly relevant to rectal dose forms because the rectum lacks the large surface area and considerable movement of contents that aid absorption higher in the gut.

Solution will be faster from a suppository that quickly melts into a fluid of low viscosity which spreads into a film of large surface area than from one that remains entire throughout its dissolution. Generally, a fatty base more suitable for medicaments required to act locally while a water miscible or water soluble base is superior for giving the quick release required to systematically active drugs.

f) Presence of adjuvants in base

Emulsifying agents such as emulsifying wax, wool fat, wool alcohols, macrogol stearates and polysorbates may be included in suppository bases to facilitate incorporation of aqueous solutions or polar liquids, but they should be used with caution as their effects on release and absorption are not always predictable. The presence of
emulgents may complicate preparation of suppositories by causing foam in the base and bubbles in the product. The possibility that conclusion of a powerful surface active agent may cause greatly increased absorption of a medicament, with consequent toxic effects must be borne in mind.

The major limiting factor in rectal absorption appears to be the rate at which the drug diffuses to the rectal mucosa and therefore, if a high blood concentration of a systematically active drug is required quickly, rapid release from the suppository is essential. Absorption from different bases can be compared in animals by rinsing the rectum and analyzing the residue, or by analyzing of body fluids. Often in a suppository, a dose 50 to 200% more than the oral dose must be administered to obtain an adequate response.

1.8 Physical and Chemical Qualities of the Drug

The successive events guiding to drug absorption from the anorectal area can be diagrammatically represented as provided:\textsuperscript{61, 62}:

\textbf{Drug (vehicle) }\rightarrow\textbf{ Drug (colon fluids) }\rightarrow\textbf{ Absorption (rectal mucosa)}

In order for the drug to be available for absorption, it must be released from the suppository and distributed by the surrounding fluids to sites of absorption. By dissolving in the fluids, there is wide contact of the drug with the lumen walls, thereby increasing drug contact with a large number of absorption sites. The drug has a lipid-water coefficient prefer fat solubility the drug is released slowly from its suppository excipient. \textit{Allawala} and \textit{riegelman} report that a drug that is very soluble in cocoa butter and present at levels at or close to saturation. Thus water soluble, oil not soluble, salts are preferred in
fat base suppository. For water-soluble suppository type bases, from which the drug is released as the vehicle dissolves, water soluble kind salt is the one of select for quicker drug in take. For example, to increase the absorption rate from suppositories, e.g. ephedrine sulphate, quinine hydrochloride, sodium barbital sodium salicylate, are preferred to their corresponding bases & acids.

Rate regulating step in drug absorption from suppositories is the separation of the dissolved drug from the melted base and not the rate of solution of the drug in the body fluids. Riegelman and crowell have shown that the rate at which the diffuse to the surface of the suppository, the particle size of the suspended drug and the presence of surface active agents are factors that affect drug release from suppositories. Solution of the drug in solid polyethylene glycol and oleaginous bases resulted in prolonged absorption times, because the drug is slowly eluted in to the surrounding fluids. As would be expected, the larger the particle size, the slower the rate of solution, and as a consequence, the drug absorption rate is decreased with an increase in drug particle size. Surfactants can both enhance & reduce drug absorption rate. For instance in the case of sodium iodide, absorption is accelerated in the presence of surfactants and appears to be proportional to the relative surface tension lowering of the vehicle.

In addition, Riegelman and Crowell state that the acceleration of sodium iodide absorption might also be attributed to the mucus-peptizing action of the vehicle. The rectal membrane is covered by a continuous mucus blanket, which may be more readily washed away by colonic fluids that have reduced surface tension. Cleaning activity caused by the surfactant having vehicle may make extra pore spaces available for drug
absorption rate is decreased in the presence of surfactants probably because of the formation of a drug surfactant complex.

*Schanker* showed that the absorption if several acid and base compound in the solution as in a retention enema was not affected over a 10-fold range of concentration. In the case of retention enema, the absolute amount of drug absorbed was directly proportional to the initial saturation concentration present and not to any excess beyond this amount. If the luminal concentration of drug is above a particular amount, which varies with the drug, the rate of absorption does not change with further increase in drug. Thus, colonic absorption of drugs is a matter of simple diffusion across the colonic membrane. In suppositories however concentration dose play a role in knowing the rate of release of drug from suppository bases.

Once the drug is released from the suppository base and reaches the area of absorption on the lumen wall, lipid soluble un dissociated drug is the most readily absorbed form. Completely ionized drugs like quaternary ammonium mixtures and sulfonic acid derived products are poorly absorbed. Unionized substances that are lipid insoluble also are poorly absorbed.

There is relation between the degree of ionization and the rate of absorption of drugs. Weak acids with a pKa < 4.3 and weak bases with a pKa < 8.5 are usually readily absorbed. Highly ionized compounds are poorly absorbed. Acids having pKa values below 3.0 and pKa values for bases above 10.0 indicate negligible absorption rates. This reaction suggests that the anorectal and colonic mucosa are selectively permeable to the uncharged drug molecule, whereas the ionized drugs penetrate the mucosa poorly or
negligibly. Thus drug absorption can be increased by the use of buffer solution or salts that convert the pH of the anorectal area to a value that increases the concentration of unionized drug.

In summary, absorption of drugs from the anorectal area is affected by such physiologic factors as colonic contents, circulation, pH, lack of buffering capacity, physiologic state, and the mucous blanket on the lumen wall. The physico-chemical characteristics of drugs affecting absorption are the lipid/water partition coefficient and the degree of ionization. When the amount of drug in the rectal fluid is above the rate determining level, marked increases in drug concentration play no role in altering established drug absorption rates. The presence of surfactant may or may not aid absorption, depending on concentration and possible interaction with the drug. Drug particle size is directly related to absorption rate.

1.8.1 Physicochemical characteristics of the base and adjutants

Various properties of the suppository base can affect drug absorption. Heinmann et al., reported that with use of sodium Phenobarbital, the absorption rate is faster from fatty bases having a lower melting range. It was also shown that absorption rate increases along with hydroxyl values\textsuperscript{63, 64}.

Since fatty bases may harden for several months after molding, this rise in melting range certainly would affect absorption. Adjuvants in the formula can affect the drug absorption through changes in the rheological properties of the base at body temperature, or by affecting the dissolution of the drug in the media of the dosage form.
In emulsion type bases it was shown that the quantity of water soluble drug release enhanced with the water quantity of the base and that the rate of drug released could be extended by the adding the aqueous polymer. Addition of hydrophobic colloidal silicon oxide to fat base suppositories dramatically changed the rheologic behavior of the mass. Salicylates were identified to enhance the rectal absorption of water soluble antibiotics in lipophilic bases\textsuperscript{64}.

Drug release from cylindric hydrogels of hydroxethyl methacrylate decreased as increasing percentage of the cross linking agent ethylene glycol dimethacrylate were used.

1.8.2 Blood levels from different dosage forms

The literature is replete with conflicting information concerning the effectiveness of drugs administered in suppository form. The information is difficult to correlate because of different or inadequate methods for determining blood levels, the nature of the drug and the suppository base as well as the inability of many patients to retain the suppository. Rudolf \textit{et al.}, reported on blood levels resulting from the oral, rectal and intravenous administration of theophylline derivatives. Rectal retention enemas and intravenous injections showed that these two routes are similarly effective in allowance is made for the approximately 30min delay required for drug absorption from the rectum.

The fact that the rectum or colon is a dependable site for drug absorption seems well established, but not all investigators agree that the suppository dosage form yields therapeutically adequate blood levels. Several investigators report adequate absorption of drug from suppositories. Enesco and co-workers made a comparative study on the
absorption time of six drugs, namely sodium salicylate, chloral hydrate, methylene blue, atropine, morphine, and sodium iodide. The first five drugs are absorbed rectally more quickly and at therapeutically more effective levels than with oral administration. Absorption of sodium iodide is slower by the rectal route than by the oral route, but varies considerably from one individual to another. Shichiri et al., reported increased intestinal absorption of insulin from a suppository. Copidos and Ward-McQuaid found pentazocine suppositories equal in relief of moderate pain to pethidine injection and show less side effects with the suppository. Turrell, morino, and nerb report the same dosage requirement for sulfonamide in glycerinated gelatin suppositories as in tablets. Higher concentrations of the sulfonamide are found in the blood following its administration by enema than by suppository, thus in some cases, the suppository dose yield effective therapeutic blood levels, although the enema yields faster and higher concentrations of drug in the blood. To maintain the therapeutic effectiveness of drug in a suppository requires, therefore, a wise choice of drug salt and the suppository base\textsuperscript{65, 66}. 