1.1 MODIFIED RELEASE DOSAGE FORM: [1-10]

Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption.

The term modified release dosage form is used to describe products that alter the timing and rate of release of the drug substance. A modified release dosage form is defined as one for which the drug – release characteristics of time course and / or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. To achieve therapeutic effect of drug, it should be available at certain minimal concentration for a specific duration. The conventional dosage forms gives prompt release of drugs showing fluctuations in drug concentration in the body and necessitates multiple dosing to maintain the therapeutic level. So to achieve and maintain uniform concentration of drug in the therapeutically range the modified dosage forms are developed.

The goal in designing modified release dosage forms is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. The basic goal of therapy is to achieve a steady state drug in blood level for extended periods of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and dosage forms are terms used to identify drug delivery system. Although these terms have been used by manufacturer's interchangeably, these are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period may vary from day to months. In the case of orally administered dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has been associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral injectable and topical use and inserts for placement in the body cavities.

Sustained release drug delivery system, which mainly consists of two parts: an immediately available dose and a sustaining part. The immediately available dose is
normally directly added to the sustaining part of the tablet or alternatively is incorporated in the tablet coating with the sustaining portion in the core of the tablet i.e., a portion (initial priming dose) of the drug is released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of the drug (maintenance dose) is then released slowly thereby resulting in therapeutic drug / tissue level, which is a prolonged but not maintained constant.

**Different Terminologies used in modified release:**

1. Sustained release
2. Delayed release
3. Prolonged release
4. Extended release
5. Controlled release
6. Site-specific targeting and receptor targeting

**Drawbacks of Conventional dosage forms:**

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley in plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects specially of a drug with small Therapeutic Index (TI) whenever over medication occur.

**Advantages of modified release formulations:**

1. Improved patient compliance and convenience due to reduction in dosing frequency.
2. Reduction in fluctuation in steady state level and therefore better control of disease condition due to constant plasma drug level over a long period of time.
3. Minimize the drug accumulation with chronic dosing.
4. Minimize or eliminate local and systemic side effects.
5. Maximum utilization of the drug enabling reduction in total amount of dose administered.
6. Increased safety margin of high potency drugs due to better control of plasma drug level.

Disadvantages of modified release formulations:
1. Administration of modified release medication does not permit prompt termination of therapy.
2. The physician has less flexibility in adjusting dosage regimens.
3. Possibility of dose dumping due to food, physiological or formulation variables or chewing and grinding of oral formulations by the patient and thus increased risk of toxicity.
5. More costly process and equipments are involved in manufacturing SRDFs.
6. Drugs absorbed at specific sites can’t be given in this dosage form.

Modified release dosage form:

Oral dosage form
- Extended release (eg. Controlled release, sustained release, prolonged release)
- Delayed release (eg. Enteric coated)

Intramuscular Dosage Forms
- Depot injection
- Water-immiscible injections (eg. Oil)

Subcutaneous Dosage Forms
- Implants

Transdermal Delivery System

Targeted Delivery Systems
- Colon targeted

1.2 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM \[^{11-13}\]

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account three major
factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms.

The solubility classification of a drug in the BCS is based on the highest dose strength in an IR product. A drug substance is considered highly soluble when the highest strength is soluble in 250 ml or less of aqueous media over the pH range of 1.0–7.5; otherwise, the drug substance is considered poorly soluble. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. Animal or in vitro models capable of predicting the extent of intestinal absorption in humans may be used as alternatives, e.g., in situ rat perfusion models and in vitro epithelia cell culture models. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable.

PRINCIPLE CONCEPT BEHIND BCS:-
Principle concept behind BCS is that if two drugs products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration. This concept can be summarized by application of Fick’s first law in the following equation

\[ J = P_w C_w \]  \hspace{1cm} (1)

Where,

‘\( J \)’ is the flux across the gut wall,

‘\( P_w \)’ is the permeability of the gut wall to the drug, and

‘\( C_w \)’ is the concentration profile at the gut wall.

In terms of bioequivalence, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate bioequivalence of two drug products.
According to the BCS the drugs can be categorized into four basic groups on the basis of their solubility and permeability GIT mucosa.

**DRUG CHARACTERISTICS OF VARIOUS BCS CLASSES:**

**Class I drugs:**
Exhibit a high absorption number and a high dissolution number. Bioavailability and dissolution is very rapid. Bioavailability and bioequivalence studies are unnecessary for such product. These compounds are highly suitable for design of SR and CR formulations. Examples include Propanolol, Metoprolol, Diltiazem, Verapamil etc.

**Class II drugs:**
Have a high absorption number but a low dissolution number. This drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. IVIVC is usually expected for class II drugs. Examples include Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Felodipine, Nicardipine, Nisoldipine etc.

**Class III drugs:**
Permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability. Examples include Acyclovir, Alendronate, Captopril, Enalaprilat Neomycin B etc.

**Class IV drugs:**
These drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability and gastric emptying form the rate limiting steps for the drug absorption. These are unsuitable for controlled release. Examples include Chlorthaizide, Furosemide, Tobramycin, Cefuroxime etc.
1.3 SELECTION OF DRUG CANDIDATE FOR ORAL SUSTAINED RELEASE SYSTEMS: [1, 4, 7, 8]

The design of sustained release systems depends upon various factors as the route of administration, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of drug. These are either physicochemical or biological properties of drug.

**Physicochemical properties:** - These includes

1) **Aqueous solubility:**
Absorption of poorly soluble drug is often dissolution rate limited. Such drug do not require any further control over their dissolution rate and thus may not seems to be good candidate for sustained release systems. Drugs with good aqueous solubility are good candidate for oral sustained release formulations.

2) **Partition coefficient:**
Drugs that are very lipid soluble or very water soluble i.e. extremes in partition coefficient will demonstrate either low flux into the tissue or rapid flux followed by accumulation in tissue. Both cases are undesirable for sustained release formulation. Drugs with balanced partition coefficient are good candidate for oral sustained release formulations.

3) **Drug stability:**
As most oral sustained release systems are designed to release their content over much of the length of GI tract. Drugs, which are unstable in the environment of intestine, are difficult to formulate into prolonged release systems.

4) **Protein binding:**
Extensive protein binding can be evidenced by long half life of elimination for the drug, and such drugs do not require sustained release dosage form. However, drugs that exhibit high degree of binding to plasma protein also might bind to biopolymer in the GI tract, which could have influence on sustained drug delivery.
5) Molecular size and diffusivity:
Drugs in many sustained release system must diffuse through a rate controlling membrane or matrix, in addition to diffusion through various biological membranes. The ability of drug to pass through the membranes, it’s so called diffusivity, is a function of its molecular size (or molecular weight). An important influence upon the value of diffusivity, D in polymers is the molecular size of diffusing species. The value of diffusivity is related to the size and shape of cavities as well as the size and shape of diffusing species. Generally, the values of diffusion coefficient for intermediate molecular drugs i.e. 150-400, through flexible polymer range from $10^{-6}$ to $10^{-9}\text{cm}^2/\text{sec}$, with values of the order $10^{-8}$ being most common. For drugs having molecular weight greater than 500 it is difficult to quantify.

6) Biological half-life:
The usual goal of sustained released product is to maintain therapeutic blood level over an extended period. For this, the rate that drug enter the circulation must be approximately equivalent to the rate of its elimination which is quantitatively described by its half-life. Drugs with shorter half-life (2-4 hrs) make excellent candidate for sustained release preparation since this can reduce dosing frequency.

Biological properties: - These includes

1) Absorption:
To maintain a constant blood or tissue level of drug it must be uniformly released from the sustained release system and then uniformly absorbed. Usually, the rate-limiting step in drug delivery from a sustained release product is release from the dosage form, rather than inherent absorption control. The fraction of drug absorbed from a single non-sustained dose of drug can be quite low due to drug degradation, binding to proteins or dose dependent absorption. Even if the drug is incompletely but uniformly absorbed, a successful sustained release product can be made.

Dicoumarol and the amino glycosides, gentamicin and kanamycin are examples of drugs, which are erratically absorbed after oral administration, making the design of a sustained release product more difficult. Similarly drugs absorbed by specialized transport processes and at specific sites of the gastro-intestinal tract are poor candidates for sustained release products, e.g. riboflavin.
2) **Distribution:**
The distribution of drugs into tissues is a major factor in the overall drug elimination kinetics. Drugs with high apparent volume of distribution, which in turn influences the rate of elimination for the drugs are, poor candidates. It influences the concentration and amount of drug either in the blood or in the tissues.

3) **Metabolism:**
Metabolic alteration of a drug mostly occurs in the liver. Metabolism is reflected in the elimination constant of a drug. The complex metabolic patterns make the design more difficult, particularly when biological activity is due to a metabolite. If the drug, on chronic administration induces or inhibits enzyme synthesis, it will make a poor candidate for a sustained release product because of the difficulty of maintaining uniform blood level.

4) **Duration of Action:**
The biological half life and hence the duration of action of a drug is influenced by its distribution, metabolism and elimination patterns and plays a key role in determining the candidature of the drug for preparation as sustained release product. There is little justification to prepare sustained release formulation for drugs with long biological half-lives. If there are no significant differences in effectiveness when a drug is given as a single large dose per day or in several smaller doses throughout the day, the need for a prolonged action dosage form is doubtful e.g. phenylbutazone and phenothiazines.

5) **Side effects:**
Controlled release formulations can minimize the incidence of side effects by controlling the plasma concentration of the drug e.g. controlled release levodopa has lowered the incidence of side effects and increased patient tolerance to a larger total daily dose. The technique of controlled release has been more popularly used to lower the incidence of gastro-intestinal side effects than that of systemic side effects. Thus, drugs that are prone to cause gastric irritation are better tolerated in sustained release dosage forms, e.g. Ferrous sulphate and Potassium chloride.
6) Margin of safety:

Margin of safety of a drug is commonly indicated by its therapeutic index. A drug is considered to be relatively safe if its therapeutic index exceeds 10.

\[
\text{Therapeutic Index} = \frac{\text{Median toxic dose}}{\text{Median effective dose}} = \frac{\text{TD}_{50}}{\text{ED}_{50}}.
\]

Table 1.1: Properties of drugs to be considered for modified release

<table>
<thead>
<tr>
<th>Drugs Suitable</th>
<th>Drugs not Suitable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physicochemical</strong></td>
<td></td>
</tr>
<tr>
<td>1 Compound with low molecular weight</td>
<td>1 Large molecular size/weight (proteins and peptides for oral)</td>
</tr>
<tr>
<td>2 Good aqueous solubility, pH independent (Penoxophylline)</td>
<td>2 Very low aqueous solubility (0.1 mg/ml) (Nifedipine, Griseofulvin)</td>
</tr>
<tr>
<td>3 With non-aqueous solubility (for Parenteral; Steroids)</td>
<td>3 Largely in ionized form in the G.I. tract</td>
</tr>
<tr>
<td>4 Unionized (at least 0.1%-5%) in G.I. tract</td>
<td>4 Strong bases (pKa &gt; 11.0) e.g: Guanethidine</td>
</tr>
<tr>
<td>5 Very weak bases pKa &lt; 5.0 (Theophylline pKa=0.7, Diazepam pKa = 3.7)</td>
<td>5 Strong acids (pKa &lt; 2.5) eg: Cromolyn sodium</td>
</tr>
<tr>
<td>6 Very weak acids pKa &gt; 8.0 (Pentobarbital pKa =8.1) Unionized at all pH, absorb well</td>
<td></td>
</tr>
<tr>
<td>7 Moderately weak acids pKa 2.5-7.5 Aspirin (3.5), Ibuprofen (4.4).</td>
<td></td>
</tr>
<tr>
<td>8 Moderately weak bases (pKa 5.0-11.0), Codeine (8.2) Ionization depends on pH</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacokinetic</strong></td>
<td></td>
</tr>
<tr>
<td>1 Short ½ (2-5 hr) Theophylline (4 hr) Sodium diclofenac (2 hr) Nifedipine (2.5 hr) Diltiazem(3.5 hr) Glipizide (3.4hr)</td>
<td>1 Drugs that exhibit Slow absorption</td>
</tr>
<tr>
<td>2 Well absorbed from all regions of G.I. tract</td>
<td>2 Carrier mediated transport (several vitamins)</td>
</tr>
<tr>
<td></td>
<td>3 Site specific absorption (Vit B12)</td>
</tr>
<tr>
<td></td>
<td>4 Degradation in GI tract (Nitroglycerine, Penicillin G, Erythromycin)</td>
</tr>
<tr>
<td></td>
<td>5 First pass hepatic metabolism (Nitroglycerin, Propranolol)</td>
</tr>
<tr>
<td></td>
<td>6 That induce or inhibit metabolism (Rifampicin, Barbiturates, Allopurinol, PAS)</td>
</tr>
<tr>
<td><strong>Pharmacodynamic</strong></td>
<td></td>
</tr>
<tr>
<td>1 Therapeutic range of blood conc.- wide enough</td>
<td>1 Having large dose</td>
</tr>
<tr>
<td>2 Response ∝ blood conc.</td>
<td>2 Drugs whose metabolites are also active</td>
</tr>
</tbody>
</table>
1.4 DESIGN OF ORAL SUSTAINED RELEASE SYSTEMS (MODIFIED RELEASE DOSAGE FORM) \textsuperscript{[1,4,6,8-10]}

Most sustained release systems are solids. The following way of classification of such systems includes not only the conceptual approach of design, but some elements of physiology of the GI system as well.

1. Continuous-release systems
   a. Dissolution control systems
   b. Diffusion control systems
   c. Dissolution and diffusion control systems
   d. Ion-exchange resins complexes
   e. Osmotically controlled devices
   f. Slow-dissolving salts or complexes
   g. pH-independent formulations

2. Delayed-transit and continuous-release systems
   a. Density-based systems
   b. Size-based systems
   c. Bioadhesive based systems

3. Delayed-release systems
   a. Intestinal release systems
   b. Colonic release systems

1. Continuous-release systems:
   a. Dissolution control systems:

   Continuous release for extended periods can be obtained by employing dissolution as the rate-limiting step in drug release. Certain drugs are slow-dissolving due to their intrinsic low aqueous solubility and thus act as natural sustained-release products. Digoxin a cardiotonic and Griseofulvin an antifungal drug are examples of slow-dissolution drugs. For compounds with high aqueous solubility, one needs to reduce the solubility rate by some mechanism. The approach to control the rate of dissolution of such compounds will be based on either or both of the following techniques:

   1. Stagnant-layer control
   2. Encapsulation or coating, which erodes or dissolves slowly
Stagnant-layer control:
If the dissolution process is diffusion layer-controlled, i.e., the rate limiting step is diffusion through an unstirred layer on the solid surface to the bulk of solution, an increase in the stagnant diffusion layer works effectively.
Matrix is the most commonly employed system to achieve such dissolution control. The rate of drug availability is controlled by the rate of penetration of the dissolution media. This penetration can be controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet.

A major disadvantage of stagnant layer-controlled systems is that they fail to give a zero-order release; i.e., release rate progressively decreases with time. This is a result of an increased diffusional distance and decreased surface area at the penetrating solvent front.

Encapsulation dissolution control:
The basic approach in encapsulation is the coating of drug particles with a slowly dissolving material. Coated particles can be compressed directly into tablets or placed into gelatin capsules. Since the time required for dissolution of the surface coat is a function of coat thickness and its aqueous solubility, good control of the release rate can be achieved.

b. Diffusion control systems:
Diffusion controlled systems fall into two basic categories:

1. Reservoir devices
2. Matrix devices

Reservoir devices:
In reservoir devices, a water insoluble polymeric material encases drug. Drug release through the system is governed by partitioning of drug through the coating membrane. Drug penetrates the membrane and diffuses to the other side, and eventually enters into the dissolution media. Insoluble coatings can be applied to a drug core by a variety of techniques. Commonly used approaches are press coating and air-suspension coating. For smaller particles intended for tablets or capsules, microencapsulation techniques are generally used. Uncoated drug may be enclosed in the system to provide an initial rapid dose.
Matrix devices:
The matrix approach employs a system where the drug is compressed with a slowly
dissolving or insoluble polymer. The rate of drug availability is controlled by the rate of
penetration of the dissolution medium through the matrix. As the drug dissolves and
diffuses out, the diffusional path length increases because the polymer matrix is
insoluble. Once pores have been created, drug will be released soon. Obviously, the
rate of release will not be zero order. However, if one uses a slowly dissolving polymer
matrix, where the matrix itself dissolves at a certain rate so as to keep the diffusional
length more or less the same, it can result in nearly a zero-order release.
The rate of drug release is dependent on the rate of drug diffusion but not on the rate of
solid dissolution. Higuchi’s equation can be used to express the release rate from such
systems:

\[
Q = \frac{DE}{T (2A - EC) CSt}^\frac{1}{2}
\]

Where
\(Q\) = drug released in g per unit surface area.
\(D\) = diffusion coefficient of drug.
\(E\) = porosity of the matrix.
\(T\) = tortuosity of the matrix.
\(Cs\) = solubility of drug in release medium (g/ml)
\(A\) = concentration of drug in the tablet (g/ml)
\(t\) = time

C. Dissolution and diffusion controlled systems:
Some systems employs diffusion as well as dissolution control over the drug release
rate. The dosage form consists of a drug core encased in a partially soluble membrane.
When placed in the appropriate milieu, the soluble part of the membrane dissolves
away, creating pores in the remaining coat. This allows dissolution of the drug. An
example of such a coating would be a polymer coating consisting of ethyl cellulose and
methylcellulose. Methyl cellulose dissolves, leaving the ethyl cellulose coat intact.
Varying the fraction of soluble material in the coating one can easily control surface area in such a system. Also, by incorporating more than one soluble material with different rates of solubility, one can increase the release rate after a certain period of time.

d. Ion-exchange resins:
Ion-exchange resins are water insoluble cross-linked polymers containing salts forming groups in repeating position on the polymer chain. Drug release from the drug resin complex depends on pH and electrolyte concentration within the GI tract and on the properties of the resin. Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract as shown below,

\[
\begin{align*}
\text{Resin}^+ \cdot \text{Drug}^- + X^- & \rightarrow \text{Resin}^+ \cdot X^- + \text{Drug}^- \\
\text{Resin}^- \cdot \text{Drug}^+ + Y^+ & \rightarrow \text{Resin}^- \cdot Y^+ + \text{Drug}^+
\end{align*}
\]

Where \( X^- \) and \( Y^+ \) are ions in the GI tract.

The rate of release depends on the extent of cross-linking in the resin. Coating the drug resin can make a further modification of the release rate complex with a hydrophobic rate-limiting polymer such as ethyl cellulose or waxes\textsuperscript{13}.

e. Osmotically controlled devices:
Osmotically controlled systems utilize osmotic pressure as the driving force to release drug at a constant rate. It consists of a drug core surrounded by a semi permeable membrane coating, which has one orifice. Water imbibed from the environment crosses the membrane at a controlled rate and causes the drug solution to exit through the delivery orifice. It delivers drug at a rate independent of gastrointestinal pH and motility. The delivery rate is controlled by osmotic properties of the core as well as membrane area, thickness, and permeability to water. An elementary osmotic pump is shown in Figure 1.1.

Fig. 1.1: Schematic representation of an elementary osmotic pump
f. Slow dissolving salts or complexes:
A salt or complex of drug that is only slightly soluble in GI fluids can provide an extended release of drug. The process of complex formation is usually a simple acid-base reaction, as in the case of amines and tannic acid. Solutions of both compounds in suitable solvents are mixed together and the resulting complex is precipitated by the addition of another solvent or salt.

g. pH-independent formulations:
Since the pH in the GI tract varies considerably and continuously as the formulation moves through it, pH-independent formulations are particularly attractive for oral use. These formulations are prepared by blending an acidic or basic drug with one or more buffering agents; e.g., primary, secondary, or tertiary salts of citric acid, granulated and are coated with appropriate materials. When gastrointestinal fluid passes through the membrane, buffering agents adjust the pH to an appropriate, predetermined, constant pH at which the drug dissolves and permeates out at a constant rate regardless of the external pH.

2. Delayed-transit and continuous-release systems:
The length of in-vivo delivery by oral CR products is severely limited due to short GI-transit time of solids and liquids. In addition, GI transit time tends to show considerable inter and intra-subject variations. This can also make the drug delivery both variable and unpredictable. As a result, most oral dosage forms are limited to a 12-hour period. For prolonging residence time of the delivery devices in the GI tract the only viable approach appears to be to delay gastric emptying; because once a dosage form is emptied from the stomach, little can be done to retard its movement through the intestine.

1) Density based systems.
2) Size based systems.
3) Bioadhesive systems.

3. Delayed-release systems:
Delayed release systems for oral controlled delivery are aimed at delivering drug to a particular area of the GI tract, instead of delivering the drug continuously and
immediately after ingestion. This site-specific delivery can be aimed at systemic absorption, as in case of enteric-coated tablets, or for local effects. Delivering drugs specifically in the desired area could treat certain disease conditions of the colon and rectum. These systems can provide one or more of the following advantages over the oral CR systems:

1. Bypass areas of potential drug degradation, e.g., the stomach for acid-labile drugs, the stomach and jejunum for peptidase labile drugs.
2. Achieve local effects in the lower GI tract without much systemic absorption or side effects.
3. Reduce discomfort in the upper GI area
4. Deliver drugs to a specific absorption site to achieve a high concentration at the absorptive membrane, e.g., delivery of Peyer’s patches or colon bacteria.

**Intestinal release:**
Enteric-coated tablets are examples of the intestinal-release approach. This approach is usually used for acid-labile drugs. In case of aspirin, prevention of gastric irritation is the aim. However, enteric-coated formulations tend to be unpredictable in their bioavailability. Enteric-coated erythromycin tablets are well known for their unpredictable and variable bioavailability.

**Colonic release:**
Despite a small absorptive surface area, the potential for drug delivery through the colonic mucosa still exists because the desired rate of absorption from CR formulations is generally not very high.

There are basically two approaches toward delivering drugs through the colon: (1) use of bioerodible polymers to protect drug during its passage through the upper GI tract, and (2) use of prodrugs that are activated by bacterial degradation or metabolism.

1.5 **SUSTAINED RELEASE MATRIX DRUG DELIVERY SYSTEM**
**(MODIFIED RELEASE DOSAGE FORM)**

1) **Hydrophilic matrix tablet.** [1,4,7,9,14-16]
The hydrophilic matrix tablet is prepared using various hydrophilic polymers such as HPMC, Xanthan Gum, Polyox, Carbopol etc. There are too much factors involved in
drug release from hydrophilic matrix systems. The most important factors to be taken into account when developing a formulation based on hydrophilic matrices are the percentage, solubility and drug particle size, the type of polymer, the percentage incorporated, its degree of viscosity and the polymer particle size. Also important are the drug/polymer ratio and the amount of water entering the matrix. Other factors have been shown to be involved in the release of drugs, such as the percentage and mixtures of polymers and the dimensions of the matrix. The compression force is important among the formulation factors to the extent that it determines the amount of air trapped in the matrix.

These delivery systems are also called swellable-soluble matrices. In general they comprise a compressed mixture of drug and water-swellable hydrophilic polymer. The systems are capable of swelling, followed by gel formation, erosion and dissolution in aqueous media.

On contact with water the hydrophilic colloid components swell to form a hydrated matrix layer. This then controls the further diffusion of water into the matrix. Diffusion of drug through the hydrated matrix layer controls its rate of release. The outer hydrated matrix layer will erode as it becomes more dilute; the rate of erosion depends on the nature of the colloid.

The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

**Cellulose derivatives:**
Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC), Sodium carboxymethylcellulose (NaCMC) and Methylcellulose.

**Non-cellulose natural or semisynthetic polymers:**
Agar-agar, Carob Gum, Xanthan gum, Guar gum, Chitosan.

**Polymers of acrylic acid:**
Polymers which are used in acrylic acid category are Carbopol, Eudragit.
ii) Hydrophobic matrix tablet (Wax matrix tablet): [17-22]

The matrix compacts are prepared from blends of powdered components. The active compound is contained in hydrophobic matrix that remains intact during drug release. Release depends on dissolving the channeling agent, which leaches out of the compact, so forming a porous matrix of tortuous capillaries. The active agent dissolves in aqueous medium and by way of water-filled capillaries, diffuses out of the matrix. Hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release.

The hydrophobic matrix tablet are prepared using various hydrophobic polymer such as Ethyl cellulose, Acrylate related polymer, Polyvinyl chloride, Cellulose acetate and Polystyrene etc.

Wax matrices are a simple concept. They are easy to manufacture using standard direct compression, roller compaction or hot melt granulation. The drug can be incorporated into wax, by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. Examples of wax substances are Compritol, Precirol, Hydrogenated vegetable oil, Stearic acid, Bees wax, Cetyl alchol, cetostearyl alcohol etc.

Advantages of matrix systems:

1. Excipient is generally cheap and is usually GRAS (generally regarded as safe).
2. Capable of sustaining high drug load and high molecular weight compounds.
3. Reproducible release profile.
4. Uses readily available pharmaceutical manufacturing equipment.
5. Possible to obtain different type of release profile: zero order, first order, bimodal etc.
6. Easy to manufacture.
7. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.
1.6 FACTORS AFFECTING DRUG RELEASE FROM SUSTAINED RELEASE SYSTEM\(^\text{[1,3,4,9]}\)

1. **Polymer hydration:**
Polymer dissolution includes absorption/adsorption of water in more accessible place, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linkage, separation of polymeric chain, swelling and finally, dispersion of polymeric chain in the dissolution medium.

The Methocel K polymer, because of low content of methoxy groups, hydrate quickly, which justifies its application in controlled release matrices. Larger sized fraction of HPMC hydrates more rapidly than smaller fraction.

2. **Polymer viscosity:**
With cellulose ether, polymer viscosity is used as an indication of the matrix weight. Increasing the molecular weight increases viscosity of the polymers in the matrix formulation and thus slows the drug dissolution.

3. **Drug solubility:**
Absorption of poorly soluble drugs is often dissolution rate limited. Such drug does not require any further control over their dissolution rate; During the Preformulation phase it is necessary to determine drug solubility not only in water but also at various pH values.

4. **Polymer drug proportion:**
The release rate increases for lower amount of HPMC with slightly soluble drug. The proportion is dependent on gel consistency, since it is affected by gel proportion.

5. **Tablet hardness and density:**
In previous studies with different compression forces no significant difference observed in drug release patterns from tablets of different densities.

6. **Effect of diluents:**
In few studies it is observed, the addition of water-soluble diluents (lactose) and water insoluble diluents (Dibasic calcium phosphate), divergence was obtained in the release profile, because of the difference in the solubility of the diluents and their subsequent
effect on the tortuosity factor. As the water-soluble diluents dissolve, it diffuses outward and decreases the tortuosity of the diffusion path of the drug. But dibasic calcium phosphate does not diffuse outward, but rather become entrapped within the matrix and affected the release of the drug by the fact that its presence necessarily decreases the gum concentration.

1.7 MELT GRANULATION (Wax Matrix Tablet)\(^{[1,6,7,19-23]}\)

In melt granulation, stearic acid, hydroxypropyl methyl cellulose, wax material and hydrophobic polymers are used. PEG has been widely used in melt granulation due to its properties like low-melting point, rapid solidification rate. Melt granulation involve elimination of water or organic solvents. This decreases any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, process required less time and energy.

**Techniques of Melt Granulation:**

1. **Spray Congealing:**

Spray congealing is a melt technique of high versatility. In addition to manufacture multiparticulate delivery system, it can be applied to process the raw meltable materials into particles of defined size and viscosity values for the melt agglomeration process. Processing of meltable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glyceride into an air chamber below the melting point of the meltable materials or at cryogenic temperature. Spray-congealed particles (10–3000 µm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation.

2. **Tumbling Melt Granulation:**

A powdered mixture of meltable and nonmeltable materials is fed onto the seeds in a fluid-bed granulator (Fig. 1.2). The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity.
Fig. 1.2: Process of Tumbling Melt Granulation

Materials used in Wax Matrix Systems:
Wax are considered as an alternative to polymer in the design of sustained drug delivery systems due to their advantages such as the low melt viscosity (thus avoiding the need of organic solvents for solubilization) absence of toxic impurities such as residual monomer catalysis and initiators, potential biocompatibility and biodegradability. The various meltable binders used for the sustained drug delivery systems are mentioned in the table.

Table 1.2: Hydrophobic Meltable Substances in the Melt Granulation Technique

<table>
<thead>
<tr>
<th>Hydrophobic Meltable Binder</th>
<th>Melting Range (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeswax</td>
<td>56–60</td>
</tr>
<tr>
<td>Carnauba wax</td>
<td>75–83</td>
</tr>
<tr>
<td>Glyceryl behenate (Compritol)</td>
<td>67–75</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>47–63</td>
</tr>
<tr>
<td>Glyceryl palmitostearate (Precirol)</td>
<td>48–57</td>
</tr>
<tr>
<td>Glyceryl stearate</td>
<td>54–63</td>
</tr>
<tr>
<td>Hydrogenated castor oil</td>
<td>62–86</td>
</tr>
<tr>
<td>Microcrystalline wax</td>
<td>58–72</td>
</tr>
<tr>
<td>Paraffin wax</td>
<td>47–65</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>46–69</td>
</tr>
<tr>
<td>Stearic alcohol</td>
<td>56–60</td>
</tr>
</tbody>
</table>
Melt Agglomeration:
Melt agglomeration is a process by which the solid fine particles are bound together into agglomerates, by agitation, kneading, and layering, in the presence of a molten binding liquid. Dry agglomerates are obtained as the molten binding liquid solidifies by cooling. Typical examples of melt agglomeration processes are melt pelletization and melt granulation.

During a melt agglomeration process, the meltable binder may be added as molten liquid, or as dry powder or flakes. In the latter, the binder may be heated by hot air or by a heating jacket to above the melting point of the binder. Typically, the melting points of meltable binders range from 50 to 80°C.

Modes of melt agglomeration:

Fig 1.3: Modes of melt agglomeration: (a) Distribution and (b) Immersion

In agglomeration by the distribution mode, a distribution of molten binding liquid on the surfaces of primary particles will occur, and agglomerates are formed via coalescence between the wetted nuclei (Fig.1.3). In agglomeration by the immersion mode, nuclei are formed by immersion of the primary particles onto the surface of a droplet of molten binding liquid (Fig.1.3).

1.8 MULTILAYERED TABLETS: [24-26]
The tablets in this category are prepared for two reasons: to separate physically or chemically incompatible ingredients and to produce repeat action/ prolonged action tablet.
1. Tablet in tablet technology

2. Layered tablets – two to three component systems (Bilayer and Trilayer system)

Compression coated tablets – tablet within a tablet.

Inlay tablet – coat partially surrounding the core.

When two or more incompatible active ingredients are needed to be administered simultaneously, then it is better to formulate multilayered tablet. Granules of different drugs are compressed together. Each layer is fed from separate hopper.

**Tablet in Tablet Technology**[^27-29]

**Compression coated tablets**

This type of tablet has two parts, internal core of active ingredient and surrounding coat. The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied.

![Compression Coated Tablet](image)

**Inlay tablets**

In this method, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.

It has some advantages over compression coated tablets:

i) Less coating material is required.

ii) Core is visible, so coreless tablets can be easily detected.

iii) Reduction in coating forms a thinner tablet and thus freedom from capping of top coating.

![Inlay Tablet](image)
1.9 BILAYER TABLET TECHNOLOGY\textsuperscript{[30-33]}

Introduction:-

Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit is possible.

They are preferred for the following reasons:
1) To co-administer two different drugs in the same dosage form.
2) To minimize physical and chemical incompatibilities.
3) IR and SR part of drug in the same tablet, for chronic condition

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner.

1.10 MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEMS\textsuperscript{[34-37]}

a) Diffusion- controlled systems:

Diffusion controlled release systems are divided into matrix systems (also referred to as monolithic systems) and reservoir systems. The release unit can be a tablet or a nearly spherical particle of about 1 mm in diameter (granule).

Drug releases from a diffusion-controlled release unit in two steps:

1) The liquid that surrounds the dosage form penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.

2) The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released.

A dissolution step is thus normally involved in the release process, but the diffusion step is the rate-controlling step.

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a water-insoluble polymer, such as polyvinyl chloride (Fig.1.6). Initially, drug particles located at the surface of the release unit will be dissolve and the drug release rapidly.
If the release of drug from matrix is diffusion controlled, the amount of drug released versus the square root time will be linear.

\[ M = k \cdot t^{1/2} \]

If this is the case, one may control the release of drug from a homogeneous matrix system by varying the following parameters.

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer systems forming the matrix
- Solubility of drug

**b) Dissolution Controlled systems:**

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare sustained release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by,

- Preparing an appropriate salt or derivative
- Coating the drug with a slowly dissolving material- encapsulation dissolution control
- Incorporating the drug into a tablet with a slowly dissolving carrier- matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

c) Erosion-Controlled Systems:
In erosion-controlled extended-release systems the rate of drug release is controlled by the erosion of a matrix in which the drug is dispersed. The erosion in its simplest form can be described as a continuous liberation of matrix material (both drug and excipient) from the surface of the tablet, i.e. surface erosion. Drug release from an erosion system can thus be described in two steps:

1) Matrix material, in which the drug is dissolved or dispersed, is liberated from the surface of the tablet.
2) The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

The eroding matrix can be formed from different substances. One example is lipids or waxes, in which the drug is dispersed. Another example is polymers that gel in contact with water (e.g. hydroxyethylcellulose).

The gel will subsequently erode and release the drug dissolved or dispersed in the gel. Diffusion of the drug in the gel may occur in parallel.

1.11 DRUG RELEASE KINETIC STUDY
I) Model independent Analysis\textsuperscript{[39-42]}

The difference and similarity factors, commonly known, as $f1$ and $f2$ fit factors are model independent pair wise comparisons. These parameters are currently recommended for use in most guidance documents published by regulatory agencies for the comparison of dissolution profiles. The regulatory requirement as set by the FDA specifies that a minimum of 12 dosage units from each manufactured batch should be tested with suitable sampling times.

$$f1 = \frac{\sum_{t=1}^{nt} |R_t - T_t|}{\sum_{t=1}^{nt} R_t} \times 100$$
Where \( n \) is the number of time points, \( R \) is the dissolution value of the reference batch (Marketed product) at time \( t \), and \( T \) is the dissolution value of the test (optimized batch) batch at time \( t \). For curves to be considered similar, \( f1 \) values should be close to 0, and \( f2 \) values should be close to 100. Generally, \( f1 \) values up to 15 (0–15) and \( f2 \) values greater than 50 (50–100) ensure equivalence of the two curves and, thus, that of the performance of the test (optimized batch) and reference product.

II) Model Dependent Analysis \([37, 38, 43, 44]\)

The application of mathematical modeling using defined equations is useful in the design of new controlled release dosage forms as it can provide information on mass transport release mechanisms that govern the release of a drug from a specific system. In addition, these models can be used to quantitatively predict the kinetics of drug release from specific dosage forms.

Drug release kinetics from monolithic matrix device systems may be influenced by a variety of factors including the composition of the matrix device \( i.e., \) type and amount of drug, the geometry of a system, the solubility of the drug in the matrix material and the dynamics of the gel layer in which the drug is dissolved, including thickness and viscosity. In addition, drug release may be limited by the rate of dissolution medium infiltration into the drug delivery device.

There are simple empirical or semi-empirical models such as those defined by Higuchi and Korsmeyer-Peppas, also known as the “power law” that can be applied to characterize drug release profiles and elucidate the mechanisms of drug release from monolithic devices. In addition, more mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously have also been defined.

The Zero Order Model

The dissolution of an API from dosage forms that do not disintegrate or disaggregate and release drug at a constant rate may be characterized or represented by a zero order model.
Dosage forms that follow a zero-order model release mechanism, release the API in a constant amount per unit time. Zero order release is an ideal target for sustained drug delivery formulation development. It is represented by following equation

\[ Q_t = Q_0 + K_0 t \]

Where,
- \( Q_t \) = the amount of drug released at time = \( t \)
- \( Q_0 \) = the initial amount of drug in solution at \( t = 0 \)
- \( K_0 \) = the zero-order release rate constant
- \( t \) = time

**The First Order Model**

The first order kinetic model was used to describe and characterize the absorption and/or elimination of certain drugs from biological systems. This model may be applied to dissolution testing were sink conditions exist, as the percentage of drug dissolved at a certain time point may be equivalent to the percentage surface area at that time point. The first order kinetic model can be represented by following equation.

\[ \ln Q_t = \ln Q_0 + K_1 t \]

Where,
- \( Q_t \) = the amount of drug released at time = \( t \)
- \( Q_0 \) = the initial amount of drug in solution at \( t = 0 \)
- \( K_1 \) = the first order release rate constant
- \( t \) = time

**The Higuchi Model**

Higuchi described drug release by diffusion process, dependent on the square root of time. This description of drug release can be used to characterize the dissolution process from several types of modified release systems and a simple form of Higuchi equation is shown in Equation

\[ F_t = KH t^{1/2} \]

Where,
- \( KH \) = Higuchi dissolution rate constant
- \( F_t \) = the amount of drug released at time = \( t \)
- \( t \) = time
The “Power Law”
A simple semi-empirical model that relates drug release to elapsed time with an exponential function has been reported. This relationship is referred to as the Korsmeyer-Peppas model or the “Power law” and is represented mathematically using Equation

\[ \frac{M_t}{M_\infty} = K t^n \]

\( M_t/M_\infty = \) fraction of drug released at time \( t \)
\( K = \) kinetic constant
\( n = \) diffusion exponent for drug release

This model has been applied to various systems in which the value for \( n \) is used to describe different release mechanisms. Specific values for \( n \) represent different mechanisms (Table 1.3).

<table>
<thead>
<tr>
<th>Diffusion Exponent (n)</th>
<th>Diffusion Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45</td>
<td>Fickian Diffusion</td>
</tr>
<tr>
<td>0.45 &lt; n &lt; 0.89</td>
<td>Anomalous (non-Fickian) diffusion</td>
</tr>
<tr>
<td>0.89</td>
<td>Case-II transport</td>
</tr>
<tr>
<td>n &gt; 0.89</td>
<td>Super case-II transport</td>
</tr>
</tbody>
</table>

1.12 Stability study: [45-48]
Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. Any considerable deviation from the appropriate release would render the controlled release product useless. The in-vitro and in-vivo release rates of controlled release product may be altered by atmospheric or accelerated conditions such as temperature and humidity.
Definition: Stability is defined as “the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity” (FDA 1987).

Objective and Purpose:
Most recently a guideline issued by the International Conference on Harmonization (ICH, 1993) indicates that the purpose of stability testing is to provide evidence on how the quality of a drug substance or the drug product varies with time under the influence of variety of environmental factors, such as temperature, humidity and light, and enables recommended storage conditions, retest periods, and shelf life to be established. Basically, there are two types of stability studies:
- Short –term stability studies
- Long - term stability studies

A typical short-term stability study is an accelerated stability testing study under stressed storage conditions. The purpose of it is not only to determine the rate of chemical and physical reactions but also predict a tentative expiration-dating period under ambient marketing conditions.

1.13 FACTORIAL DESIGN: [49-52]
Factorial designs are used in experiments where the effects of different factors or condition on experimental results are to be elucidated. Independent variables are formulation and process variable directly under the control of the formulator. Dependent variable are responses of independent variables. The result of Factorial design may be used a) To help interpret the mechanism of an experimental system. b) To recommended or implement of practical procedure c) as guidance for further experimentation.

The simplest factorial experiments consist of four trials two factors each at two levels. If three factors A, B and C each at two level, eight trials are necessary for a full factorial design. This is also called as $2^3$ experiments. If two factors each at three levels are called as $3^2$ experiments.

In $3^2$ factorial design study, two independent factors, A and B are to be set at three levels. High, medium and low levels of each factor are to be coded as +1, 0 and –1, respectively. The range of a factor must be chosen in order to adequately measure its
effects on the response variables. Stepwise linear regression analysis is to be used to find out the control factors that significantly affect response variables.

\[ Y = b_0 + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2 \]

Y is dependent variables, A and B are independent variables, \( b_0 \) is the arithmetic mean response of 9 runs and \( b_i \) is the estimated coefficient for the factors A and B. The main effects (\( b_1 \) and \( b_2 \)) of A and B represent the average result of changing one factor at a time from its low to high value. The interaction terms \( b_3 \) of (AB) shows how the response changes when 2 factors are changed simultaneously.
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