CHAPTER 1

Controlled Drug Delivery Systems

Introduction, terminology/definitions and rationale, advantages, disadvantages, selection of drug candidates Approaches to design-controlled release formulations based on diffusion, dissolution and ion exchange principles, Physicochemical and biological properties of drugs relevant to controlled release formulations


Introduction

Drugs are administered through various routes such as oral, topical, parenteral, etc. Among all these routes, the oral route is the most common, convenient and popular. There are various reasons for such popularity. The most important and common reasons for their popularity are the convenience of administration, easy to carry and the ease of preparation on an industrial scale. About 80% of the dosage forms sold in the market are tablet dosage form. These dosage forms have been used since long, but these are found to have the following limitations.

1. The frequency of administration in a day, 'dosage regimen' is high.
2. It is difficult to monitor the daily-dose; in many cases, it is not exactly maintained.
3. There is a greater chance of missing dose.
4. Non-specific administration
5. The careful calculation is required to prevent overdosing; it is difficult to calculate the exact dose for a child or elderly patient who should not receive the adult dose.
6. The drug goes to non-target cells and can cause damage; orally administered drug must reach circulatory bloodstream every time and pass through the liver. Thus, the drug is available in the sites which are not affected.
7. Low concentrations can be ineffective. After oral administration fraction of the dose may not be absorbed, a fraction of dose is metabolized; hence, the amount of drug must be sufficient to elicit its therapeutic action.

8. High concentrations can be toxic, causing side effects or damage to organs.
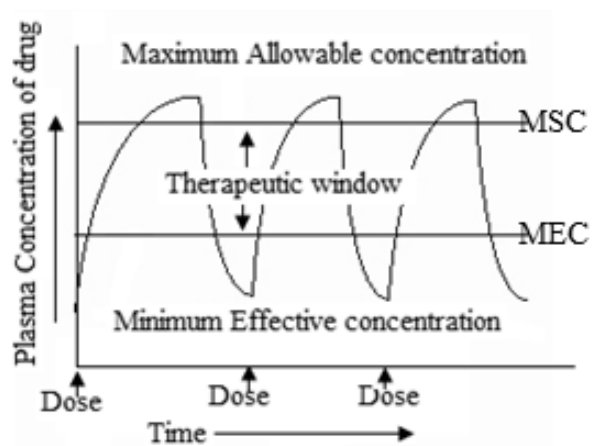9. Consumption of more drug than necessity.

After oral administration of a drug, the concentration of the drug increases gradually with time (absorption phase) as shown in **Fig. 1.1**.
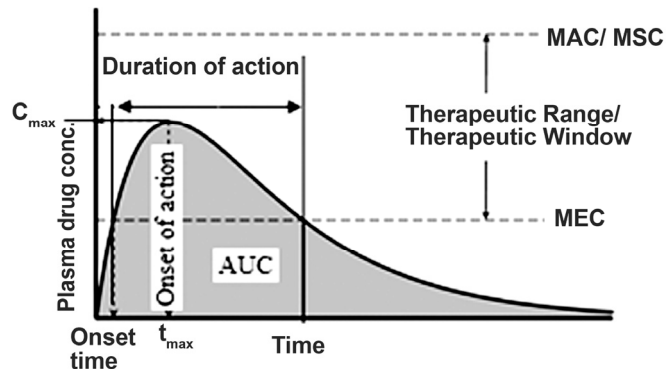
Fig. 1.1: Bioavailability profile of drug after oral administration. The curve plotted between plasma drug concentration vs. time, showing all the pharmacokinetic parameters, where; MEC- minimum effective concentration; MSC- maximum safe concentration; AUC- area under curve; C_{max}- maximum drug concentration and t_{max}- maximum time.

During this phase, absorption >> elimination. Therapeutic action starts when the concentration of the drug reaches the minimum effective concentration (MEC); the ascending portion of the curve. Once the concentration reaches to peak level, the descending phase starts (elimination phase); the metabolism and elimination phase predominates. During this phase elimination >> absorption. The therapeutic effect is observeduntil the concentration remains above the MEC. The period during which the concentration of the drug remains above the MEC is

Fig. 1.2: Fluctuation in plasma concentration of drug following conventional dosage forms

called *duration of action*. After the concentration falls below the MEC, a second dose is required to achieve continuous therapeutic action of the drug; this is shown in **Fig. 1.2**.

Terminology/Definitions

A. **Immediate release dosage forms:** The conventional dosage forms belong to this class. The dosage form releases the drug present in it after administration to achieve rapid and complete systemic absorption. After absorption of the drug from the dosage form, plasma concentration of the drug starts decreasing according to its pharmacokinetic profile. Finally, the concentration falls below the minimum therapeutic concentration (MEC) and therapeutic activity ceases. The period at which the drug concentration remains within the therapeutic window is called the *duration of action* and the time at which the maximum concentration is attained is called the *onset of action*. To maintain a steady state concentration, the next dose is administered. Thus, a conventional dosage form shows 'see-saw' or 'peak and valley' pattern of drug concentration in plasma and tissue compartments (**Fig 2**). Depending on the drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals, the magnitudes of these fluctuations varies.

B. **Modified release dosage form:** The dosage forms, in which the rate of release of the drug and the time at which the release of the drug would take place are different from conventional type, are called modified release dosage form. An enteric coated tablet can be considered as a common example of a modified release dosage form. For example, erythromycin gets decomposed in the stomach; hence it is formulated as an enteric coated tablet. The multi-layered tablet is a further advancement of the modified release delivery systems.

C. **Site-specific targeting:** These systems refer to targeting the release of a drug straight to a particular biological location. In this case, the target is adjacent to or in the diseased organ or tissue.

D. **Receptor targeting:** These systems refer to targeting a specific biological receptor. In this case, the target is the specific receptor for a drug within an organ or tissue. Site-specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

E. **Delayed release dosage form:** When a dosage form does not release the drug immediately after administration like immediate release or conventional dosage form but releases the drug in portions at a predetermined time or at times, it is called delayed release dosage form. However, in some cases, a portion of the drug may be released immediately after administration.

F. **Extended-release dosage form:** If a dosage form reduces the frequency of dose at least by two-fold as compared to the frequency of administration of immediate release or conventional dosage form, the dosage form is said to be the extended release dosage form. Sustained-release, controlled-release, or long-acting dosage forms belong to this class.
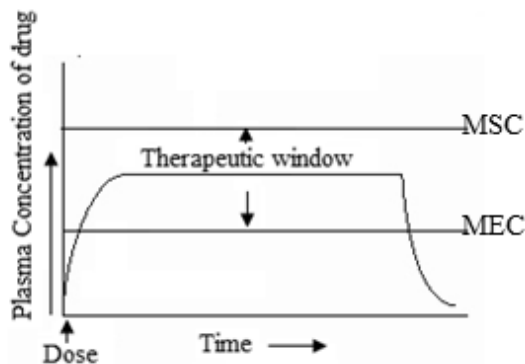
G. **Sustained release dosage form:** The drug release from sustained release dosage form exhibit a predetermined rate in order to maintain an approximately constant drug concentration in the body over a prolonged period. The rate of release of drug follows first-order kinetics. Usually, the drug content of one dose of SR dosage form is more than that of its conventional or immediate release dosage form.

H. **Prolonged action dosage form:** In this type of dosage form the drug is released at a rate relatively slower rate, but for a long period; so that, the therapeutic action of the drug remains for an extended period. In this type of dosage form, one dose of the drug is released immediately after administration and later on, the second dose is released.

Rationale of Controlled Drug Delivery

Therefore, extensive researches have been conducted to reduce the frequency of administration. The outcome is the development of controlled or sustained release drug delivery system. Controlled delivery of the drug is possible by combining a polymer with the drug or active agent; so that, the release of the drug can take place at the right time, at a predetermined rate and the right place. In this system, the release of drug can bepre-designed. Thus, controlled release dosage forms have gradually gained acceptance of the medical practitioner and popularity among the patients.

Compared to conventional dosage forms such delivery systems offer numerous advantages including improved efficacy, reduced toxicity, and improved patient compliance and convenience. All controlled release systems are developed to improve the therapeutic effectiveness of the drug.

According to the patent history, the earliest patent on SR dosage form was filed by Israel Lipowskiin 1938, who coated the pellets/particles. The basic objective of this therapy is to maintain a steady state therapeutic concentration of drug in blood or tissue for an extended period, as shown in **Fig. 1.3**. The controlled or sustained release dosage form can be defined as; *The dosage forms that release a drug at a predetermined rate so that a constant drug*

Fig. 1.3: No fluctuation in plasma concentration of drug following controlled release dosage form

concentration is maintained for a specific period with a minimum side effect. A single dose of such dosage form is used for extending the therapeutic action. The dose size is more than a single conventional dose, but the total daily dose is reduced.

The primary reason for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamic properties of the drug substance. This is possible by using a novel drug delivery system or by modifying the molecular structure and physiological parameters. A properly designed dosage form should provide the drug action for a prolonged period. The key objective of controlled drug delivery is to confirm safety and to improve the efficiency of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and frequency of dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary for each drug. For every drug, there is a definite therapeutic window. Below the MEC, the therapeutic effect of the drug is ineffective, and above MSC toxic side effects are elicited. The therapeutic index is defined as the ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}). The rationale of controlled release dosage form can be summarized as below:

- To provide a location-specific action within the GIT.
- To avoid an undesirable local action within the GIT.
- To provide a programmed delivery pattern.
- To increase the rate and extent of absorption/bioavailability.
- To extend the duration of action of the drug.

General Advantages

The release of the active ingredient (drug) may be constant over a long period; it may be cyclic. The environment or other external events may trigger it. Controlled release drug delivery systems provide one or more of the following advantages.

- Maintenance of drug level within the desired range
- Delivery of 'difficult' drugs: the slow release of water-soluble drugs, and/orfast release of poorly soluble drugs
- Reduces dosing frequency
- Eliminates over or underdosing
- Prevention or reduction of side effects
- Reduction in total health care cost
- Improved efficacy in the treatment
- Reduction in adverse side effects and improvement in tolerability
- Improved patient compliance
- Employ less amount of total drug
- Minimizes or eliminates local or systemic side effects
- Minimal drug accumulation on chronic usage
- Cures or controls the condition more promptly
- Reduces the fluctuation in drug level

- Improves the bioavailability of some drugs
- Makes use of special effects

Disadvantages

Various disadvantages of the controlled drug delivery systems are mentioned below:
- Likely to be costly
- Unpredictable and often provide poor *in-vitro – in-vivo correlations*
- May cause dose dumping, if the release design is failed
- Provides less scope for dosage adjustment
- May increase the first pass clearance
- Poor systemic availability in some cases
- Effective drug release period is influenced and limited by the gastric residence time

Clinical Advantages of Control Release Dosage Forms
- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage, when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)
- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient

Commercial / Industrial Advantages
- Illustration of innovative/technological leadership
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension

Major Limitations
- Delay in the onset of action
- The possibility of dose dumping in the case of a poor formulation strategy
- Increased potential for first-pass metabolism
- Greater dependence on the gastric residence time of the dosage form
- The possibility of less accurate dose adjustment in some cases
- Cost per unit dose is higher when compared with conventional doses
- All drugs are not suitable for formulating into ER dosage form

Selection of Drug Candidates

All the drugs cannot be formulated as their controlled release dosage forms. A drug must have the following characteristics for the formulation of controlled release dosage forms.

- Very short elimination half-life
- Very long elimination half-life
- Narrow therapeutic index
- Rate of absorption
- Mechanism of absorption
- First pass effect

Factor Influencing the Design and Performance of Controlled Drug Delivery System

1. Biopharmaceutic characteristics of the drug
   - The molecular weight of the drug
   - The aqueous solubility of the drug
   - Apparent partition coefficient
   - Drug pKa and ionization physiological pH
   - Drug stability
   - Mechanism and site of absorption
   - Route of administration.
2. Pharmacokinetic characteristics of the drug
   - Absorption rate
   - Elimination half-life
   - Rate of metabolism
   - Dosage form index
3. Pharmacodynamic characteristic of the drug
   - Therapeutic range
   - Therapeutic index
   - Plasma–concentration-response relationship

The fabrication of the formulation depends on the physicochemical properties of the drug and on the pharmacokinetic behavior of the drug. In conventional dosage form, the rate-limiting step in drug's bioavailability is usually absorption through the bio-membrane; where as in controlled drug delivery system the rate-limiting step is the release of drug from the dosage form.

Approaches to Design Controlled-release Formulations

Primarily there are two approaches or concepts to design and prepare controlled/sustained release dosage form:

(a) Modification of the drug molecule, and (b) Modification of the dosage form.

There are hundreds of commercial products based on controlled release technologies. Only a few show distinct mechanisms of controlled drug release. Oral controlled-release formulations are designed mainly based on physical mechanisms. The chemical degradation, enzymatic degradation, and prodrug approach are less. **Table 1.1** presents different classes of marketed products based on controlled release mechanisms. All controlled-release formulations are designedby one mechanism or combination of a few mechanisms.

Table 1.1: Marketed formulations of drugs with the technology used

S.No.	Drug	Branded Formulation	Technology
1	Bupropion	WellbutrinWL	Diffusion controlled-release
2	Zolpidem tartarate	Ambien CR	Matrix system (Tablet)
3	Chlorpheniramine Polistirex and Hydrocodone Polistirex	TussionexPennkinetic ER suspension	Ion-exchange system
4	Chlorpheniramine Maleate Glipizide	Efidac 24® Glucotrol XL®	Osmosis-based system Elementary osmotic pump Push-pull osmotic system
5	Propranolol HCl	Inderal ® LA	pH independent formulation
6	Levodopa and Benserazide	Modapar	Altered density formulation

The modified-release dosage form can be categorized into the following;

- Delayed release
- Extended-release
- Sustained release
- Controlled release
- Timed release
- Prolonged release

Broadly the modified release dosage form can be classified as below **(Fig. 1.4),**
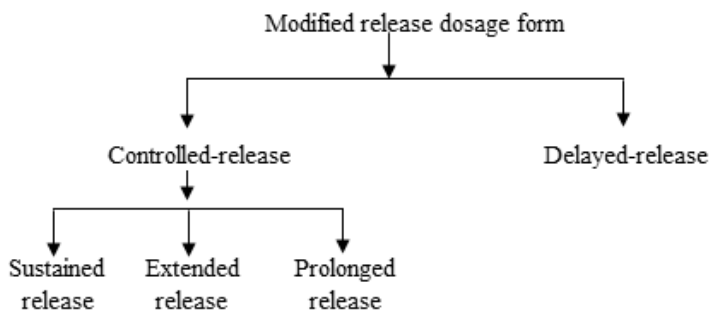
Fig. 1.4: Classification of modified release dosage form.

Based on the mechanism of drug-release and carrier used, the modified-release dosage form can be classified into the following six categories;

1. Diffusion sustained system
    (a) Reservoir type   (b) Matrix type
2. Dissolution sustained the system.
    (a) Reservoir type   (b) Matrix type
3. Methods using Ion-exchange
4. Methods using osmotic pressure
5. pH-independent formulations
6. Altered-density formulations

Dissolution Controlled-release

The simple preparation of this category is sustained-release oral products, where dissolution is the rate-limiting step. When the rate of dissolution of a drug is high, the drug is mixed with a carrier having a slow rate of dissolution, and a tablet is prepared to sustain or control the release of the drug.

When the dissolution process is diffusion layer controlled, the rate of diffusion of the drug from the solid surface to the bulk solution through an unstirred liquid film is the rate-limiting step. Insuch case, the dissolution process at steady-state would be described by Noyes-Whitney equation,

$$\frac{dC}{dt} = K_D A(C_s - C) \qquad \qquad .....(1.1)$$

Where, $\frac{dC}{dt}$ = Dissolution rate.

K_D = Dissolution rate constant.

C_s = Saturation solubility of drug, and

C = The concentration of drug in bulk of the solution.

There are two ways to prepare dissolution-controlled preparations:

- Dissolution-controlled encapsulated/coated system
- Dissolution-controlled matrix system
- **Dissolution-controlled encapsulation:** In this method, the particles or granules of the drug are coated individually with slowly dissolving coating material (**Fig. 1.5**). The coated particles are compressed into a tablet directly; such as space tabs or Spansules.
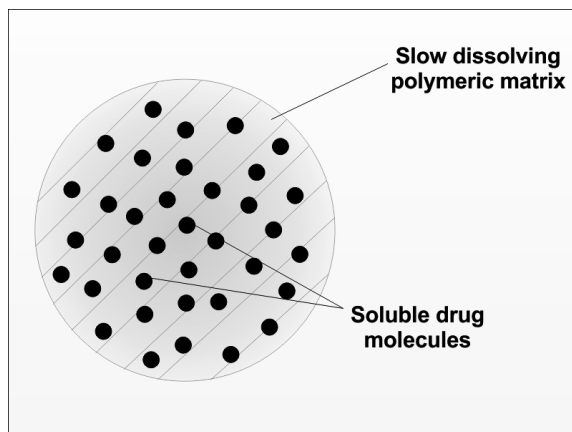
Fig 1.5: Schematic diagram of the drug release from the reservoir system by dissolution of polymeric matrix.

Erosion-controlled systems

Erosion-controlled drug delivery systems are alternatively called *stimuli-induced systems*. These systems are activated by an external stimulus, such as pH, temperature, enzymes or osmotic pressure and release the drug. Drug release occurs depending on the mechanism of erosion surface or bulk. If the pH of the environment is not favorable for dissolution of the dosage form, the drug release will not occur (pH sensitive dosage form). Polymers are commonly used for coating of the pH-sensitive systems. Usually acrylates (methacrylic acid copolymers) and cellulose esters (cellulose acetate phthalate) are used for coating; however, these can also be used to make matrix systems (**Fig. 1.6**).
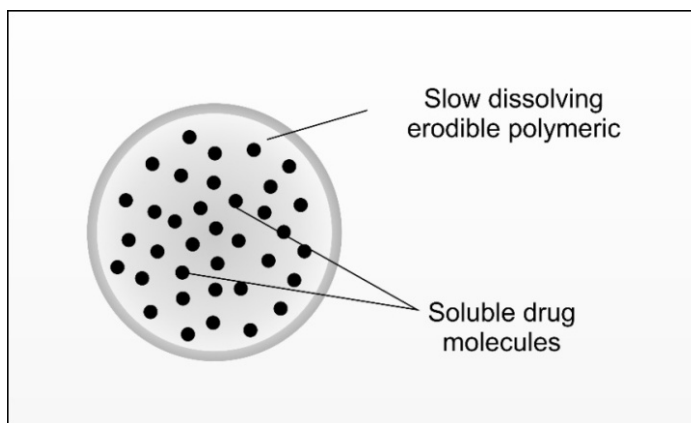
Fig. 1.6: Schematic representation of an erosion controlled system

Dissolution-controlled matrix

In this method, the drug is mixed with a slowly dissolving carrier to prepare a matrix material, which is then compressed. The rate of bioavailability of the drug is controlled by the rate of penetration of the dissolution fluid into the matrix. The penetration of the medium is controlled by the porosity of the tablet matrix, the presence of hydrophilic material, the wettability of the tablet, and the particle surface.

Poorly water-soluble drugs (BCS class II and IV) inherently show sustained release. In the case of water-soluble drugs, a water-insoluble carrier is incorporated in the formulation to reduce the rate of dissolution of the drug particles, which are pre-coated with this type of materials; such as polyethylene glycol. In this type of formulation disintegrating agent may not be used to help delayed release.

Hybrid systems

These are a combination of the robustness of matrix systems with the constant-release kinetics of reservoir systems. The drug is incorporated (entrapped) into a release-controlled matrix, and the matrix is then coated with a polymer. High molecular weight compounds can also be incorporated. The advantages of this system are many folds –

- Cost-effectiveness,
- Easy to manufacture, and
- Can be prepared by conventional processes and equipment.

Diffusion-controlled release

These systems may be of two types:

1. Diffusion-controlled encapsulation, and
2. Osmotic pressure is rate limiting.

Diffusion controlled encapsulation

In diffusion-controlled formulations, drug molecules diffuse through a polymer membrane or a polymer matrix and are released. Depending on whether a polymer membrane surrounds a drug or distributed within the polymer matrix, diffusion-controlled formulations can be divided into categories:

- Reservoir system, and
- Monolithic systems.

In nonporous reservoir systems, drug molecules diffuse through the polymer membrane; but in microporous reservoir systems, the drug molecules are released by diffusion through micropores. The micropores are usually filled with either water or oil.

In addition to nonporous and microporous systems, diffusion-controlled monolithic systems can be further classified by the concentration of the loaded drug. In the monolithic system, the drug is loaded by soaking a polymer matrix in a drug solution. The concentration of drug inside the matrix cannot be higher than the solubility of the drug; if

the partition coefficient of a drug is 1. If the drug loading is higher than the drug's solubility, the monolithic system is called monolithic dispersion.

Fick's law gives the flux of the drug J (in amount/area - time), across a membrane in the direction of decreasing concentration.

$$J = - D \, dc/dx$$

Where, D = diffusion coefficient in area/ time,

dc/dx = change of concentration 'c' with distance 'x'

A release rate of the drug characterizes diffusion systems is dependent on its diffusion through inert water insoluble membrane barrier. There are two types of diffusion devices.

(a) Reservoir Type: In the system, a water-insoluble polymeric material encloses a core of drug, which controls release rate.

The drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. The additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate. The rate of drug released (dm/dt) can be calculated using the following equation

$$\frac{dm}{dt} = ADK\frac{\Delta c}{l}$$

Where, A = Area,

D = Diffusion coefficient,

K = Partition coefficient of the drug between the drug

core and the membrane,

ℓ = Diffusion path length and

ΔC= Concentration difference across the membrane.

Advantage
- Zero-order delivery is possible with this method,
- Release rates variable with polymer type.

Disadvantages
- The system must be physically removed from implant sites.
- Difficult to deliver high molecular weight compound,
- Generally increased cost per dosage unit,
- Potential toxicity may occur if the system fails.

(b) Matrix Type: A solid drug powder is homogeneously dispersed within a rate controlling medium, an insoluble matrix. The waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc. are used to prepare the matrix. These waxes

control drug dissolution by controlling the rate of dissolution in fluid and subsequent penetration into the matrix. The medium alters the porosity of the tablet, decreases its wettability or dissolves at a slower rate. The drug release from such matrices follows the first order kinetics. The wax-the embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same. The rate of drug release is subject to the rate of drug-diffusion, not on the rate of dissolution of the drug.

Advantages

- Production of this system is more accessible than reservoir or encapsulated devices,
- High molecular weight compounds can be delivered.

Disadvantages

- Cannot provide zero order release,
- Removal of the remaining matrix is necessary for the implanted system.

Osmosis-Based Formulations: Osmosis is the movement of a solvent (water) from its higher concentration to its lower concentration through a semipermeable membrane. While diffusion is the movement of solute from its higher concentration to lower concentration.This principle of osmosis has been used for the development of zero-order release drug delivery systems.

These systems are made-up by encapsulating an osmotic drug core (**Fig 1.7**) comprising an osmotically active drug (or a blend of an osmotically inactive drug with an osmotically active salt such as NaCl, **Fig 1.8A**) within a semi-permeable membrane made from biocompatible polymers, such as cellulose acetate. Once a difference (gradient) in osmotic pressures is created, the drug (solute) is continuously pumped out of tablet through small delivery orifice present in tablet coating. This continues for a prolonged period, about 24hrs. This type of drug system provides drug solutes continuously at a zero-order rate and release of the drug is independent of the environment of the gastrointestinal tract but depends on the osmotic pressure of the release medium. However, the manufacturing process is complicated. Basic osmotic systems can deliver only water-soluble drugs. Water-insoluble drugs can be delivered by "push-pull" osmotic systems (**Fig 1.8B**). There is a non-swelling solubilizing agent that enhances the solubility of insoluble drugs and a non-swelling agent that enhances the contact-surface area of the drug substances with the incoming aqueous liquid when it is dispersed throughout the composition. Different polymer membranes have different water vapor transmission value. The semipermeable membrane should be selected based on the nature of the application.
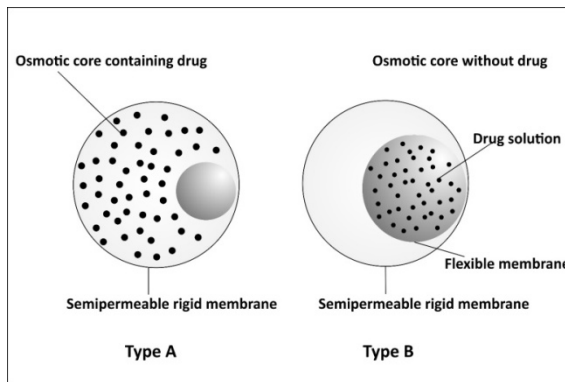
Fig. 1.7: Schematic representation of drug encapsulation in Osmotic system; Type A: Drug present in the osmotic core and Type B: Osmotic core without drug and the drug is present inside a flexible membrane.
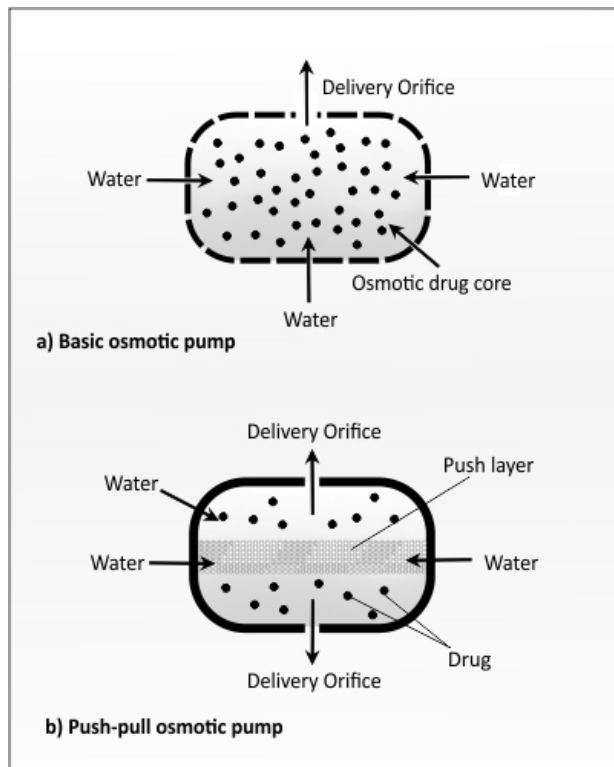
Fig. 1.8: Schematic representation of different types of osmotic pumps; (a) represents the basic osmotic pump and (b) represents the Push-pull osmotic pump.

Based on Ion exchange Principles

Ion exchange resins are also used to control the release of drugs. The water-insoluble polymeric materials containing ionic groups are used as resins. Through electrostatic interaction, the drug molecules attach onto the oppositely charged ionic groups of the resin. The drug molecules can be exchanged with other ions having the same charge and accordingly, the drug molecules are released from the ion-exchange resin. This principle is used to prepare the controlled-release dosage form of anionic or ionizable drug. The method of preparation is simple:

(a) The ionized drug is absorbed onto the ion-exchange resin granules; for example, codeine base (drug) is absorbed onto amberlite (resin).
(b) The resins are filtered from the alcoholic medium,
(c) The filtered drug-resin complex granules are coated with a water permeable polymer, such as a modified copolymer of polyacrylic and methacrylic ester, by spray drying method.

The drug is released by replacing with appropriately charged ions in the GIT, and then the drug diffuses out of the resin. The release of the drug depends on;

(a) the strength and type of ionic environment (pH, electrolyte conc.) and
(b) the properties of the resin.

The rate of diffusion is controlled by:

(a) the area of diffusion,
(b) diffusion path length, and
(c) the rigidity of resin.

$$Resin^+\text{-}Drug^- + X^- \longrightarrow Resin^+\text{-} X^- + Drug^-$$
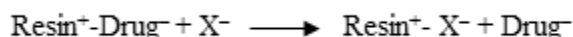
Advantage

- It offers a protective mechanism by temporarily changing the substrate.
- Suitable for the drugs which are highly susceptible to degradation by enzymatic processes.

Limitation

- The release rate is proportional to the concentration of the ions present in the proximity of the granules in the site of administration.
- The rate release varies with diet, water intake, and intestinal contents.

Processes used to prepare controlled-release formulations

Based on the mechanism of drug-release such as dissolution, diffusion, and osmosis, the oral controlled- release (CR) formulations are developed. Accordingly, the approaches/technology used to develop CR formulations can be roughly divided into three types: (A) matrix tablets, (B) multi-particulates, and (C) osmotic tablets; although different processes can be used in a particular formulation approach.

(A) Matrix Tablets: Both hydrophilic CR systems and lipophilic CR systems can be present in Matrix tablets. From hydrophilic systems, the drug is released through both diffusion and dissolution (i.e., matrix erosion), and from lipophilic systems, the drug-release takes place only through diffusion mechanism.

In general, the processes such as direct compression, roller compaction, wet granulation, fluid bed granulation, foam granulation, and melt extrusion granulation have been used to prepare both types of matrix tablets.

The selection of a process for the preparation of matrix tablets is similar to that used for immediate release tablets. The major factors influencing the process selection are;

- Drug loading,
- Flowability, and
- Compatibility.

For moisture-sensitive drugs, both wet granulation and fluid bed granulation would not be suitable. The melt extrusion granulation would not be suitable for thermally unstable drugs. For different processes, generally, the maximal drug loading follows approximately in the order of melt extrusion granulation>wet granulation >roller compaction ≈ fluid bed granulation> direct compression.

(B) Multi-particulates: Multi-particulate CR systems constitute both drug layered beads and microspheres. Fluid bed coating has been found very useful in preparing different multi-particulate CR systems. The process uses three different spraying methods – top spray, bottom spray (Wurster process), and tangential spray. Commonly the top spray method is used for fluid bed granulation; in some cases, for particle coating also. For the coating of particles/beads, the bottom spray(Wurster) coating is usually followed.

For the preparation of the multi-particulate CR systems, Wurster coating has been found very useful for layering of the drug on nonpareils as well as functional coating. Similar film quality can be achieved by the tangential spray (rotary) method as is obtained by Wurster coating. However, it is more difficult to scale up the technology. Besides fluid bed granulation, many other processes have been used to prepare microspheres or beads, such as;

- Extrusion and spheronization,
- Hot-melt extrusion granulation,
- Spray congealing, and
- Roller compaction.

For making pellets Extrusion–spheronization (palletization process) is usually used. The pellets can be used for the preparation of both immediate and controlled release formulation. If a solution of calcium chloride is added to sodium alginate solution, insoluble calcium alginate precipitates out, and the beads are formed. These beads have been widely used for preparing controlled release formulation. The beads can be collected by filtering and drying, or by one-step spray drying.

(C) Osmotic Tablets: The method of preparation of osmotic tablets can be roughly divided into three operations:
1. formation of drug layer and/or sweller layer,
2. formation of a membrane(s), and
3. making of microscopic hole(s) for drug release.

The drug layer and the sweller layer can be made by using the traditional method of granulation to prepare granules. To prepare an elementary osmotic pump, monolayer tablets can be compressed easily. For the 'pull-push' osmotic pump, that is, both drug layer and sweller layer need to be compressed into bilayer tablets. After membrane(s) has been coated onto the core tablets, holes for releasing drug from membrane are normally created by laser drilling technique. In Merck osmotic delivery system, high concentrations of porosigens are incorporated inside cellulose acetate, which generates holes for drug release.

Physicochemical Properties of Drugs Suitable for Controlled Release Formulations

For designing a controlled drug delivery system, the following physicochemical properties of drugs must be considered:

1. **The molecular weight of the drug:** Drugs of lower the molecular weight, more accurately, of lower molecular size, are absorbed faster and more completely. Through passive diffusion, about 95% of the drugs are absorbed. Diffusivity is well-defined as the ability of a substance (drug) to diffuse through the membrane. It is inversely related to the molecular size. Thus, drugs with large molecular weight rather large molecular size are not ideally suitable for oral controlled release systems.

2. **The diffusion coefficient and molecular size:** After reaching the systemic circulation, the drug needs to diffuse (1) through rate-controlling polymeric membranes or matrix (in case of extended-release or matrix system), and through (2) different biological membranes. The capacity of a drug to diffuse through these membranes is called diffusibility or diffusion coefficient (D). Diffusibility of the drug depends on its molecular size or molecular weight. The diffusivity of a drug through a polymer can be interrelated with its molecular size or weight as follows;

$$\log D = -S_v \log V + k_v = -S_M \log M + k_m \qquad .....(1.1)$$

Where V is the molecular volume, M is the molecular weight; S_v, S_M, k_v, and k_m are constants. Thus, the value of D depends on the size and shape of the drug. Usually, drugs having a molecular weight within 150 to 400 Da (Dalton) possess diffusivity of 10^{-6} –10^{-9} cm^2/sec through flexible polymers. The drugs having molecular weight more than 500 Da have very small diffusivity such as 10^{-12} cm^2/sec. It is challenging to measure such a low diffusivity. High molecular

weight drugs usually show very slow release kinetics in extended release dosage form; if the mechanism of drug release is diffusion control.

3. **The aqueous solubility of the drug:** For oral controlled release dosage form, the drug should have excellent aqueous solubility and are independent of pH; such drugs are good candidates. The solubility of the drug is a factor for selection of the mechanism to be employed for preparing CRDDS. For example, the diffusional systems are not appropriate for poorly soluble drugs. Absorption of poorly soluble drugs is dissolution rate-limited; hence, control release device does not control the absorption process. So, they are poor candidates.

Solubility refers to the concentration of solute in a saturated solution. In other words, solubility can be expressed as the amount of solute remaining in a solution containing a given volume of solvent with some undissolved solute in equilibrium–saturated solution. Solubility is a thermodynamic property of solute. The amount of drug absorbed into systemic circulation is a function of the amount of the drug present in anunionized form in a solution of G.I fluid. This is the intrinsic solubility of the drug and permeation of drug under such condition is called intrinsic permeability.

Before absorption, the drug must go into a solution of GI fluid and then partitions into the absorbing membrane. Thus, absorption of a drug is related to its partitioning between the lipid layer and an aqueous phase, and the rate of dissolution is related to its aqueous solubility. The Noyes-Whitney equation can express the relation between the rate of dissolution and aqueous solubility as below;

$$\frac{dC}{dt} = k_D.A.C_S \text{ (under sink condition)} \qquad .....(1.2)$$

Where, $\frac{dC}{dt}$ is the rate of dissolution, k_D is the dissolution rate constant, A is the total surface area of the drug particle, and C_S is the saturation solubility of the drug. Thus, drugs which are soluble in water are generally absorbed adequately when administered orally. On the other hand, poorly soluble drugs have low dissolution rates, and their bioavailability becomes a problem when administered orally.

Since most drugs are either weak acids or weak bases, their aqueous solubility greatly influenced by the pH of dissolution medium. The aqueous solubility of a weak acid can be expressed as;

$$S_t = S_u \left(1 + \frac{K_a}{[H^+]} \right) \qquad .....(1.3)$$

Where S_t is the total solubility (both ionized and nonionized forms) of the weak acid, S_u is the solubility of the unionized form, K_a is the dissociation constant of the

acid, and $[H^+]$ is the hydrogen ion concentration of the medium. Similarly, the aqueous solubility of weakly basic drugs can be expressed as;

$$S_t = S_u \left(1 + \frac{[H^+]}{K_a} \right) \qquad \qquad .....(1.4)$$

Where, S_t is the total solubility (both conjugate acid and free base forms) of the weak base, S_u is the solubility of the free-base form, K_a is the dissociation constant of the conjugate acid, and $[H^+]$ is the hydrogen ion concentration of the medium.

The equations 3 and 4 indicate that the pH of the medium can influence the total solubility of a weakly acidic or weakly basic drug having a given pKa.

According to the pH-partition hypothesis, the unionized form of a weakly acidic drug present in the stomach (pH ≈ 1–2) will be absorbed very well. Similarly, weakly basic drugs predominantly remain unionized in the small intestine (pH ≈ 5–7) and will be excellently absorbed; but these drugs remain in ionized form in the stomach resulting poor absorption.

Therefore, the above discussion can be summarized as: *for better absorption in GI tract (oral route) the drug must have an adequate aqueous solubility, must be released from the dosage form at a required rate, and be available as unionized form at the site of its absorption.*

The ratio of equation 2 and 3 indicates the driving force, R for absorption based on the pH gradient. Then,

$$R = \frac{\left(1 + 10^{p^{Hb}} - p^{K_a} \right)}{\left(1 + 10^{p^{Hg}} - p^{K_a} \right)} \qquad \qquad .....(1.5)$$

When, pHb = 7.4 (pH of blood), pHg = 2 (pH of gastric fluid), and if the pKa value of the drug is 3.4 then the value of R becomes $10^{3.8}$. It indicates that the drug would be absorbed in the stomach. Similarly, by using the pH value of intestinal fluid, the value of R can be calculated, and the potential site of absorption can be speculated.

The effect of three major factors -solubility, dissolution, and intestinal permeability on oral drug absorption can be measured with the help of biopharmaceutical classification (BCS) system. According to BCS, the drugs are of 4 classes:

Class I: high solubility-high permeability,

Class II: low solubility-high permeability,

Class III: high solubility-low permeability,

Class IV: low solubility-low permeability.

High solubility means the largest dose of a drug is dissolved in 200 – 250 ml of water over a pH range from 1 to 8 and when the extent of absorption is more than 90% the drug is said to be highly permeable. Accordingly, the drugs of class III and IV are not suitable for SR/CR formulation. Usually, the drugs whose solubility is less than 0.1mg even up to 10mg per ml are challenging to be formulated as SR/CR dosage form.

4. **Apparent partition coefficient:** Larger the apparent partition coefficient of a drug ($K_{o/w}$), greater its lipophilicity and hence, greater would be its rate and extent of absorption. These types of drugs even cross the highly selective blood-brain barrier. This parameter is also significant in deciding the release rate of a drug from a lipophilic matrix or device.

Both permeation of a drug across the biological membrane and diffusion through the rate controlling membrane or matrix depend on the partition coefficient of the drug. After administration and before elimination from the body the drug is supposed to diffuse through various biological membranes. These membranes perform primarily as a lipid-like barrier. The apparent oil/water partition coefficient of a drug is considered as a measure of its membrane permeability. The apparent oil/water partition coefficient, K is defined as;

$$K = \frac{\text{The concentration of drug in oil}}{\text{The concentration of drug in water}} = \frac{C_o}{C_w} \qquad \qquad .....(1.6)$$

Where, C_o represents the equilibrium concentration of all forms of the drug in an organic phase, usually in n-octanol, and C_w represents the equilibrium concentration of all forms of the drug in the aqueous phase. Drugs having a high value of K are readily soluble in oil and partition easily into membranes. *Hansch correlation* describes the parabolic relationship between the logarithm of the ability of a drug to be absorbed and the logarithm of its partition coefficient. This relationship expresses that the activity of a drug is a function of the ability to cross the membranes and interact with the receptor. There should be an optimum partition coefficient for required permeability. When the value of partition coefficient is more than the optimumvalue, the aqueous solubility of a drug is reduced, and the lipid solubility is increased; under this circumstance of once the drug enters into lipid membrane cannot diffuse out of the lipid membrane. Usually, the optimum value of K is 1000 when measured using the n-octanol/water system. Drugs having partition coefficient value more than or less than the optimum values are not suitable candidates for making extended-release formulation.

5. **Drug pKa and ionization at physiological pH:** The pKa value can indicate the strength of an acid or a base. Thus, at a particular pH, the charge on a drug molecule can be determined through its pKa value. Drug molecules are therapeutically active only in their unionized form and in this form the drug can easily penetrate the lipoidal membrane.

The amount of drug that remains in unionized form is a function of its dissociation constant and pH of the fluid at the site of absorption. Thus, the drug which remains in ionized form at its absorption site is not suitable for SR/CR dosage form.

For optimum passive absorption, the drugs should be non-ionised at the site for an extent of 0.1–5%. Drugs, such as hexamethonium, exist largely in ionized forms are poor candidates for controlled delivery systems.

6. **Drug stability:** Drugs which are unstable in the GI environment are not suitable candidates for controlled release systems. Drugs which are unstable in gastric pH can be designed for release in the intestine with limited or no release in stomach

and drugs which are unstable in intestinal pH (alkaline pH) can be designed for release in the stomach with limited or no release in the intestine.

Some amount of the drug administered orally may be lost in the GI tract due to acid hydrolysis and metabolism in the liver. Omeprazole, pantoprazole, lansoprazole, rifampicin, erythromycin, riboflavin, etc. are the most common examples of acid-susceptible drugs; i.e., these are unstable in the stomach. While captopril, ranitidine, etc. are not stable in the intestine; (alkaline media). Hence, the stability of the drug in the GI tract is an essential factor. The relative bioavailability of a drug which is unstable in the stomach can be improved significantly by making a slowly releasing or controlled releasing formulation. However, it would be most beneficial when the formulation can control the release of the drug only in the intestine.

Similarly, there are drugs which are unstable in the intestine. Their stability can be increased significantly by making a sustained/controlled release formulation which can slowly release the drug in the stomach only. Hence, the drugs which have stability problem in any region of the gastrointestinal tract can be formulated as sustained/controlled/extended release formulation; but the release characteristics must be decided based on absorption site where the drugs are most stable. The desired physicochemical properties of a drug are summarized in the **Table 1.2.**

Table 1.2: Physicochemical properties of drug

Physicochemical properties	Desired value
Molecular weight/size	< 1000 Daltons
Solubility	> 0.1g/lt at pH 1 to 7.8
Apparent Partition coefficient	High
Absorption mechanism	Diffusion control
General absorbability	Throughout entire GI tract
Drug release	Should not depend on enzyme and pH

7. **Mechanism and site of absorption:** Drugs which are absorbed by carrier-mediated transport procedure or through a window are not entirely suitable candidates for the development of controlled release systems, such as Vitamin B.

8. **Route of administration:** Oral and parenteral routes are the most preferred for controlled release, this is followed by transdermal.

   (i) *Oral route*: The drug should have the following properties to be a successful candidate

   - It must get absorbed through the entire length of GIT.
   - The main limitation is transit time (mean of 14 hours), which can be extended for 12-24 hours.
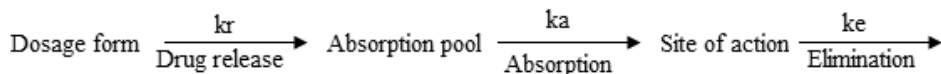
- Dose as high as 1000mg can be given through this route.

(ii) *Intramuscular/subcutaneous route:* This route is preferred because

- The action is to be prolonged for 24 hours to 12 months.
- A small amount of drug is administered (2mL/2gm).
- Factors important are solubility of the drug in surrounding tissue, molecular weight, partition coefficient and pKa of the drug.

(iii) *Transdermal route:* This route is selected for drugs which show extensive first-pass metabolism upon oral administration or drugs with a low dose. Important factors to be considered are:

- The partition coefficient of drugs,
- Contact area,
- Skin condition,
- Skin permeability of drug,
- Skin perfusion rate, etc.

# Biological Properties of Drugs Suitable for Controlled Release Formulations

Pharmacokinetic Properties of a Drug

(a) Dose and Release rate:

To achieve a sustained or extended action, the concentration of the drug is to be maintained within the therapeutic window for a long period. For this, it is essential to provide a therapeutic concentration immediately after administration;

so that the absorption pool of drug is maintained. Using a conventional or immediate release dosage form this can be done.This can be illustrated schematically as follows;

$$\text{Dosage form} \xrightarrow[\text{Drug release}]{k_r} \text{Absorption pool} \xrightarrow[\text{Absorption}]{k_a} \text{Site of action} \xrightarrow[\text{Elimination}]{k_e}$$

Where, kr, ka, and ke are release rate constant, absorption rate constant, and overall elimination rate constant respectively. Absorption pool indicates the amount of drug present at the site of absorption. When the drug is released immediately as in case of the conventional dosage form, kr>>> ka. Thus, the absorption of the drug becomes the rate-limiting step for the drug to reach its site of action. On the other hand, for a dosage form which does not release the drug immediately, kr<<< ka and release of drug at the site of absorption become the rate-limiting step for the drug to reach its site of action.

$$\text{Dosage form} \xrightarrow[\text{Drug release}]{\text{kr}} \text{Site of action} \xrightarrow[\text{Elimination}]{\text{ke}}$$
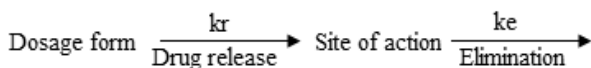
The three-step process is reduced to the two-step process. This indicates that once the drug is released from the dosage it is immediately absorbed, and it reaches its site of action. Thus, to design or develop a sustained/extended release dosage form attention should be paid towards altering the rate of release (*alteration of the* kr). While designing or developing an SR/CR dosage form, it is theoretically expected that the plasma concentration of the drug should remain at a constant level. In fact, practically it is complicated and, in most cases, not necessary also to maintain the constant level. The concentration of the drug should remain within the therapeutic window throughout the period. Ideally, an extended release dosage form should release the drug at the desired site and at a rate as per the need of the body. Many attempts have been, and no commercial product is available that fulfills this requirement. Since there is no feedback information about the rate at which a drug should be infused into the body to maintain the steady-state blood concentration; the drug may be administered at a rate equivalent to the rate of elimination from the body.This means that the drug should be administered at a constant rate over a period without considering the amount of drug remaining in the dosage form. Thus, the drug would be released from the dosage form following zero-order kinetics;

$$K_r^o = k_e C_d V_d = \text{Rate of administration} = \text{Rate of elimination} \qquad .....(1.7)$$

Where, K_r^o is the zero-order rate constant for the drug release (amount/time), k_e is the first, order rate constant for theoverall elimination of the drug from the body (time^{-1}), C_d is the desired drug concentration in plasma (amount/volume), and V_d is the apparent volume of distribution of the drug in the body (volume).

The equation 7 may be used to calculate the amount of drug to be released per unit time for maintaining a constant plasma drug concentration. This may be used in the simple case where elimination of the drug from the body follows first order kinetics.

- *Use of Zero order release technique*

    There are many drugs whose elimination is a complex process and disposition of drugs is influenced by several factors. These influence the release kinetics of the dosage form for maintaining constant drug level in the body. Although theoretically zero order release kinetics is desired for sustaining or extending the action, in some cases non-zero order release has been found to be equally clinically useful. However, there are intra- and inter-subject variations. Depending on the degree of such variations the clinical performance of some drugs may vary. In some cases, due to this intra- and inter-subject variations average change in drug concentration in tissues does not show a significant change in the clinical performance of the drug. As a result, the difference

between the clinical effects of constant plasma drug level and of non-constant plasma drug level becomes insignificant.

The purpose of SR/CR dosage form is to provide an immediate effect and to extend this effect for a more extended period. Hence, there are two parts of SR/CR dosage form – immediate or initial dose (Di) and sustaining or maintenance dose (Dm). The sum of these doses makes the total dose, W.

$$W = Di + Dm \qquad .....(1.8)$$

When the maintenance dose releases the drug by zero order process for a definite period, the total dose may be calculated as;

$$W = Di + K_r^o T_d \qquad .....(1.9)$$

Where, T_d is the total time required for the extended release of drug from one dose. If the maintenance dose starts releasing the drug along with the initial dose (when t = 0), the total amount of drug released shall be more than the amount released from the initial dose. In such case, a correction is necessary to account for the extra amount (amount released from maintenance dose, $K_r^o T_p$) and the equation is rewritten as;

$$W = Di + K_r^o T_d - K_r^o T_p \qquad .....(1.10)$$

Where, T_p is the time required for attaining peak drug level, C_{max}. In fact, the maintenance dose starts releasing the drug after the time, T_p. This is an ideal situation; making the maintenance in such a way that it releases the drug following zero-order kinetics is the simplest way to achieve this.

- *Use of First order release technique*

  A constant drug level can be maintained by formulating the initial dose and maintenance dose which releases the drug by first order process. Total dose for such a system can be calculated as;

$$W = Di + (\frac{k_e C_d}{k_r})V_d \qquad ....(1.11)$$

Where, k_e, C_d, and V_d carry the same meaning as described earlier; k_r is the first order release rate constant.

Now, in this case also if the maintenance dose releases the drug along with the initial dose (when t = 0), a correction factor needs to be included as indicated below;

$$W = Di + (\frac{k_e C_d}{k_r})V_d - Dm.k_e.T_p \qquad .....(1.12)$$

The conventional dose of a drug provides some information of the amount of drug required to be present in an extended release dosage unit. This has been mentioned earlier that both dose-size and half-life of drugs are essential characteristics of a drug to become suitable for SR/CR dosage form (**Table 1.3**).

Table 1.3: Pharmacokinetic properties of the drug

Pharmacokinetic properties	Desired value
Absolute bioavailability	> 75%
Intrinsic rate of absorption	Greater than the release rate
Elimination half-life	0.5 to 8 hr
Elimination rate constant	As necessary for the design
The apparent volume of distribution, V_d	Should not be large
Minimum effective concentration, MEC	Should not be high; if both MEC and V_d are less, the dose size of SR/CR dosage form will be small.
Toxic concentration	Toxic concentration or maximum safe concentration should be large; i.e., wider therapeutic window can provide safety of the dosage form.

(b) Absorption rate

A drug which is fabricated into a controlled release system should be absorbed efficiently. The rate-limiting step is the rate of drug release. A drug which is slowly absorbed is a poor candidate for such dosage forms; since continuous release will result in a pool of unabsorbed drug. If a drug is absorbed by active transport, or transport is limited to a specific region ofthe intestine, sustained-release preparations may be disadvantageous to absorption; hence should be avoided.

For an extended release dosage form, the rate, extent, and uniformity of absorption of the drug are important factors to be considered. When the formulation is prepared for oral route, these are most critical; because for smooth and regular absorption from GI tract the release of the drug must be very less than the rate of absorption, i.e., $k_r<<<k_a$.

If the transit time of a drug in the gastrointestinal tract is assumed to be within 9 – 12 hours, the maximum absorption half-life would be 3 – 4 hours. Then the minimum absorption rate constant, Ka would be 0.17 – 0.23/hr for about 80 – 95% absorption during 9 – 12 hours.

When a drug is very slowly absorbed ($K_a<< 0.17$), the first order release rate constant, k_rWould be less than 0.17/hr and the drug is considered to be very poorly bioavailable in many patients. Such poorly bioavailable drug is not suitable for formulating extended release dosage form. Because for extended release dosage form $k_a>>>k_r$.

The absorptive surfaces of the gastrointestinal tract vary. If the absorption of a drug is erratic in the GI tract, e.g., iron, dicoumarol; it becomes difficult to design an extended/controlled release dosage.

Drugs which are not suitable for formulating sustained/controlled/extended release dosage form can be categorized into four types by biological factors;

➢ Drugs which are absorbed by active transport system; e.g., Methotrexate, pyridoxine, riboflavin, nicotinamide, enalapril, methyl-dopa, 5-fluorouracil, 5-bromouracil, etc.

➢ Drugs which are absorbed through amino acid transporter in the intestine; e.g., cephalosporin, baclofen, gabapentin, methyl-dopa, levodopa, etc.

➢ Drugs which are absorbed through oligo peptide transporters; e.g., cephalexin, cefadroxil, cefixime, captopril, lisinopril, etc.

➢ Drugs used for local therapeutic effect in the stomach; e.g., antacids, 5-fluorouracil, misoprostol, anti-helicobacter pylori agents, etc.

The normal pH range and enzyme present in different areas of gastrointestinal tract mentioned in **Table 1.4**;

Table 1.4: The pH range and Enzyme present in different region of GIT.

Part of GIT	pH range	Enzymes present
Mouth	7.4	Amylase
Stomach	0.8 – 5.0	Pepsin, lactase
Small intestine	5.0 – 6.5	Lactase, Bile, Protease, Amylase, Lipase
Colon	6.0 – 8.0	

● *Absorption window*

The term 'absorption window' refers to the area or range of areas of the gastrointestinal tract where the drug is absorbed beyond which there is no/negligible absorption. Different regions of the gastrointestinal tract have different pH; accordingly, solubility and stability of some drugs vary from region to region due to change in pH and enzymatic degradation. For the formulation of a controlled/extended release dosage form, the rate, extent, and uniformity of absorption of a drug are essential factors. In a controlled or extended release system the release of the drug is the rate limiting step for absorption. Once the drug crosses the absorption window, it is almost wasted. Thus, absorption window is one more limiting factor for bioavailability of orally administered drugs. It can appear as a major constraint in developing SR/CR dosage form. Drugs show site absorption in the GI tract is metformin, acyclovir, captopril, ranitidine, levodopa, furosemide, sulphonamides, salbutamol, cephalosporins, tetracycline, verapamil, thiamine, quinolines, etc.

Table 1.5: Apparent volume of distribution of different drugs.

S. no.	Drug	Apparent volume of distribution (L)
1.	Amiodarone	4620
2.	Azithromycin	2170
3.	Chloroquine	12950
4.	Doxepin	1400
5.	Digoxin	500
6.	Flurazepam	1540
7.	Haloperidol	1400

- *Distribution*

In overall elimination kinetics, the distribution of a drug in vascular and extravascular spaces in the body is an important factor to be considered. The distribution characteristic of a drug is expressed using its apparent volume of distribution and ratio of drug in tissues to the drug in plasma (T/P). The larger volume of distribution means the more considerable amount of drug is bound to the tissues and drug present blood is relatively less. The drug present in circulating blood is exposed to hepatic or renal clearance. That is if the apparent volume of distribution of a drug is less most of the drug is in blood and is exposed to renal or hepatic clearance.

Some drugs such as chloroquine are widely bound to extravascular tissues. Their apparent volumes of distributions are more significant than the real volume of distributions, and their elimination half-lives are reduced. In such cases, the drugs go away from the body slowly provided their rate of elimination be limited by the rate of release from tissue binding sites. If the amount of drug released from the tissues is within the therapeutic range, therapeutic action of the drugs becomes sustained. The **Table 1.5** shows some drugs whose apparent volume of distribution is more than the real volume of distribution.

Use of apparent volume of distribution to assess drug present in the body may sometimes create ambiguity. To avoid this ambiguity the ratio T/P may be used for this purpose. If the amount of drug present in the blood (P) is known, the amount of the drug present in the peripheral compartment (T) and hence, T/P can be calculated as;

$$T/P = k_{12}(k_{21} - \beta) \qquad\qquad .....(1.13)$$

Where β represents the slow disposition rate constant of the drug. T/P indicates the relative distribution of the drug in peripheral and central compartments, while V_d indicates the apparent distribution of the drug in the body. Some use the V_{dss}, the volume of distribution at the steady state level in place of V_d; but it does not yield any conclusion. However, the values of T/P and of V_{dss} can be correlated, and some interpretations can be made (**Table 1.6**).

Table 1.6: Relation of T/P ratio, total body clearance and disposition characteristics

T/P ratio	Total body clearance	Disposition characteristics
High	High	Weak tissue binding
High	Low	Strong tissue/protein binding
Low	Low	Strong protein binding
Low	High	Weak plasma protein binding

- *Metabolism*

  Metabolism is a process which converts the drug in the body. Through metabolism either an inactive molecule is converted into therapeutically active metabolite or a therapeutically active molecule is converted into an inactive metabolite. When the process of metabolism is complex, it becomes difficult to design an SR/CR dosage form particularly if the metabolite is an active molecule. There are two situations related to metabolism which affect the design of SR/CR dosage form significantly.

  1. A drug will be considered a poor candidate for SR/CR formulation if it induces or inhibits synthesis of the enzyme when it is administered for an extended period (chronic administration).

     (i)   Drugs which induce enzymes are primidone, phenytoin, griseofulvin, rifampicin, barbiturates, meprobamate, cyclophosphamide, etc.

     (ii) Drugs which inhibit enzymes are erythromycin, Fluconazole, ketoconazole, isoniazid, cimetidine, Amiodarone, MAO-inhibitors, 4-aminosalicylic acid, allopurinol, coumarins, etc.

  2. A drug will be considered a poor candidate for SR/CR formulation, if there is a varying concentration of it in the blood either due to tissue/intestinal metabolism or due to hepatic metabolism (first pass effect). Other reasons are: most of the process can be saturated, depending on the dose the amount or fraction of the drug would be lost, and due to this loss, the bioavailability of the drug may reduce appreciably. An appreciable reduction in bioavailability will result particularly when the drug is released slowly as in case of SR/CR dosage form.

     Drugs which are metabolized in the intestine are chlorpromazine, clonazepam, hydralazine, levodopa, salicylamide, isoproterenol, etc.

- *Elimination half-life*

  Time is taken for the amount of a drug in the body (plasma concentration) to be reduced by 50% 0f its initial concentration is called elimination half-life. The half-life elimination can be determined by using clearance (Cl) and volume of distribution (V_d).

  $$t_{\frac{1}{2}} = 0.693 V_d / Cl \qquad .....(1.14)$$

  According to the eqn. 14 the elimination half-life increases when the volume of distribution, V_d is increased or when clearance, Cl is decreased. When the volume of distribution is high, the drug remains distributed more in tissues than in blood. Similarly, if the volume of distribution is less the drug is present more in the blood and less in tissues. The drug is subjected to elimination. The effect of clearance and volume of distribution on the elimination of some drugs has been presented in the **Table 1.7**.

Table 1.7: The effect of drug clearance and volume of distribution on elimination half-life.

Drug	Clearance (L/hr)	Volume of Distribution (L)	Elimination half-life (hr)
Morphine	63	280	3.0
Haloperidol	46	1400	20.0
Chloroquine	45	12950	200
Flucytosine	8	4.9	4.2
Digoxin	7	420	40.0
Ethosuximide	0.7	49	48.0

When a drug follows linear kinetics its elimination half-life is found to remain constant, does not depend on the dose of the drug or its concentration. When a drug follows non-linear kinetics, its elimination half-life and clearance change with a change in dose or concentration.

(c) Biological half-life

In the case of an ideal CRDD system, the rate of drug absorption should be equal to the rate of drug elimination. If the biological half-life($t_{1/2}$) of a drug is small (less than 2 hours), then more amount of drug would be present in a single dose of the controlled release dosage form. Drugs having $t_{1/2}$ in the range of 2-4 hours are ideal candidates for controlled release system. Drugs with long half-life should not be formulated into controlled release dosage form.

(d) Metabolism

Drug-selected for controlled release system should be completely metabolized, but the rate of metabolism should not be too rapid. A drug which encourages or inhibits metabolism is a poor candidate; because steady states are challenging to achieve.

(e) Drug-Protein Binding

The drugs can bind to the components like blood cells and plasma proteins and also to tissue proteins and macromolecules. Drug-protein binding is a reversible process. As the free drug concentration in the blood declines, the drug-protein complex dissociates and liberates the free drug to maintain equilibrium. Due to high molecular size, a protein bound drug is unable to enter into hepatocytes; as a result, the metabolism of the drug is reduced. The bound drug is not presented as a substrate for liver enzymes there by the rate of metabolism is further reduced. The glomerular capillaries do not permit the way of plasma-protein anddrug-protein complexes. Hence, the only unbound drug is eliminated. The elimination half-life of drugs usually increases when the percent of the bound drug to plasma increases. Such drugs should not be formulated as sustained/controlled release formulations.

(f) Dosage form index

Dosage form index is defined as the ratio of $C_{ss.max}$ to $C_{ss.min}$. Its value must be nearer to unity.

Pharmacodynamic Properties of the Drug

(a) **Therapeutic range:** For controlled release drug delivery system, a drug should have its therapeutic range wide enough so that any variation in the release rate do not produce its concentration beyond this level.

(b) **Therapeutic index:** It is the most widely used parameter to measure the margin of safety of a drug. Therapeutic index = TD_{50}/ED_{50}. The longer the value of the therapeutic index, the safer is the drug. A drug is considered to be safe, if its therapeutic index value is greater than 10. Drugs with a very small value of therapeutic index are not suitable candidates for the formulation of sustained release products.

(c) **Plasma concentration-response relationship:** Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for the controlled-release system.

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Exercise

A. Multiple Choice Questions

1. Which of the following statements is incorrect?
    - (a) Controlled release formulation can provide a location specific action
    - (b) Controlled release formulation can provide a local action
    - (c) Controlled release formulation cannot provide a location specific action
    - (d) Controlled release formulation increases duration of action
2. Which of the following statements is correct?
    - (a) Therapeutic window of a drug is the ratio of LD_{50} to ED_{50}
    - (b) Therapeutic window of a drug is the ratio of ED_{50} to LD_{50}
    - (c) Therapeutic window of a drug is its duration of action
    - (d) Therapeutic window of a drug is its dosing frequency
3. Which of the following statements is correct?
    - (a) Controlled release formulation can reduce the tolerability
    - (b) Controlled release formulation can improve the tolerability
    - (c) Controlled release formulation can increase the potential first-pass clearance
    - (d) Controlled release formulation can extend the product's life cycle
4. Which of the following statements is incorrect?
    - (a) CR dosage form cannot provide the scope of dose adjustment
    - (b) CR dosage form can cause dose dumping
    - (c) CR dosage form can delay the onset of action of the drug
    - (d) CR dosage form fails to delay the onset of action of the drug
5. Which of the following statements is correct?
    - (a) Drug having short biological half-life is suitable for CR dosage form.
    - (b) Drug having long biological half-life is suitable for CR dosage form.
    - (c) Drug having narrow therapeutic window is suitable for CR dosage form.
    - (d) Drug having large dose size is suitable for CR dosage form.
6. Which of the following statements is correct?
    - (a) Drugs absorbed mainly in lower intestine are suitable for designing CR dosage form
    - (b) Drugs with large elimination rate are suitable for designing CR dosage form
    - (c) Drugs which is immediately absorbed are suitable for designing CR dosage form
    - (d) Drugs with undesirable side effects are suitable for designing CR dosage form
7. Which of the following statements is correct?
    - (a) Stimuli-induced systems are dissolution-controlled CR system
    - (b) Stimuli-induced systems are erosion-controlled CR system
    - (c) Hybrid system contains drug in a release controlled-matrix
    - (d) Hybrid system contains drug in a matrix which is again coated with a polymer

8. Which of the following is a biopharmaceutical factor?
    (a) Therapeutic range
    (b) Elimination half-life
    (c) Drug pKa and ionization at physiological pH
    (d) Rate of metabolism

7. Which of the following is pharmacodynamic factor?
    (a) Mechanism and site of drug absorption
    (b) Route of drug administration
    (c) Rate of metabolism
    (d) Plasma concentration-response relationship

9. Which of the following is pharmacokinetic factor?
    (a) Dosage form index
    (b) Therapeutic index
    (c) Mechanism and site of absorption
    (d) Therapeutic range

10. Which of the following statements is correct?
    (a) In case of dissolution-controlled matrix penetration of the medium is controlled by porosity of the tablet matrix.
    (b) In case of dissolution-controlled matrix penetration of the medium is controlled by presence of hydrophilic material in the tablet matrix.
    (c) In case of dissolution-controlled matrix penetration of the medium is controlled by particle surface.
    (d) All of the above.

11. Which of the following statements is correct?
    (a) In nonporous reservoir system, drug molecules are released through micropores by diffusion.
    (b) In nonporous reservoir system, drug molecules diffuse through polymer membrane.
    (c) In nonporous reservoir system, drug molecules diffuse from lower concentration to higher concentration.
    (d) None of the above.

12. Which of the following statements is correct?
    (a) The release of the drug from ion-exchange resin is independent on the pH and electrolyte concentration in its surroundings.
    (b) The release of the drug from ion-exchange resin is dependent on the pH and electrolyte concentration in its surroundings.
    (c) The release of the drug from ion-exchange resin is independent on the properties of resin itself.
    (d) The release of the drug from ion-exchange resin is independent on the rigidity of resin itself.

13. Which of the following statements is not correct?
    (a) To prepare osmotic tablet drug layer and/or sweller layer is to be formed,
    (b) To prepare osmotic tablet membrane(s) need to be formed
    (c) To prepare osmotic tablet microscopic holes are to be formed
    (d) None of the above

14. Diffusibility of drug from a matrix tablet depends on?
    (a) Molecular weight of the polymer used
    (b) Method of preparation of the polymer
    (c) Molecular weight of the drug
    (d) Average weight of the tablet

15. Which of the following statements is correct?
    (a) Solubility of a drug is its thermodynamic property.
    (b) Solubility of a drug is not its thermodynamic property.
    (c) Absorption of a drug into system circulation from GIT is independent of the solubility of the drug in gastric fluid.
    (d) None of the above.

16. Which of the following statements is correct?
    (a) For better absorption of drug in GIT, the drug must be smaller in size.
    (b) For better absorption of drug in GIT, the drug must have adequate aqueous solubility.
    (c) For better absorption of drug in GIT, the drug must be available in ionized form.
    (d) For better absorption of drug in GIT, the drug must not be smaller in size.

17. Which of the following statements is correct?
    (a) Highest value of partition coefficient would be 10.
    (b) Highest value of partition coefficient would be 100.
    (c) Highest value of partition coefficient would be 1.
    (d) None of the above.

18. Which of the following statements is correct?
    (a) Erythromycin estolate tablet is a conventional dosage form.
    (b) Erythromycin estolate tablet is a sustained release dosage form.
    (c) Erythromycin estolate tablet is a controlled release dosage form.
    (d) Erythromycin estolate tablet is a modified release dosage form.

19. Which of the following statements is correct?
    (a) The rate of drug release from a reservoir system is directly proportional to the diffusion coefficient of the drug.
    (b) The rate of drug release from a reservoir system is not proportional to the area.

(c) The rate of drug release from a reservoir system is directly proportional to the diffusion path length.

(d) The rate of drug release from a reservoir system is independent on partition coefficient of the drug.

B. Short Questions

1. Define controlled-release dosage form. What are modified-release and delayed-release dosage form?
2. Briefly justify the reason for development of controlled release dosage form.
3. Define minimum therapeutic index, maximum safe concentration and therapeutic window.
4. What is site specific targeting, receptor targeting and extended release dosage form?
5. Briefly mention the advantages and disadvantages of controlled release dosage form.
6. What are the characteristics of the drug to be considered for selection of a drug for CR dosage form?
7. Explain dissolution-controlled release systems.
8. Explain diffusion-controlled release systems.
9. Write a note about CR dosage form using the principle of ion-exchange.
10. What do you understand by osmosis-based formulation for controlled drug delivery?

C. Long Questions

1. Discuss why CR dosage form is more beneficial.
2. Explain the rationale of controlled-release dosage form.
3. Explain with relevant example the approaches used for designing CR dosage form.
4. Explain the concepts or approaches used to design controlled drug delivery system. Classify the CR drug delivery systems.
5. Write down the principle of dissolution-controlled release. Write notes on diffusion-controlled matrix and reservoir systems.
6. Write down briefly the effect of molecular weight, diffusion coefficient, apparent partition coefficient of drugs, and its route of administration on the design of CR dosage form.
7. Explain the effect of following characteristics on CR dosage form design: (1) aqueous solubility of drug, (2) pKa-value and ionization of drug at physiological pH, (3) stability of drug.
8. Explain the pharmacokinetic properties with respect to dose, release rate, and absorption rate of drug suitable for CR dosage form.

9. Explain the pharmacokinetic properties with respect to absorption window, distribution, and metabolism of drug suitable for CR dosage form.
10. Explain the biological half-life, drug-protein binding, therapeutic range, therapeutic index, and plasma concentration-response relationship of a drug selected for CR dosage form.