A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Among all drug delivery systems, oral drug delivery is the most preferred route for administration for various drugs. Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral sustained release (SR)/Controlled release (CR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamic properties of drugs. It also reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through which 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. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body.

Keywords: Sustained / Controlled-release, Conventional tablet, Oral controlled release system, Matrix tablet.

INTRODUCTION

In recent years, the study of controlled release of drugs and other bioactive agents from polymeric devices has attracted many researchers from around the world. Controlled drug delivery applications include both sustained delivery over days/weeks/months/ years and targeted (For example - to a tumor, diseased blood vessel, etc.) delivery on a one-time or sustained basis. Controlled release formulations can be used to reduce the amount of drug necessary to cause the same therapeutic effect in patients. The convenience of fewer and more effective doses also increases patient compliance[1-3]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems[4,5]. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.
Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients[6].

Advantages of Sustained/Controlled Release Dosage Forms

- Reduced fluctuations in circulating drug levels.
- Avoidance of night time dosing.
- Increased patient compliance.
- More uniform effect.
- The frequency of drug administration is reduced.
- Drug administration can be made more convenient.
- The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced.
- Safety margin of high potency drug can be increased.

Disadvantages of Sustained/Controlled Release Dosage Forms

- Unpredictable or poor in-vitro and in- vivo correlation.
- Dose dumping.
- Reduced potential for dosage adjustment.
- Poor systemic availability in general.

Types of Modified Release Drug Products

1. Extended Release Dosage Forms

A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form.

For example - Controlled release, Sustained release.

Sustained release: It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a pre-determined rate.

Controlled release: It includes any drug delivery system from which the drug is delivered at a predetermined rate over a prolonged period of time.
2. **Delayed Release Dosage Forms**

   A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration.

   For example- Enteric coated dosage forms.

3. **Targeted Release Dosage Forms**

   A dosage forms that releases drug at/near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics.

4. **Repeat Action Dosage Forms**

   It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a latter time.

5. **Prolonged Action Dosage Forms**

   It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period of time.

**ORAL CONTROLLED RELEASE SYSTEMS**

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1) **Continuous Release Systems**

   These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow,

   A. Dissolution controlled release systems
   B. Diffusion controlled release systems
   C. Dissolution and diffusion controlled release systems
   D. Ion exchange resin- drug complexes
   E. pH dependent formulation
   F. Osmotic pressure controlled systems

   A. Dissolution controlled release systems
These types of systems are easiest to design. The drug present in such system may be the one

- With inherently slow dissolution rate for example-Griseofulvin and Digoxin.
- That produces slow dissolving forms, when it comes in contact with GI fluids.
- Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate.

i) Matrix (or monolithic) dissolution controlled systems

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolithic system. It is very common and employ waxes such as beeswax, carnauba wax.

ii) Reservoir dissolution controlled systems

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like Cellulose and Polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

B. Diffusion controlled release systems

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix.

i) Matrix Diffusion Controlled Systems

In this type, the drug is dispersed in an insoluble matrix of rigid, non-swellable hydrophobic material or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as Poly-vinyl chloride and Stearic acid\textsuperscript{[7,8]}. 

THEORIES OF DISSOLUTION

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of
liquid/solid interface, temperature and solvent composition. The basic step in drug dissolution is the reaction of the solid drug with the fluid and/or the components of the dissolution medium. This reaction takes place at the solid-liquid interface and therefore dissolution kinetics are dependent on three factors, namely the flow rate of the dissolution medium toward the solid-liquid interface, the reaction rate at the interface and the molecular diffusion of the dissolved drug molecules from the interface toward the bulk solution. Scientists have reviewed the factors which can affect the dissolution of tablets and these include the stirring speed, temperature, viscosity, pH, composition of the dissolution medium and the presence or absence of wetting agents. Physical models have been set up to account for the observed dissolution of tablets. According to Higuchi, there are three models which either alone or in combination, can be used to describe the dissolution mechanisms\(^9\). These are as below.

(i) The Diffusion layer model

This model (Fig 1) assumes that a layer of liquid, H cm thick, adjacent to the solid surface remains stagnant as the bulk liquid passes over the surface with a certain velocity.

![Diffusion Layer Model](image)

Figure 1
Diffusion Layer Model

The reaction at the solid/liquid interface is assumed to be instantaneous forming a saturated solution, Cs, of the solid in the static liquid film. The rate of dissolution is governed entirely by the diffusion of the solid molecules from the static liquid film to the bulk liquid according to Fick’s first law,

\[
J = - D_f \frac{dc}{dx}
\]

Where,
\[ J = \text{Amount of substance passing perpendicularly through a unit surface area per time,} \]
\[ D_f = \text{Diffusion coefficient} \]
\[ \frac{dc}{dx} = \text{Concentration gradient.} \]

After a time \( t \), the concentration between the limit of the static liquid layer and the bulk liquid becomes \( C_t \). Once the solid molecules pass into the bulk liquid, it is assumed that there is rapid mixing and the concentration gradient disappears. The theory predicts that, if the concentration gradient is always constant i.e. \( C_s - C_t \) is constant because \( C_s >> C_t \) (“sink” conditions which usually mean \( C_s > 10 C_t \)) then a uniform rate of dissolution is obtained.

(ii) The Interfacial Barrier Model

In the interfacial barrier model (Fig 2), it is assumed that the reaction at the solid/liquid interface is not instantaneous due to a high activation free energy barrier which has to be surmounted before the solid can dissolve. Thereafter the dissolution mechanism is essentially the same as in (i) above, with the concentration at the limit of the static layer of liquid becoming \( C_t \) after time \( t \).

![Diagram](image.png)

**Figure 2**

Diagrammatic representation of the free energy barrier to dissolution

(iii) The Danckwert’s Model

The Danckwert’s model (Fig 3) assumes that macroscopic packets of solvent reach the solid/liquid interface by eddy diffusion in some random fashion.
At the interface, the packet is able to absorb solute according to the laws of diffusion and is then replaced by a new packet of solvent. This surface renewal process is related to the solute transport rate and hence to the dissolution rate. Though the diffusion layer model is the most commonly used, various alterations have been proposed. The current views of the diffusion layer model are based on the so-called effective diffusion boundary layer, the structure of which is heavily dependent on the hydrodynamic conditions. Ahmed et al proposed a scheme which holds that dissolution occurs only when the drug is in small particles. Whitney modified this idea and showed that dissolution occurs from both the intact tablet and the aggregates and/or granules produced after disintegration by using a plot of the percentage of drug dissolved versus time on logarithmic probability graph papers[^10,11].

**MATRIX TABLET**

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, the drug and retardant blend may be granulated prior to compression. The materials most widely used include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is
critical to the rapid formation of gelatinous layer on the tablet surface\textsuperscript{[12,13]}. Hydroxypropylmethylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems\textsuperscript{[14,15]}.

One of most important characteristics of the matrix tablet is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion\textsuperscript{[16,17]}. Then, the incorporated drug diffuses out of the system. For the design of new controlled drug delivery systems which are based on HPMC and aimed at providing particular, pre-determined release profiles, it is highly desirable (i) to know the exact mass transport mechanisms involved in drug release and (ii) to be able to predict quantitatively the resulting drug release kinetics. The practical benefit of an adequate mathematical model is the possibility to simulate the effect of the design parameters of HPMC-based drug delivery systems on the release profiles\textsuperscript{[18]}.

In the ideal case, the required composition (type and amount of drug, polymer and additives) and geometry (size and shape) of the new controlled drug delivery system designed to achieve a certain drug release profile can be predicted theoretically. Thus, the number of necessary experiments can be minimized and the development of new pharmaceutical products significantly facilitated.

**PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS**

**Release Rate and Dose**

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suppositories. For purposes of this discussion, these dosage forms can be considered to release these active ingredients into an absorption pool immediately. This is illustrated by the following simple kinetic scheme.

\[
\begin{array}{c}
\text{Dosage form} \\
\rightarrow
\end{array} \quad \begin{array}{c}
k_r
\quad \text{Absorption Pool}
\quad \rightarrow
\quad k_a
\quad \text{Target Area}
\quad \rightarrow
\quad k_e
\end{array}
\]

Drug release \quad \begin{array}{c}
\text{Absorption}
\end{array} \quad \begin{array}{c}
\text{Elimination}
\end{array}

The absorption pool represents a solution of the drug at the site of absorption and the terms \(k_r\), \(k_a\) and \(k_e\) are the first order rate constants for drug release, absorption and overall elimination, respectively. Immediate release from a conventional dosage form
implies that kr>>>ka or alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate limiting step in delivery of the drug to its target area. For non immediate-release dosage forms, kr<<<kw that is, release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to,

\[
\begin{align*}
\text{Dosage form} & \xrightarrow{k_r} \text{Target Area} & \text{Elimination} \xrightarrow{k_e} \\
\text{Drug release} & & \\
\end{align*}
\]

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared with the drug release phase. Thus, the effort to develop a non-immediate-release delivery system must be directed primarily to altering the release rate by affecting the value of kr. Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal starting goal of an extended-release delivery system. In fact, in some cases optimum therapy is achieved by providing oscillating, rather than constant drug levels. An example of this is antibiotic therapy, where the activity of the drug is required only during the growth phase of the microorganism\(^{[19]}\).

If the dose of a drug is high (For example - those that requiring a daily dose exceeding 500 mg), it becomes more challenging to develop sustained release oral dosage forms. For short half-life drugs, to provide a once a day tablet, it requires not only that a large amount of drug to be incorporated in a dosage unit to provide the daily dose, but also the dosage units be small in size to allow for ease of swallowing by the human. The requirement for small sizes would leave little space in the dosage unit for other ingredients needed to control the drug release. The size of the dosage unit becomes even more critical with highly water-soluble drugs since even a larger amount of inactive ingredients (For example - more than 50% of the total weight) is usually needed to provide the sustained release property, according to the conventional SR methods\(^{[20]}\).

**BIOLOGICAL FACTORS**

**Half Life**

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at
approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half life \( (t_{1/2}) \).

Half life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half and is determined by both clearance (Cl) and volume of distribution (VD).

\[ t_{1/2} = \frac{0.693.Vd}{Cl} \]

Half life is increased by increasing in volume of distribution or a decrease in clearance and vice-versa. The larger the volume of distribution the more the drug is concentrated in the tissues compared with the blood\(^{[21,22]}\).

**Absorption**

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system. The most critical in case of oral administration is \( Kr<<Ka \). Assuming that the transit time of drug through the absorptive area of gastrointestinal tract is between 9-12 hours, the maximum absorption half life should be 3-4 hours. This corresponds to a minimum absorption rate constant Ka value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12hr transit time\(^{[23]}\).

**Drugs absorbed by active transport system are unsuitable for sustained/controlled drug delivery system**

Methotrexate, Enalapril, Riboflavin, Pyridoxine, 5-Fluorouracil, 5-Bromouracil, Nicotinamide, Fexofenadine, Methyl-dopa.

**Drugs absorbed through amino acid transporters in the intestine**

Cephalosporines, Gabapentine, Baclofen, Methyl-dopa, Levo-dopa.

**Drugs transported through Oligo – peptide transporters**

Captopril, Lisinopril, Cephalexine, Cefadroxil, Cefixime.

**Drugs required to exert a local therapeutic action in the stomach are unsuitable for sustained/controlled drug delivery.**

Misoprostol, 5-Fluorouracil, Antacids, antibelicobacter pylori agents.

**Absorption Window**

Some drugs display region specific absorption which is related to differential drug solubility and stability in different regions of G.I.T, as a result of changes in
environmental pH, degradation by enzymes, etc. These drugs show absorption window, which signifies the region of G.I tract where absorption primarily occurs. Drugs released from sustained/controlled release systems, after absorption window has been crossed goes waste with little/no negligible absorption.

Drugs exhibiting the site specific absorption in stomach or upper parts of small intestine

- Acyclovir, Captopril, Metformin, Gabapentin, Atenolol, Furosemide, Ranitidine, Levo-dopa, Sotalol, Salbutamol, Riboflavin, Sulfonamides, Loratadine, Cephalosporines, Tetracyclines

Distribution

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in the overall elimination kinetics. Apparent volume of distribution and ratio of drug in tissue to plasma (T/P) concentration are used to describe the distribution characteristics of a drug. For drugs which have apparent volume of distribution higher than real volume of distribution i.e., drugs which are extensively bound to extra vascular tissues For example - Chloroquine, the elimination half life is decreased i.e., the drug leaves the body gradually provided drug elimination rate is limited by the release of drug from tissue binding sites and that drug is released from the tissues to achieved concentrations exceeding the threshold level or within the therapeutic range, one can assume that such drugs are inherently sustained.

Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

- Drug should have low half-life (<5 hrs).
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- Drug should be absorbed throughout the GIT.

There are two areas of concern related to metabolism that significantly restrict SR product design. First, if a drug upon chronic administration is capable of either inducing
or inhibiting enzyme synthesis, it will be a poor candidate for a S/R/CR. Product because of the difficulty of maintaining uniform blood levels of a drug. Second, if there is a variable blood level of a drug through either intestinal (or tissue) metabolism or through first pass effect, this also will make formulation of SR dosage form difficult, since most of the process are saturable, the fraction of the drug loss would be dose dependent and that would result in significant reduction in bioavailability, if the drug is slowly released over a extended period of time[24].

Fluctuating drug blood levels due to intestinal metabolism upon oral dosing

  Salicylamide, Isoproterenol, Chlorpromazine, Clonazepam, Hydralazine and Levodopa.

Fluctuating drug blood levels due to first pass hepatic metabolism upon oral dosing

  Nortriptyline, Phenacetin, Morphine, Propranolol.

Fluctuating blood levels due to enzyme induction are poor candidates for Sustained/controlled Release dosage forms

  Griseofulvin, Phenytoin, Primidone, Barbiturates, Rifampicin, Meprobamate, Cyclophosphamide.

Fluctuating blood levels due to enzyme inhibition are poor candidates for Sustained/Controlled Release dosage forms

  Isoniazid, Cimetidine, Amiodarone, Erythromycin, Fluconazole, Ketoconazole, MAO-inhibitors, Para -aminosalicyclic acid, Allopurinol, Coumarins.

Drug-Protein Binding

  The drug can bind to components like blood cells and plasma proteins and also to tissue proteins and macromolecules. Drug protein binding is a reversible process. As the free drug concentration in the blood decreases, the drug-protein complex dissociates to liberate the free drug and maintain equilibrium. Due to this reversible binding of a drug, the free drug levels of the drug are maintained for long time in the blood leading to a long biological half-life. A protein bound drug due to its high molecular size is unable to enter into hepatocytes, resulting in reduced metabolism. The bound drug is not available as a substrate for liver enzymes there by further reducing the rate of metabolism.

Therapeutic Index

  It is most widely used to measure the margin of safety of a drug.
TI = TD50/ED50

The longer the value of TI, the safer the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its TI value is greater than 10.

Duration of Action

Duration of action is the time period for which the blood levels remain above the MEC and below the MSC levels (or) more specifically within the therapeutic window. Drugs acting for long duration are unsuitable candidates for formulation into S.R/C.R forms.

Conclusion

By the above discussion, it can be easily concluded that sustained release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient’s compatibility. Drug transport inside pharmaceutical systems involves multiple steps provoked by different physical or chemical phenomenon.

REFERENCES

17. Peppas LB and Peppas NA: The equilibrium swelling behavior of porous and non porous hydrogels: Elsevier Amsterdam, 1990; 67-102.


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