

THE PHARMA INNOVATION

Controlled Release Drug Delivery Systems

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Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. Continuous oral delivery of drugs at predictable and reproducible kinetics for predetermined period throughout the course of GIT. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance.

Keyword: Controlled Drug Delivery, High Blood Level, Extended Release, Drug Toxicity

INTRODUCTION: 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 the

higher cost of controlled-release systems compared with traditional pharmaceutical formulations. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent

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a toxic level, and a minimum value, below which the drug is no longer effective.

POLYMER USED IN CONTROL DRUG DELIVERY SYSTEM

Polymers are becoming increasingly important in the field of drug delivery. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. The review focuses on the significance of pharmaceutical polymer for controlled drug delivery applications. Sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of the medicines they need to fight a variety of human ailments, including cancer. Controlled Drug Delivery (CDD) 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 pre-designed manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing.

CONTROL RELEASE DOSAGE FORM

The United States Pharmacopoeia (USP) defines¹ the modified-release (MR) dosage form as “the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms”. One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic

performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms “controlled release (CR)”, “prolonged release”, “sustained or slow release (SR)” and “long-acting (LA)” have been used synonymously with “extended release”.

Nearly all of the currently marketed monolithic oral ER dosage forms fall into one of the following two technologies:

1. Hydrophilic, hydrophobic or inert matrix systems: These consist of a rate controlling polymer matrix through which the drug is dissolved or dispersed.
2. Reservoir (coated) systems where drug-containing core is enclosed within a polymer coating. Depending on the polymer used, two types of reservoir systems are considered.
 - (a) Simple diffusion/erosion systems where a drug-containing core is enclosed within hydrophilic and/or water-insoluble polymer coatings. Drug release is achieved by diffusion of the drug through the coating or after the erosion of the polymer coating.
 - (b) Osmotic systems where the drug core is contained within a semi-permeable polymer membrane with a mechanical/laser drilled hole for drug delivery. Drug release is achieved by osmotic pressure generated within the tablet core.

Advantages and Limitations of Control Release Dosage Forms

Clinical Advantages^{2,6}

- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)

- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient

Commercial / Industrial Advantages

- Illustration of innovative/technological leadership
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension

Potential Limitations

- Delay in onset of drug action
- Possibility of dose dumping in the case of a poor formulation strategy
- Increased potential for first pass metabolism
- Greater dependence on GI residence time of dosage form
- Possibility of less accurate dose adjustment in some cases
- Cost per unit dose is higher when compared with conventional doses
- Not all drugs are suitable for formulating into ER dosage form

Selection of drug for formulation into extended release dosage form is the key step. Following candidates are generally not suitable for ER dosage forms

Characteristics That May Make A Drug Unsuitable For Control release Dosage Form

- Short elimination half-life^{3, 4, 5}
- Long elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect

Control release dosage form Formulation Designs

1. Dissolution controlled release⁸

- Encapsulation Dissolution control
 - Seed or granule coated
 - Micro encapsulation
 - Matrix Dissolution control
2. Diffusion controlled release⁷
 - Reservoir type devices
 - Matrix type devices
 3. Diffusion and Dissolution controlled systems
 4. Ion exchange resins
 5. Osmotically controlled release

BIOPHARMACEUTIC AND PHARMACOKINETIC ASPECTS IN THE DESIGN OF CONTROLLED RELEASE PER ORAL DRUG DELIVERY SYSTEMS

Controlled release drug delivery systems^{9, 21} are dosage forms from which the drug is released by a predetermined rate which is based on a desired therapeutic concentration and the drug's pharmacokinetic characteristics

Biological half-life ($t_{1/2}$)

The shorter the $t_{1/2}$ of a drug the larger will be the fluctuations between the maximum steady state concentration and maximum steady state concentration upon repetitive dosing. Thus drug product needs to be administered more frequently.

Minimum effective concentration (MEC)

If a minimum effective concentration, MEC is required either frequent dosing of a conventional drug product is necessary or a controlled release preparation may be chosen.

Dose size and Extent of duration

The longer the extent of duration the larger the total dose per unit delivery system needs to be. Hence there is a limitation to the amount of drug that can be practically incorporated into such a system.

Relatively long $t_{1/2}$ or fluctuation desired at steady state

It is the belief of some that neither a SR nor a CRDDS is needed or useful for drugs having a $t_{1/2}$ of 12 hours or more. This is not so because there are two cases for which a 12 or 24 CRDDS seems to be indicated:

1. A drug having a $t_{1/2}$ between 12 and 72 hours may be designed for a CRDDS permitting application for every two to three days. The decline of the blood level time curve after release of the drug from the system will depend on the drug's $t_{1/2}$. Naturally, fluctuation between $C_{ss\ max}$ and $C_{ss\ min}$ may accordingly be relatively large in other words on adds slow release to the slow elimination process.

For some drugs having a $t_{1/2}$ between 20 and 100 hrs, and which are intended for long term use, one may desire small fluctuations between peaks and troughs at steady

2. states either to achieve a certain therapeutic effect or because the therapeutic range is narrow.

DESIRED BIOPHARMACEUTIC CHARACTERISTICS OF DRUG TO QUALIFY FOR CDDS

Molecular weight or size

Small molecules may pass through pores of a membrane by convective transport. This applies to both, the drug release from the dosage form and the transport across a biologic membrane. For biologic membranes the limit may be a molecular weight of 150 and 400 respectively for spherical molecules and chain like compounds respectively.

Solubility

For all mechanisms of absorption the drug must be present at the site of absorption in the form of solution. During the Preformulation study it is necessary to determine the solubility of the drug

at various pH values. If the solubility is less than 0.1 $\mu\text{g/ml}$ (in acidic medium) one may expect variable and reduced bioavailability. If the solubility is less than 0.01 $\mu\text{g/ml}$ absorption and availability most likely become dissolution limited. Hence driving force for diffusion may be inadequate.

It seems that drugs are well absorbed by passive diffusion from the small intestine upon per oral administration if at least 0.1 to 1% is non ionised form.

Apparent partition coefficient (APC)

Drugs being absorbed by passive diffusion must have a certain minimal APC. The higher the APC in an n-octanol/buffer system the higher is the flux across a membrane for many drugs. The APC should be determined for the entire pH range in the GI tract. The APC must also be applied for partition of the drug between CRDDS and the biological fluid.

General absorption mechanism

For a drug to be a variable candidate for per oral CRDDS, its absorption mechanism must be by diffusion throughout the entire GI tract. The term diffusion here refers to the dual pathway of absorption either by partitioning into the lipid membrane (across the cells) or by passing through water filled channels (between the cells). It is also important that absorption occurs from all segments of the GI tract which may depend on the drug's pKa, the pH in the segment, binding of drug to mucus, blood flow rate, etc. The absorption process seems to be highly dependent on the hydrodynamics in the GI lumen.

Even though that first order and square root of time release can result in highly effective drug delivery systems it is widely believed that the ultimate goal is zero order release profile.

Zero order release *invitro* release will produce zero order *in vivo* release and zero order *in vivo* absorption only if; (1) the entire GI tract behaves as a one compartment model, i.e. the various segments throughout the GI tract are

homogeneous with respect to absorption, and (2) drug release rate is the rate limiting step in the absorption process.

With first order release on the other hand, smaller and smaller amounts are released per unit of time with increasing time. Assuming that rate of absorption gets slower past the small intestine due to increased viscosity, decreased mixing, and decreased intestinal surface area, less drug is absorbed.

In any case, the drug release from the CRDDS should not be influenced by pH changes within the GI tract, by enzymes present in the lumen, peristalsis, etc

For all practicality, the one compartment open model is quite suitable to design CRDDS for most drugs.

Pharmacokinetic parameters

Elimination half life ($t_{1/2}$)

Drugs having a $t_{1/2}$ of 8 hours are ideally suited for CRDDS. If the $t_{1/2}$ is less than 1 hour the dose size required to be incorporated for a 12 hour or 24 hour duration dosage form may be too large. If the $t_{1/2}$ is very long there is usually no need for a CRDDS, unless it is simply intended for a reduction in fluctuation of steady state blood levels.

Total clearance (CL)

CL is a measure of the volume of distribution cleared of drug per unit of time. It is the key parameter in estimating the required dose rate for CRDDS, and predicting the steady state concentration.

Terminal disposition rate constant (K_e or λ_z)

The terminal disposition rate constant or elimination rate constant can be obtained from the $t_{1/2}$ and is required to predict a blood level time profile.

Apparent volume of distribution (V_z)

The V_z is the hypothetical volume of a drug would occupy if it were dissolved at the same

concentration as that found in blood. It is the proportionality constant relating the amount of drug in the body to the measured concentration in the blood.

Among the trio CL, V_z , and $t_{1/2}$, the former two parameters are the independent variables and the last one is the dependent variable.

The V_z or CL is required to predict the concentration time profile.

Absolute bioavailability (F)

The absolute bioavailability is the percentage of drug taken up into systemic circulation upon extravascular administration. For drugs to be suitable for CRDDS one wants an F value to be close to 100%.

Intrinsic absorption rate constant (K_a)

The intrinsic absorption rate constant of the drug administered peroral in the form of a solution should be high, generally by an order of magnitude higher than the desired release rate constant of the drug from the dosage form, in order to insure that release process is the rate controlling step.

Therapeutic concentration (C_{ss})

The therapeutic concentrations are the desired or target steady state peak concentrations ($C_{ss \max}$), the desired or target steady state minimum concentrations ($C_{ss \min}$), and the mean steady state concentration ($C_{ss \text{ avg}}$). The difference between $C_{ss \max}$ and $C_{ss \min}$ is the fluctuation. The smaller the desired fluctuation the greater must be the precision of the dosage form performance.

The lower C_{ss} , the smaller V_z , the longer $t_{1/2}$, the higher F and The less amount of drug is required to be incorporated into a CRDDS.

POLYMERS AS BIOMATERIALS FOR DELIVERY-SYSTEMS

A range of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were

originally intended for other, nonbiological uses, and were selected because of their desirable physical properties, for example:

- Poly(urethanes) for elasticity.
- Poly(siloxanes) or silicones for insulating ability.
- Poly(methyl methacrylate) for physical strength and transparency.
- Poly(vinyl alcohol) for hydrophilicity and strength.
- Poly(ethylene) for toughness and lack of swelling.
- Poly(vinyl pyrrolidone) for suspension capabilities.

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Some of the materials that are currently being used for controlled drug delivery include

- Poly(2-hydroxy ethyl methacrylate)
- Poly(N-vinyl pyrrolidone).
- Poly(methyl methacrylate).
- Poly(vinyl alcohol).
- Poly(acrylic acid).
- Polyacrylamide.
- Poly(ethylene-co-vinyl acetate).
- Poly(ethylene glycol).
- Poly(methacrylic acid).

However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body, few of them among these include:

- Polylactides (PLA).
- Polyglycolides (PGA).
- Poly(lactide-co-glycolides) (PLGA).
- Polyanhydrides.
- Polyorthoesters.

Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment.

These degradation products both desirable and potentially nondesirable must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials. The various important factors indicating the breadth of structural, chemical, and processing properties that can affect biodegradable drug delivery systems are listed below:

- Chemical structure
- Chemical composition
- Distribution of repeat units in multimers
- Presence of ionic groups
- Presence of unexpected units or chain defects.
- Configuration structure.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semi crystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Annealing.
- Sterilization process.
- Storage history.
- Shape.
- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.).
- Physicochemical factors (ion exchange, ionic strength, pH).
- Physical factors (shape and size changes, variations of diffusion coefficients,

mechanical stresses, stress- and solvent-induced cracking, etc.).

- Mechanism of hydrolysis (enzymes versus water).

Controlled drug delivery:

The most exciting opportunities in controlled drug delivery lie in the arena of responsive delivery systems, with which it will be possible to deliver drugs through implantable devices in response to a measured blood level or to deliver a drug precisely to a targeted site. Much of the development of novel materials in controlled drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features. Such systems include:

- Copolymers with desirable hydrophilic/hydrophobic interactions.
- Block or graft copolymers.
- Complexation networks responding via hydrogen or ionic bonding.
- Dendrimers or star polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents.
- New biodegradable polymers.
- New blends of hydrocolloids and carbohydrate-based polymers.

MODELLING AND COMPARISON OF DISSOLUTION PROFILE

Several theories and kinetic ^{10, 11, 12, 13} models were described the drug release characteristics of immediate release and modified release dosage forms, by using dissolution data and quantitative interpretation of values obtained in dissolution assay if facilitated by the usage of the generic equation dosage form that mathematically translates the dissolution curve in function of some parameters related with pharmaceutical dosage form.

In the present work, some analytical models were used to study the mechanism of drug release of extended release by following models

Zero order

Drug dissolution from pharmaceutical dosage form that doesn't disaggregates and release the drug slowly can be represented by the following equation

$$Q_t = Q_0 + K_0 t$$

Where

Q_t = amount of drug released in time t

Q_0 = initial amount of drug in solution

K_0 = zero order release constant

Application:

This relation can be used to describe the drug dissolution of several types of modified release dosage forms as in the case of transdermal systems and matrix tablets with low solubility of drugs, coated forms, osmotic systems etc

Pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is ideal method of drug release in order to achieve a pharmacological prolonged action

First order model

Application of this model to drug dissolution study was first proposed by Gibaldi and Feldman (1967) later by Wagner (1969)

In this model the decimal logarithm of amount remained VS time will be linear. It indicates first order release and expressed by following equation

$$\log Q_t = \log Q_e + (K_i t / 2.303)$$

Q_t = amount of drug released in time t

Q_e = initial amount of drug in solution

K_i = first order release constant

Higuchi model

Higuchi in (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in solid matrices; mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as diffusion media and this model describes the drug release characteristics as diffusion process based on Fick's law related

with square root of time dependent and it expressed by using the formula

$$Q_t = K_H \sqrt{t}$$

Where

Q_t = amount of drug released in time t

K_H = Higuchi Constant

\sqrt{t} = dependent square root of time

Application: Higuchi model can be used to describe the drug dissolution of several types of modified release dosage forms as in the case of transdermal systems and matrix tablets with low solubility of drugs

Korsmayer’s and Peppas’s model

Korsmayer’s and Peppas’s in 1983 developed a simple empirical model relating exponentially the drug release to the elapsed time by using ‘ n ’ values, in order to characterize several release mechanisms. Under some experimental conditions the release mechanism deviate from the fick’s equations following an anomalous behaviour in this case it should be expressed by the following equation

$$\log(m_t / m_\infty) = \log K + n \cdot \log t$$

Where

m_t = amount of drug released at time t

m_∞ = amount of drug released at infinite time t

K = release rate constant

n = diffusion expression (drug release mechanism)

Application This model generally used to analyze the release of pharmaceutical polymeric dosage form, when the release mechanism is not well known or when more than one type release mechanism could be involved.

Hixson-Crowell model

Hixson-Crowell (1931) recognising that particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner:

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where

W_0 is the initial amount of drug in the pharmaceutical dosage form

W_t is the remaining amount of drug pharmaceutical dosage form at time t

K_s is the constant incorporating the surface volume relation.

Release exponent (n)			Drug Transport Mechanism
Thin film	cylinder	Sphere	
0.5	0.45	0.43	Fickian transport
0.5?n?1	0.45?n?0.89	0.43?n?0.85	Non Fickian transport
1.0	0.89?n?1	0.85?n?1	Case II transport(zero order)

SUSTAIN RELEASE DRUG DELIVERY SYSTEM

There are certain considerations for the formation of sustained release formulation:

- If the active compound has a long half-life (over 6 hours), it is sustained on its own.
- If the pharmacological activity of the active compound is not related to its blood levels, time releasing then has no purpose.
- If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
- Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

The difference between controlled release and sustained release is that controlled release is a perfectly zero order release; that is, the drug releases over time irrespective of concentration. Sustained release implies slow release of the drug

over a time period. It may or may not be controlled release.

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. 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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