

Controlled Drug Delivery System

S. Deepu^{1*}, Molly Mathew² and MS. Shamna¹

¹Mar Dioscorus College of Pharmacy, Mount Hermon, Sreekariyam, Thiruvananthapuram, Kerala, India.

²Malik Deenar College of Pharmacy, Kasaragod, Kerala, India.

¹Mar Dioscorus College of Pharmacy, Mount Hermon, Sreekariyam, Thiruvananthapuram, Kerala, India.

ABSTRACT

Controlled release drug delivery systems provide uniform concentration of drug to the absorption site and thus allow the maintenance of plasma concentration within the therapeutic range which minimizes not only the side effects but also the frequency of administration. Oral Sustained release (SR) products provide an advantage over conventional dosage forms by optimizing properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.

Keywords: Controlled drug delivery system, Sustained drug delivery system.

INTRODUCTION

Controlled drug delivery system

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of controlled release drug delivery system. The role of drug delivery today is to take a therapeutically effective molecule with sub-optimal physiochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective with added benefits. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the health care system. These systems can be characterized as controlled drug release systems and targeted drug delivery systems.

The term "controlled release" has a meaning that goes beyond the scope of sustained drug action. It also implies predictability and reproducibility in the release rate kinetics, which mean that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another.

Controlled release drug delivery systems provide uniform concentration of drug to the absorption site and thus allows the maintenance of plasma concentration within the therapeutic range which minimizes not only the side effects but also the frequency of administration.

Classification of rate controlled drug delivery systems:

Based on their technical sophistication – controlled drug delivery systems can be classified into

1. Rate – pre programmed drug delivery systems
2. Activation modulated drug delivery systems
3. Feed back regulated drug delivery systems
4. Site-targeting drug delivery systems.

Advantages of Controlled Release Dosage Forms

- Avoid patient compliance problems
- Employ less total drug
- Minimization or elimination of local or systemic side effects.
- Minimal drug accumulation on chronic usage.
- Improve efficiency of treatment.
- Cure or control the condition more promptly.

- Reduce the fluctuation in drug level.
- Improves the bioavailability of some drugs.
- Make use of special effects.

E.g. Sustained release Aspirin for morning relief of arthritis by dosing before bed times.

Disadvantages

- The physician has less flexibility in adjusting the dosage regimen. This is fixed by dosage form design.
- Administration of this type of dosage form does not permit the prompt termination of therapy.
- Economic factors include more costly processes and equipments that are involved in manufacturing many controlled release dosage forms.
- All drugs are not suitable candidates for controlled release medication.
- Drugs with long biological half life (e.g. Digoxin-34 hours) are inherently long acting and thus are viewed as questionable candidates for sustained release formulations.
- Drugs with narrow requirements for absorption (e.g.: drugs which depend on position of GIT for optimum absorption are also poor candidates).
- Drugs like Riboflavin and ferrous salt, which are not effectively absorbed in lower intestine are poor candidates.
- Drugs which are having very short half life (<1 hour) e.g.: Penicillin, Furosemide are poor candidates for SR formulations.

Before proceeding with designing of sustained release formulation of a drug, a formulator should have an understanding of the pharmacokinetics of the candidates. It should be assured that pharmacological effect can be correlated with drug blood level and should be knowledgeable about the therapeutic dosage range, including the minimum effective and maximum safe doses. Oral route is the most convenient and common mode of administration of controlled release system. Oral controlled release systems include coated pellets, matrix tablets, microcapsules, mixed release granules, poorly soluble drug complexes, ion exchange resin complexes, osmotic pumps etc.

Oral drug delivery system

Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience.

By definition oral controlled release products refer to those formulations in which a "controlling technology or component" is incorporated that is critical to modulate the drug release pattern in a predictable fashion or that controls the timing and subsequently the location of drug release within GIT.

All the pharmaceutical products formulated for systemic delivery via oral route of administration, irrespective of the mode of delivery – (immediate, sustained or controlled release) and the design of dosage forms (either solid, liquid or dispersion) must be developed within the intrinsic characters of GI physiology. Therefore a fundamental understanding of various disciplines including GI physiology, pharmacokinetics, pharmacodynamics and formulation design, is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The scientific frame work required for the successful development of an oral delivery system consist of basic understanding of following 3 aspects:

1. Physiochemical, pharmacokinetic and pharmacodynamic characteristic of the drug.
2. The anatomic and physiologic characters of GIT (surface area, length and transit time).
3. Physiochemical characteristics and drug delivery mode of dosage form design. Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.

Areas of potential

- Development of a drug delivery system.
- Modulation of GI transit time.
- Minimization of hepatic first pass elimination.

Rationale for modifying drug release in the GIT

- To provide a location specific action within the GIT.
- To avoid an undesirable local action within the GIT.
- To provide programmed delivery pattern.
- To increase the extend of absorption/bioavailability.
- To extend the time of action of drug after administration.

Oral controlled drug delivery system

Oral route has been one of the most popular commonly employed routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms.

Potential areas to be considered are

- The various pH that the dosage form would encounter during its transit
- The gastrointestinal motility,
- The enzyme system and its influence on the drug and the dosage form.

Conventional oral drug delivery system involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration. These dosage forms have been found to have the following serious limitations.

- Inconvenient due to periodic administration
- Difficult to monitor
- Non-specific administration
- Careful calculation necessary to prevent overdosing
- Drug goes to non-target cells and can cause damage
- Low concentrations can be ineffective
- High systemic concentrations can be toxic, causing side effects or damage to organs
- Expensive (using more drug than necessary)

Factor Influencing The Design And Performance Of Controlled Drug Delivery System

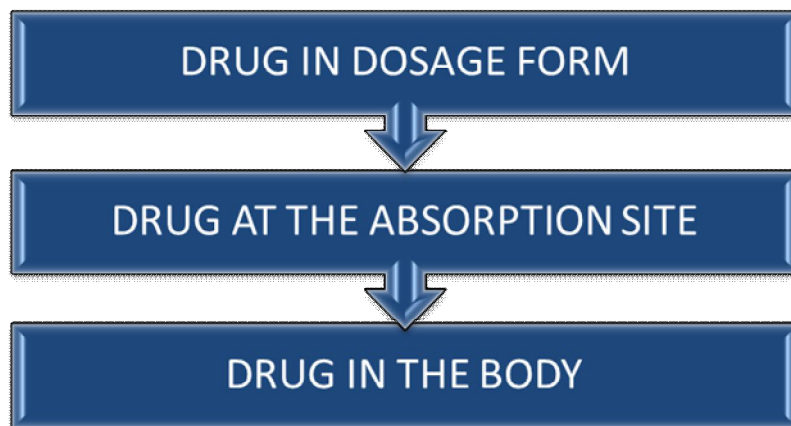
1. Biopharmaceutic characteristic of the drug
 - a) Molecular weight of the drug
 - b) Aqueous solubility of the drug
 - c) Apparent partition coefficient
 - d) Drug pKa and ionization physiological PH
 - e) Drug stability
 - f) Mechanism and site of absorption
 - g) Route of administration.
2. Pharmacokinetic characteristic of the drug
 - a) Absorption rate
 - b) Elimination half life
 - c) Rate of metabolism
 - d) Dosage form index
3. Pharmacodynamic characteristic of the drug
 - a) Therapeutic range
 - b) Therapeutic index
 - c) Plasma-concentration-response relationship

Biopharmaceutical characterization of drug

The performance of a drug presented as a controlled release system depends upon

- Release from the formulation
- Movement within the body during its passage to the site of action.

Among these the former depends upon the fabrication of the formulation and the physicochemical properties of the drug and the later depends on the pharmacokinetic of the drug. In conventional dosage form the rate limiting step in drug availability is usually absorption through the biomembrane, whereas in controlled drug delivery system the rate limiting step is the release of drug from the dosage form.



For designing a controlled drug delivery system the following biopharmaceutic properties of drugs must be included

- a) Molecular weight of the drug: Lower the molecular weight, faster and more complete the absorption. About 95% of the drugs are absorbed by passive diffusion. Diffusivity is defined as the ability of a drug to diffuse through the membrane is inversely related to the molecular size. Thus drugs with large molecular weight are poor candidates for oral controlled release systems.
- b) Aqueous solubility of the drug: A drug with good aqueous solubility, especially if pH independent, serves as a good candidate for oral controlled release dosage form. Solubility of drug can limit the choice of mechanism to be employed for CRDDS, for example the diffusional systems are not suitable 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.
- c) Apparent partition coefficient: Greater the apparent partition coefficient of a drug, greater its lipophilicity and thus greater is its rate and extend of absorption. These types of drugs even cross the highly selective blood brain barrier. This parameter is also important in deciding the release rate of a drug from lipophilic matrix or device.
- d) Drug pKa and ionization at physiological pH: For optimum passive absorption, the drugs should be non-ionised at that site for an extend of 0.1-5%. Drugs that are existing largely in ionised forms are poor candidates for controlled delivery systems eg: hexamethonium.
- e) Drug stability: Drugs that are unstable in the GI environment are not suitable candidates for controlled release systems. Drugs that are unstable in gastric pH can be designed to release in intestine with limited or no release in stomach and vice versa.
- f) Mechanism and site of absorption: Drugs that are absorbed by carrier mediated transport process or through a window are poor candidates for controlled release systems, eg: Vitamin B.
- g) Route of administration: For controlled release oral and parenteral routes are

the most preferred which is the followed by transdermal.

- i. Oral route: the drug should have following properties to be a successful candidate
 - It must get absorbed through the entire length of GIT.
 - 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.
 - Intramuscular/subcutaneous route: This route is preferred because
 - The action is to be prolonged for 24 hours to 12 months.
 - Small amount of drug is administered (2ml/2gm).
 - Factors important are solubility of drug in surrounding tissue, molecular weight, partition coefficient and pKa of drug.
- ii. Transdermal route: This route is selected for drugs which show extensive first pass metabolism upon oral administration or drugs with low dose. Important factors to be considered are partition coefficient of drugs, contact area, skin condition, skin permeability of drug, skin perfusion rate, etc.

Pharmacokinetic characteristic of a drug

- a) Absorption rate: A drug which is fabricated into a controlled release system its absorption must be efficient since the desired rate limiting step is rate of drug release. A drug with slow absorption is a poor candidate for such dosage forms, as 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 of intestine, sustained-release preparations may be disadvantageous to absorption.
- b) Biological half life: An ideal CRDDS is one in which the rate of drug absorption is equal the rate of drug elimination. If the $t^{1/2}$ is smaller (less than 2 hours) for a given drug then more amount of drug is to be incorporated into 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 need not be formulated into such formulations.

- c) Metabolism: Drug selected for controlled release system should be completely metabolized but the rate of metabolism should not be too rapid. A drug which induces and inhibits metabolism is a poor candidate because steady states are difficult to achieve.
- d) Drug-Protein Binding: The drug can bind to 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 decreases, the drug-protein complex dissociates to liberate the free drug and maintain equilibrium. A protein bound drug due to its high molecular size is unable to enter into hepatocytes, resulting in reduced metabolism. The bound drug is not available as a substrate for liver enzymes there by further reducing the rate of metabolism. The glomerular capillaries do not permit the passage of plasma-protein and drug protein complexes. Hence only unbound drug is eliminated. The elimination half-life of drugs generally increases when the percent of bound drug to plasma increases. Such drugs need not be formulated into sustained/controlled release formulations.
- e) Dosage form index: It is defined as the ratio of $C_{ss,max}$ to $C_{ss,min}$. its value must be close to as possible as one.

Pharmacodynamic characteristics of the drug

- a) 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 concentration beyond this level.
- b) Therapeutic index: It is most widely used to measure the margin of safety of a drug. $TI = TD_{50} / ED_{50}$. The longer the value of T.I the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 10.
- c) Plasma concentration-response relationship: Drugs such as reserpine whose pharmacological activity is independent of its concentration are

poor candidates for controlled-release system.

CONCLUSION

Oral Sustained release (SR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutic, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.

REFERENCES

1. Sarika Pundir. International Journal of Drug Research and Technology. 2013;(1):12-20.
2. Brahmkar HA and Jaiswal SB. Biopharmaceutics and Pharmacokinetics A Treatise Vallabh Prakashan. Reprint Edition. 2009;348-357 and 337.
3. Kumar Kiran S, Rao Rama T and Jayaveera KN. Matrix Tablets as Controlled drug delivery systems. Indo American Journal of Pharmaceutical Research. 2011;1(4):343-350.
4. Shargel L, Yu Andrew BC and Wu-Pong Susanna. Modified release drug products. Applied Biopharmaceutics and Pharmacokinetics, 5th Edition, McGraw Hill. 1999;170-173.
5. Siepmann J and Peppas NA. HPMC matrices for controlled drug delivery. new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics. Pharm Research. 2000;16:1748-1756.
6. Kumar Sunil, Kumar Anil, Gupta Vaibhav, Malodia Kuldeep and Rakha Pankaj. Oral Extended Release Drug Delivery System. A Promising Approach. Asian J Pharm Tech. 2012;2(2):38-43.
7. Robinson Joseph R. Controlled-Release Drug-Delivery Systems. Chapter-27, Remington: The Science and Practice of Pharmacy. Lippincott Williams & Wilkins. 20th ed, 2002;1:903-914.
8. Ashok V Bhosale, Rahul V Takawale and sanjay D Sawamy. Oral novel drug delivery system. The Eastern pharmacist. 2000;41-43.

9. Lachman L, Lieberman HA and Kanig Joseph L. The theory and practice of Industrial pharmacy. Verghese publishing house, 3rd edition, 1990;337-38.
10. Gibaldi M. Biopharmaceutics and Clinical Pharmacokinetics, 4th ed. Lea & Febiger, London, England. 1991;61-79.
11. Bourne DWA. Pharmacokinetics. In: Banker GS, Rhodes CT, Modern Pharmaceutics, 4th ed., Marcel Dekker Inc, New York, 2002;67-92.
12. Aher KB, Bhavar GB, Joshi HP and Chaudhari SR. Recent advances in compression-coated tablets as a controlled drug delivery system. Saudi pharmaceutical journal. 2011;01.
13. Loyd V Allen, Nicholas G Popovich and Howard C Ansel. Ansel's Pharmaceutical dosage forms and drug delivery system. 8th edition, 260-263.