

Review Article



Sustained Release Oral Drug Delivery System: A Concise Review

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ABSTRACT

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. Sustained release system are considered a wiser approach for the drug with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. The basic objective of these dosage forms is to optimize the delivery of medications so as to achieve a measure of controls on therapeutic effect in the face of uncertain fluctuation in the in vivo environment in which drug release takes place. Sustained release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. Sustained Release is also providing promising way to decrease the side effect of the drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The basic rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of the drug in such a way that utility is maximized, side-effects are reduced and cure of the disease is achieved. The principal goal of sustained release forms is the improvements of drug therapy assessed by the relationship between advantages and disadvantages of the use of sustained release system.

Keywords: Sustained release, Dose Frequency, physicochemical properties of drugs, Biological Half life.

INTRODUCTION

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms¹. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form as term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose². In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced

toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapy¹.

Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage forms there is need to take 3-4 times dosage in a day to achieve the same therapeutics action. The key role behind administering a single dose of a drug is sustained release dosage forms is that it can be released over an extended period of time to maintain uniform concentration of a drug in a blood this may lead to better patient compliance and provide enhanced clinical output of the drug³.

Rational for development of SRDDS

1. Formulations of SRDDS minimize dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.
2. To reduce cost of treatment by reducing number of dosage requirement.
3. To minimize toxicity due to overdose which is often conventional dosage form.
4. To enhance the activity duration of a drug possessing short half-life^{1,4}.

Terminology Related to SRDDS

Delayed release

Delayed release systems are those which use repetitive, intermittent dosing of a drug. These systems are



composed of one or more immediate releasing units in a single dosage form. The delay release may be based on time or due to the influence of environment conditions, like gastrointestinal pH

Extended release

a. Sustained release

It is defined as any drug or dosage form modification that prolongs the therapeutic activity of drug.

b. Controlled release

The drug delivery system which designed to deliver the medication at a predetermined rate over an extended period of time. This system follows zero-order release (independent upon initial concentration of drug) whereas SRDDS follows first order release⁵.

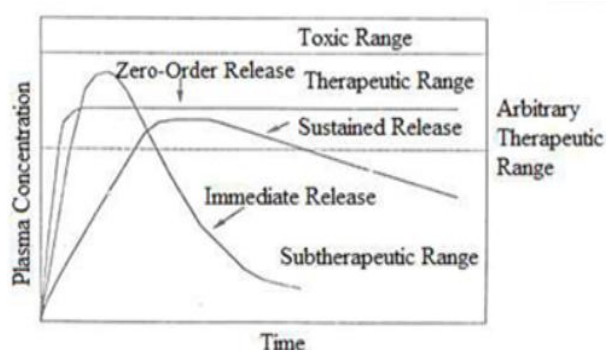


Figure 1: Arbitrary therapeutic range of different dosage form in blood⁶

Advantages of Sustained Release System

Patient Compliance

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patients to comply with the regimen.

Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule.

Also the complexity of therapeutic regimen, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering sustained release drug delivery system.

Reduced 'see-saw' fluctuation

Administrations of a drug in a conventional dosage form [except via IV infusion at drug concentration a constant rate] often result in 'see-saw' pattern of drug concentration in systemic circulation and tissue compartment. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak & valley' pattern is more striking in case of

drugs with biological half lives of less than four hours since prescribed dosing intervals are rarely less than four hours since prescribed dosing intervals are rarely less than four hours.

A well-designed sustained release drug delivery system can significantly reduce the frequency of drug dosing & also maintain a more steady drug concentration in blood circulation & target issue cells.

Reduced total Dose

Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition by reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to great economy.

Improved efficiency in treatment

Optimal therapy of a disease requires efficient delivery of active drugs to the tissues, organ that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable toxicological & immunological effects in non-target tissue to sustained release dosage form leads to better management of the acute or chronic disease condition.

Economy

The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over a prolonged period of time may be less^{5,7}.

Disadvantages of Sustained Release System

Inhibition of prompt termination of therapy

Administration of sustained release medication does not permit the prompt termination of therapy such as might be encountered if significant adverse effects are noted, cannot be accommodated.

Dosage form design

The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

Patient variation

Sustained release forms are designed for the normal population i.e. on the basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition, significant patient variation and so forth are not accommodated.

Economic factors

Economic factor must also be assessed since more costly processes & equipment are involved in manufacturing many sustained release forms

Poor In-Vivo and In-Vitro correlations

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

Dose dumping

Dose dumping is a phenomenon where by relatively large quantities of drug in sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

Limited choice of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablets can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured^{5,7,8}.

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

1. If the active compounds has a long half-life (over 6 hours), it is sustained on its own.
2. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
3. If the absorption of the active compound involves an active transport, the development of a time release product may be problematic.
4. 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 recommended⁷.

Table 1: Characteristics of Drug unsuitable for Peroral Sustained Release Forms

S. No.	Characteristics	Drugs
1.	Not effectively absorbed in the lower intestine.	Riboflavin, ferrous salt
2.	Absorbed and excreted rapidly, short biological half-lives (<1 hr)	Penicillin G, Furosemide
3.	Long biologic half-lives(>12h)	Diazepam, phenytoin
4.	Large doses required(>1g)	Sulfonamides
5.	Cumulative action and undesirable side effects; drugs with low therapeutic indices	Phenobarbital, digitoxin

6.	Precise dosage titrated to individual is required.	Anticogulants, cardiac glycosides
7.	No clear advantages for sustained released formulation	Grisofulvin ^{6,8}

Criteria to be met to incorporate the drug in sustained release dosage form

Table 2: Physicochemical parameter for drug selection

S. No.	Parameters	Criteria
1.	Molecular size	< 1000 Daltons
2.	Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General absorbability from all GI segments	Release should not be influenced by pH and enzyme

Table 3: Pharmacokinetic parameter for drug selection

S. No.	Parameters	Comments
1.	Elimination half-life	Between 2 to 8 hrs
2.	Absolute bioavailability	Should be 75% or more
3.	Absorption rate constant(K_a)	Must be higher than release rate
4.	Apparent volume of distribution(V_d)	Larger V_d and MEC, larger will be the required dose
5.	Total clearance	Not dependent on dose
6.	Elimination rate constant	Required for design
7.	Therapeutic concentration(C_{ss})	The lower C_{ss} and smaller V_d , the less amount of drug required
8.	Toxic concentration	Apart the value of MTC and MEC safer the dosage form ^{8,9}

Classification of Sustained Release System

The controlled release system for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanism in the control of release rate of drug.

Depending upon the manner of drug release three systems are classified as follows:

1. Continuous Release systems
2. Delayed transit and controlled release systems
3. Delayed release system



Continuous release system

Continuous release 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 system under this category are as follow:

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

Diffusion controlled release system

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 increase 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 system.

The two types of diffusion-controlled release are:

1. Matrix diffusion controlled systems
2. Reservoir devices

Dissolution-controlled release systems

The drug present in such system may be the one:

- a) Having high aqueous solubility and dissolution rate
- b) With inherently slow dissolution rate e.g. Grisofulvin and digoxin
- c) That produces slow dissolving forms, when it comes in contact with GI fluids.

Dissolution-controlled release can be obtained by slowing the dissolution rate of drug in GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules, with polymeric material of varying thickness.

Dissolution and diffusion controlled release systems

In such systems the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of membrane which permit entry of aqueous medium into the core and hence drug diffusion of dissolved drug out of the system.

Ion exchange resin-drug complexes

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanges in gastrointestinal tract and release with excess of Na^+ and Cl^- present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer.

They contain salt forming function group is repeating position on a polymer chain.

pH independent formulation

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation to help to maintain to constant pH thereby retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane the buffering agent adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release⁹.

FACTORS GOVERNING THE DESIGN OF SUSTAINED RELEASE DOSAGE FORMS

Physico-chemical Properties

Molecular size and Diffusivity

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The ability of drug to diffuse in polymers, its so called diffusivity (diffusion coefficient D), is a function of its molecular size (or molecular weight)^{3,10}. For most polymers, it is possible to relate $\log D$ empirically to some function of molecular size as,

$$\log D = -S_v \log u + k_v = -S_M \log M + k_m$$

Where,

V = Molecular volume

M = Molecular weight

S_v, S_M, k_v, k_m = Constant

The value of D , thus is related to the size and shape of the cavities as well as size and shape of drugs.

Aqueous Solubility

Solubility is defined as the amount of material that remains in solution in a given volume of solvent containing undissolved material. It is the thermodynamic property of a compound. The fraction of drug absorbed into the portal blood is a fraction of the amount of drug in the solution in the G.I. tract, i.e., the intrinsic permeability of the drug. For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and the partition into the absorbing membranes¹¹. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membranes. Diffusion rate is related to aqueous solubility, as shown



by the Noyes-Whitney equation that, under sink condition is,

$$dC/dt = k_D A C_s \quad (1)$$

Where,

dC/dt = Diffusion rate,

k_D = Diffusion rate constant,

A = Total surface area of the drug particles,

C_s = Aqueous saturation solubility of the drug.

The dissolution rate is constant only if it remains constant, but the important point to note is that the initial rate is directly proportional to C_s . Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility of weak acids or bases is governed by the pK_a of the compound and the pH of the medium.

For a weak acid,

$$S_t = S_0 (1 + K_a / (H^+)) = S_0 (1 + 10^{pH - pK_a}) \quad (2)$$

Where,

S_t = Total solubility (both the ionized and unionized forms) of the weak acid,

S_0 = Solubility of the unionized form,

K_a = Acid dissociation constant,

(H^+) = Hydrogen ion concentration in the medium⁴.

Similarly, For a weak base

$$S_t = S_0 (1 + (H^+) / K_a) = S_0 (1 + 10^{pK_a - pH}) \quad (3)$$

Where, S_t = Solubility (both the conjugated acid and free base forms) of the weak base,

S_0 = Solubility of the free base form,

K_a = Acid dissociation constant for the conjugated acid.

Equation 2 and 3 predict that the total solubility of weak acid or base with a given pK_a can be affected by the pH of the medium. Considering the pH partition hypothesis, the importance of equation 2 and 3 relative to drug absorption is evident.

Class I : High solubility-High permeability

Class II: Low solubility-High permeability

Class III : High solubility-Low permeability

Class IV : Low solubility-Low permeability

High solubility

Largest dose dissolves in 250 ml of water over a pH range 1-8.

High permeability

Extent of absorption is > 90% Class II and Class IV drugs are poor candidates for sustained release dosage forms. Compound with solubility below 0.1 mg/ml face

significantly solubilization obstacles and often compounds with solubility below 10 mg/ml present difficulties related to solubilization during formulation. In general, extremes in aqueous solubility of a drug are undesirable for formulation in an extended-release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into an extended release system may not provide considerable benefits over conventional dosage form. Even, if a poorly soluble drug were considered a candidate for formulation into an extended-release system a constraint would be placed on the type of delivery system that could be used. For example, any system relying on diffusion of the drug through a polymer as the rate limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is drug concentration in the polymer or solution and this concentration would be low. For a drug with very high solubility and a rapid dissolution, it is often quite difficult to decrease its dissolution rate and slow its absorption¹³. A drug of high water solubility can dissolve in water or gastrointestinal milieu readily and tends to release from its dosage forms in a burst and thus is absorbed quickly, leading to a sharp increase in the drug blood concentration. Compared to less soluble drugs, it is often difficult to sequester a highly water soluble drug in the dosage form (such as tablet) and retard the drug release, especially when the drug dose is high. Preparing a slightly soluble form of a drug with normally high solubility is one possible method for producing extended release dosage forms. The pH dependent solubility, particularly in the physiological pH range would be another problem for SR/CR formulation because of the variation in the pH throughout the gastro intestinal tract and hence variation in dissolution rate.

Examples of Drug Which are Poor Candidates for Sustained Release Systems

- i. Drug limited in the absorption by their dissolution rates are: Digoxin, Warfarin, Griseofulvin and Salicylamide.
- ii. Drug poorly soluble in the intestine (acid soluble basic drugs) are Diazepam, Diltiazem, Cinnarizine, Chlordiazepoxide and Chlorpheniramine¹.

pK_a - Ionization Constant

The pK_a is a measure of the strength of an acid or base. The pK_a allows determining the charge on drug molecule at any given pH. Drug molecules are active in only the undissociated state and also unionized molecules cross the lipoidal membranes much more rapidly than the ionized species. The amount of drug that exists in unionized form is a function of dissociation constant of a drug and pH of fluid at absorption site. For a drug to be absorbed, it must be in unionized form at the absorption site. Drug which exist in ionized form at the absorption



site are poor candidate for sustained/controlled dosage form¹³.

Partition Coefficient

Partition coefficient influences not only the permeation of drug across the biological membranes but also diffusion across the rate controlling membrane or matrix between the time when a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes (1.1. its membrane permeability) in its apparent oil/water partition coefficient defined as,

$$K = C_o / C_w \dots \dots \dots (5)$$

Where,

C_o = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,

C_w = Equilibrium concentration of all forms in an aqueous phase

In general, drugs with extremely large values of K are very oil-soluble and will partition into membrane quickly readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the Hansch correlation, which describes a parabolic relationship between the logarithm of activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. As a first approximation the more effectively a drug crosses membranes, the greater its activity. There is also an optimum partition coefficient below this optimum result in decreased lipid solubility and the drug will remain localized in the first aqueous phase it contacts. Values larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility and the drug will not partition out of lipid membrane once it gets in. The value of K at which optimum activity is observed is

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 first order rate constants for drug release, absorption, and overall elimination, respectively. Immediately release from a conventional dosage form implies that $k_r \gg k_a$ or alternatively, that absorption of drug across a biological

approximately 1000/1 in n-octanol/ water. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poorer candidates for formulation into extended release dosage forms¹⁴.

Stability

One important factor for the loss of drug is through acid and/or metabolism in the GIT when administered orally. It is possible to significantly improve the relative bioavailability of a drug that is unstable in G.I.T by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach the most appropriate controlling unit would be one that release its contents, only in the stomach. The release in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling such as in this case would be one that release its content, only in the stomach. So drugs with significant stability problems in any particular area of the G.I. tract are less suitable for formulation into controlled release systems that deliver the contents uniformly over the length of GIT^{15,16}.

Acid Unstable Drugs (Stomach)

For example Rabeprazole, Pantoprazole, Omeprazole, Omeprazole, Lansoprazole, Esomeprazole, Rifampicin, Mesalazine Erythromycin, Riboflavin.

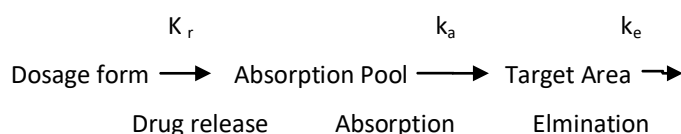
Alkaline Unstable Drugs (Drugs that are Unstable in Intestine and Colon)

For example Captopril, Ranitidine¹⁷

Pharmacokinetic and Pharmacodynamic Consideration

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.



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, $k_r \ll k_w$ that is release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to,



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 k_r . 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 microorganism.

The ideal goal in designing an extended-release system is to deliver drug to the desired site at a rate according to the needs of the body (i.e. a self-regulated system based on feedback control). However this is a difficult assignment. Although some attempts have been made to achieve this goal, such as with the self-regulating insulin pump, there is no commercial product representing this type of system as yet. In the absence of feedback control we are left with a simple extending effect. This pivotal question is at what rate should a drug be delivered to maintain a constant blood drug level. This constant rate should be the same as that achieved by continuous intravenous infusion where a drug is provided to a patient at a constant rate just equals to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. This is, release from dosage form should

$$k_r^0 = \text{Rate In} = \text{Rate Out} = k_e \cdot C_d \cdot V_d$$

Where,

k_r^0 = Zero-order rate constant for drug release (amount/time)

k_e = First-order rate constant for overall drug elimination (time⁻¹)

C_d = Desired drug level in the body (amount/volume)

V_d = Volume of the space in which the drug is distributed.

The values of k_e , C_d and V_d needed to calculate k_r^0 are obtained from appropriately designed single-dose pharmacokinetics studies. The above equation provides the method to calculate the zero-order release rate constant necessary to maintain a constant drug blood or tissue level for the simplest case, where the drug is eliminated by first order kinetics. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affect the nature of the release kinetics necessary to maintain a constant drug blood level¹⁸. It is important to recognize that while zero-order release may be equivalent clinically to constant release in many cases. Aside from the extent of constant inter and intra subject variation is the observation that for many drugs, modest changes in drug tissue level do not result in an improvement in clinical performance. Thus a non-constant drug level may be indistinguishable clinically from a constant drug level. To achieve a therapeutic level promptly and sustain the level for a given period of time,

the dosage form generally consist of two parts: an initial priming dose D_i , that releases drug immediately and maintenance or sustaining dose D_m , that release drug immediately and maintenance or sustaining dose, D_m . The total dose, W , thus required for the system is,

$$W = D_i + D_m$$

For a system in which the maintenance dose release drug by zero-order process for a specific period of time, the total dose is,

$$W = D_i + k_r^0 T_d - k_r^0 T_p$$

Where,

T_d = Total time required from extended release from one dose

If the maintenance dose begins release of drug at the time of dosing ($t=0$), it will add to what which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose,

$$W = D_i + k_r^0 T_d - k_r^0 T_p$$

The correction factor $k_r^0 T_p$ is the amount of drug provided during the period from $t=0$ to the time of the peak drug level T_p . No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time T_p . It already has been mentioned that a perfectly invariant drug blood or tissue level versus time profile is the ideal starting goal starting goal of an extended release system. The way to achieve this, in the simplest case, is use of a maintenance dose that releases its drug by zero-order kinetics. However, satisfactory approximations of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first order process. The total dose for such a system is,

$$W = D_i + (k_e C_d / k_r V_d)$$

Where,

k_r = First-order rate constant for drug release (time⁻¹)

k_e, C_d, V_d = As defined previously.

If the maintenance dose begins releasing drug at $t=0$, a correction factor is required just as in the zero-order case. The correct expression in this case is,

$$W = D_i + (k_e C_d / k_r) V_d - D_m k_e T_p$$

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most extended-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal extended-release system that releases drug by zero-order kinetics, the multiple dosing regimens is analogous to that used for a constant intravenous infusion¹¹. Since in extended-release system is designed to alleviate repetitive dosing, it

naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in a conventional dosage form will give some indication of the total amount of drug needed in an extended release preparation. For the drugs requiring large conventional doses, the volume of sustained dose may be too large to be practical or acceptable, depending on the route of administration. The same may be true of drugs that require a large release rate from the extended release system (for example drugs with short half-lives). If the dose of drug is high (for example those that require 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 be incorporated in a dosage unit to provide the daily dose, but also the dosage unit to 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.

Biological Factors

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 $K_r \ll K_a$. 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 absorptive rate constant K_a value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12 hr transit time⁷. For a drug with a very slow rate of absorption ($K_a < 0.17$ /hr), the first order release rate constant K_r less than 0.17/hr results in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drug will be difficult to be formulated into extended release systems where the criterion $K_r \ll K_a$ must be met¹⁷. If the drug was erratically absorbed because of variable absorptive surface of gastrointestinal tract, design of the sustained release product would be more difficult or prohibitive. Example, The oral anticoagulant Dicoumarol, Iron.

Drugs Absorbed by active Transport System are Unsuitable for Sustained/Controlled Drug Delivery System

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

Drug Absorbed Through Amino Acid Transporters in the Intestine

Cephalosporines, Gabapentine, Baclofen, Methyldopa, Levodopa.

Drugs Transport through Oligo-Peptide Transporters

Cephalosporines, Gabapentine, Baclofen, Methyldopa, Levodopa, Captopril, Lisinopril, Cephalexin, Cefixime.

Drug Required to Exert a Local Therapeutic Action in the Stomach are Unsuitable for Sustained Controlled Drug Delivery

Misoprostol, 5-Fluorouracil, Antacids, Anti helicobacter 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. Hence absorption window can limit the bioavailability of orally administered compounds and can be major obstacles to the development of sustained/controlled drugs.

Examples of Drugs Exhibiting the Site Specific Absorption in Stomach or Upper Parts of Small Intestine (Absorption Window) are

Acyclovir, Captopril, Metformin, Gabapentine, Atenolol, Furosemide, Rantidine, Levodopa, Sotalol, Salbutamol, Riboflavin, Sulfonamide, Loratadine, Cephalosporin, Tetracycline, Varapamil, Thiamine, Sulpiride, Baclofen, Nimesulide, Cyclosporine, Quinolones^{19,20}.

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 characteristic 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 examples, Chloroquine, this 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 achieve concentrations exceeding the threshold level or within the therapeutic range, one can assume that such drugs are inherently sustained. The larger the volume of distribution, the more the drug is concentrated in the tissues compared with the blood. It is the drug in the blood that is exposed to hepatic or renal clearance, so that when the distribution volume is larger



these mechanisms have fewer drugs to work on. By contrast, if the volume of distribution is small, most of the drug in the body is in the blood and is accessible to the elimination process. To avoid the ambiguity inherent in apparent volume of distribution as estimation of amount of drug in body, the T/P ratio is used. If the amount of drug in central compartment 'P' is known, the amount of drug in peripheral compartment 'T' and hence the total amount of drug in the body can be calculated by,

$$T/P = k_{12}(k_{21} - \beta)$$

Where,

β = Slow disposition rate constant.

Metabolism

The metabolism of a drug can either inactivate an active drug or convert an inactive drug to active metabolite. Complex metabolic patterns would make the sustained release design much more difficult particularly when biological activity is wholly or partly due to a metabolite as in case of Isosorbide 2,5-dinitrate. 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 SR/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 sustained 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 an extended period of time.

Fluctuating Drug Blood Levels Due to Intestine Metabolism upon Oral Dosing

For example, Salicylamide, Isoproterenol, Chlorpromazine, Clonazepam, Hydralazine and levodopa.

Fluctuating Drug Blood Levels Due to First Pass Hepatic Metabolism upon Oral Dosing

For example, Nortriptyline, Phenacetin, Morphine, Propranolol.

Fluctuating Blood Levels Due to Enzyme Induction are Poor Candidates for Sustained Release Dosage Forms

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

Fluctuating Blood Levels Due to Enzyme Inhibition are Poor Candidates for Sustained Release Dosage Forms

Isoniazide, Cimetidine, Amiodarone, Erythromycin, Fluconazole, Ketoconazole, MOA-Inhibitor, P-Aminosalicylic acid, Allopurinol, Coumarins.

Dose Dependent Bioavailability

In case of Propoxyphene bioavailability is dose dependent. Only 18% of 65 mg dose, 28% of 130 mg dose, 33% of 195 mg dose reaches the systemic circulation due to first pass effect. It makes the SR/CR dosage form less desirable.

Elimination Half Life

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).

$$t_{1/2} = 0.693 V_d / Cl$$

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. If the volume of distribution is small, most of the drug in the body is in the blood and is accelerated to the elimination process. For drug that follows linear kinetics, the elimination half life is constant and does not change with dose or drug concentration. For drugs that follow non-linear kinetics, the elimination half-life and drug clearance both change with dose or drug concentration. Drug with short half-lives (<2hrs) and high dose impose a constraint on formulation into sustained/controlled release systems because of the necessary dose size and drug with long half-lives (>8hrs) are inherently sustained¹². Sustained released products for drugs with intrinsically long biologic half-lives are available. As expected, little or no therapeutic advantages have been demonstrated in these products over conventional dosage forms. For examples, Meprobamate (11.3hr), Amitriptyline (21 hr). Sustained release corticosteroids are unnecessary from the stand point of therapy, undesirable from the point of view side effects and un-physiological from that of the diurnal variations in Cortisol secretions. Infact, sustained formulations of Prednisolone have been shown to be equally effective as conventional oral tablets offering no advantages over the latter.

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 complexes dissociate to liberate the free drug and maintain equilibrium. Due to the 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 thereby further reducing the rate of metabolism. The glomerular capillaries do not permit the passage of plasma-protein



and drug protein complexes. Hence only unbound drug is eliminated. The elimination half life of drugs generally increases when the percent of bound drug to plasma increases. Such drugs need not be formulated into sustained/controlled release formulations. Since blood proteins are mostly re-circulated, not eliminated, high drug protein binding can serve as a depot for drug producing a prolonged drug action. The role of protein binding as a factor in formulation of SR/CR dosage form can be explained by considering angiotensin-II antagonist class of drugs. The drugs of this class are highly protein bound (99%). Tasosarten is a long acting AT-II receptor blockers with a protein binding of 99.8%, while its long acting active metabolite Enoltasosartan has a protein binding 99.9%. In a study AT-II receptor blockade effect of single dose of Tasosarten (100 mg oral, 25 mg iv) and Enoltasosartan (25 mg iv) were compared. It was found that Tasosarten induced rapid and sustained blockade of AT-II receptors. Tasosarten induced rapid and sustained blockade of AT-II receptors. Tasosarten blocked 80% of AT-II receptors 1-2 hrs of drug administration and still had 40% effect at 32 hrs. In contrast the blockade induced by the Enoltasosartan was markedly delayed and hardly reached 60-70% despite i.v administration and high plasma level. This delayed in-vivo blockade effect for Enoltasosartan appears to be due to high and tight protein binding, leading to decrease in affinity for receptors and slower receptors association rate²¹.

Duration of Action

Duration of action is the time period for which the blood levels remain above the EMC and below the MSC levels (or) more specifically within the therapeutic window. Drugs acting for long duration are unsuitable candidates for formulation into SR/CR forms. Receptor occupation, Tissue binding, Half life, Metabolism, Partition coefficient, Irreversible binding to cells are some parameters which are responsible for long duration of actions of drugs²².

Therapeutic Index

It is most widely used to measure the margin of safety of a drug.

$$TI = TD_{50} / ED_{50}$$

The longer the value of TI the safer is 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 T.I value is greater than 10^{1,23}.

CONCLUSION

From the above discussion it is concluded that sustained release dosage form is one of the most effective dosage form. It is helpful in increasing patient compliance and also improves efficiency in treatment. Certain criteria like molecular size, aqueous solubility must be met to incorporate the drug in sustained release dosage form. Sustained release dosage form undergo certain mechanisms for medicament release. Various pharmacokinetic and pharmacodynamic parameter

should be taken under consideration before formulating a drug into sustained release dosage form.

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