### CHAPTER-1

**INTRODUCTION**

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CHAPTER-1
INTRODUCTION

1.1. ORAL DRUG DELIVERY[1]

Oral dosage forms like tablets & capsules are prepared to release active pharmaceutical ingredient right after administration. This achieves faster and complete oral absorption and also relative pharmacodynamic effect. The drug concentration in plasma declines, once drug absorption from dosage form is finished, as per its pharmacokinetic profile. As a result, drug concentration in plasma falls below minimum effective concentration (MEC), therapeutic activity of that drug is lost. If a sustained effect is desired another dose of same drug is given before it reaches MEC. Alternatively a sustained release dosage form of a drug can be used to maintain drug concentration in plasma.

Modified-release dosage forms are products that change the timing and/or the rate of drug release from the dosage form. They conveniently accomplish therapeutic objectives which are not usually seen with conventional oral dosage forms.

1. Extended-release drug products:
   Dosage frequency can be reduced to a great extent compared to regular immediate release dosage forms.
   Ex: Controlled-release dosage forms and Sustained-release dosage forms.

2. Delayed-release drug products:
   This dosage form releases drug in discrete portions.
   Ex: Enteric-coated dosage forms.

3. Targeted-release drug product:
   This dosage form releases drug exactly at or in close vicinity of the desired physiologic site of action. These dosage forms either have immediate release or extended-release characteristics.
<table>
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<th>Route of Administration</th>
<th>Drug Product</th>
<th>Examples</th>
<th>Comments</th>
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<td>Extended release</td>
<td>Diltiazem HCl extended release</td>
<td>Once-a-day dosing.</td>
</tr>
<tr>
<td></td>
<td>Delayed release</td>
<td>Mesalamine delayed-release</td>
<td>Coated for drug release in terminal ileum.</td>
</tr>
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<td></td>
<td>Oral mucosal drug delivery</td>
<td>Oral transmucosal fentanyl citrate</td>
<td>Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth.</td>
</tr>
<tr>
<td>Transdermal drug delivery systems</td>
<td>Transdermal therapeutic system (TTS)</td>
<td>Clonidine transdermal therapeutic system</td>
<td>Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest.</td>
</tr>
<tr>
<td></td>
<td>Iontophoretic drug delivery</td>
<td></td>
<td>Small electric current moves charged molecules across the skin.</td>
</tr>
<tr>
<td>Ophthalmic drug delivery</td>
<td>Insert</td>
<td>Controlled-release pilocarpine</td>
<td>Elliptically shaped insert designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye.</td>
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<td>Parenteral drug delivery</td>
<td>Intramuscular drug products</td>
<td>Depot injections</td>
<td>Lyophilized microspheres containing leuprolide acetate for depot suspension.</td>
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<tr>
<td></td>
<td>Water-immiscible injections</td>
<td>Medroxyprogesterone acetate (Depo-Provera®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subcutaneous drug products</td>
<td>Controlled-release insulin</td>
<td>Basulin is a controlled-release, recombinant human insulin delivery.</td>
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</table>
Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form. Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

1.2. Oral controlled release drug delivery systems [2, 3]

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

To overcome fluctuations in dose release of conventional dosage forms, extensive research has paved way to develop controlled drug delivery system brought about drastic changes in medication techniques with innumerable therapeutic benefits.
1.2.1. Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.
- Make use of special effects, e.g. Sustained-release aspirin, when taken before bed, it can produce relief in the morning in case of arthritis patients.
- Reduction in health care costs i.e. Economy, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.
1.2.2 Disadvantages of Controlled Drug Delivery Systems

- Increased variability among dosage units.
- Poor \textit{in vitro} – \textit{in vivo} correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Withdrawal of drug from the body is difficult in case of poisoning, toxicity and hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counseling.
- Reduced potential for dose adjustment of drugs.

\textbf{Fig 1.1} - Conventional multiple dosing and several unit (single) doses of sustained as well as controlled delivery formulations.

(MSC = maximum safe concentration, MEC = minimum effective concentration).
1.3. SELECTION OF DRUG CANDIDATE FOR SUSTAINED DOSAGE FORM

The physico chemical properties of the drug such as pKa, partition coefficient, biological half life, molecular weight, dose of the drug etc., have to be considered before selection [4,5]

**Characteristics of drugs suitable for formulation as Sustained Release Products**

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

**Characteristics of drugs unsuitable for formulation as Sustained Release Products**

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (anticoagulants)
7. No clear advantage for sustained release formulation (Griseofulvin)

1.4. Types of oral controlled release drug delivery systems

A number of techniques are used to achieve controlled release of drugs via the oral cavity. Most of these drugs depend on either dissolution mechanism or diffusion mechanism or both mechanisms to produce slow release of drug from dosage form.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems
- Gastro retentive drug delivery systems
Electrically stimulated release devices
Ion-exchange resins

1.4.1. Dissolution controlled release systems [6]

A drug which has slow rate of dissolution will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. Therefore sustained release dosage form of drugs can be prepared by lowering their dissolution rate. Dissolution controlled systems can be made either by

- Varying concentration of rate controlling coats or polymers (Matrix Dissolution Systems) or
- By administering the drug in groups made of beads having coatings of varying thickness (Encapsulated Dissolution Systems)

Matrix Dissolution Systems are prepared by compressing the tablet with a slowly soluble polymer carrier into tablet form. Wax matrices are prepared either by congealing or dispersion the drug-wax mixture in water.

Encapsulated Dissolution Systems contain beads that have different coating thickness, their release occurs progressively. Thin layers deliver the initial dose and layers of thicker coating deliver maintenance levels. This dissolution process at steady state is described by the Noyes-Whitney equation.

\[
dc / dt = KD A (C_s - C) = DA / h (C_s - C)
\]

\[
dc / dt = \text{dissolution rate.}
\]
\[
K_D = \text{dissolution rate constant.}
\]
\[
D = \text{Diffusion coefficient.}
\]
\[
C_s = \text{saturation solubility of the solid.}
\]
\[
C = \text{concentration of solute in the bulk solution}
\]
Commerically available products belonging to this category are given below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamox Sequels</td>
<td>Acetazolamide</td>
<td>Lederle</td>
</tr>
<tr>
<td>Nicobid Temples</td>
<td>Nicotinic acid</td>
<td>Rorer</td>
</tr>
</tbody>
</table>

1.4.2. Diffusion Controlled Release Systems

Diffusion through a water insoluble polymer determines release rate of drugs. They are classified into two types of diffusion device

1.4.2.1. Reservoir devices:

Reservoir devices possess a core which contains drug (reservoir). A polymeric membrane surrounds the core and mostly its nature controls rate of drug release.

The Reservoir type devices include micro-encapsulation of drug particle & coating of tablets containing drug cores.

*Advantages*

i) These devices can offer zero-order release of the drug.

*Disadvantages*

i) Device must be taken off from the implant site.

ii) It is tedious to deliver compounds with high molecular weight.

Commerically available products belonging to this category are given below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nico-400</td>
<td>Nicotinic acid</td>
<td>Jones</td>
</tr>
<tr>
<td>Nitro span</td>
<td>Nitroglycerin</td>
<td>Rorer</td>
</tr>
</tbody>
</table>
1.4.2.2. Matrix devices: [70, 71, 72]

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method of preparation is to mix the drug with the matrix material and then compress the mixture. Drug releases through porous or granular matrix can be described by

\[ M = (D_s C_a \{P/T\} \{2C_0 - PC_a\}t)^{1/2} \]

Where
- \( P \) = Porosity of the matrix
- \( T \) = Tortuosity
- \( C_a \) = Solubility of the drug in the release medium
- \( D_s \) = Diffusion coefficient in the release medium

Advantages
- i) Can deliver high molecular weight compounds.

Disadvantages
- i) Cannot obtain zero order release
- ii) Remaining matrix must be necessarily removed in case of implanted systems.

Commercially available products belonging to this category are given below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fero-Gradumet</td>
<td>Ferrous sulfate</td>
<td>Abbott</td>
</tr>
<tr>
<td>Choledyl SA</td>
<td>Oxtriphylline</td>
<td>Parke-Davis</td>
</tr>
</tbody>
</table>

1.4.3. Diffusion and dissolution controlled systems

In those systems the release rate of drug depends on both the diffusion and dissolution mechanisms.

1.4.4. Osmotically controlled release systems

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an Osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant
amount of drug per unit time or by the use of a "push–pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is released via a single laser-drilled hole in the tablet.

A representative osmotic oral drug product is the "push–pull" system called Gastrointestinal Therapeutic System (GITS), developed by Alza Corporation for Nifedipine (Procardia XL) and other drugs. The system consists of a semipermeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer.

**1.4.5. Gastro retentive drug delivery systems**

Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery Systems (GRDDS). These forms constantly release drug over an extended period of time. These systems are used for drugs with high absorption window and enhance their controlled delivery to ensure optimum bioavailability.

Ex: Bioadhesive systems, swelling and expanding systems, High density systems and Low density (Floating) systems.

**1.4.5.1. Bioadhesive systems**

Bioadhesion is the process whereby synthetic and natural macromolecules adhere to the biological membranes in the body and remain there for an extended period of time. If the membrane substrate is mucosal layer then the process is referred to as mucoadhesion. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

**1.4.5.2. Swelling and expanding systems**

These systems increase the residence time of the dosage form in the stomach. Particles greater than 10mm are unable to enter the duodenum and are retained in the stomach. The swelling systems incorporate hydrogels which are polymers that can swell up to 100 times their dry weight. The hydrogels used must be biodegradable.
1.4.5.3. High density systems

In High density systems the bulk density of the dosage form must be around 1.40 and is in excess to that of stomach. To prepare these forms, drug is coated over a core using heavy and inert materials like barium sulfate or titanium dioxide. The pellet is weighed and then coated with a membrane controlled by diffusion.

1.4.5.4. Low density systems / Floating systems:

Bulk density of floating drug delivery systems (FDDS) is lesser to that of gastric fluids so that they exist buoyant in stomach with no effect on rate of gastric emptying over a prolonged duration of time. The drug is slowly released at a predetermined rate from these floating systems. When the drug release is complete the residual entity is removed from the stomach. The net result is an increase in GRT with a better control of fluctuations in plasma drug concentration. These systems are suitable for drugs that are poorly soluble or unstable in the intestinal medium.

1.4.6. Electrically Stimulated Release Devices

These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile. In order to optimize drug therapy, drug release from the devices which are implanted in the body must be controlled precisely with respect to its quantity and timing. Electrically-controllable drug release from polyelectrolyte hydrogels is helpful in achieving these goals.

Ex: Ejection of drug from gel where fluid phase synereses out, drug diffusion across concentration gradient, electrophoresis of charged drugs and release of entrapped drug when gel complex erodes.
1.4.7. Ion-Exchange Resins

Cross linked polymers which are water insoluble are used as resins. They contain a repetitive functional groups spread all over the resin intended to form salts with opposite charges. Drug is attached to these groups on resin and can be released when exchanged with suitably charged ions come into contact.

\[
\text{Resin}^+ \cdot \text{Drug}^- + X^- \rightarrow \text{Resin}^+ \cdot X^- + \text{Drug}^-
\]

Conversely,
\[
\text{Resin}^- \cdot \text{Drug}^+ + Y^+ \rightarrow \text{Resin}^- \cdot Y^+ + \text{Drug}^+
\]

\(X^-\) and \(Y^+\) indicate ions present in the GIT. Thus free form of drug can now diffuse out. In a chromatography column, the resin and drug are constantly exposed to each other or they are kept in contact for prolonged period by forming a solution. Either of the two methods can be used to prepare a drug-resin complex.

Factors that control rate of diffusion of drug from resin include diffusion area, path length and resin rigidity. An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethylcellulose or wax. These systems rely on the polymer coat to govern the rate of drug availability.

A representative listing of ion-exchange resins is given below

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphetamine capsules</td>
<td>Amphetamine, Dextroamphetamine</td>
<td>Fisons</td>
</tr>
<tr>
<td>Ionamin capsules</td>
<td>Phenteramine</td>
<td>Pennwalt</td>
</tr>
</tbody>
</table>
1.5. Factors controlling Design and Performance of Sustained release products [7]

The design of controlled-release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance.

Physicochemical factors

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Diffusivity

Biological factors

- Absorption
- Distribution
- Elimination
- Biological half life and Duration of action
- Side effects and Margin of safety
- Dose size
- Disease state

1.6. PHYSICOCHEMICAL FACTORS [8, 9]

- Aqueous solubility

Dissolution rate of a drug is influenced by its aqueous solubility. As a result a concentrated solution is formed which acts as gradient for diffusion across membrane. The choice of mechanism for oral sustained release systems is limited by aqueous solubility of the drug. Diffusion systems fail to be in use for drugs with low solubility because the driving force required for diffusion; the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system.
Partition coefficient

Partition coefficient ($K_{o/w}$) is the relative solubility of the drug with respect to oil and water phases when they exit together. It can be written as ratio of solubility in oil and water.

\[ K = \frac{C_o}{C_w} \]

Where
\[ C_o = \text{amount of drug in oil phase} \]
\[ C_w = \text{amount of drug in aqueous phase} \]

Lipid soluble drugs have high $K_{o/w}$ and they have low water solubility. So these drugs remain in the body for long periods as they can localize in the lipid membranes of cells. (e.g.: Phenothiazines). Compounds with very low $K_{o/w}$ will have difficulty in penetrating membranes. Bioavailability of such drugs is low. Polymer membranes also work on same principles of partition for diffusion and this nature of drug largely decides the choice of diffusion membrane. If the partition coefficient of a drug is greater or lesser than the optimum or normal value (i.e., 1000/1), they are poor candidates for formulation into SR dosage forms.

Drug stability

Drugs given by oral route may undergo degradation due to hydrolysis by acid or base or by enzymatic breakdown. Propantheline is delivered in such a way that it releases drug in intestine because it is unstable in stomach. For drugs which are unstable in intestine they are designed to release drug in stomach. In general, drugs having a problem of stability in any given portion of the gastrointestinal tract are less suitable for formulation into sustained release systems.

Protein binding

Many drugs bind to plasma proteins with a significant influence on the duration of drug action. For protein bound drugs, their distribution is controlled by the respective dissociation from the drug - protein complex. This complex serves as a reservoir and helps to achieve a controlled release of drug into extra vascular tissues. These drugs
possess longer elimination half-life and they need not be made as a sustained release dosage form.

- **Molecular size and Diffusivity**

  The efficiency of sustained release drugs to diffuse across membranes that control diffusion rate is known as diffusivity (diffusion coefficient). This diffusivity largely depends on its molecular size (even molecular weight). The equation that shows this relation is

  \[
  \log D = S_v \log V + K_v = S_m \log M + K_m
  \]

  Where
  - \( D \) = diffusivity
  - \( M \) = molecular weight
  - \( V \) = molecular volume
  - \( S_v, S_m, K_v \) and \( K_m \) = constants in a particular system.

  In general the denser the medium, the smaller is the diffusivity.

**Biological Factors [10, 11]**

  The design of sustained release products should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing.

- **Absorption**

  When a drug is made as sustained release dosage form, its rate of absorption, extent of absorption and uniformity of absorption are considered as crucial factors. To maintain a constant blood or tissue level of drug, it must be uniformly released from the sustained release system and then uniformly absorbed. Rate determining step is drug release from a dosage form, so for a successful system the absorption rate should be higher than its release. For sustained release dosage form, the rate constant for drug release is much less than the constant for drug absorption (i.e., \( K_r << K_a \)). Assuming that the transit time of a drug through the absorption area of the gastrointestinal tract is between 9 and 12 hrs, the maximum absorption half-life should be 3 to 4 hrs. This value
is given assuming minimum rate constant of absorption would be $K_a$ of 0.17 to 0.23 hr$^{-1}$ necessary for about 80 to 95% absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption (i.e., $K_a >> 0.23$ hr$^{-1}$), the above discussion implies that a first order release rate constant $K_r < 0.17$ hr$^{-1}$ is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into sustained release dosage forms.

### Distribution

Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution ($V_d$) and the ratio of drug concentration in the tissue to that in plasma (T/P ratio) at the steady state. In general, the bound portion of drug can be considered inactive and unable to cross membranes. At high binding one sees prolonged drug action. The magnitude of drug distribution and its binding to the components inside the body are often described by using apparent volume of distribution. The total apparent volume of distribution for a drug at steady state can be calculated from the following equation.

$$V_{dss} = \frac{(k_{12}+k_{21})}{k_{21}}V_p$$

Where

$V_{dss}$ is the apparent volume of distribution at steady state

$K_{12}$ and $K_{21}$ are the constants for the distribution of drug from the central to peripheral compartment and from peripheral to central compartments respectively.

$V_p$ is the volume of central compartment.

### Elimination

Elimination of a drug involves two aspects i.e., metabolism and excretion. Drug metabolism can occur in two ways. An active drug can convert to inactive metabolite or an inactive drug can convert to active metabolite. Bioavailability of a drug is decreased if it is metabolized in the intestine even before its absorption particularly from slowly releasing dosage forms. Metabolism of a drug will be reflected in the elimination rate
constant. This property can be used for designing of sustained release dosage forms. If the therapeutic activity of a drug is due to its metabolite then its design is more difficult.

Ex: Isosorbide 2, 5-dinitrate.

**Biological half life and duration of action**

The main aim of sustained release systems is to achieve and maintain blood levels of drug above therapeutic level for extended time period. Half-life is the measure of elimination rate. Before designing these systems it is essential to consider biological half-life of a drug and its duration of therapeutic action. Compounds having a shorter biological half-life are better choice to make sustained-release systems as it decreases dosage frequency. Limitations include, for drugs having very short half lives, higher quantities of drug must be placed into each dosage unit for maintaining sustained effect. Ideal candidates for designing sustained release systems are those having biological half lives between 2 – 8 hrs.

**Side effects and margin of safety**

Side effects can decreased by controlling plasma concentration of a drug at any give time, and hence controlled release formulations appear to offer a solution to this problem. By slowing the rate at which the drugs are released, the chances of gastrointestinal irritation will be reduced due to a smaller amount of drug exposed to the gastrointestinal mucosa at the given time. The most widely used measure of the margin of safety of a drug is its therapeutic index (TI).

\[ TI = \frac{TD_{50}}{ED_{50}} \]

Where

- \( TD_{50} \) = median toxic dose
- \( ED_{50} \) = median effective dose

Drugs having lesser therapeutic window are also poor choice for sustained release products.

**Dose Size**

For oral forms the maximum dose is 0.5 to 1gm in case of conventional dosage forms. Same can be followed for sustained release systems.
Disease State

Sometimes the disease states are considered before the designing of an oral SR dosage form. This can be explained by taking the example of Aspirin (for rheumatic arthritis) which is not a suitable candidate for sustained release dosage form. However, it is used for maintaining drug concentrations at therapeutic level entire night, to alleviate morning stiffness.