SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. This article contains the basic information regarding sustained-release drug delivery system.
Key Words: Sustained-release, Advantages And Disadvantages, Designing, Matrix tablet.

INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug-delivery, greater attention has been focused on development of sustained or controlled-release drug-delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist the effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. If one were to imagine the ideal drug-delivery system, two prerequisites would be required, first. It would be a single dose the duration of treatment, whether it is for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body. It is obvious that this imaginary delivery system will have changing requirements for different disease states and different drugs. Thus we wish to deliver the therapeutic agent to a specific site for a specific time. In other words, the objective is to achieve both spatial and temporal placement of drug. Currently, it is possible to only partially achieve both of these goals with most drug-delivery systems[1]. 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. Numerous sustained release oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, and intense research has recently focused on the fabrication of sustained release systems for poorly water-soluble drugs[2].
Sustained release, sustained action, prolonged action controlled release, extended released, depot release are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other sid. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion. In some SR formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface. There are certain considerations for the formation of sustained-release formulation, If the active compound has a long half-life (over 6 hours), it is sustained on its own. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.[3]

Characteristic that makes a drug unsuitable for extended-release formulation:
1. Short elimination half-life,<2 hr
2. Long elimination half-life, >8 hr
3. Narrow therapeutic index
4. Large doses
5. Poor absorption
6. Low or slow solubility
7. Extensive first-pass clearance

Characteristics That Makes Drugs Suitable For Extended- Release Formulation Biological Characteristics [4,5]

1. Biological half life
2. Absorption
3. Metabolism

Biological half life
The usual goal of an oral sustained release 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 (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life (2-8 hr.) are generally are excellent candidate for sustained release formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for sustained release preparation. Compounds with long half-lives, more than hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples of drugs having long life.

Absorption
Since the purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the gastrointestinal tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, sustained release preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio-adhesive materials.

Metabolism
Drugs those are significantly metabolised before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form.

Physicochemical characteristics[4,5]
1. Dose size
2. Ionization, pKa and aqueous solubility
3. Partition coefficient
4. Stability

Drawbacks Of Conventional Dosage Forms
1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index(TI) whenever over medication occur.[6,7]

Advantages Of Sustained Release Formulations Include
1. Uniform release of drug substance over time.
2. Reduction in frequency of intakes.

3. Reduced adverse side effects.
4. Better patient compliance.
5. A sustained release dosage form can be created using lipid excipients to form either a water insoluble matrix or a hydrophobic film around an active drug.[8]

**DESIGNING SUSTAINED-RELEASE DRUG DELIVERY SYSTEM**
Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system[16].

PRINCIPLE OF SUSTAINED RELEASE DRUG DELIVERY
The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.
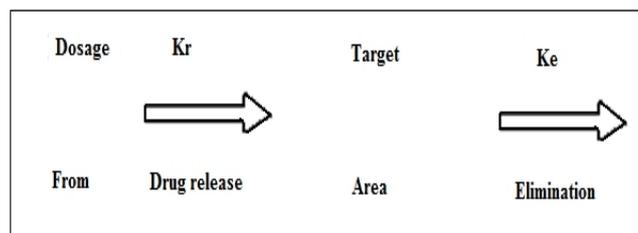
The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This causes the above Kinetic scheme to reduce to the following.
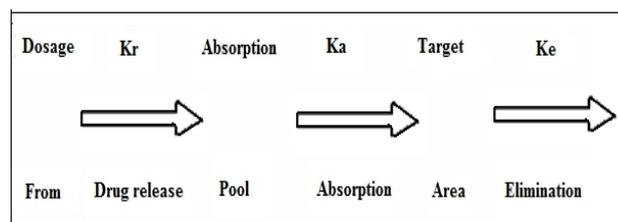
Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed primarily at altering the release rate. The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant

rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

$Kr° = $ Rate in = Rate out = $Ke\ Cd\ Vd$----- (1.1)

Where,

$Kr°=$ Zero-order rate constant for drug release-Amount/time

Ke = First-order rate constant for overall drug elimination-time-1

$Cd=$ Desired drug level in the body - Amount/volume, and

$Vd=$ Volume space in which the drug is distributed-Liters

The value of Ke, Cd and Vd are obtained from appropriately designed single dose pharmacokinetic study. The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theoretically, non zero-order release may be equivalent clinically to constant release in many cases.

Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this being of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system[9,10,11].

DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERYSYSTEMS

Table 1 Parameters for drug selection parameter preferred value

Molecular weight/size	<1000
Solubility	>0.1 mg/ml ph 1 to ph 7.8
Apparent partition coefficient	High
General absorbability	From all GI segments
Release	Should not be influenced by ph and enzyme

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G.I. tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient[11,12,13].

Table 2 Pharmacokinetic parameters for drug selection[11,12]

Parameter	Comment
Elimination half life	Preferably between 0.5 to 8h
Total clearance	Should not be dose dependent
Elimination rat constant	Required for design
Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be required dose size
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Tharapeutic concentration Css av	The lower Css, av and smaller Vd loss among of drug required
Toxic concentration	Apart the value of MTC and MEC,safer the dosage form. Also suitable for drug with very short half life.

MOST WIDELY USED APPROACH TO SUSTAINED DRUG RELEASE

Matrix tablet is one of the most widely approach to sustained the drug release. 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 drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in following table 1, which includes 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[14,15]

Table 3: Examples of two classes of retardant material used to formulate matrix tablet

Matrix Characteristics	Material
Insoluble, inert	Polyethylene, Polyvinyl chloride, Ethyl cellulose
Insoluble, erodible	Carnauba wax, Stearic acid, Polyethylene glycol

Matrix Tablets can be classified as,
1.Hydrophilic Matrix Tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. Figure 2 indicating sequential steps for drug release from sustained release matrix tablet. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrixrequires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug-release behaviour from compressed hydrophilic matrices has been studied by number of investigators.
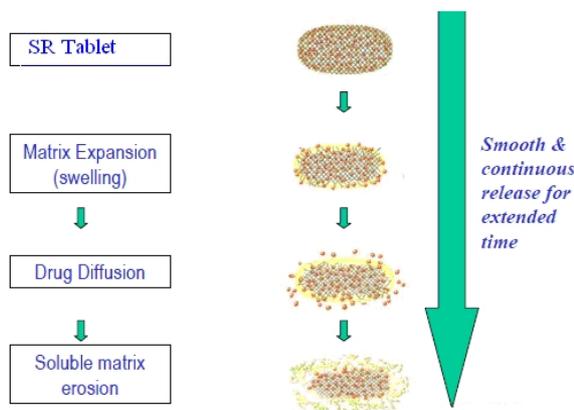

Figure 1: Release mechanism in case of extended release tablet

The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow, Cellulose Derivatives: Hydroxyethyl cellulose, Hydroxypropyl

methylcellulose (HPMC) 100, 4000 and 15000 cps, Sodium carboxymethyl cellulose and Methylcellulose 400 and 4000 cps. Non-Cellulose Natural Or Semisynthetic Polymers: Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and galactose, chitosan and modified starches. Polymers of Acrylic Acid: Polymers which are used in acrylic acid category is Carbopol 934.

Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

2.Fat-Wax Matrix Tablet

The drug can be incorporated into fat-wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix. iii) Plastic matrix tablet (hydrophobic matrices) The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be communicated or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.

2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.

3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. Examples of excipients used to form hydrophobic matrices are Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

CONCLUSION

Wide range of drugs is formulated now in a variety of different per oral extended-release dosage forms. However, only those which result in a significant reduction in dose frequency and/or a reduction in toxicity resulting from high concentration in the blood or gastrointestinal tract are likely to improve therapeutic outcomes. To be a successful extended-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and may be absorbed at a rate and will replace the amount of drug being metabolized and excreted. In a nut shell, sustained-release formulations are a promising way to improve the patient's compliance by reducing dosing intervals and minimizing adverse effects.

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