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Review Article

Dosage from design of sustained release drug delivery systems: An overview

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ABSTRACT

Aim: In Oral drug delivery is the most prefer and convenient option as the oral route provides most active surface area among all drug delivery system for administration of different drugs. Frequently conventional dosage form produces extensive range of fluctuation in drug concentration in the bloodstream and tissues with consequent unwanted toxicity and poor efficiency. The maintenance of concentration of drug molecules in blood plasma within therapeutic index is very critical for efficient treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption direct to the concept of oral sustained release dosage formulations. **Methodology:** Various reports were taken from review or research articles and other online available literature. **Conclusion**: In this review articles covers all the biopharmaceutical and physiochemical factors of formulation and development of sustained release dosage forms, which gives idea for selection of drug molecules to develop of sustained release dosage formulation successfully.

Keywords: Sustained release drug delivery system, Controlled release drug delivery system, Biopharmaceutics.

Introduction

Over the past 30 years, with related respect of the therapeutic advantages of sustained drug delivery, greater attention is being paid on the development of oral sustained or controlled drug delivery systems [John et al., 2002]. There are several reasons for the pleasant appearance of these dosage forms. The goal of designing sustained release dosage forms is to reduce the frequency of the dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery [Robinson et al., 1987].

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Sustained release (SR) dosage forms are designed to release an initial therapeutically effective amount of a drug followed by maintaining this efficient level over an extended period of time. This is achieved by aim approaches. The advantages of sustained release dosage forms include maintenance of therapeutic effect for a longer time, reduced frequency of administration, and enhanced patient compliance. The hydrophilic polymer matrix is widely used for formulating a sustained release dosage form. The role of sustained release dosage forms is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma [Lee et al., 1987].

The immediate release (IR) drug delivery system lacks some features like dose continuation, sustained release rate & site targeting. The oral sustained drug dosage has some potential advantage like sustained release rate & dose

maintenance in plasma. The SR dosage forms have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.

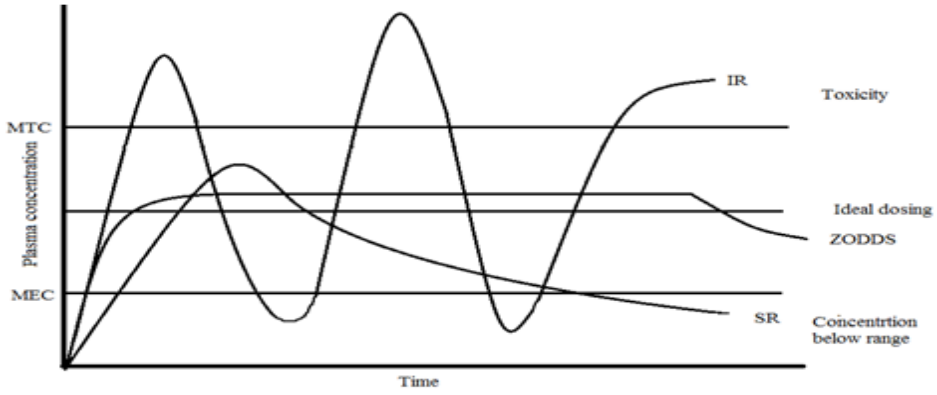

Figure: 1. shows the relation between plasma concentration verses time

The conventional or normal dosage form requires regular delivery of doses. It can overshoot or undershoot the therapeutic window, reducing not only the effectiveness of the drug but also easily creating side effects. An ideal sustained drug dosage forms should be able to maintain plasma concentration of the drug over an extended period of time. Sustained-release dosage forms developed so far mimic zero-order release through a slow first release. On the other hand, a controlled release dosage forms delivers bioactive agent at a controlled rate for an extended period of time. Properly designed, it will provide steady-state drug delivery within the therapeutic window. Normally, it follows zero-order kinetics. It may also target drug action by spatially targeting the drug at the site. Figure shows a hypothetical plasma concentration outline of the drug versus time for conventional, controlled, and sustained drug delivery techniques [Ho WH et al., 1987].

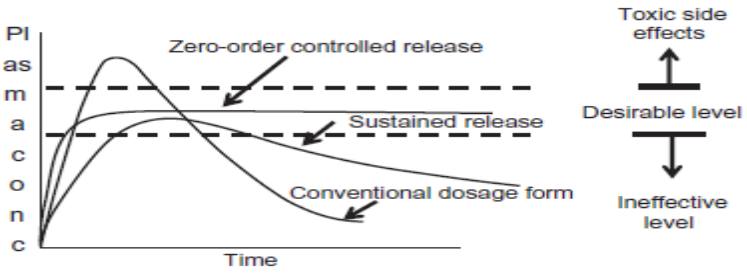

Figure 2: Plasma drug concentration versus time for zero-order controlled release, sustained release and release from conventional dosage forms

a. Advantages of Sustained release drug delivery dosage forms over the conventional dosage form

a) Since the frequency of drug administration is reduced, patient compliance can be improved, and drug administration can be made more convenient as well.
b) The blood level variation characteristic of multiple dosing of conventional dosage forms is reduced.
c) In addition, better control of drug absorption can be attained, since the blood level peaks that may be observed after administration of a dose of a high-availability drug can be reduced by sustained release dosage forms.
d) The safety margin of high-potency drugs can be increased, and incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

e) Overall, administration of sustained release forms enables increased reliability of therapy.

b. Disadvantages sustained release dosage forms

a. Administration of sustained release dosage forms does not permit the prompt termination of therapy. Immediate changes drug need during therapy, such as might be encountered if considerable adverse effects are noted, cannot be accommodated.
b. The physician has less elasticity in adjusting dosage regimens. This is fixed by the sustained release drug delivery systems.
c. Economic factors must be assessed since more costly processes and equipment are involved in manufacturing many sustained release dosage forms [Jain et al., 1997].

Factors affecting dosage from design of controlled and sustained release drug delivery systems

The fundamental rational of a controlled and sustained release drug delivery systems (SRDDS) is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of the drug in such a way that its efficacy is maximized through decrease in side effects and cure or control of diseases condition in the shortest feasible time by using smallest quantity of drug, administered by the most appropriate route.

A. Biopharmaceutic characteristics of a drug in the design of CRDDS and SRDDS

The performance of a drug existing as a sustained release system depends upon its:

a. Release from the dosage forms
b. Movement within the body throughout its passage to the site of action [Shukla AK et al., 2017].

The former depends upon the fabrication of the formulation and the physiochemical properties of the drug molecules while the latter element is depend upon pharmacokinetics properties of drug. In comparison to conventional or normal dosage from, where the rate-limiting step in drug availability is usually absorption through the biomembrane, the rate determing step in the release of drug from sustained release system is the rate of release of drug from the dosage from which is much lesser than the intrinsic absorption rate for the drug molecules.

The type of delivery system and the route of administration in sustained release formulation depend upon the physicochemical properties of the drug molecules and its biopharmaceutic characteristics. The desired biopharmaceutic properties of a drug to be used in a sustained release drug delivery system are discussed under [Brahmankar et al., 2015].

a. Molecular weight of the drug molecules

Lesser the molecular weight, faster and more complete the absorption. For drugs absorbed by pore transport mechanism based, the molecular size threshold is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. However, more than 95% of drugs molecules are absorbed by passive diffusion. Diffusivity, defined as the capacity of a drug to diffuse through the membranes surface, is inversely related to molecular size of drug. The upper limits of drug molecular size for passive diffusion are 600 Daltons. Drugs with large molecular size are poor candidates for oral sustained release dosage formulations e.g. peptides and proteins.

b. Aqueous solubility of the drug molecules

A drug with good aqueous solubility, particularly if pH independent serves as a good candidate for the formulation of sustained release dosage forms. The lower limit of solubility of a drugs molecules to be formulated as SRDDS is 0.1mg/ml. Drugs with pH dependent aqueous solubility e.g. phenytoin, or drugs with solubility in non-aqueous solvents e.g. steroids, are suitable for parenteral (e.g. i.m. depots) sustained release dosage formulations since. Upon injection, the drug precipitates at the injection site and its

release is slowed down due to change in pH or contact with aqueous body fluids. Solubility of drug molecules can limit the choice of mechanism to be employed in CRDDS or SRDDS, for example, diffusional systems are not appropriate for poorly soluble drugs. Absorption of poorly water soluble drugs is dissolution rate-limited which means that the sustained release device does not control the absorption process; hence, they are poor candidates for such dosage forms.

c. Apparent partition coefficient/lipophilicity of the drug of molecules

Higher the apparent partition coefficient of a drug molecules, greater its lipophilicity and thus, greater is its rate and extent of absorption. Such drugs have improved tendency to cross even the more selective barriers like BBB. The apparent volume of delivery of such drugs also increases due to increased portioning into the fatty tissues and since the blood flow rate to such tissues is always lesser than that to an aqueous tissue like liver, they may show characteristics of models having two or more compartments. The parameter is also significant in determining the release rate of a drug from lipophilic matrix or device.

d. Drug pKa and ionization at physiological pH

The pKa range for acidic drug molecules whose ionization is pH sensitive is 3.0 to 7.5 and that for basic drugs is 7.0 to 11.0. For optimum passive absorption, the drug molecules should be non-ionised at that site at least to an extent 0.1 to 5%. Drugs existing largely in ionized forms are poor candidates for sustained release dosage formulations e.g. hexamethonium.

Lipophilicity of drug, expressed as log P.

Polarility of drug molecules which is measured by the number of H-bond acceptors and number of H-bond donors.

Molecular size of drug.

The influence of these properties has been discussed earlier.

e. Drug stability

Drugs which are unstable in GI environment, that drug cannot be administered as oral sustained release formulation because of bioavailability problems like nitroglycerine. A different route of administration should then be preferred such as the trans-dermal route. Drugs unstable in gastric pH like as propantheline can be designed for sustained delivery in intestine with limited or no delivery in stomach. On the other hand, a drug unsteady in intestine like probanthine can be formulated as gastro retentive dosage form.

f. Mechanism and site of absorption of drug

Dogs which are absorbed by carrier mediated transport processes and those absorbed through a window are poor candidates for sustained release dosage forms like several B vitamins.

1.1.3 Biopharmaceutical aspects of route of administration

Oral and parenteral (i.m) routes are the mainly popular followed by trans-dermal application. Route of minor importance in sustained dosage forms are buccal/sublingual, rectal, nasal, ocular, pulmonary, vaginal and intrauterinal. The desirable characters for a drug to be given by a particular route are discussed under.

a. Oral route

For a drug to be successful as oral sustained release dosage forms, it must get absorbed through the entire length of GIT. Since the main limitation of this route is the transit time (a mean of 14 hours) the period of action can be extended for 12 to 24 hours. The route is suitable for drugs given in dose as high as 1000 mg. A drug, whose absorption is pH dependent, destabilized by GI fluids/enzymes, undergoes widespread pre-systemic metabolism (e.g. nitroglycerine), influenced by gut motility, has an absorption window and/or absorbed activity (e.g. riboflavin), is a poor candidate for oral sustained release systems.

b. Intramuscular/subcutaneous routes

These routes are appropriate when the duration of action is to be prolonged from 24 hours to 12 months. Only a small quantity of drug, about 2 ml

or 2 grams, can be administered by these routes. Factors significant in drug release by such routes are solubility of drug molecules in the surrounding tissues, molecular weight, partition coefficient and pKa of the drug and contact surface between the drug and the surrounding tissues.

c. Transdermal route

The route is best suitable for drugs performance widespread first pass metabolism upon oral administration or drugs with low dose such as nitroglycerine. Important factors to be measured for percutaneous drug absorption are partition coefficient of drug, contact area, skin condition, skin permeability of drug, skin perfusion rate etc.

In short, the main determinants in deciding a route for management of sustained release dosage forms are physicochemical properties of the drug, dose size, absorption efficiency and preferred duration of action.

B. Pharmacokinetic characteristics of a drug in the design of CRDDS

Detail knowledge of the ADME characteristics of a drug molecule is essential in the design of a sustained release dosage forms. An optimum range of a given pharmacokinetic parameter of a drug is needed beyond which sustained delivery is difficult or impossible.

a. Absorption rate

For a drug to be administered as sustained release dosage, its absorption must be proficient since the desired rate-limiting step is rate of drug release Kr<< Ka. A drug which having low absorption window is a poor candidate for such dosage forms since uninterrupted release will results in a pool of unabsorbed drug like iron. Water soluble but poorly absorbed potent drugs like decamethonium are also unsuitable candidates since a slight difference in the absorption may precipitate potential toxicity.

b. Elimination half life

An ideal SRDDS is the one forms which rate of drug of absorption (for extended period of time) is equivalent to the rate of elimination. For drugs with $t_{1/2}$ less than 2 hours, a very large dose may be needed to maintain the high release rate. Drugs with half life in the range 2 to 4 hours make good candidates for sustained release drug delivery systems e.g. MAO inhibitors; the duration of action is longer than that predicted by their half lives. A candidate's drug should have t ½ that can be correlated with its pharmacological response. In terms of MRT, considerably longer than that from conventional dosage forms.

c. Rate of metabolism

A drug which is widely metabolized is suitable for sustained release systems as long as the rate of metabolism is not too fast. The extent of metabolism should be equal and predictable when the drug is administered by different routes. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a invention since steady-state blood levels would be difficult to maintain.

d. Dosage form index

It is defined as the ratio of Css, max to Css, min. Since the purpose of sustained release dosage forms is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels inside the therapeutic window, ideally, its value should be as close to one as possible.

Pharmacodynamic characteristics of a drug in the design of SRDDS

a. Drug dose

In common, dose strength of 1.0 gram is considered maximum for a SRDDS.

b. Therapeutic range

A candidate drug for sustained release dosage forms should have a therapeutic range wide enough such that variations in the release rate do not results in a concentration beyond this level.

c. Therapeutic index

The release rate of a drug with narrow therapeutic index must be like as that the plasma concentration attained is within the therapeutically safe and effective range. This is essential because such drugs have toxic concentration closer to their therapeutic range. Precise control of release rate of a potent drug with narrow border of safety is

difficult. A drug with short half life and narrow therapeutic index should be administered more regularly than twice a day. One must also considered the activity of drug metabolites since prohibited delivery system controls only the release of potent drug but not its metabolism.

d. Plasma concentration response (PK/PD) relationship

Drugs such as reserpine whose pharmaceutical activity is independent of its concentration are poor candidates for sustained release dosage forms.

Market opportunities of sustained release dosage forms

The global market for better drug delivery systems amounted to $134.3 billion in 2008 and was projected to increase to $139 billion in 2009. The estimate for 2014 is $196.4 billion, for a compound annual growth rate (CAGR) of 7.2% in the 5-year period. drug delivery, which reached $50.9 billion in 2009 and is expected to increase to $80.2 billion in 2014, for a CAGR of 9.5%.Sustained-release dosage forms have the second-largest market share, with estimated sales of $36.1 billion in 2009 and $45.8 billion in 2014, for a CAGR of 4.9%. Sustained release dosage forms reduce frequent dosing and thus better compliance reduces variations in plasma/blood levels for more consistent result [Sampath et al., 2010].

Application of natural polymers in controlled and sustained drug delivery system

Protein, enzymes, muscle fibers, polysaccharides and gummy exudates are the natural polymers being used effectively in formulating the variety of pharmaceutical dosage forms. The well-known natural polymers used in pharmacy and others fields such as chitosan, carrageenan, acacia, agar, gelatin, shellac, guar gum, xanthan gum, tamarind gum, Fenugreek gum and locust bean gum etc. [Patel et al., 2011, Shukla et al., 2018, Shukla et al., 2017]

Selection of natural polymers depends upon the nature of formulations, for example in sustained and controlled drug delivery system; the water-soluble drugs (model drugs) release rate can be persistent by cross-linking natural gum method. These cross-linked gums are reported to have better control on drug release [Vyas and Khar et al., 2002]

In oral drug delivery dosage forms, hydrophilic matrices have been used since a long time to control the drug release. A number of natural and modified polysaccharides have been used in sustained release dosage forms by various researchers.

Conclusions

The sustained release drug delivery formulation aims to release the drug at the desired rate over extensive period of time to maintain the therapeutic level in blood plasma. Currently, the oral route of administration for sustained release drug delivery system has received more awareness due to its less flexibility, reduced dosing frequency and better patient compliance. The design of oral sustained release drug delivery system depends on various factors such as, physic-chemical properties of drug, type of delivery system, disease being treated, patient condition, and treatment duration, presence of food, gastrointestinal motility and co-administration of other drugs. We can conclude that the sustained release drug delivery system is very supportive in increasing the efficiency of the dose as well as the patient compliance. Moreover; the reasonable cost of oral sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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