

Development of Sustained Release Drug Delivery System: A Review

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ABSTRACT

Sustained release drug delivery system can be a major advance toward solving the problem concerning drugs have a short half-life are eliminated quickly from blood circulation require frequent dosing. To avoid this problem, oral sustained release formulations have been developed in an attempt to release the drug slowly into the g.i.t and maintain a constant drug concentration for long period of time. Purpose of review article is designing sustained release drug delivery system is to reduce the frequency of dosing, reduce the dose and provide uniform drug delivery. Present review article compile various formulation approaches for sustained release drug delivery system such as objectives of SRDDS, disadvantages of conventional dosage form, advantages, factors in designing of SRDDS, drug selection, polymers used, models and comparison of dissolution profile, characterization of sustained release tablets.

Key words: Dissolution profile, Gastro intestinal tract, half life, drugs pharmacokinetic, Sustained release drug delivery system,

Introduction

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pellets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s [1]. The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [2,3]. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system.

If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design[4]. Sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of 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 [5]. In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop sustained release dosage forms for many drugs. The primary objective of this system is to ensure safety and to improve efficacy of the drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Pharmacokinetic

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theory suggests that the ultimate method for reducing the plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}) ratio is to have zero-order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists.

Successful commercialization of an extended release formulation is usually challenging and involves consideration of many factors such as physiochemical properties of the drug, physiological factors, and manufacturing variables [6,7].

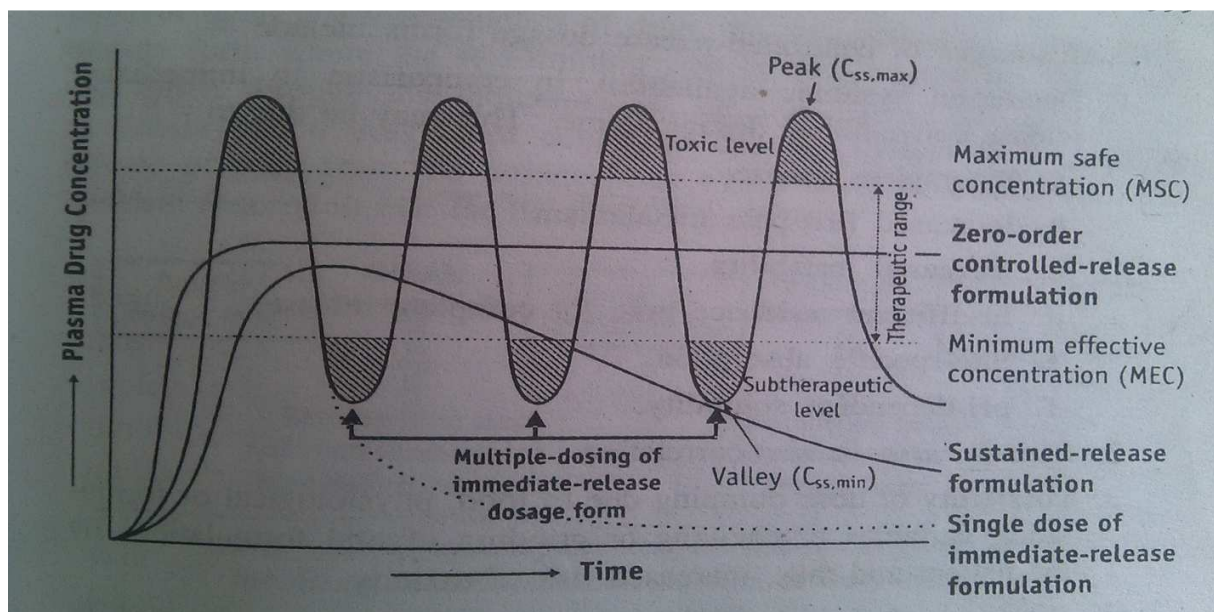


Figure 1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation

Objectives of oral sustained released dosage form

- To maintain the concentration of drug at constant level for a desired period of time.
- To reduce the frequency of doses administrated as compared to conventional dosage form
- It should deliver active entity directly to site of action, minimizing or eliminating side effects.
- This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
- The safety margin of potent drugs can be increased.
- Incidence of both local and systemic adverse side effects can be reduced in sensitive patient [8,9,10,11].

Disadvantages of conventional dosage forms

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur [12,13].

Advantages of sustained release drug delivery system

Clinical advantages

- Patient compliance can be improved.
- Reduction in fluctuation in steady levels and better control of disease condition and reduced intensity of local and systemic side effects.
- Increased safety of margin of high potency of drugs.

- Maximum utilization of drug enabling reduction in total amount of dose.
- Improve therapy cost
- Shorter treatment period
- Lower frequency of dosing [14].

Commercial / Industrial Advantages

- Illustration of innovative /technological
- Leadership
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension[15]

Challenges to sustained release drug delivery

1. Biocompatibility
2. Cost of formulation, preparation and processing
3. Fate of controlled release system if not biodegradable
4. Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers etc [16].

Factors in the designing of sustained release drug delivery systems

A. Biopharmaceutics characteristics of drug in the design of SRDDS

- **Molecular size and diffusivity**
Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10^{-6} - 10^{-9} cm²/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10^{-12} cm²/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.
- **Partition coefficient (P (o/w))**
Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes through biological membrane, if partition co-efficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have

higher partition coefficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

- **Drug pKa and ionization at physiological pH**

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%.

- **Drug stability**

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation [17].

- **Aqueous Solubility**

Most of the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout

the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption. Class III (High solubility- Low permeability) & Class IV (Low solubility- Low permeability) drugs are poor candidates for Sustained release dosage form compound with solubility < 0.1 mg/ml face significant solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation formulation. In general, highly soluble drugs are undesirable for formulation in to a Sustained release product [18].

B. Pharmacokinetic characteristics of drug in the design of SRDDS

- **Absorption rate**
A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug e.g iron.
- **Rate of metabolism**
Drug which is extensively metabolized is suitable for SRDDS as long as the rate of metabolism is not too rapid.
- **Elimination half life**
An ideal SRDDS is of the one from which rate of drug of absorption is equal to the rate of elimination. Smaller $t_{1/2}$, larger the amount of drug to be incorporated in dosage form. Drugs with half life in the range 2 to 4 hours make good candidate for this system e.g propranolol.
- **Dosage form index**

It is define as the ratio of $C_{ss,max}$ to $C_{ss,min}$. since the goal of sustained-release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window.

C. Pharmacodynamic characteristics of drug in the design of SRDDS

- **Dose of drug**
Maximum dose strength for SRDDS is 1gm.
- **Therapeutic range**
Drugs for SRDDS should have a wide therapeutic range [19].
- **Therapeutic index**
Drugs with low therapeutic index are unsuitable for incorporation in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity.
- **Plasma concentration response relationship**
Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system [20].

Drug selection for sustained release drug delivery system

The scientific frame work required for successful development of oral drug delivery system consists of basic understanding of following aspects includes physicochemical, pharmacokinetics and pharmacodynamic characteristics of a drug, anatomical and physiomechanical characteristics of GI track, and physiomechanical characteristics of drug delivery mode of the dosage form to be designed. A number of physicochemical and pharmacokinetic parameters for the selecting of the drug to be formulated in sustained release dosage form which mostly includes the knowledge on the absorption mechanism of the drug form the GI tract [21]. Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system [22].

Table 1. Physicochemical and pharmacokinetic parameters for drug selection

| Parameters | Criteria for drug selection |
|--|--|
| Physicochemical parameters for drug selection | |
| Molecular size | < 1000 Daltons |
| Aqueous Solubility | More than 0.1 mg/ml for pH 1 to pH 7.8 |
| Apparent partition coefficient | High |
| Absorption mechanism | Diffusion |
| General absorbability from all GI segments | Release Should not be influenced by pH and enzymes |
| Pharmacokinetic parameters for drug selection | |

| | |
|--|---|
| Elimination half-life (t_{1/2}) | Between 2 to 8 hours |
| Absolute bioavailability | Should be 75% or more |
| Absorption rate constant (K_a) | Must be higher than release rate |
| Apparent volume of distribution (V_d) | Larger V _d and MEC, Larger will be the required dose |
| Total clearance | Not depend on dose |
| Elimination rate constant | Required for design |
| Therapeutic concentration (C_{ss}) | The lower C _{ss} and smaller V _d , the loss among of drug required. |
| Toxic concentration | Apart the value of MTC And MEC safer the dosage for |

Types of polymer

Since the structural and physicochemical characteristics of the polymer are decisive in the drug release mechanism, some will be more suitable than others, depending on the aim pursued and the drug desired [23,24].

Hydrophilic polymers

a) Cellulosic

- Methylcellulose
- Hydroxypropylmethylcellulose (Hypromellose, HPMC)
- Hydroxypropylcellulose (HPC)
- Hydroxyethylcellulose (HEC)
- Ethylhydroxyethylcellulose (E-HEC)
- Sodium carboxymethylcellulose (Na-CMC)

b) Non-cellulosic

- Sodium alginate
- Xanthan gum
- Carrageenan
- Chitosan
- Guar gum
- Pectin
- Cross-linked high amylose starch
- Polyethylene oxide
- Homopolymers and copolymers of acrylic acid

Hydrophobic polymers

- Ethylcellulose
- Hypromellose acetate succinate
- Cellulose acetate
- Cellulose acetate propionate
- Methacrylic acid copolymers
- Polyvinyl acetate

MODELLING AND COMPARISON OF DISSOLUTION PROFILE

Several theories and kinetic models were described the drug release characteristics of immediate release and modified release dosage forms, by using dissolution data and quantitative interpretation of values obtained

in dissolution assay if facilitated by the usage of the generic equation dosage form that mathematically translates the dissolution curve in function of some parameters related with pharmaceutical dosage form. In the present work, some analytical models were used to study the mechanism of drug release of extended release by following models

Zero order

It is ideal method of drug release in order to achieve a pharmacological prolonged action. Drug dissolution from pharmaceutical dosage form that doesn't disaggregates and release the drug slowly can be represented by the following equation

$$Q_0 = Q_0 + K_0 t$$

Where

Q_t = amount of drug released in time t

Q₀ = initial amount of drug in solution

K₀ = zero order release constant

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\ln(1-Q) = -K_1 t$$

Where, Q is the fraction of drug released at time t and k₁ is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = K_2 t^{1/2}$$

Where, K₂ is the release rate constant. A plot of the fraction of drug released against square root of time

will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Power Law

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas's and Korsmeyer equation (Power Law).

$$M_t/M_\alpha = K t^n$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α , thus the M_t/M_α is the fraction of drug released at time t , k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppas's and Korsmeyer equation and the slope of this plot represents "n" value (diffusion coefficient) which describes mechanism of diffusion [25].

Hixson-Crowell model

Hixson-Crowell (1931) recognising that particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where

W_0 is the initial amount of drug in the pharmaceutical dosage form

W_t is the remaining amount of drug pharmaceutical dosage form at time t

K_s is the constant incorporating the surface volume relation [26].

Characterization of sustained release tablets

Before marketing a sustained release product, it can be evaluated and characterized by using different parameters including in vitro, ex vivo and by in vivo (Clinical) procedures, and it is must to assure the strength, safety, stability and reliability of a product. A number of techniques have been used to characterize SRDDS and determine the various feasibility or flexibility of their formulation process. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

- **Pre and post compression parameters :** Most widely used parameters are bulk density, tapped density, compressibility index, hausner ratio, total porosity, flow rate, angle of repose, hardness, friability, weight variation test and uniformity of drug content etc.

In-Vitro Methods

The various types of methods used are beaker, rotating disc, rotating bottle, rotating basket, stationary basket, oscillating tube, dialysis and USP dissolution method.

In-Vivo Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are clinical response, blood level data, urinary excretion studies, nutritional studies, toxicity studies and radioactive tracer techniques.

- Stability Studies
- In vitro- In vivo Correlation (IVIVC)
- Bioavailability Testing
- In vitro drug release characterization models: Mathematical Models .The various types of modals used are zero order release kinetics, first order release kinetics, Higuchi model, Hixson-Crowell cube root law and Korsmeyer-Peppas model [27].

Conclusion

There are several reasons for attractiveness of sustained release drug delivery system, provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. From the above discussion, we can concluded that development of SRDDS depend upon various factors such as Biopharmaceutics, Pharmacokinetic and Pharmacodynamic characteristics of drug. Sustained release formulations are a promising way to improve the patient compliance by reducing dosing interval and minimizing adverse effect.

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List of abbreviations

SRDDS – sustained release drug delivery system

g – gram

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