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REVIEW ON CONTROLLED RELEASE DOSAGE FORMS

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ABSTRACT
The paper Explain about the Controlled release dosage forms are designed to alter the release mechanism of a drug from the formulation. The key goals in designing controlled release systems are to reduce the frequency of dosing, increase the effectiveness of the drug by localizing it at the desired site, and improve patient compliance. Controlled release technologies have applications across a wide range of drugs and delivery routes, from oral dosage forms to transdermal patches. They are used in both pharmaceutical and nutraceutical products. The design and optimization of controlled release systems involves a balance between various formulation and process parameters to achieve the desired drug release profile and therapeutic benefits.

KEYWORDS: Oral drug delivery System, Extended-release Drug, Control drug release, Kinetic studies.

INTRODUCTION

Oral drug delivery is the predominant method for systemic drug administration across various dosage forms. The oral route is favored for its natural, convenience, safety, and cost-effectiveness. Oral pharmaceutical products primarily consist of immediate release systems aimed at rapid drug absorption.

However, immediate release dosage forms present several challenges:

1) Drugs with short half-lives necessitate frequent dosing, which may impair patient adherence.
2) A typical plasma concentration profile complicates the achievement of steady-state conditions.
3) Fluctuations in drug concentration can result in inadequate or excessive medication, as Css values may exceed therapeutic limits.

Such concentration variability can precipitate adverse effects, particularly for drugs with narrow therapeutic indices during instances of over-medication.

1.1. EXTENDED-RELEASE DOSAGE FORMS

Extended-release dosage forms achieve at least a twofold decrease in dosing frequency compared to conventional forms like solutions or prompt-releasing solids.

These formulations ensure prolonged availability of the active ingredient within its therapeutic range, thereby minimizing dosing frequency relative to traditional dosage forms.

They encompass

- Controlled Release (Ideal Zero-Order)
- Prolonged Release

The comparison of various modified release dosage formulations can be illustrated through a plasma concentration versus time figure.1.1.

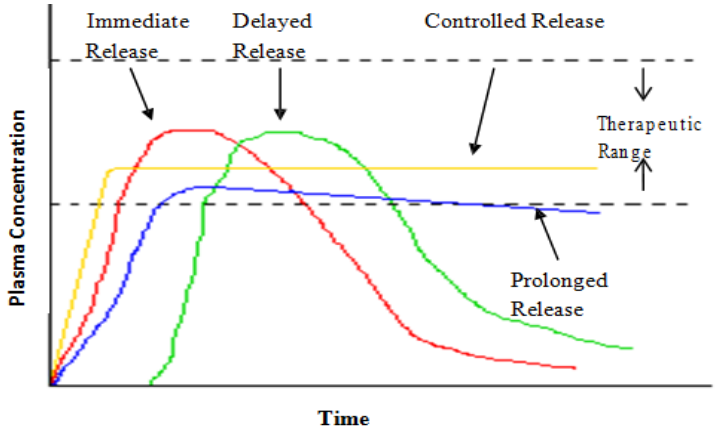


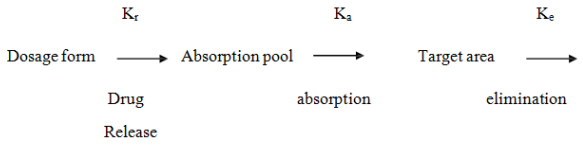
Figure 1.1: Plasma concentration vs. Time curve for different type of dosage forms.

Modified-release products are also referred to by various terms such as extended-release and controlled-release. These formulations are characterized by a diminished release rate of the active ingredient. Generally, these terminologies are synonymous.

A delayed-release product is a type of modified-release, but it is not classified as extended-release. Such products can release specific amounts of the drug after administration, as seen in enteric-coated formulations that have a lag phase with minimal absorption. Although several modified-release products exist as both prescription and over-the-counter medications, only a few demonstrate a significant therapeutic benefit.

Release Rate and Dose Consideration[15]

Conventional dosage forms include solutions, capsules, tablets, emulsions, etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.



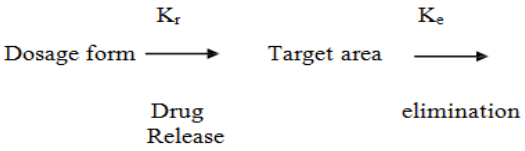
Where,

K_r = First order rate constant for drug release.

K_a = First order rate constant for drug absorption.

K_e = First order rate constant for overall drug elimination.

- For immediate release dosage formulations, the permeability coefficient (Kr) is greater than the absorption coefficient (Ka), or conversely, the translocation of the pharmacological agent across a biological barrier represents the critical rate-limiting factor in the administration of the drug to its intended site of action.
- In contrast, for non-immediate release dosage formulations, the permeability coefficient (Kr) is significantly less than the absorption coefficient (Ka).



Terminology[16]

Controlled drug delivery or modified release delivery systems may be defined as follows: -

Controlled – Release formulation

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systemically, for a specific period of time.

Repeat action preparations

A dose of the pharmaceutical agent is initially released promptly following administration, which is typically commensurate with a singular dosage of the traditional drug formulation. After a specified duration, a subsequent single dose is released. In certain formulations, a tertiary single dose is released after a designated time has elapsed, subsequent to the second dosage. The principal advantage is that it affords the convenience of delivering supplementary dose(s) without necessitating re-administration. However, it is associated with the disadvantage that the plasma concentrations continue to exhibit the "Peak and valley" characteristic inherent in conventional intermittent pharmacotherapy.

Extended-Release formulations

Extended-Release formulations are typically engineered to diminish the frequency of dosing while sustaining a relatively stable or level plasma drug concentration. This strategy is instrumental in mitigating the adverse effects associated with elevated drug concentrations.

Delayed release preparations
The pharmaceutical agent is liberated at a subsequent interval following administration. The delayed pharmacological action is facilitated through the integration of specialized coatings, such as enteric coatings, or alternative temporal barriers including the formaldehyde treatment of both soft and hard gelatin capsules. The objectives of such formulations encompass the mitigation of side effects associated with the drug's presence in the gastric environment and the preservation of the drug's integrity against degradation within the highly acidic pH of gastric fluids.

Site specific targeting
These systems pertain to the precise targeting of a pharmaceutical agent directly to specific biological locales. In this context, the target is situated adjacent to or within the affected organ or tissue.

Receptor targeting
These systems are concerned with the precise targeting of a pharmaceutical agent to specific biological sites. In this scenario, the target constitutes a particular receptor for the drug situated within an organ or tissue. Both site-specific targeting and receptor-targeting systems fulfill the spatial criteria of drug delivery and are also classified as controlled drug delivery systems.

1.2 ADVANTAGES AND DISADVANTAGES OF ORAL EXTENDED-RELEASE DOSAGE FORMS

All controlled release dosage forms have a common goal of improving the drug therapy compared to that achieved by their non sustained counter parts.

Advantages
- Avoid patient compliance problems
- Employ less quantity drug.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Reduce dosing frequency and fluctuation of therapeutic plasma concentration
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.
- Improves efficiency in treatment
- Cures or control conditions more promptly.
- Improves control of condition i.e., reduces fluctuations in drug level.
- Improves bioavailability of some drugs.
- Makes use of special effects in sustained release aspirin for morning relief of Arthritis by dosing before bedtime.

Disadvantages
- May be costly,
- Unpredictable and often provide poor in-vitro – in-vivo correlations,
- May cause dose dumping, if the release design is failed,
- Provides less scope for dosage adjustment,
- May increase the first pass clearance,
- Poor systemic availability in some cases

1.3 ORAL CONTROLLED – RELEASE PRODUCTS

Based on the release mechanism these are classified as follows[17]
1. Diffusion-controlled products.
2. Dissolution-controlled products.
3. Erosion products.
4. Osmotic pump systems.
5. Ion exchange resins.

1. Diffusion – Controlled products
In these systems, there is water – insoluble polymer which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the controlled release device. The diffusion can occur through pores in the polymer matrix or by passing between polymer chains. These are broadly divided into two categories:-
A. Reservoir Devices. B. Matrix Devices.
The basic mechanisms of drug release from these two systems are fundamentally different.

A. 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 particles (or) tablet.

The active agent is released to the surrounding environment by diffusion process through the rate limiting membrane. In the reservoir systems the drug delivery rate remains fairly constant.

B. Matrix Devices
In the matrix devices the drug or active is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into 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.

2. Dissolution-controlled products
In these products, the rate of dissolution of the drug is controlled by slowly soluble polymers or by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. Some preparations contain a fraction of the total dose as an immediate-release component to provide a pulse dose soon after administration. The pellet dosage forms of diffusion- or dissolution- controlled products can be encapsulated or prepared as a tablet.

Dissolution-controlled products can be sub-divided into two types

A. Encapsulation Dissolution controls.
B. Matrix Dissolution control.

A. Encapsulation Dissolution control

These systems method involves coating of individual particles (or) granules of drug with a slow dissolving material. The coated particles can be compressed directly into tablets (or) placed in capsules. The rate of dissolution of the drug (and thereby availability for absorption) is controlled by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled.

These products should not be chewed as the coating may be damaged. One of the advantages of encapsulated pelleted products is that the onset of absorption is less sensitive to stomach emptying.

The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating sustained-release tablet formulations.

B. Matrix Dissolution control

In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wet ability of system and surface of particle.

3. Erosion products

In this system drug or active agents are mixed with biodegradable polymers. These materials degrade within the body as a result of natural biological processes and drug release occurs at constant rate.

Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. The release if drug from these products is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion.

4. Osmotic pump systems

The osmotic pump is similar to a reservoir device but contains an osmotic agent (e.g., the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane.

Oral controlled release dosage forms

Based on the release mechanism, these formulations can be categorized as follows[17]

1. Diffusion-controlled products.
2. Dissolution-controlled products.
3. Erosion products.
4. Osmotic pump systems.
5. Ion exchange resins.

1. Diffusion-Controlled Products

In these systems, a water-insoluble polymer governs the ingress of water and the resultant liberation of the solubilized drug from the dosage form. The process of diffusion transpires when a drug traverses the polymer forming the controlled release apparatus. Diffusion may occur through the porosity of the polymer matrix or by interstitial movement between polymer chains. These products are broadly segmented into two distinct categories:

A. Reservoir Devices. B. Matrix Devices

The fundamental mechanisms governing drug release from these two systems exhibit significant disparities.

A. Reservoir Devices

In this configuration, a water-insoluble polymeric substance envelops a core of the drug. The drug partitions into the membrane and exchanges with the surrounding fluid of the particles (or) tablet.

The active pharmaceutical ingredient is released into the ambient environment through a diffusion mechanism across the rate-limiting membrane. In reservoir systems, the drug delivery rate remains relatively consistent.

B. Matrix Devices

In matrix devices, the drug or active ingredient is uniformly dispersed within a polymer matrix, thereby forming a homogeneous system referred to as a matrix system. The diffusion process occurs when the drug migrates from the polymer matrix into the external environment. As the release progresses, the rate typically diminishes, as the active agent must traverse an increasingly longer distance, necessitating an extended diffusion time for release.

2. Dissolution-Controlled Products

In these formulations, the dissolution rate of the drug is regulated by slowly soluble polymers or through microencapsulation techniques. Upon the dissolution of the coating, the drug becomes accessible for dissolution. By adjusting the thickness and composition of the coating, the drug release rate can be precisely controlled. Certain formulations include a segment of the total dosage as an immediate-release component to facilitate a pulse dose shortly after administration. Pellet dosage forms of diffusion- or dissolution-controlled products may be encapsulated or fabricated as tablets.

Dissolution-controlled products can be further categorized into two types:

A. Encapsulation Dissolution Controls.
B. Matrix Dissolution Control.

A. Encapsulation Dissolution Control

This method entails the coating of individual particles

(or) granules of the drug with a material that dissolves slowly. The coated particles can be directly compressed into tablets (or) encapsulated within capsules. The rate of dissolution of the drug (and consequently its availability for absorption) is regulated by microencapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thickness and composition of the coating, the drug release rate can be meticulously controlled.

These products are contraindicated for mastication, as such action may compromise the integrity of the coating. A significant advantage of encapsulated pellet formulations is that the onset of absorption is less affected by gastric emptying.

The entry of the pellets into the small intestine (where the predominant drug absorption occurs) is generally more uniform compared to non-disintegrating sustained-release tablet formulations.

B. Matrix Dissolution Control

In this approach, the drug is compressed with a slowly dissolving carrier. In this scenario, the rate of drug release is modulated by the rate at which the dissolution fluid penetrates the matrix, as well as the matrix's porosity, the presence of hydrophobic additives, and the wettability of the system and particle surface.

3. Erosion Products

In this system, the drug or active agents are amalgamated with biodegradable polymers. These materials undergo degradation within the biological milieu as a result of natural biological processes, leading to a consistent rate of drug release.

Most biodegradable polymers are engineered to degrade through the hydrolysis of polymer chains into biologically acceptable and progressively smaller entities. The release of the drug from these formulations is governed by the erosion rate of the carrier matrix. The release rate is contingent upon the erosion kinetics.

4. Osmotic Pump Systems

The osmotic pump functions analogously to a reservoir device, but it incorporates an osmotic agent (for instance, the active agent in a salt form), which facilitates the absorption of water from the surrounding medium via a semi-permeable membrane.

Pressure is generated internally within the device, propelling the active agent out of the device through an orifice (designed to minimize solute diffusion while preventing the accumulation of a hydrostatic pressure head, which would otherwise reduce osmotic pressure and alter the dimensions of the device). The principal advantage of this product type is that the constant release remains unaffected by the gastrointestinal environment, relying solely on the influx of water into the dosage form.

The release rate can be modulated by varying the osmotic agent and the orifice dimensions.

5. Ion exchange resins

Drug-resin complexes, commonly referred to as "resonates," have been recognized for their efficacy in extended release applications and have been successfully implemented in commercial settings. The drug molecules are tethered to the resin and subsequently released through a process of exchange with suitably charged ions that interact with the ion exchange functional groups. This methodology is pertinent to specific pharmaceuticals that exhibit distinctive characteristics regarding their relative affinity for the utilized polymers.

1.4 DRUG PROPERTIES RELEVANT TO CONTROLLED-RELEASE FORMULATIONS

The degree of variation in drug concentration at a steady state is influenced by the comparative magnitude of the elimination half-life and the dosing interval. When a drug is administered at an interval that corresponds to its elimination half-life, a two-fold disparity is observed between the peak and trough concentrations at steady state.

Certain pharmaceutical compounds that exhibit relatively high solubility at low pH levels, coupled with a short biological half-life, are deemed inappropriate for traditional oral dosage formulations, as their high acid solubility characteristics lead to swift drug absorption and clearance, resulting in significant and undesirable fluctuations in plasma concentration.

For pharmaceutical agents characterized by short half-lives and a clear correlation between concentration and therapeutic response, it becomes imperative to administer doses at regular, frequent intervals to sustain the concentration within the therapeutic window. Increased dosing at less frequent intervals is likely to yield elevated peak concentrations, thereby raising the risk of toxicity. In the case of certain medications that possess wide therapeutic margins, such an approach may be deemed acceptable; for instance, amoxicillin, which has a half-life of approximately one hour, is administered every eight hours.

The prudent selection of the drug substance constitutes the most critical aspect of the successful development of controlled-release formulations. Various categories of drugs possess the potential for enhanced therapeutic efficacy via controlled-release oral delivery systems, including but not limited to antianginal, anti-inflammatory, antihistaminic, antigastric resistant agents, antipsychotic agents, and antidiabetic drugs. The overarching objective for extended duration is to achieve administration twice daily or, where feasible, once daily. Numerous intrinsic properties of the drug can facilitate the realization of a prolonged release oral dosage form spanning 12 to 24 hours. However, several characteristics may impede the successful development,

which include the following:

1. An exceedingly short half-life and/or a relatively large single dose.
2. A prolonged half-life.
3. A potent drug with a narrow therapeutic margin.
4. Poor solubility and/or inadequate absorption.
5. Biological activity not contingent upon core integration within the blend.
6. Absorption primarily occurring through a "window."
7. Significant first-pass metabolism

The selection of both the active pharmaceutical ingredient and the retardant polymers, alongside the filler excipients, will significantly influence the mechanism and rates of drug release from the dosage formulation. Various physicochemical and biological attributes of a drug, along with its biopharmaceutical characteristics, play a crucial role in product design and performance.

A. Physicochemical Properties

1. Aqueous Solubility

A drug that exhibits favorable aqueous solubility represents an excellent candidate for controlled-release dosage forms, exemplified by pentoxifylline. Compounds characterized by very low aqueous solubility typically encounter oral bioavailability challenges due to the limited gastrointestinal transit time of the undissolved drug particles, as well as constrained solubility at the site of absorption.

2. Partition Coefficient

During the interval between drug administration and its subsequent elimination from the body, it is requisite for the drug to traverse a variety of biological membranes, which primarily function as lipid-like barriers. A key criterion in evaluating a drug's capacity to penetrate these lipid membranes is its apparent oil/water partition coefficient, which is defined as...

$$K = C_O / C_W$$

Where

C_O = total concentration of all forms of the drug, e.g. ionized and unionized, in some organic phased at equilibrium, and

C_W = total concentration of all forms in an aqueous phase at equilibrium.

Drugs with a partition coefficient that either is extremely higher or lower that the optimums are, in general, poorer candidates for formulation into modified- release dosage forms.

3. Drug Stability

Stability constitutes a crucial physicochemical attribute that must be meticulously evaluated in the formulation of sustained-release systems. Pharmaceuticals that exhibit instability in the gastric environment are designed to release their active constituents exclusively within the intestinal tract. Consequently, these compounds can be formulated into a slowly soluble form.

Stability investigations are of paramount importance, allowing pharmaceutical manufacturers to accurately forecast the shelf-life stability of novel products based on accelerated storage stability data. Pharmaceuticals exhibiting notable stability concerns in any specific segment of the gastrointestinal tract are generally considered less amenable to formulation into controlled release systems.

4. Protein binding

The formation of drug-protein complexes can function as a reservoir, facilitating a prolonged release profile for drugs that demonstrate a significant degree of binding to plasma proteins. The primary intermolecular forces responsible for such binding include van der Waals forces, hydrogen bonding, and electrostatic interactions. Drugs that are bound to mucin may enhance their absorption, exemplified by quaternary ammonium compounds that interact with mucin in the gastrointestinal tract.

5. Molecular Size and diffusivity

In addition to permeating biological membranes, many sustained-release systems necessitate diffusion through a polymeric membrane or matrix engineered to regulate their release kinetics. The capacity of a drug to diffuse through a polymeric membrane or matrix, employed for controlling release kinetics, is intrinsically linked to its diffusivity, quantified as the diffusion coefficient.

A significant determinant influencing the diffusivity value (D) within polymers is the molecular size (or molecular weight) of the diffusing entity. In the majority of polymeric matrices, it is feasible to empirically correlate log D to a function of molecular size. Hence, the diffusivity value (D) is associated with both the size and shape of the cavities, as well as the dimensions and geometry of the drugs.

Typically, the diffusion coefficients for drugs of intermediate molecular weight, specifically in the range of 150-400, through flexible polymers vary from 10^-6 to 10^-9 cm²/sec, with values approximating 10^-8 being the most prevalent.

B. Biological Factors

1. Absorption

The rate, extent, and consistency of drug absorption are critical considerations when evaluating its formulation into a controlled release system. Given that the rate-limiting step in drug delivery from a controlled release system is its release from a dosage form, as opposed to absorption, a rapid absorption rate relative to the drug's release is imperative for the system's success. To achieve a stable concentration of the drug in the bloodstream (or tissue), it must be released uniformly from the controlled release system and subsequently absorbed in a consistent manner. The design of controlled release products presents greater challenges when considering the oral administration route, as exemplified by quaternary

ammonium compounds and aminoglycosides such as gentamicin.

2. Distribution

The distribution of a drug across vascular and extravascular compartments within the organism is a significant determinant of its overall elimination kinetics. Two parameters are utilized to elucidate the characteristics of drug distribution. The term "apparent volume of distribution" is frequently employed to quantify the extent of distribution for a given pharmaceutical. In the context of a two-compartment model, the total apparent volume of distribution for a drug at steady state can be computed using the following equation.

$$Vd_{ss} = [(K_{12} + K_{21}) / K_{21}] V_p$$

Where,

Vd_{ss} = Apparent volume of distribution at study state.

K_{12} = Constant for central to peripheral compartment.

K_{21} = Constant from peripheral to central compartment.

V_p = Volume of central compartment

3. Metabolism

The metabolic transformation of a pharmaceutical agent into an alternative chemical entity is typically considered in the formulation of a controlled-release system for that specific agent. There exist two critical factors correlated with the metabolic processes of certain pharmaceuticals. One factor pertains to the drug's capacity to induce or inhibit the synthesis of enzymes, while the other concerns the variability in drug plasma concentrations attributable to the hepatic first-pass effect. For instance, the organ predominantly accountable for metabolic processes is the liver. The metabolism of a pharmaceutical compound is manifested in the elimination constant associated with that compound.

4. Elimination and biological half-life

The elimination kinetics of a pharmaceutical agent is quantitatively characterized by its biological half-life, which is intrinsically linked to its apparent volume of distribution (V) and its systemic clearance rate.

$t_{1/2} = 0.693\ V/Cl_S = 0.693\ V\ AUC/dose$

Where,

Cl_S = systemic clearance.

A drug with a short half-life requires frequent dosing, and this makes it a desirable candidate for a controlled-release formulation. On other hand, a drug with a long half-life is dosed at greater time intervals, and thus there is need for a controlled- release system.

5. Side effects

Most of the drugs will produce side effects. For some drugs, the incidence of Side effects is believed to be a function of plasma concentration, and it can be minimized by controlling the concentration at which the drug exist in plasma, and hence controlled release formulations appear to offer a solution to this problem.

6. Margin of safety

The Margin of safety of a drug mostly used to measure its therapeutic index. In sign of controlled release one can consider to be therapeutically safe and effective in drug therapy monitoring. Especially for potent drugs, whose therapeutic concentration range is narrow, the value of therapeutic index is small. **e.g.:** Cardiac glycosides, Antiarrythmic drugs etc.

7. Total clearance

Clearance is defined as the theoretical of body fluid containing drug, from which the drug is completely removed in a given period of time, it is expressed in ml/min (or) liters / hour. Clearance is given by,

$$Clerance = \frac{Dose}{Dosong\ intervel \times Cocentration}$$

8. Mean residence time (MRT)

Mean residence time is defined as time of drug molecule residence in the body. It is the time corresponding to 63.2% elimination from the body. It is calculated from AUC and AUMC.

MRT = AUMC/ AUC

Where,

MRT = Mean residence time.

AUMC = Area under the first-moment curve.

AUC = Area under the zero-moment curve.

1.5. MATRIX TECHNOLOGY

Matrix technologies are popularly used because of the simplicity of the manufacturing processes required, level of reproducibility, stability of the raw materials and dosage form as well as ease of scale up operation, validation and favorable in-vitro in-vivo correlation (IVIVC). Classically, simple matrix delivery systems exhibit first order or square root of time release kinetics.

These systems improve patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, a controlled-release formulation maintains therapeutic blood level of a drug for a specific period of time. A number of oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects. In order to overcome all those problem mentioned above, the matrix tablets has additional advantage like, Matrix tablets are resistant to dose dumping. They are simple in nature of the formulations, and due to robustness they are unaffected by variations in ingredients.[12,18]

Matrix tablets containing hydrophilic polymers are a common and commercially successful means of prolonging oral drug delivery. A common problem observed with hydrophilic matrix systems containing water soluble drugs is an initial burst effect of the drug release.[12,18]

Process of Manufacturing Matrix Tablets

One of the commonly employed processes for the manufacture of extended release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which the drug is embedded in the matrix core of retardant. Alternately, the retardant-drug blends can be granulated prior to compression.

Matrix devices are of two types: Matrix dissolution controlled and matrix diffusion controlled drug delivery devices.[18]

Matrix Diffusion Controlled Drug Delivery Devices

Matrix diffusion devices are prepared by dispersing a solid drug in an insoluble polymer matrix carrier system, i.e. a drug reservoir is formed by homogenous dispersion of solid drug particles throughout a lipophilic or hydrophilic polymer matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. The equation describing drug from this system T. Hugichi has derived this system.[18]

$$Q = \sqrt{\frac{Cs\,t}{D\varepsilon\,(2A - \varepsilon\,Cs)}}$$

Where,

Q = Weight in grams of drugs in the unit surface area.
D = Diffusion coefficient of drug in the release medium.
ε = Porosity of the matrix.
τ = Tortuosity of the matrix.
Cs = Solubility of the drug in release medium and,
A = Concentration of drug in the tablet expressed as g/ml.

The following assumptions were made in deriving the above equation: A pseudo-steady state is maintained during release. A>>Cs i.e. excess solute is present. C = 0 in solution at all times (perfect sink condition) Drug particles are much smaller than those in the matrix. The diffusion coefficient remains constant. No interactions between the drug and the matrix occur. One many control drug release from a homogenous matrix by varying the following parameters.

Initial concentration of drug in the matrix.
Drug solubility.
Porosity
Tortuosity
Leaching solvent composition.
Polymer system making up matrix.

Matrix Dissolution Controlled Drug Delivery Devices

Matrix dissolution devices can also be formulated by compressing the drug with a slowly dissolving polymer carrier into a tablet form. There are two general methods of preparing drug-wax particles: congealing method and aqueous dispersion method. In congealing method the drug is mixed with wax material and either spray congealed or congealed and screened. In the aqueous dispersion method, the drug-wax mixture is sprayed or placed in water and the resultant particles are collected.

Matrix tablets are made by direct compression of mixture of drug, polymer and excipients. The rate limiting step in controlling release from these formulations is liquid penetration into the matrix. Some channeling agents (wetting agents) can be incorporated with the blend of mixture to promote permeation of polymer matrix by water, which allows drug dissolution and diffusion from the channels created in the matrix. Formulations should be designed, so that pore diffusion becomes the rate- controlling step.

Drug bioavailability, which is critically dependent on the drug: polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in low-milligram-potency formulations.

Drug release is controlled by penetration of water through a gel layer produced by hydration of polymer and diffusion of drug through swollen, hydrated matrix, in addition to erosion of the gelled layer. The polymer selected for formulation as well as the drug polymer ratio controls the extent to which diffusion or erosion which controls release of the drug from the formulation.[18]

CONCLUSION

The intent of controlled release dosage forms is to alter the release mechanism from the formulation, as a freely soluble drug is generally not suitable for controlled release. Controlled drug delivery systems aim to deliver the drug at a predetermined rate, either locally or systemically, for a specified period of time. Modified release drug products, including controlled release formulations, have been shown to be more effective therapeutic alternatives compared to conventional or immediate release dosage forms. Controlled release dosage forms are designed to provide more consistent and prolonged drug exposure, leading to improved therapeutic efficacy and reduced side effects compared to conventional formulations.

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