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A REVIEW ON CONTROLLED DRUG DELIVERY SYSTEM

A Hariom Prakash Rao*, V.T. Iswariya , V Lokeswara Babu and A Srinivasa Rao

Dept. of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar, Yenkapally (V), Moinabad (M), RR Dist, 500075, India

***Corresponding author e-mail:** lokshv83@gmail.com

ABSTRACT

Controlled-release systems are used to control the plasma concentration of the drug after administration by various possible routes. These are the systems in which the drug is released in a predetermined pattern over a fixed period of time. The release kinetics is usually zero-order. Ideally the release rate from the dosage form should be the rate-determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. The controlled release formulations will reduces the dosing frequency required for daily. This article provides an ideal requirements, advantages, properties and different approaches involved in the development of controlled release formulations for the better delivery of drugs.

Keywords: Controlled release, Dosing frequency, Drug concentration, Plasma Concentration, Zero order

INTRODUCTION

Controlled release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the market place. Such advancements have come about by the simultaneous convergence of many factors, including the discovery of novel polymers, formulation optimization, better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities, and the introduction of biotechnology and bio-pharmaceutics in drug product design. The major benefits of these products lie in the optimization of drug input rate into the systemic circulation in order to achieve an appropriate pharmacodynamic response. This in turn should added to product safety and reduce the extent and incidence of major adverse drug reactions due to a more strict control of blood levels. Furthermore, with less frequent dosing, it is speculated that this should improve patient compliance and possibly maximize drug production efficacy in therapeutics. Recently numerous hydrophilic polymers have been investigated and are currently used in the design of complex controlled release systems [1] in many cases the formulator depends on the inherent rate controlling mechanisms of the polymer to provide constant rate drug delivery. Among desirable features, the polymer should possess inherent physicochemical characteristics which provide for the attainment of high gel-state viscosity upon swelling, ability to maintain constant gel layer integrity over a prolonged period of time and hence low erosion rate, and complete dissolution of polymer upon exhaustion of drug release. Alternatively a programmed system is sought for which swelling and erosion is the key factors in controlling drug liberation. The ideal polymer would permit these processes to operate synchroniously, i.e. offering a balance between the principle processes of swelling, erosion, and dissolution. Among the most widely used polymers, such as the nonionic hydroxypropyl methyl cellulose (HPMC), hydroxypropyl Cellulose (HPC) polyethylene oxide (PEO) types the cationic chitosan types and anionic alginate types, the attainment of high gel-state viscosity, maintenance of constant gel layer, in a monolithic sense for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. Since the various dynamic phases in the rate processes of polymer relaxation, distanglement, and or erosion

during dissolution are manifested in a non constant manner, realization of zero-order drug release from such monolithic devices is difficult.

In the past, alkaline compounds or buffers have been included in solid oral formulations of several acidic drugs that undergo dissolution rate-limited absorption. The same principle of addition of buffers, osmotically active agents like surfactants or combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques. However, no specific strategy has been employed to apply the same principle to design a simple, directly compressible, monolithic, and controlled- release system with provision of zero-order kinetics. In general, the application of buffers and ionizable compounds in dosage from design has essentially been limited to the minimization of localized gastrointestinal tract adverse effects and the pH-solubility dependency of poorly soluble compounds [2].

Controlled Drug Delivery Systems

In recent years, considerable attention has been focused on the development of new drug delivery systems. There are a number of reasons for the intense interest in new systems. First, recognition of the possibility of repatenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new drug delivery systems. Second, new systems are needed to deliver the novel, genetically engineered pharmaceuticals, i.e., peptides and proteins, to their site of action without incurring significant immunogenicity or biological inactivation. Third, treating enzyme deficient diseases and cancer therapies can be improved by better targeting. Finally, therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement with in the body, thereby reducing both the size and number of doses.

In general, control delivery attempts to:

1. Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.
2. Localize drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue or organ.
3. Target drug action by using carriers or chemical derivatization to deliver drugs to a particular "target" cell type.

CHARACTERISTICS OF DRUGS SUITABLE FOR CONTROLLED RELEASE:

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the GI tract.
3. Administered in relatively small doses.
4. Possess a good margin of safety.

FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF CONTROLLED RELEASE PRODUCTS

To establish criteria for the design of controlled release products, a number of variables must be considered.

1. Drug properties

The physicochemical properties of a drug, including stability, solubility, partitioning characteristics, charge and protein binding property play a dominant role in the design and performance of controlled release systems.

2. Route of drug delivery

The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. Performance of the controlled release systems may also be influenced by physiological constraints imposed by the particular route, such as first pass metabolism, G.I.motility, blood supply, and sequestration of small foreign particles by the liver and spleen.

3. 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.

4. Acute or chronic therapy

Consideration of whether one expects to achieve cure or control of a condition and expected length of drug therapy are important factors in designing controlled release systems. Moreover, long term toxicity of rate controlled drug delivery systems is usually different from that of conventional dosage forms [3].

5. The disease

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

6. The patient

Whether the patient is ambulatory or bed ridden, young or old, obese or gaunt, etc can influence the design of a controlled release product. For example, single unit controlled release products are particularly

prone to intra and inter subject variation because of variability in individual G.I.motility.

PHYSICOCHEMICAL PROPERTIES OF A DRUG INFLUENCING DRUG PRODUCT DESIGN AND PERFORMANCE:

1. Aqueous solubility

Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site [4].

2. Partition coefficient and molecular size

Partition coefficient and molecular size influence not only the permeation of a drug across biological membranes, but also diffusion across or through a rate controlled membrane or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity, is related to its molecular size by the following equation.

$$\text{Log } D = -S_V \text{ Log } V + K_V = -S_M \text{ Log } M + k_m$$

Where D is diffusivity, M is molecular weight, V is molecular volume and S_V, SM, KV and k_m are constants in a particular system.

3. Drug stability

The stability of a drug in the environment to which it is exposed is another physicochemical factor to be considered in the design of controlled release systems. Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine.

4. Protein binding

Blood proteins are for the most part recirculated and not eliminated, drug protein binding can serve as a depot for drug producing a prolonged release profile/ especially if a high degree of drug binding occurs. Quaternary ammonium compounds bind to mucin in the G.I. tract. Drugs bound to mucin may increase absorption, if the bound drugs act as a depot.

BIOLOGICAL FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF CONTROLLED RELEASE PRODUCTS [5]

The design of controlled release product should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing. In the following discussion, it is assumed that the level of drug in blood or body tissue parallels biological activity of the drug.

1. Absorption

To maintain constant blood or tissue level of drug, it must be uniformly released from the controlled release system and then uniformly absorbed. The fraction of drug absorbed from a single non controlled dose or drug can sometimes be quite low for a variety of reasons such as drug degradation due to solvolysis or metabolism, binding of drugs to proteins, physical loss, or perhaps site - or dose-dependent absorption. If the drug were erratically absorbed, as might occur in a route of administration with variable absorptive surface, such as the G.I.tract, design of a controlled release product would be more difficult or prohibitive with respect to the oral route, it is well known that the absorptive character of the different segments of the G.I tract varies [6], which in turn can influence the amount and rate of absorption of certain drugs. The oral anticoagulant dicoumarol [7], the quaternary ammonium compounds [8] and the amino glycosides such as Gentamycin [9] are examples of such drugs.

2. Distribution

The distribution of drugs into tissues can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extra cellular fluids.

3. Metabolism

Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Metabolic alteration of a drug can occur in a variety of tissues, some of which are richer in enzymes than others. For example, the organ most responsible for metabolism is the liver and thus the greatest metabolic conversion occurs after a drug has been absorbed into the general-circulation.

4. Duration of action

The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for controlled release. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns.

5. Side effects

It is believed that for some drugs, the incidence of side effects is a function of plasma concentration [10]. Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear to offer a solution to this problem. The technique of controlled release has been more widely used to lower the incidence of GI side effects than that of systemic side effects and appears to produce more satisfactory results. It is postulated that by slowing the rate at which the drugs are released, the likely hood of GI irritation would be reduced due to a smaller amount of drug exposed to the GI mucosa at any given time.

6. Margin of safety

Decisions on margin of safety of a drug perhaps can be better made on the basis of its therapeutic index in combination with the range of plasma combination with in which the drug is considered to be therapeutically safe and effective. This approach has been very valuable as a therapeutic guide in monitoring drug therapy.

7. Total clearance (Cl)

The CL is that the hypothetical volume of distribution of unmetabolised drug that is cleared per unit of time by any pathway of drug removal. The value of CL can be determined from the dose administered D, and absolute bioavailability and AUC.

$$Cl = D.F / AUC$$

The Cl is the key to estimate the dose rate R° for controlled release dosage forms and is related to the mean steady state concentration.

8. Mean Residence Time (MRT)

The MRT is the mean time a drug molecule resides in the body, it is the time corresponding to 63.2 % elimination from the body. It is calculated from AUC and AUMC i.e. the area under the first movement curve.

9. Dosage form Index (DI)

DI is the ratio between the peak (C_{SS} max) and trough (C_{SS} min) values with in dosing intervals [11].

ADVANTAGES AND DISADVANTAGES OF CONTROLLED RELEASE PREPARATIONS

Advantages [12]

1. Decreased incidence and/or intensity of adverse effects and toxicity.
2. Better drug utilization.
3. Controlled rate and site of release.
4. More uniform blood concentrations.
5. Improved patient compliance.
6. Reduced dosing frequency.
7. More consistent and prolonged therapeutic effect.
8. A greater selectivity of pharmacological activity.

Disadvantages

1. Increased variability among dosage units
2. Stability problems.
3. Toxicity due to dose dumping.
4. Increased cost.
5. More rapid development of tolerance.
6. Need for additional patient education and counseling.

TYPES OF CONTROLLED DRUG DELIVERY SYSTEMS

Controlled drug delivery systems are broadly classified as follows:

- Oral controlled release systems
- Targeted delivery systems
- Dental systems
- Ocular systems
- Transdermal systems
- Vaginal & uterine systems
- Injections & implants.

ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

The majority of oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms to generate slow release of drug to the gastrointestinal milleu.

A. DISSOLUTION CONTROLLED RELEASE

Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare.

1. Encapsulation dissolution control:

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in Space tabs or placed in capsules as in the Spansule Products. Since the time required for dissolution of the coat is a function of its thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide spectrum of coated particles of varying thickness respectively.

2. Matrix dissolution control:

An alternative approach is to compress the drug with a slowly dissolving carrier of some sort into a tablet form. Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This, in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particles surface

B. DIFFUSION CONTROLLED RELEASE

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.

There are basically two types of diffusion controlled systems which have boon developed over the past two decades, reservoir devices and matrix devices.

1. Reservoir devices:

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the membrane, diffuse to the periphery, and exchange with the surrounding media.

2. Matrix devices:
In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution.

C. DIFFUSION AND DISSOLUTION CONTROLLED SYSTEMS
The main feature of this system is that the drug core is enclosed with a partially soluble membrane. Dissolution of part of the membrane allows for diffusion of the contained drug through pores in the polymer coat.

D. ION-EXCHANGE RESINS
Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with the drug solution for extended periods of time. The drug-resin is then washed to remove contaminant ions and dried to form particles or beads. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecules is exchanged and diffuses out of the resin to the bulk solution.

E. pH - INDEPENDENT FORMULATIONS
The granules are designed for the oral controlled release of basic or acidic drugs at a rate that is independent of the pH in the GI tract. (Pederson, A.M, German patent). They are prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients, and finally, coating with a gastrointestinal fluid permeable film-forming polymer. When the GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH, thereby rendering a constant rate of drug release.

F. OSMOTICALLY CONTROLLED RELEASE
In this type of drug delivery systems, osmotic pressure is the driving force that generates constant drug release. This system 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 delivery orifice is drilled in each system by laser or by a high -speed mechanical drill [13].

G. ALTERED DENSITY FORMULATIONS
It is reasonable to expect that, unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery systems in the GI tract. One such approach is the bioadhesion approach [14], which is based on the adherence of bioadhesive polymers to the mucin on epithelial surface of the GI tract. The other approach is to alter the formulation's density by using either high or low density pellets.

1. High - density approach:
In this approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4 [15]. In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder, and zinc oxide. The weighed pellet can then be covered with a diffusion controlled membrane.

2. Low-density approach:
Globular shells which have an apparent density lower than that of gastric fluid can be used as carrier of drug for sustained release purposes [16]. Polystyrol, poprice, and even popcorn are all candidates as carriers. The surface of these empty shells is undercoated with sugar or with a polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by a mixture of drug with polymers such as ethyl cellulose and hydroxyl propylcellulose. The final product floats on the gastric fluid for a prolonged period, while slowly releasing drug.

Oral CONTROLLED RELEASE SYSTEM ADOPTED IN THE PRESENT INVESTIGATION

1. Matrix devices:
A matrix device, as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix as represented in *figure 2.* In the model, drug in the outside layer expose to the bathing solution is dissolved first and then diffuse out of the matrix. This process continues with the interfacial between the bathing solution and the solid drug moving towards the interior obviously, for this system to be diffusion-controlled, the rate of diffusion of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Advantages of matrix diffusion system:
1. Easier to produce than reservoir devices.
2. Can deliver high molecular weight compound.
3. Accidental release of the total drug component is less.

Disadvantages of matrix diffusion system:
1. Cannot obtain zero order release.

2. Removal of remaining matrix is necessary for implanted systems.

The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. The appropriate equation describing drug release from this system has been derived by Higuchi. T. [17]

$Q = [D\varepsilon / T (2A-\varepsilon Cs) Cs t]^{½}$

Where, Q is weight in grams of drug released per unit surface area

D is diffusion coefficient of drug in the release medium

ε is porosity of the matrix: T is Tortuosity of the matrix

Cs is solubility of drug in the release medium and

A is concentration of drug in the tablets expressed as gm/ml.

The assumptions made in deriving the equation are follows;

1. A pseudo-steady state is maintained during release.
2. A>>Cs, i.e., excess solute is present.
3. C=0 in solution at all times (perfect sink)
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction between the drug and the matrix occurs.

For the purpose of data treatment the above equation is usually reduced to:

$Q=Kt1/2$

Therefore, a plot of amount of drug release verses the square root of time should be linear if drug release from the matrix is diffusion controlled. In this instance, one may control drug release from a homogeneous matrix by varying the following parameters:

1. Initial concentration of drug in the matrix.
2. Drug solubility.
3. Porosity.
4. Tortuosity.
5. Leaching solvent composition.
6. Polymer system making up matrix.

POLYMERS USED FOR CONTROLLED RELEASE POLYMERIC SYSTEMS

For many years, the major focus of drug related research has been the synthesis or discovery of potent drugs with new kinds of biological activity. Which continues to be an important area of research, increasing attention is being devoted to the manner in which these drugs are delivered. One way has been incorporation of drugs in solid polymers. Controlled release polymeric systems are the most promising as they increase patient compliance due to reduced frequency of administration, improve the safety and efficacy of drug substance and reduce undesirable side-effects. The number of polymers and the range of formulation variables available to control the rates of drug release from controlled-release devices are broad. Selection among these variables is based upon the desired release rate and duration, the physical and chemical properties of the drug and the intended site of administration.

Characteristics of Ideal polymer system

An ideal polymer system should possess the following characteristics:

1. It should be inert and compatible with the environment.
2. It should be non-toxic.
3. It should be easily administered.
4. It should be easy and inexpensive to fabricate.
5. It should have good mechanical strength.

CRITERIA FOLLOWED IN POLYMER SELECTION

Polymer chosen as potential drug carrier must exhibit certain properties, as listed below:

1. The polymer must be soluble and easy to synthesize; it must have a finite molecular weight and narrow distribution.
2. It should provide drug attachment or release sites for the possibility of Incorporation of drug-polymer linkages.
3. The polymer should be compatible with the biological environment, i.e. non-toxic, non-antigenic and non-provocative in any other respect.
4. It should be biodegradable or be eliminated from the organism after the fulfillment of its function.

POLYMERS USED FOR CONTROLLED RELEASE MATRIX SYSTEMS

Three classes of retardant material are used to formulate matrix tablets. Each class demonstrates a different approach to the matrix concept. The first class consists of retardants that form insoluble or "skeleton" matrices; the second class represents water insoluble materials that are potentially erodible and the third class consists of polymers that form hydrophilic matrices. The polymers used for matrix tablets formulations are given in Table 1.1

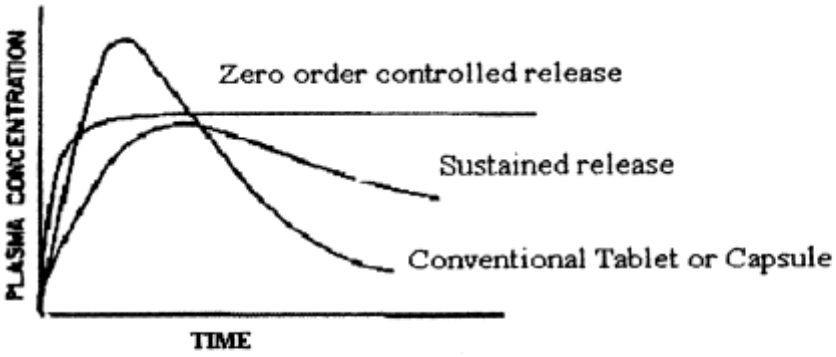

Fig.1.1 shows comparative blood drug level profiles obtained from administration of conventional, controlled as well as prolonged release dosage forms.

Figure.2 **Matrix diffusion system before drug release (time = 0) and after partial drug release (time = t).**

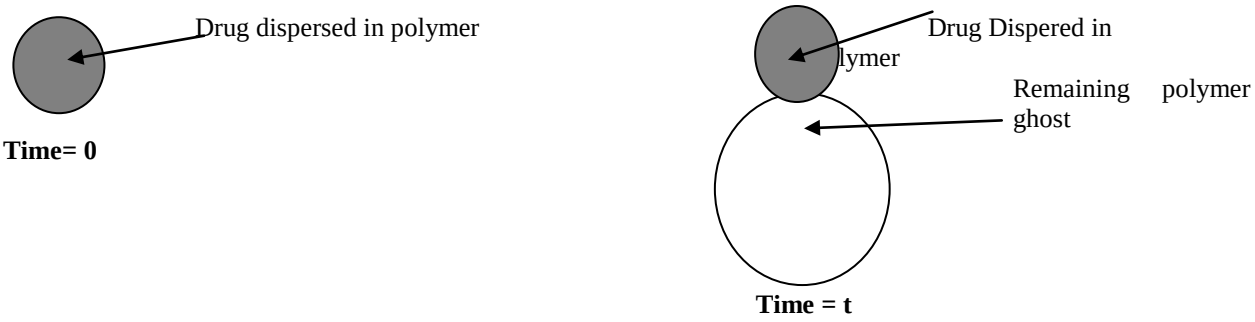

Table 1.1**; Polymers used as Retardants in Control Release Tablet Formulations**

Matrix characteristics	Materials
Insoluble, Inert	Poly ethylene Polyvinyl chloride Methylacrylate – Methacrylate Copolymer Ethylcellulose Cellulose acetate.
Insoluble , erodible	Carnauba wax Stearyl alcohol Stearic acid Poly ethylene glycol Castor wax Triglycerides Polyethylene glycol monosterate.
Hydrophilic	Methyl cellulose (400cps, 4000cps) Hydroxyl ethyl cellulose Hydroxypropyl methyl cellulose {high viscosity grades, K4M, K100M etc} Sodium carboxy methyl cellulose Carboxy polymethylene Galacto mannose Sodium alginate. Guar gum.

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