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CONTROLLED DRUG DELIVERY SYSTEMS: AN OVERVIEW ON ADVANCES AND NEW TECHNOLOGIES

Vijay Patel[1], Arvind Singh Jadon[2], Prateek Jain[1], Basant Khare[1], Bhupendra Singh Thakur[1], Rubeena Khan[1], Deepshikha Ray[3] and Anushree Jain[1]*

[1]Adina College of Pharmacy, Sagar, Madhya Pradesh, India-470001.
[2]Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India-474001.
[3]Baba Loknath Institute of Pharmaceutical Sciences, Sagar, Madhya Pradesh, India-470001.

Corresponding Author: Anushree Jain
Adina College of Pharmacy, Sagar, Madhya Pradesh, India-470001.

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ABSTRACT

Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time into the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. Drug delivery systems aim to improve patient compliance and convenience, such as, for example, fast-dissolving tablets. One of the most important goals of pharmaceutical science is localizing the pharmacological activity of the drug at the site of action. Drug delivery systems are molecular tools which, without undesired interactions at other sites, target a specific drug receptor. Keeping in view the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and, because of increased patient demand, these dosage forms are expected to become more popular.

KEYWORDS: Controlled Drug Delivery, Extended Release, Drug Release.

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. Controlled delivery of the drug is possible by combining a polymer with the drugor active agent; so that, the release of the drug can take place at the right time, at a predeterminedrate and the right place.In this system, the release of drug can be pre-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.*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. Theprimary 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 of controlled drug delivery system

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 of the controlled drug delivery systems

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
- 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

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 onthe 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, modification of the drug molecule, and modification of the dosage form.

There are hundreds of commercial products based on controlled release technologies. Only a few shows distinct mechanisms of controlled drug release.

Oral controlled-release formulations are designed mainly based on physical mechanisms. The chemicaldegradation, enzymatic degradation, and prodrug approach are less. All controlled-release formulations are designedby one mechanism or combination of a few mechanisms.

Dissolution Controlled-release Preparations

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.

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 ofthe drug are coated individually with slowly dissolving coating material (Fig. 1.1).The coated particles are compressed into a tablet directly; such as space tabs orSpansules.

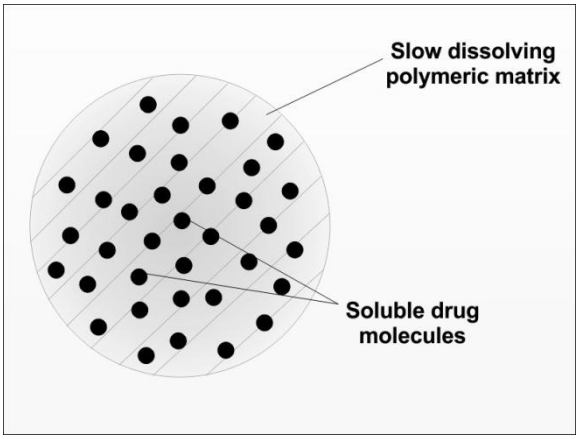

Fig. 1.1: Schematic diagram of the drug release from the reservoir system by dissolution of polymeric matrix.

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-sensitivesystems. 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. 1.2).

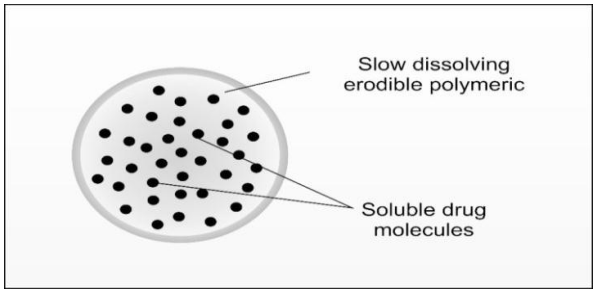

Fig. 1.2: Schematic representation of an erosion-controlled system.

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 controlledby 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 throughmicropores. 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.

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 byencapsulating an osmotic drug core (Fig 1.3) comprising an osmotically active drug (or a blend of an osmotically inactive drug with an osmotically active salt such as NaCl, Fig 1.4A) 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 1.4B). 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 vapour transmission value. The semipermeable membrane should be selected based on the nature of the application.

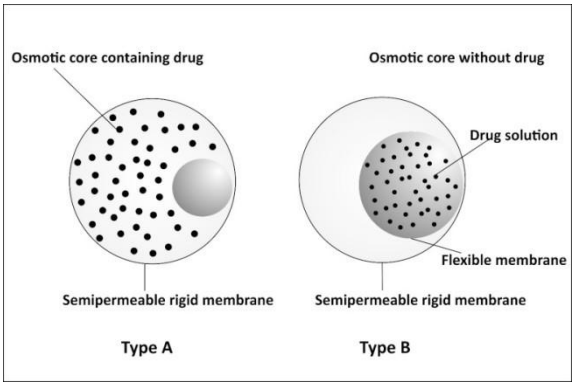

Fig. 1.3: Schematic representation of drug encapsulation in Osmotic system; Type A: Drug present in the osmotic core and Type B: Osmotic core without drug and the drug is present inside a flexible membrane.

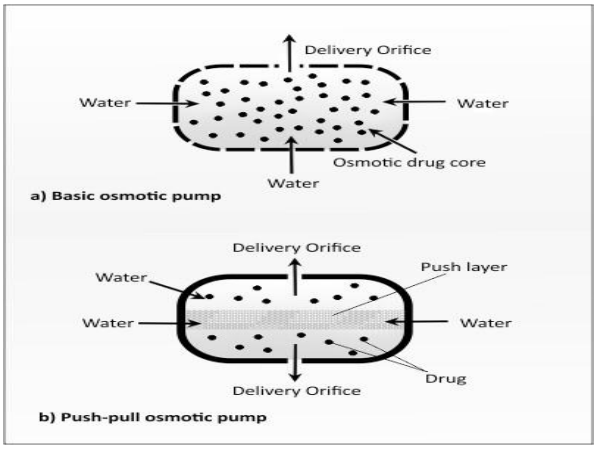

Fig. 1.4: Schematic representation of different types of osmotic pumps; (a) represents the basic osmotic pump and (b) represents the Push-pull osmotic pump.

Based on the mechanism of drug-release such as dissolution, diffusion, and osmosis, the oral controlled-release (CR) formulations are developed. Accordingly, theapproaches/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.

Matrix Tablets: Both hydrophilic CR systems and lipophilic CR systems can bepresent 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 granulationhave 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 drugloading follows approximately in the order of melt extrusion granulation>wet granulation >roller compaction ≈ fluid bed granulation> directcompression.

(B) Multi-particulates: Multi-particulate CR systems constitute both drug layeredbeads 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 spherization,
- 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 Merckosmotic delivery system, high concentrations of porosigens are incorporated inside celluloseacetate, which generates holes for drug release.

Physicochemical Properties of Drugs Suitable for Controlled Release Formulations

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

1. The molecular weight of the drug: Drugs of lower the molecular weight, moreaccurately, oflower 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 systemiccirculation, 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 infusibility or diffusion coefficient.
3. The aqueous solubility of the drug: For oral controlled release dosage form, thedrug 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 ununionized 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 dissolutionis related to its aqueoussolubility. Thus, drugs which are soluble in water are generally absorbed adequately whenadministered orally. On the other hand, poorly soluble drugs have low dissolution rates, and theirbioavailability becomes a problem when administered orally.

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.

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 suitablecandidates for controlled release systems. Drugs which are unstable in gastric pH can be designed for release inthe intestine with limited or no release in stomachand 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 inthe 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 suitablecandidates for the development of controlled release systems, such as Vitamin B.

Biological Properties of Drugs Suitable for Controlled Release Formulations

Pharmacokinetic Properties of a Drug

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

releasesystem the releaseof 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 1.2: 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.

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.

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. 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.

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.

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.

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.

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 releaseformulations.

Pharmacodynamic Properties of the Drug

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.

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 oftherapeutic index are not suitable candidates for the formulation of sustained release products.

Plasma concentration-response relationship

Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for the controlled-release system.

CONCLUSION

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and higher cost of controlled-release systems compared with traditional pharmaceutical formulations.However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity.

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