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REVIEW ARTICLE

Oral Controlled Drug Delivery System – A Review

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ABSTRACT:
The new generation of oral controlled release drug delivery system technologies brings valuable benefits to patients. Oral route is the most convenient and commonly route of drug delivery. Oral controlled release formulations are designed to deliver a drug at a pre determined rate by achieving a constant drug level for a specified period of time with lower side effects. Controlled release drug delivery have become a significant priority worldwide, it may be possible to achieve rapid absorption of drug and increased bio availability, reduced toxicity and improved patient compliance. This article mainly focuses the requirement of controlled drug delivery system, their advantages, disadvantages, formulation, various methods and use of controlled release system.

KEYWORDS: Controlled release drug delivery system, prolonged release, Zero-order, Half life Diffusion controlled.

INTRODUCTION:
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 controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist[1]. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

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TERMINOLOGY:
In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent)[2]. Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval. Delayed release systems, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun. Enteric-coated tablets are an example of this

type of dosage form[3].

The ideal of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems, this approximation is achieved by creating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, entero hepatic recycling, sweat, fecal, and so on. Since for most drugs these elimination processes are first order, it can be said that at a certain blood level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period. This is represented mathematically as

Rate in = rate out = $k_{elim} x C_d x V_d$

Where C_d is the desired drug level, V_d is the volume of distribution, and k_{elim} is the rate constant for drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve by administration routes other that intravenous infusion. Noninvasive routes (e.g., oral) are obviously preferred[1].

Oral systems:

Historically, the oral route of administration has been used the most for both conventional and novel drug delivery systems. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. The types of sustained- and controlled-release systems employed for oral administration include virtually every currently known theoretical mechanism for such application. This is because there in more flexibility in dosage design, since constraints, such a sterility and potential damage at the site of administration, axe minimized[4]. Because of this, it is convenient to discuss the different types of dosage forms by using those developed for oral administration as initial examples.

In order to maintain a constant drug level in either plasma or target tissue, release rate from the controlled released system should be equal to the elimination rate from plasma or target tissue. The most conventional method to achieve a constant plasma level is the use of intravenous infusion. However this would be inconvenient for most therapeutic situations so that other noninvasive routes such as the oral or transversal route are preferred.

Various designations such as “smart” “targeted” “intelligent” “novel” and “therapeutic” have been given to controlled release systems. Therapeutic systems have also been used interchangeably with rate controlled release systems. These usually operate on an advanced engineering system control approach, consisting of a logic element with or without a sensor. Three types of therapeutic systems are available, namely, passive preprogrammed, active preprogrammed, and active self programmed. Most rate controlled system fail in the category of passive preprogrammed in which the release rate is predetermined and is irresponsive to the external biological environment. Examples of active preprogrammed are few and include most metered insulin pumps, whose release rate can be altered by a source external to the body[5].

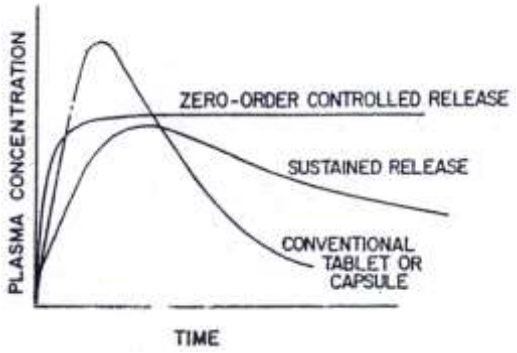


Fig. I Plasma drug concentration profiles for conventional tablet or capsule formulation a sustained release formulation and a zero order controlled release formulation.

Figure I shows comparative blood drug level profiles obtained from administration of conventional, controlled as well as prolonged release dosage forms. Thus the conventional tablet or capsule/provides only a single and transient burst of drug. As long as the amount of drug is above the minimum effective concentration, a pharmacological response is observed. Problems occur when the therapeutic range is very narrow or when the peak is greater than the upper limit of this range. Indeed one of the main purpose of controlled release is to improve safety and minimize side effects of the drug by reducing fluctuations in drug level. Prolonged release dosage forms also reduce fluctuations in plasma drug levels by slowing down the absorption rate due to slower drug release rate. In many cases, this is achieved by intermittently releasing a small burst of drug over a prolonged period of time as in the case of repeat action dosage forms[6].

Controlled drug delivery occurs when a polymer whether natural or synthetic is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, or it may be triggered by the environment or other external events.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled release systems can respond to changes in the biological environment and deliver or cease to deliver – drugs based on these changes.

Controlled Drug Delivery System:
The primary objectives of controlled drug delivery system (CDDS) are to ensure safety and enhance efficacy of drug with improved patient compliance[4].

An ideal CDDS is the one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.

An ideal targeted DDS as the one which delivers the drug only to its site of action and not to the non target organs or tissues[5].

The goal of a sustained release (SR) dosage form is to maintain therapeutic blood or tissue level of the drug for an extended period. This is usually accomplished by attempting to obtain zero – order release from the dosage from[1].

Terms used in CDDS:
Controlled release system provides a release profile predominantly controlled by the design of the system. Various terms like "Smart" "targeted". "Intelligent" "Novel" and "Therapeutic" have been assigned to controlled release system[4].

There are several terms used interchangeably VIZ.
- Controlled release
- Programmed release
- Sustained release
- Prolonged release
- Timed release
- Slow release
- Extended release

Controlled release system differ from sustained release system which simply prolong the drug release and hence plasma drug levels for an extended period of time (i.e. not necessarily at a predetermined rate)[5].

The term "Sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe the pharmaceutical dosage form formulated to retard the release of therapeutic agent such that it's appearance in the systemic circulation is delayed and / or prolonged and its plasma profile as sustained in duration the onset of its pharmacologic action is sustained.

The term "Controlled release" has a meaning that goes beyond the scope of sustained drug action. It also implies the predictability and reproducibility in the drug release kinetics which means 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[6].

Advantages of CDDS[1, 7]:
- Increased patient compliance
- Reduction an dosing frequency
- Avoidance of night time dosing
- Reduced fluctuations in circulatory drug levels
- More uniform effect
- Decreased side effects like reduced GI irritation
- Delivery of drug in the vicinity of site of action
- More efficient utilization of active agent
- Reduction in health care cost through improved therapy

Disadvantages of CRDDS[7]:
- Poor invitro – in vivo correlation
- Toxicity due to dose dumping
- High cost
- Reduced potential for dosage adjustments
- Increased patient clearance
- Poor systemic availability in general
- Stability problem

Characteristic futures of drug to design CDDS[1]:
The optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug
To design the controlled release product, a number of variables must be considered.

Drug properties:
The physiochemical properties of the drug including stability, solubility, partitioning characteristics, charge, and protein binding property, play dominant role in the design and performance of controlled release system.

Route of drug delivery:
The drug delivery system in certain route of administration can exert a negative influence on drug efficacy, particularly during chronic administration, and hence other routes of administration may also be considered.

Performance of the CR system may also influenced by physiological constraints imposed by the particular route, such as first pass metabolism, GI motility, blood supply and sequestration of small foreign particles by

the liver and spleen.

Target sites:
In order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue this can be partially achieved by local administration or by the use of carriers[8].

Acute or chronic therapy:
Consideration of weather one expects to achieve cure (or) control the diseased condition and the expected length of drug therapy are important factors in designing controlled release systems.

Long term toxicity of rate controlled drug delivery system is usually different from that of conventional dosage forms.

The disease:
Pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system.

For example, in attempting to design an ocular controlled release products for an external inflammation, the time course of changes in protein content in ocular fluids and in the integrity of the ocular barriers would have to take into consideration[9].

The patient:
The patient is ambulatory or bedridden, young or old, obese or gaunt etc. can influence the design of a controlled release product.

All of these variables are important in the design of controlled and targeted release delivery systems.

To establish a basis for discussions of the influence of drug properties and the route of administration on sustained / controlled release product design, it is worth while focusing on

Behavior of the drug in its delivery system
Behavior of the drug and it's delivery system in the body.

Principles (or) mechanisms[8]:
There are three primary mechanisms by which active agents can be released from the delivery system.

- Diffusion
- Degradation
- And swelling followed by diffusion

Diffusion occurs when a drug or other active agent combines with the polymer that forms the controlled release device and the diffusion can occurs on macroscopic scale – as through pores in the polymer matrix or on a molecular level, by passing between polymer chains

The polymers and active agent have been mixed uniformly to form a matrix system and the diffusion occurs when the drug passes from polymer mat matrix in to the external environment. As the release continues its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release[10].

The drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In this system the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores.

Swelling – controlled release systems are initially dry and, when placed in the body, will absorb water or other body fluids and swells.

The swelling increases the aqueous solvent content within the formulation as well as the polymer particle size, enabling the drug to diffuse through the swollen network in to the external environment[11]

Most of the materials used in swelling controlled release system are based on hydro gels which are polymers that will swell without dissolving when placed in water or other biological fluids.

Depending upon the polymer and the environmental conditions such as pH, temperature or ionic strength the system can either shrinks or swell upon a change in any of these environmental factors.

Properties of drug that are unsuitable for CDDS[1]:

- Short long elimination half life.
- Large doses.
- Narrow therapeutic index.
- Poor absorption.
- Active absorption.
- Low aqueous solubility.
- Extensive first Pass clearance.
- Drugs with half life less than 2hrs should not be used.
- Drugs having half life more than 8hrs.

Properties of drug that should be considered for CR formulation[9]:

- Solubility and permeability of drugs: High solubility and high permeability (best case for controlled release), low solubility and low permeability (worst case for CR).
- Biological half life between 2 to 6 hour to avoid accumulation in the body including gut metabolism.
- Permeability coefficient: $P < 0.5X\ 10^{-6}$ mms^{-1} not

suitable for CR dosage form.
- Inactivation or metabolism of the drug in the body, including gut metabolism.
- Effect of age, sex and smoking.
- Non linear elimination due to drug metabolism (biochemical conversation of drugs) saturation or other factors.

Design of CDDS:
The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery[12].

The Basic rationale of a controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route[5].

Classification of CDDS:
Controlled release drug delivery system can be classified into the following categories:
a) Rate programmed drug delivery system.
b) Activation – Modulated DDS.
c) Feedback – Regulated DDS.
d) Site – Targeting DDS.

All categories consists of the following common structural features
1) Drug reservoir compartment.
2) Rate controlling element.
3) Energy source[6].

Classification of controlled release system:
It can also be classified as follows:
1) Diffusion controlled:
a) Reservoir system.
b) Monolithic system.
2) Water penetration controlled :
a) Osmotic systems.
b) Swelling systems.
3) Chemically controlled:
a) Monolithic system.
b) Pendent systems.
c) Ion exchange resin.
4) Regulated systems:
a) Ultrasonically Modulated systems.
b) Magnetically Modulated systems.

Diffusion controlled system:
These systems are broadly divided in to two categories:
- Reservoir System
- Monolithic System

The basic mechanisms of drug release from these two systems are fundamentally different[10]

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer.

In these types of system me rate controlling step is not the dissolution rate. But the diffusion of dissolved drug through a polymeric barriers. The drug release rate is never zero order since the diffusional path length is increased with time as the insoluble matrix is gradually depleted of drug[4]

Reservoir system:
In a membrane controlled reservoir system the active drug is in a core surrounded by a thin polymer membrane and the active drug is released to the surrounding environment by diffusion process through the rate-limiting membrane for reservoir type of systems and the drug delivery rate remains fairly constant. These systems consist of a reservoir either solid drug dilute solution or highly concentrated drug solution within a polymer matrix, which is surrounded by a film or membrane of a rate controlling material[13].

Reservoir device as the name implies are characterized by a core of drug, surrounded by a polymeric membrane the nature of the membrane determines the rate of release of drug from the system.

The process of diffusion is generally described by a series of equations that were first detailed by Fick. The first of these states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. The equation is given as

$$J = -D \frac{dc}{dx}$$

Where,
J is Flux, given in units of amount area-time
D is the diffusion Co-efficient.

Monolithic matrix delivery system:
In monolithic matrix delivery system the therapeutic agent is dispersed in a polymer matrix and drug release is controlled by diffusion from the matrix into the surrounding environment.

To formulate such systems polymer and active agent are mixed to form a homogenous system. Diffusion occurs when the drug passes from the polymer matrix in to the external environment. The delivery rate normally decreases in these type of system since the bioactive agent has to traverse a long distance progressively and

there by requires a longer diffusion time for ultimate delivery of drug(s).

Water penetration controlled system:
In water penetration controlled delivery systems rate control is obtained by the penetration of water in to the system. Two general types of these systems.

- Osmotic ally controlled release system.
- Swelling controlled release system.

Osmotically controlled systems:
In these systems osmotic pressure provides the driving force to generate controlled release of drug consider a semi permeable membrane that is permeable to water. When this device is exposed to water or any body fluids, water will flow in to the tablet owing to osmotic pressure difference.

It is fabricated by applying a semi permeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A high speed mechanical drill, drills a delivery orifice in this product[1].

Oral osmotic pump popularly called as oros, works on the principle of osmotic pressure to release the drug at a constant zero order rate[14].

A core comprising of drug and an osmotically active substance (also called as osmogel) such as potassium chloride or mannitol is surrounded by a rigid semi permeable membrane coating such as cellulose ester or cellulose ether having an orifice 0.4mm diameter produced by laser beam for drug exit. When exposed to GI fluids, water flows through the semi permeable membrane into the tablet due to osmotic pressure difference which dissolves the drug and pumps it out through the orifice by the osmotic force[5].

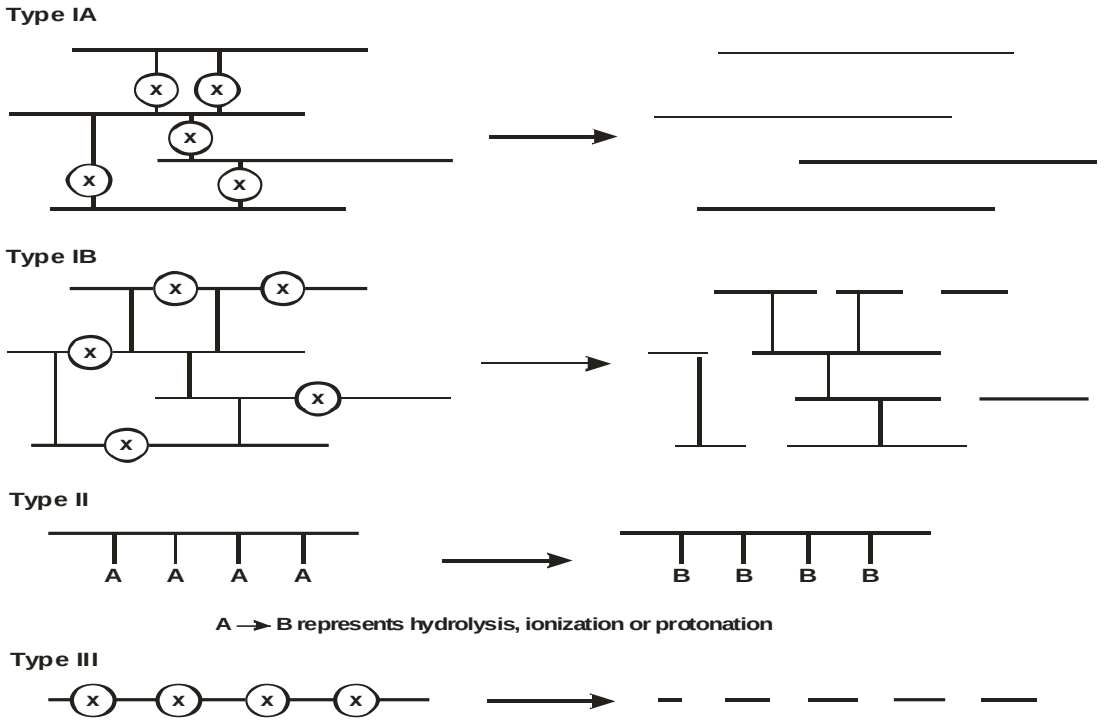
Swelling controlled systems:
When swelling controlled release systems are placed in the body, they absorb water or other body fluids and swells, swelling increase the aqueous solvent content within the formulation as well as the polymer particle size enabling the drug to diffuse through the swollen net work in the external environment. Most of the materials used in swelling controlled release system, that will swell without dissolving, when exposed to water other biological fluids.

The release of active agent from the system is a function of rate of uptake of water from the vicinity and the rate of drug diffusion[15].

Swelling mechanism can be formulated as multilayer devices, where each layer contains a different concentration of drug or even a different active agent. Thus the pattern of drug release can be regulated by adjusting the concentration of drug in different layer of device[4].

Chemically controlled:
These are delivery systems that change their chemical structure, when exposed to biological milieu. Mostly biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains in to biologically safe and progressively smaller moieties. For instance polylactides, polyglycolides and their co-polymers eventually break down to lactic acid and glycolic acid that enter the kreb's cycle and are further processed to yield carbon dioxide and water.

Monolithic systems (polymer erosion):
Polymer erosion can be defined as the conversion of water insoluble material to a water soluble material not necessarily due to a major chemical degradation. Various bio erosion mechanisms are summarized in Figure 1-26. Type I erosion is demonstrated by water soluble macromolecules that are cross-linked to form a three dimensional network. Erosion of these systems can take place by cleavage of cross-links (type IA) or disintegration of water soluble polymer backbone (type IB). As bond cleavage occurs the matrix starts to swell and ultimately it dissolves. In type II erosion water insoluble macromolecules are converted to water soluble compounds by hydrolysis, ionization or protonation of a pendant group. As there is no backbone cleavage, the solubilization does not result in any significant change in molecular weight. In type III erosion high molecular weight water insoluble polymers are transformed into small, water-soluble intermediate molecules by a hydrolytic cleavage of labile bonds in the polymer backbone.



Mechanism of drug release:

Mechanism A involves the release of active agent that is covalently attached to the backbone of biodegradable polymer by hydrolysis of bond A. It is desirable that the reactivity of bond A should be significantly higher than the reactivity of bond B. In mechanism B, the active agent is confined in a central core area and is surrounded by a bioerodible rate controlling membrane. In mechanism C, the active agent is dispersed in bioerodible polymer and diffusion, combination of diffusion and erosion or sometimes pure erosion control the release of active agent[16].

Pendent systems[11]:

Scholsky and Fitch developed a means of attaching a range of drugs such as analgesics and antidepressants, etc., by means of an ester linkage to poly (acryl ate) ester latex particles prepared by aqueous emulsion polymerization. These lattices when passed through an ion exchange resin such that the polymer end groups were converted to their strong acid form could 'self-catalyse' the release of the drug by hydrolysis of the ester link.

The researchers stated that drugs have been of attached to polymer, and also where monomers have been synthesized with a pendent drug attached. The research group have also prepared their own dosage forms in which the drug is bound to a biocompatible polymer by a labile chemical bond .

Ion exchange resins:

Ion Exchange systems generally use resins composed of water – insoluble cross linked polymers. Those polymers contain salt forming functional groups in repeating positions on the polymer chain. The drug as bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$Resin^+ - drug^- + x^- \rightarrow resin^+ - x^- + drug^-$

Conversely

$Resin^- - drug^+ + y^+ \rightarrow resin^- - y^+ + drug^+$

Where

x^- and y^+ are ions in the G1 tract

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length, and rigidity of the resin the ionic concentration of the GI tract remains rather constant with limits, the release rate of dug can be affected by variability in diet, water intake, and individual intestinal content[1].

Controlled delivery of ionizable acidic and basic drugs can be obtained by complexing them with insoluble nontoxic anion exchange and cation exchange resins respectively. The drug is released slowly by diffusion through the resin particle structure[17].

A number of basic drugs like noscapine, phenyl propanalmine and phentermine have been retarded 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[5].

Regulated systems:

Ultrasonically modulated systems:

In ultrasonic – controlled polymeric delivery systems in which release rates of substances can be repeatedly modulated externally[18]. Both non-erodible as well as bio erodible polymers were used for preparation of drug carrier's matrices. The bio erodible polymers include poly lactide, polyglycolide; poly bis (p-carboxy phenoxy) alkane anhydrides and their copolymers with sebacic acid on exposure to ultrasound enhanced polymer erosion and drug release were recorded[19].

Magnetically modulated systems:

Pulsatile drug delivery could be attained using oscillating fields. This approach involves incorporation of magnetic beads in elastic polymers. It has been shown that when an oscillating magnetic field was applied more drugs were released[4].

CONCLUSION:

Oral controlled release dosage form provides prolong drug release and helpful increasing the therapeutic efficacy as well as they also improving the patient's compliance. The controlled release oral dosage form is easy to optimizing pharmacokinetic and pharmacodynamic properties of the drug in such way that it reduces dosing frequency and maintains uniform plasma drug concentration. From the discussion it is concluded that the oral controlled release drug delivery system is the most convenient route for drug delivery.

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