Chapter

1 CONTROLLED DRUG DELIVERY SYSTEMS

♦ LEARNING OBJECTIVES ♦

***After completing this lesson, the Reader should be able to understand*:**

- **The need for controlled drug delivery**
- **Various advantages and disadvantages of controlled drug delivery systems**
- **How to select drug candidates for designing controlled drug delivery systems**
- **Various principles exploited to design controlled drug delivery systems**

1.1 INTRODUCTION

The purpose of drug dosing in any disease is to achieve the desired therapeutic concentration of drug at the site of action or at least in plasma for a stated period of time, usually for the entire duration of treatment. Hence, drugs are administered at a particular amount (dose) and at a definite time interval (frequency). The frequency of drug administration usually depends on its elimination half-life or mean residence time (MRT). Better medical treatments do not always require stronger medicines. The effectiveness of drug substances depends on the method of administration. Hence, the treatment outcomes can be improved by choosing suitable drug formulations or drug delivery systems and delivering through a proper route. If the duration of therapy offered by a single administration of a dosage form is insufficient, re-administration (multiple dosing) of the dosage form is needed so as to maintain the steady-state therapeutic drug concentration in the plasma. When a drug is delivered as a conventional dosage form such as a tablet, the dosing interval is usually shorter than the half-life of the drug resulting in a number of drawbacks:

1. Multiple dosing needed for drugs with short half-lives leading to possible poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of the steady-state condition difficult (*see* Fig 1.1).
3. The unavoidable fluctuations in the drug concentration may lead to under-medication or over-medication.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with a narrow therapeutic index whenever over-medication occurs.

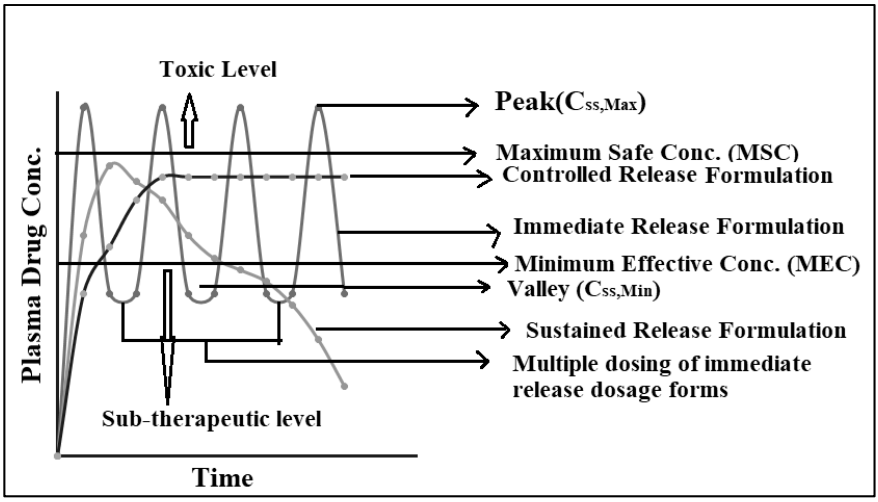

Fig.1.1 Schematic plasma drug concentration vs time profile of immediate release and controlled release drug products.

There are two ways to overcome such a situation:

1. Accelerate drug discovery strategies to develop new, better and safer drugs with longer half-lives and large therapeutic indices.
2. Re-designing of existing drugs through concepts of controlled and targeted delivery systems for effective and safer use.

Though the first approach seems very attractive, it is not a cost-effective method and therefore resulted in increased interest in the second approach. The second approach, owing to several technical advancements, has resulted in the development of drug delivery systems capable of controlling the rate of drug delivery, sustaining the duration of therapeutic action and/or targeting the delivery of drugs to a particular tissue. An ideal controlled release drug delivery system (CDDS) should deliver the drug at a rate dictated by the needs of the

body over a specified period of treatment. The two basic modalities of controlled drug delivery are:

- **Spatial drug delivery:** It relates to targeting a drug to a specific organ, tissue or cell. Such precise control over the distribution of the drug is of great significance when the natural distribution causes drug molecules to encounter normal and healthy tissues (non-targets) causing damage and/or major side effects that prohibit further treatment. This situation is often the cause of non-adherence to chemotherapy regimens leading to therapeutic failure. Moreover, in certain instances, the natural distribution of the drug does not allow drug molecules to reach their molecular site of action or receptors due to various pathophysiological barriers (e.g. blood-brain barrier). In such cases controlling the drug distribution through the targeting approach could improve the treatment outcomes.
- **Temporal drug delivery:** It refers to the delivery of a drug over an extended period of time or for a specific duration during treatment. This type of control is highly beneficial for drugs having fast elimination after administration.

An appropriately designed controlled-release drug-delivery system can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size (dose) and the number of doses (frequency) required. Controlled drug delivery may be achieved through oral or non-oral administration.

1.2 ADVANTAGES & DISADVANTAGES OF CONTROLLED DRUG DELIVERY

***The various advantages of controlled drug delivery systems include*:**

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady-state levels and therefore –
   - Better control of disease condition, and
   - Reduced-intensity of local or systemic side-effects.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in the total amount of dose administered.
5. Reduction in health care costs through –
   - Improved therapy
   - Shorter treatment period

- Lower frequency of dosing, and
- Reduction in personnel time to dispense, administer and monitor patients.

The various disadvantages associated with controlled drug delivery systems include:

1. Decreased systemic availability in comparison to immediate-release conventional dosage forms. This may be due to:
   - Partial or incomplete release
   - First-pass hepatic metabolism
   - Insufficient gastrointestinal residence time
   - Site-specific absorption of drugs having narrow absorption windows
   - pH-dependent solubility.
2. Poor *in vitro–in vivo* correlation.
3. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4. Treatment withdrawal is difficult in case of toxicity, poisoning or hypersensitivity reactions.
5. Limited or no flexibility for dosage adjustment of drugs normally administered in varying strengths.
6. Formulation cost is too high.

1.3 SELECTION OF DRUG CANDIDATES

All drugs are not candidates for controlled delivery. Hence, developmental strategies for oral controlled drug delivery warrant for a rational selection of drug candidates. Various physicochemical, pharmacokinetic and pharmacodynamic factors related to the drug candidates dictate their suitability for controlled delivery. The selection criteria are outlined as follows:

A. Physicochemical factors

The acronym LADME refers to liberation, absorption, distribution, metabolism, and excretion of drugs. Each of these LADME processes potentially affects the performance of a drug presented as a controlled-release system. The first step upon administration of a dosage form is release (liberation) of the drug (s) from the dosage form and subsequent to this is the migration to the site of action. The liberation or release of drugs from the drug delivery system (dosage form) depends upon the fabrication of the formulation and the physicochemical properties of the drug whereas the migration of the

drug to the site of action depends on the pharmacokinetics of the drug. In comparison to conventional dosage form where the rate-limiting step in drug bioavailability is usually absorption through the biomembrane, the rate-determining step in the availability of a drug from the controlled delivery system is the rate of release of drug from the dosage form which is much smaller than the intrinsic absorption rate for the drug. The desired physicochemical properties of a drug to be used in a controlled-release drug delivery system are discussed below.

1. **Molecular Weight:** Lower the molecular weight, faster and more complete the absorption. For drugs absorbed by the pore transport mechanism, the molecular size threshold is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. However, more than 95% of drugs are absorbed by passive diffusion. Drugs with large molecular size are poor candidates for oral controlled-release systems e.g. peptides and proteins.
2. **Aqueous Solubility:** A drug with good aqueous solubility, especially if pH-independent, serves as a good candidate for controlled-release dosage forms e.g. pentoxifylline. The lower limit of solubility of a drug to be formulated as CDDS is 0.1mg/ml. Drugs with pH-dependent aqueous solubility e.g. phenytoin, or drugs with solubility in non-aqueous solvents e.g. steroids, are suitable for parenteral (e.g. i.m. depots) controlled-release dosage forms; the drug precipitates at the injection site and thus, its release is slowed down due to change in pH or contact with aqueous body fluids. The solubility of drugs can limit the choice of mechanism to be employed in CDDS, for example, diffusional systems are not suitable for poorly soluble drugs. Absorption of poorly soluble drugs is dissolution rate-limited which means that the controlled-release device does not control the absorption process; hence, they are poor candidates for such systems.
3. **Lipophilicity:** Greater the apparent partition coefficient of a drug, greater its lipophilicity and thus, greater is its rate and extent of absorption. Such drugs have increased tendency to cross even the more selective barriers like BBB. The apparent volume of distribution of such drugs also increases due to increased partitioning into the fatty tissues and since the blood flow rate to such tissues is always lower than that to an aqueous tissue like liver, they may exhibit characteristics of models having two or more compartments. The parameter is also important in determining the release rate of a drug from lipophilic matrix or device.
4. **Drug pK_a and Ionisation at Physiological pH:** The pK_a range for acidic drugs whose ionisation is pH-sensitive is 3.0 to 7.5 and that for basic drugs is 7.0 to 11.0. For optimum passive absorption, the drugs should be non-ionised at that site at least to an extent 0.1 to 5%. Drugs existing largely in ionised forms are poor candidates for controlled delivery.

5. **Drug Stability:** Drugs that are unstable in GI environment cannot be administered as oral controlled-release formulation because of bioavailability problems e.g. nitroglycerine. A different route of administration should then be selected such as the transdermal route or buccal route. Drugs unstable in gastric pH, e.g. propantheline can be designed for sustained delivery in intestine with limited or no delivery in stomach. On the other hand, a drug unstable in intestine, e.g. probanthine, can be formulated as gastroretentive dosage form.
6. **Mechanism and Site of Absorption:** Drugs absorbed by carrier-mediated transport processes and those absorbed through a *window* are poor candidates for controlled-release systems e.g. several B vitamins.
7. **Biopharmaceutic Aspects of Route of Administration:** Oral and parenteral (i.m.) routes are the most popular followed by transdermal application. Routes of minor importance in controlled drug delivery are buccal/sublingual, rectal, nasal, ocular, pulmonary, vaginal and intrauterinal. The features desirable for a drug to be given by a particular route are discussed below.
   (a) Oral Route: For a drug to be successful as oral controlled-release formulation, it must get absorbed through the entire length of GIT. Since the main limitation of this route is the transit time (a mean of 14 hours), the duration of action can be extended for 12 to 24 hours. The route is suitable for drugs given in dose as high as 1000 mg. A drug, whose absorption is pH-dependent, destabilized by GI fluids/enzymes, undergoes extensive presystemic metabolism (e.g. nitroglycerine), influenced by gut motility, has an absorption window and/or absorbed actively (e.g. riboflavin), is a poor candidate for oral controlled-release formulations.
   (b) Intramuscular/Subcutaneous Routes: These routes are suitable when the duration of action is to be prolonged from 24 hours to 12 months. Only a small amount of drug, about 2 ml or 2 grams, can be administered by these routes. Factors important in drug release by such routes are solubility of drug in the surrounding tissues, molecular weight, partition coefficient and pK_a of the drug and contact surface between the drug and the surrounding tissues.
   (c) Transdermal Route: The route is best suited for drugs showing extensive first-pass metabolism upon oral administration or drugs with low dose such as nitroglycerine. Important factors to be considered for percutaneous drug absorption are partition coefficient of drug, contact area, skin condition, skin permeability of drug, skin perfusion rate, etc.

In short, the main determinants in deciding a route for administration of a controlled-release system are physicochemical properties of the drug, dose size, absorption efficiency and desired duration of action.

B. Pharmacokinetic Characteristics of Drug

A detailed knowledge of the ADME characteristics of a drug is essential in the design of a controlled-release product. An optimum range of a given pharmacokinetic parameter of a drug is necessary beyond which controlled delivery is difficult or impossible.

1. **Absorption Rate:** For a drug to be administered as controlled-release formulation, its absorption must be efficient since the desired rate-limiting step is rate of drug release K_r i.e. $K_r << K_a$. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug e.g. iron. Aqueous soluble but poorly absorbed potent drugs like decamethonium are also unsuitable candidates since a slight variation in the absorption may precipitate potential toxicity.
2. **Elimination Half-Life:** An ideal CRDDS is the one from which rate of drug of absorption (for extended period of time) is equal to the rate of elimination. Smaller the $t_{½}$, larger the amount of drug to be incorporated in the controlled-release dosage form. For drugs with $t_{½}$ less than 2 hours, a very large dose may be required to maintain the high release rate. Drugs with half-life in the range 2 to 4 hours make good candidates for such a system e.g. propranolol. Drugs with long half-life need not be presented in such a formulation e.g. amlodipine. For some drugs e.g. MAO inhibitors, the duration of action is longer than that predicted by their half-lives. A candidate drug must have $t_{½}$ that can be correlated with its pharmacological response. In terms of MRT, a drug administered as controlled-release dosage form should have MRT significantly longer than that from conventional dosage forms.
3. **Rate of Metabolism:** A drug which is extensively metabolized is suitable for controlled-release system as long as the rate of metabolism is not too rapid. The extent of metabolism should be identical and predictable when the drug is administered by different routes. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood levels would be difficult to maintain.
4. **Dosage Form Index (DI):** It is defined as the ratio of $C_{ss,max}$ to $C_{ss,min}$. Since the goal of controlled-release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to *one* as possible.

C. Pharmacodynamic Characteristics of Drug

1. **Drug Dose:** In general, dose strength of 1.0 g is considered maximum for a CDDS.
2. **Therapeutic Range:** A candidate drug for controlled-release drug delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.
3. **Therapeutic Index (TI):** The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range. Precise control of release rate of a potent drug with narrow margin of safety is difficult. A drug with short half-life and narrow therapeutic index should be administered more frequently than twice a day. One must also consider the activity of drug metabolites since controlled delivery system controls only the release of parent drug but not its metabolism.
4. **Plasma Concentration-Response (PK/PD) Relationship:** Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for controlled-release systems.

A summary of desired biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug is given in table 1.1.

Table 1.1 Factors affecting the Design of Controlled Release Systems.

	Properties of Candidate Drug	Desired Features
A.	***Biopharmaceutic Properties***	
	1. Molecular size	< 600 Daltons
	2. Aqueous solubility	> 0.1 mg/ml
	3. Partition coefficient $K_{o/w}$	Within 1 – 2
	4. Dissociation constant pK_a	Acidic drugs, $pK_a > 2.5$ Basic drugs, $pK_a < 11.0$
	5. Ionisation at physiological pH	Not more than 95%
	6. Stability in GI environment	Stable at both gastric and intestinal pH
	7. Absorption mechanism	Passive, no absorption window
B.	***Pharmacokinetic Properties***	
	1. Absorption rate constant K_a	High
	2. Elimination half-life $t_{½}$	2 – 4 hours
	3. Metabolism rate	Not too high
	4. Dosage form index	One

Table contd...

C.	*Pharmacodynamic Properties*	
	1. Dose	Not beyond 1.0 g
	2. Therapeutic range	Broad
	3. Therapeutic index	Broad
	4. PK/PD relationship	Good

1.4 DESIGN OF CONTROLLED DRUG DELIVERY SYSTEMS

The release of drug from the drug delivery device may be controlled by various principles i.e. diffusion, dissolution, etc. The optimal control on the drug release often achieved by combination of principles. The delivery can be either systemically or locally. The controlled release formulations may be classified based on the principle(s) of drug release as follows:

A. Diffusion-controlled drug delivery systems

In these types of systems, the rate of drug release from the controlled release product depends on the diffusion of dissolved drug molecules through the polymeric barriers. The rate determining step (slowest step) in these systems is diffusion. The rate-controlling element (usually polymers) in such a system is thus not soluble, not erodible nor degradable but is water-swellable or water-insoluble. Water-swellable materials include hydrophilic polymers and gums such as xanthan gum, guar gum, high viscosity grades of HPMC and HPC, alginates, etc. Water-insoluble polymers most commonly used in such systems are ethyl cellulose and polymethacrylates.

B. Dissolution-controlled drug delivery systems

In these systems the rate-limiting phenomenon responsible for imparting the controlled-release characteristics to the drug delivery device is either of the two:

(a) Slow dissolution rate of the drug: The drug present in such a system may have inherently slow dissolution rate e.g. griseofulvin, digoxin and nifedipine. Such drugs act as natural prolonged-release products. The systems may also include drugs that convert to slow dissolving forms on contact with GI fluids e.g. ferrous sulphate.

(b) Slow dissolution rate of the reservoir membrane or matrix: The drug present in such a system may be the one having high aqueous solubility and dissolution rate e.g. pentoxifylline and metformin. The challenge in designing such systems lies in controlling the drug dissolution rate by employing either or combination of following techniques:

i. Embedment in slowly dissolving or erodible matrix. The matrix in addition may have low porosity or poor wettability.

ii. Encapsulation or coating with slow-dissolving or erodible substances. In this approach, the rate of dissolution fluid penetration and/or wettability of the reservoir system are controlled.

Slowly soluble and erodible materials commonly employed to achieve these objectives include hydrophobic substances such as ethyl cellulose, polymethacrylates with pH independent solubility (e.g. Eudragit RS and RL 100) and waxes such as glyceryl monostearate, and hydrophilic materials like sodium carboxy methylcellulose.

C. Diffusion and Dissolution-controlled drug delivery systems

The rate of drug release from these systems is controlled by both diffusion of drug and dissolution of drug and/or release modifying polymer(s). Since, dual control is available, there exist more possibilities to fine tune the drug release characteristics as per the requirements in varied situations.

D. Ion-Exchange Resin based systems

Controlled delivery of ionizable acidic and basic drugs can be obtained by complexing them with insoluble non-toxic anion exchange and cation exchange resins respectively. The drug is released slowly by diffusion through the resin particle structure. The following equation represents the release of a basic drug, NH2R', from a cation exchange resin RSO_3H when in contact with GI fluid containing an ionic compound A^+B^- (either gastric HCl or intestinal NaCl):

$$RSO_3^-NH_3^+R' + A^+B^- \longrightarrow RSO_3^-A^+ + NH3+R'B^-$$

A number of basic drugs like noscapine, phenylpropanolamine and phentermine have been retarded by such an approach. The complex can be prepared by incubating the drug-resin solution or passing the drug solution through a column containing ion-exchange resin. The drug-resin complex can be coated with cellulose or hard paraffin and formulated as ion free suspension for paediatric use.

The principles mentioned above are exploited while designing of controlled drug delivery systems in broad categories like reservoir type systems and matrix type systems. Both types of systems contain appropriate type and amount of release modifying agent or polymer(s) to control the release rate of drug.

A. Reservoir type systems

In these systems, the drug is present as a core compartment encapsulated by release controlling polymeric membrane (see Fig 1.2). Hence, these systems are also called as membrane-controlled delivery systems. The drug in the core must dissolve in the micro-environment fluid, partition and diffuse through the membrane for successful drug delivery. Upon administration of the drug delivery device, the body fluid (e.g. gastrointestinal fluid in case of oral

administration) comes in contact with the system and permeate through the membrane/film to enter inside the device to reach the drug core and dissolve the drug. The dissolved drug, then, partitions and diffuses through the membrane/film. The physicochemical nature and the thickness of the membrane control the rate of fluid permeation into the drug delivery device and rate of diffusion of dissolved drug from the device. These systems include coated drug particles, crystals, granules, pellets, minitablets and tablets.

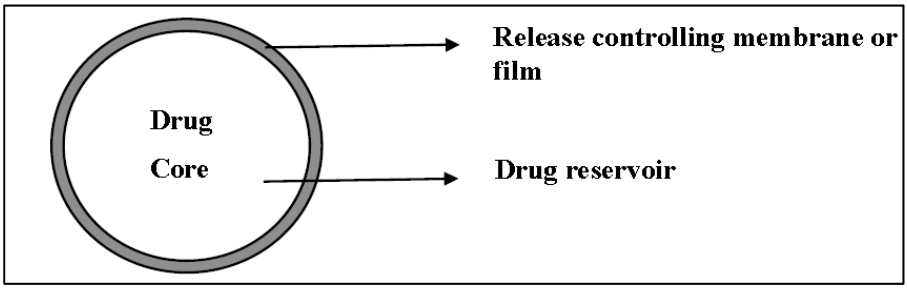

Fig.1.2 Schematic representation of Reservoir type-CDDS.

B. Matrix type systems

In these systems, the drug is uniformly distributed or dispersed in the release retarding polymeric material (see Fig 1.3). These systems are otherwise called as monolithic drug delivery systems. The matrix systems may be either hydrophilic or hydrophobic depending on the nature of release retarding materials used in the design of the drug delivery devices. The release retarding polymeric materials are water soluble/swellable or erodible in hydrophilic matrix systems and are insoluble or very slowly soluble/erodible in hydrophobic matrix systems. The hydrophilic matrix materials include HPMCs, HPC, HEC, xanthan gum, sodium alginate, guar gum, locust bean gum, PEO (polyethylene oxide) and cross-linked polymers of acrylic acid. The hydrophobic matrix materials include glyceryl monostearate, cetyl alcohol, hydrogenated vegetable oils, beeswax, carnauba wax, ethyl cellulose, polymethacrylates, etc.

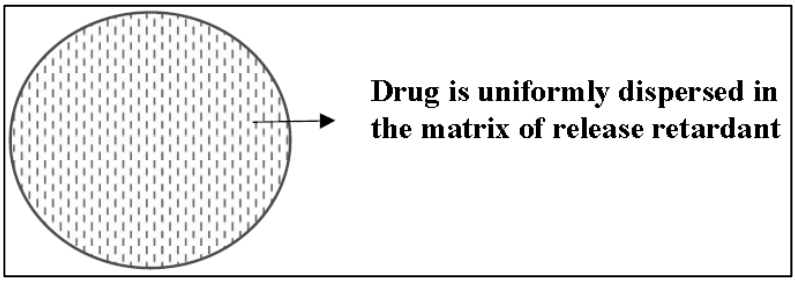

Fig.1.3 Schematic representation of Matrix type-CDDS.

C. Hybrid type systems

These systems are those where the drug in matrix of release-retarding material is further coated with a release-controlling polymer membrane. Such a device thus combines the constant release kinetics of reservoir system with the mechanical robustness of matrix system.

1.5 TIME LINE

1900	Paul Ehrlich hypothesized Magic Bullet concept
1952	First controlled release system was introduced by Smith Klein Beecham.
1953	Introduction of Eudragit
1964	Silicone based subcutaneous implants were developed
1970s	Drug eluting stents
1982	First elementary osmotic pump for indomethacin delivery.

1.6 CHAPTER AT A GLANCE

Term	Description
Conventional or immediate release dosage forms	The dosage forms in which no attempts are made to modify or control the rate of release of drugs.
Controlled release drug delivery systems (CDDS)	These are the dosage forms (more appropriately drug delivery systems) in which the release of the drug is modified or controlled by adopting suitable formulation or engineering strategies.
Spatial drug delivery	It refers to targeting a drug to a specific organ, tissue or cell.
Temporal drug delivery	It refers to the delivery of a drug over an extended period of time or for a specific duration during treatment.
Selection of drug candidates for CDDS	Physicochemical properties of the drug; Pharmacokinetic properties of the drug; Pharmacodynamic properties of the drug
Principles of CDDS	Diffusion controlled; Dissolution controlled; Hybrid control; Ion-exchange
Types of CDDS	Reservoir type; Matrix type; Hybrid type

EXERCISES

Multiple choice Questions

1. When a drug is delivered as a conventional dosage form-
   (a) the dosing interval is usually higher than the half -life of the drug
   (b) the dosing interval is usually shorter than the half-life of the drug
   (c) the dosing interval is usually equal to the half-life of the drug
   (d) none of the above
2. Fluctuations in drug levels are characteristics of-
   (a) Controlled drug delivery
   (b) Sustained drug delivery
   (c) Immediate release dosage forms
   (d) Targeted drug delivery
3. Targeting a drug to a specific organ or tissue/cell is achieved by-
   (a) Spatial delivery (b) Temporal delivery
   (c) Sustained drug delivery (d) None of the above
4. Which of the following is not an advantage of controlled drug delivery.
   (a) Fluctuating steady-state levels
   (b) Better patient compliance
   (c) Reduced dosing frequency
   (d) Better control of disease condition
5. Which of the following statement is correct?
   (a) Drugs having high molecular weight are good candidates for CDDS.
   (b) Drugs showing pH independent solubility are better candidates for CDDS.
   (c) Drugs having longer elimination half-lives are suitable for CDDS.
   (d) Drugs having narrow therapeutic window are ideal candidates for CDDS.
6. In matrix type systems, the drug release is controlled by-
   (a) The release controlling polymeric film/membrane.
   (b) Fickian diffusion
   (c) The nature of polymer matrix
   (d) All of the above
7. Fluctuation of plasma drug concentration is sometimes dangerous for-
   (a) Poorly soluble drugs (b) Lipophilic drugs
   (c) Drugs with narrow therapeutic window (d) Protein/peptide drugs

8. Which of the following is a suitable drug candidate for buccal drug delivery?
   (a) Metformin HCl (b) Nitroglycerine
   (c) Niclosamide (d) Lamivudine
9. Why a drug with slow absorption is poor candidate for CDDS?
   (a) They will form a pool of unabsorbed drug
   (b) They eliminate fast
   (c) Their bioavailability is already high
   (d) None
10. The drug release in reservoir type systems are mainly controlled by-
   (a) The nature and thickness of encapsulating membrane
   (b) Lipophilicity of drug core
   (c) o/w partition coefficient
   (d) None of the above

Short Answer Questions

1. What are the various advantages of CDDS over conventional drug delivery?
2. Explain how solubility of drugs is important while designing CDDS.
3. Why pharmacokinetic properties of drugs are considered while designing CDDS?
4. What are the key disadvantages of CDDS?
5. Explain matrix type CDDS.

Long Answer Questions

1. Discuss the various factors which influence selection of drug candidates for CDDS.
2. What are the limitations of immediate release dosage forms? Present an account of various principles adopted for designing CDDS.
3. With the help of neat diagrams explain matrix and reservoir type CDDS.
4. What are the advantages of controlled drug delivery? Explain the difference between matrix and reservoir type of devices.
5. What are the major limitations of controlled drug delivery. Add a note on diffusion and dissolution controlled systems.

Answer Key MCQs

(1) (b), (2) (c), (3) – (a), (4) – (a), (5) – (b), (6) – (c), (7) – (c), (8) – (b), (9) – (a), (10) – (a)

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