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OVERVIEW ON: CONTROLLED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Controlled Release Systems have been developed to improve the temporal and spatial presentation of drug in the body, to protect drug from physiological degradation or elimination, to improve patient compliance, and to enhance quality control in manufacturing of drugs. Controlled release (C.R) products provides an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. The goal in designing controlled/sustained drug delivery 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. The present article contains brief review on various formulation approaches for controlled release drug delivery system.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.

These immediate release dosage forms have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma conc. time profile is obtained which makes attainment of steady state condition difficult.
3) The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the C_{ss} values fall or rise beyond the therapeutic range.

Therefore, Controlled-release systems are designed to enhance drug therapy. There are several motivations for developing controlled-release systems, which may depend on the drug of interest. Controlled release systems have been devised to enable superior control of drug exposure over time, to assist drug in crossing physiological barriers, to shield drug from premature elimination, and to shepherd drug to the desired site of action while minimizing drug exposure elsewhere in the body. Controlled release systems may also increase patient compliance by reducing frequency of administration, and may add commercial value to marketed drugs by extending patent protection. Finally, use of controlled release technology may reduce variability of performance of drug products.

Controlled Release Drug Delivery System

Controlled Release system means any drug delivery system that maintains adequate and desired release of drug over an extended period of time. Hydrophilic Polymer matrix is widely used for formulating controlled dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval and at appropriate site of action to maintain therapeutic range of drug in blood plasma. 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 systematically, for a specific period of time.

Advantages of Controlled Release Drug Delivery System

1. Improved Patient compliance
2. Reducing dosing frequency
3. More consistent and prolonged therapeutic effect.
4. Reduction in health care cost
5. Decreased incidence and/or intensity of adverse effects and toxicity.
6. Better drug utilization.
7. Controlled rate and site of release
8. More consistent and prolonged therapeutic effect.
9. A greater selectivity of pharmacological activity
10. Increase the safety of margin of high potency drug.
11. Reduction in fluctuation in steady state

GOALS OF CONTROLLED RELEASE DOSAGE FORM

1. To achieve prolonged therapeutic effect.
2. Implies predictability in drug release kinetics.
3. Deliver the drug at predetermined rate locally or systemically

TERMS USED IN CONTROLLED RELEASE PRODUCTS

Repeat Action which is designed to release one dose of drug initially and a second dose of drug at a later time.

A **Prolonged action** drug product is designed to release the drug slowly and to provide a continuous supply of drug over an extended period. The prolonged action drug product prevents very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration. Most prolonged release products extend the duration of action but do not release drug at a constant rate.

A **Sustained release** drug product is designed to deliver an initial therapeutic dose of the drug (loading dose) followed by slower and constant release of drug. The rate of release of the maintenance dose is designed so that the amount of drug loss from the body by elimination is constantly replaced. With the sustained release product, a constant plasma drug concentration may be maintained with minimal fluctuation.

A **Targeted drug delivery system** is the one which delivers the drug only to its site of action and not to the non-targeted organs or tissues. (Prashar, I., et al, 2013).

CLASSIFICATION OF SUSTAINED / CONTROLLED RELEASE DOSAGE FORM

According to the formulation point of view controlled release dosage form can be classified as follow

A. SINGLE UNIT DOSAGE FORMS:

1. Monolithic devices:
   a. Hydrophobic matrix tablets.
   b. Hydrophilic swellable matrix tablets.
   c. Floating formulations
   d. Semisolid matrix system
   e. Some Mucoadhesive matrix system.
2. Complex reservoir system or multilayer system
   a. Multilayered matrix systems

B. MULTIPLE UNIT DOSAGE FORMS:

   a. Microspheres
   b. Granules or spheroids
   c. Pellets
   d. Beads
   e. Microcapsules
   f. Micro Tablets

Modified Release dosage form may be classified as

A. Delayed release

B. Extended release

   1. Sustained release
   2. Controlled release

A. Delayed release:

A delayed release dosage form is designed to release the drug at a time other than promptly after administration the delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

B. Extended release

1. Sustained Release System:

Sustained release dosage form may contain:

a) Maintenance dose, and

b) Loading dose

2. Controlled release System

Controlled release system provide drug release in an amount sufficient to maintain the therapeutic drug levels over extended period of time, with the release profiles of predominantly controlled by the special technological construction and designed itself.

TYPES OF EXTENDED RELEASE PRODUCTS

Diffusion – controlled products

In these systems, there is a water insoluble polymer, which controls the flow of water and the subsequent egress of dissolved drug from the dosage form. Both diffusion and dissolution processes are involved. In 'reservoir devices, a core of drug is coated with the polymer and, in 'matrix, systems, the drug is dispensed throughout the matrix. Cellulose derivatives are commonly used in the reservoir type, while the matrix material may be plastics e.g. methacrylate, methyl methacrylate, polyvinyl chloride, and hydrophilic polymers such as cellulose derivatives or fatty compounds including carnauba wax. Examples of this type of formulation include Plendil ER, Agon SR, Kapanol and Slow –K.

Dissolution –controlled products

In these products, the rate of dissolution of the drug (and thereby availability for absorption) is controlled by slowly soluble polymers or by microencapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thickness 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. 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 extended- release tablet formulations. An example of this type of product is Fefol.

Erosion products

The release of 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. An example of this formulation is sinemet CR. With this product, some patients may experience a later onset of effect after the morning dose, compared to conventional levodopa tablets, because of the delayed release of the drug.

Osmotic pump systems

The rate of release of drug in these products is determined by the constant inflow of water across a semi-permeable membrane into a reservoir, which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which dissolved drug is pumped at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations. The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. Altering the osmotic agent and the size of the hole can modify the rate of release. An example of this type of product is Ada

Ion exchange resins

Some drugs can be bound to ion exchange resins and, when ingested, the ionic environment within the gastrointestinal tract determines the release of drug. Examples of this type of product are Duromine containing the basic drug phentermine complexes with an anionic resin. (K, Modi., et al 2013).

METHODS OF SUSTAINED RELEASE FORMULATIONS

Sustained release formulations can be developed by

a) Drug modification

Drug modification can be done by

(1) Drug complex

(2) Drug absorbate, and

(3) Prodrug

b) Dosage Form Modification:

Dosage form modification for sustained release can be done by:

(1) Encapsulation slow release granules.

(2) Slow release tablets (granules)

(3)Tabletted Matrix

Tabletted matrix (Embedding the drug in a matrix)

In tablet matrix drug retardant material and additives are mixed and compressed directly or the retardant and the drug is granulated prior to compression. The retardant materials used are three types

(1) Insoluble inert retardant.

(2) Insoluble erodible retardation, and

(3) Hydrophilic polymers

Preparation of sustained release Matrix formulation

The formulation of sustained release dosage forms is achieved by either barrier coating11 of the drug molecules or by matrix embedment15. Out of this the preparation of matrix tablets is least complicated method15. A matrix device consists of drug dispersed homogenously throughout a polymer matrix. Two major types of materials are used in the preparation of matrix devices.

Hydrophobic carriers

1) Digestible base (fatty compounds) – glycerides – glyceryl tristearate, fatty alcohols, fatty acids, waxes - carnauba wax etc.

2) Non digestible base (insoluble plastics) methylacrylate also methyl methacrylate, polyvinyl chloride, polyethylene, ethyl cellulose etc.

Hydrophilic polymers

Methylcellulose, sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose, sodium alginate, xanthan gum, polyethylene oxide, carbopol etc. The Hydrophilic polymers are used for the preparation of matrix tablets for water soluble as well as water insoluble drugs.

Other Matrix forming material

Shellac, Starch, Eudragit , Substituted amylase, Thiolated polymers, Poly ethylene oxide Curdulan, Guar gum, Carrageenans, Hydroxy propyl cellulose, Honey locust Scleroglucan, Cellulose acetate etc. (Gupta,M., Brijesh, Ray., 2012)

FACTORS AFFECTING THE FORMULATION OF CONTROLLED RELEASE DRUG DELIVERY SYSTEM

I. PHYSICOCHEMICAL CHARACTERISTICS

1. Solubility

The drug should be in the form of the solution at the site of absorption. During the preformulation phase it is necessary to determine a drug's solubility not only in water but also at various pH values, depending upon the anticipated route of administration. Usually the pH dependant

solubility will cover the pH values, 1.5-3 (stomach), and 4.5 (acid mantle of skin, sweat), 5.5 (acidic urine), 6.5 duodenum, bile jejunum, saliva), 7.4 (plasma, ileum, cerebrospinal fluid) and 7.8 (colon, rectum). The aqueous and ph dependant solubility is of importance for drug release.

Drugs with pH- dependant solubility aqueous solubility, e.g., Phenytoin or drugs with solubility in nonaqueous solvents, eg., steroids and suitable for Parenteral (e.g. in i.m depots) controlled release dosage forms, the drug precipitates at the injection site and thus, its release is slowed down due to change in pH or contact with aqueous body fluids. Absorption of poorly soluble drugs is dissolution rate-limited which means that the controlled release device does not control the absorption process; hence they are poor candidate for such systems.

2. **Diffusion**

Most drugs are transported across membrane by Passive diffusion. It may be assumed that more than 45% of all drugs follow this pathway of transport. The transport stream Q depends on the diffusion constant of drugs in lipid material D, the surface area of the membrane A, the partition coefficient K, the membrane thickness h, and the concentration C_o and C_i on both sides of the membrane:

$$\mathbf{Q= DAK (C_o-C_i/h)}$$

Under sink conditions, such as in unrestricted absorption, where the drug is immediately carried away by the blood after crossing the membrane and is diluted within the volume of distribution, one can use Fick's first law of diffusion, the amount dq of substance diffusing in time dt across a place of area A is directly proportional to the change of concentration dC with distance travelled dx.

$$\mathbf{Dq= -D.A.\ dCdt/dx}$$

The flux of diffusion constant D decreases with increasing molecular weight. Usually the lower the molecular weight, the faster and more complete is transport.

3. **Molecular Weight**

For drugs absorbed by pore transport mechanism, the molecular size threshold is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. However, more than 95% of drugs are absorbed by Passive diffusion. Diffusivity, defined as the ability of a drug to diffuse through the membranes, is inversely related to molecular size. The upper limit of drug molecular size for diffusion is 600 Daltons. Drugs with large molecular size are poor candidates for oral controlled release systems.

4. **pK_a**

Drugs existing largely in ionized form are poor candidates for oral controlled release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of unionized drug. The non-ionized moiety is usually lipid soluble, hence may dissolve in the lipid material of a membrane and may be transported by passive diffusion, where as the ionized moiety is usually is not lipid soluble enough to permit permeation. The percent of ionization can be calculated from the Henderson equation:

% Ionized (for acidic drugs) = 100/1+antilog (pK_a-pH)

% Ionized (for basic drugs) = 100/1+antilog (pH-pK_a)

5. **Apparent Partition Coefficient (APC)**

The lipid/ water coefficient APC denotes the ratio of the concentration of drug in two immiscible phases. Whereas the "true partition coefficient applies only to completely immiscible, non-associating or dissociating species in either phase. In biopharmaceutic the apparent partition coefficient is used, since mostly non ideal conditions are found. Usually APC is determined between n-octanol and a buffer solution is certain PH at 37^oC according to equation:

APC = $(c_o{}^o\text{-}c_2{}^1)\ v_1/c_2{}^1v_2$

6. **Drug Stability**

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, or the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation.

II. PHARMACOKINETIC CHARACTERISTICS

For practically all controlled release dosage forms, a basic pharmacokinetic understanding of a given drug's disposition in the human body is essential. Most controlled release dosage forms are not intended just to release the drug at a delayed or prolonged rate, but are expected to reach and maintain a certain target concentration in blood, in plasma or at specific sites or organs. These dosage forms are multiple-dose products designed to result in steady state concentrations, $C_{ss.}$

1. **Elimination or Terminal Half-life**

The $t_{1/2}$ is the time required to reduce the concentration in blood, plasma or serum to one-half, after equilibrium is reached. The $t_{1/2}$ can be determined from the slope of the terminal line off a semilogarthmic plot of serum concentrations versus time plot by regression analysis. The $t_{1/2}$ is an important parameter for the selection of drug to be incorporated into controlled delivery system. The shorter the $t_{1/2}$, greater will be delivery system. Only drugs whose $t_{1/2}$ can be correlated with the pharmacological response are candidates for controlled drug delivery system.

2. **Area under the concentration-time curve**

The AUC is a measure of the quantity of drug in the body. If curve fitting is done, which assumes a specific model, the AUC can be determined from the coefficients and constants. However, most conveniently the AUC is determined by compartment model-independent approaches, using the linear trapezoidal rule. The AUC is very important parameter, permitting the estimation of total clearance consequently the apparent volume of distribution.

3. **Total Clearance (CL)**

The total clearance is that hypothetical volume of distribution of unmetabolized 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.

$$\mathbf{CL = D.F/AUC}$$

4. **Apparent Volume of Distribution (V_d)**

The V_d is a hypothetical volume, indicating the volume of fluid that is required to dissolve the total amount of drug in the body to the measured concentration in blood. Using the Model-independent approach, the V_d can be calculated according to equation:

$$\mathbf{V_d = D.F/AUC.K_e}$$

5. **Mean steady State Concentration (C_{ss})**

The C_{ss} is not the numeric mean between peak (C_{ssmax}) and trough ($C_{ss\ min}$) at steady state but an integrated concentration. With constant rate infusion and in ideal controlled release delivery system, no fluctuations occur at steady state, hence $C_{ss} = C_{ssmax} = C_{ss\ min}$

6. **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 (the area under the first moment curve).

$$MRT = AUMC/AUC$$

Controlled release drug delivery systems should have an MRT significantly longer than is obtainable with conventional dosage forms.

7. First-pass Effect

It is that fraction of drug which is degraded, inactivated or metabolized after its release from the dosage form. Most prominent is pressystemic loss of drug upon peroral administration, namely degradation by intestinal contents and enzymes biotransformation by the intestinal microbial flora, and the first pass-effect, the metabolism in the gut wall, portal vein and liver.

8. Dosage form Index (DI)

DI is the ratio between peak (C_{ssmax}) and trough (C_{ssmin}) values within dosing interval.

$$DI = C_{ss.max}/C_{ss.min}$$

If DI =1, then $C_{ss} = C=_{max} =C_{ss\ min,}$ Ideally, a controlled release dosage form is capable of achieving a dosage form index as close to I as possible.

CONCLUSION

The controlled release drug delivery system aims to release the drug at the desired rate over an extended period of time to achieve therapeutic level in the blood. Oral Controlled release products provide advantages over conventional dosage form by optimizing bio-pharmaceutics pharmacodynamic properties and pharmacokinetic properties of a drug that targets to reduce dosing frequency and results in patient compliance. It is concluded that Oral controlled drug delivery system is the most common and convenient route of drug delivery.

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