Journal of Integral Sciences [JIS]

[An International Open Access Journal]

Available at www.jisciences.com ISSN: 2581-5679

A COMPREHENSIVE REVIEW ON SUSTAINED RELEASE TABLETS

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Received: 25 Aug 2023 Revised: 15 Sep 2023 Accepted: 25 Nov 2023

Abstract

Sustained release is a method to reduce therapeutic drugs side effects by preventing the therapeutic concentration of the drug from fluctuating in the body. Sustained release is used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic drug so that it remains in the systemic circulation for prolonged time and its plasma profile is sustained in duration. Sustained release drug delivery system has been formulated in form of tablets to slow down release of drug from tablets. It works on various mechanisms to control the release rate of drugs. Formulation approaches that have been utilized are drug dissolution, drug diffusion, matrix erosion. Present review work deals with the different aspect of the sustained release tablets.

Keywords: Sustained release, tablets.

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DOI: https://doi.org/10.37022/jis.v6i4.65

Produced and Published by
South Asian Academic Publications

Introduction

The aim of any delivery system is to treat disease by providing therapeutic drug to the site of action. Another aim of delivery system is to maintain steady state blood level for a long period of time without reaching toxic range [1, 2]. But available conventional dosage forms offers following limitations:

1- Poor bioavailability
2- High first-pass metabolism
3- Fluctuations in plasma drug level
4- Rapid excretion
5- Frequent dosing
6- Dose dumping

However these limitations can be overcome by sustained release delivery system which is a novel drug delivery system. Most commonly used and easily accessible dosage form is tablets. Thus sustained release tablets become a subject of interest [3, 4].

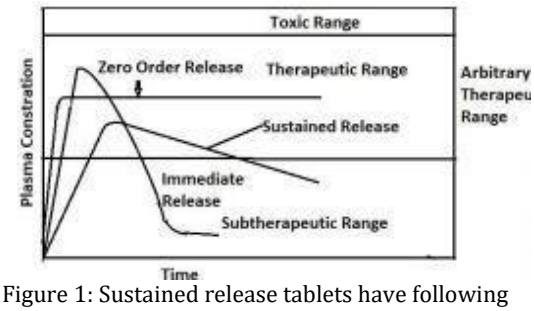

Figure 1: Sustained release tablets have following advantages:

1) **Patient compliance-** Success of treatment depends upon patient ability to stick to the treatment regimen in case of chronic diseases. Various factors affecting patient compliance are: knowledge about disease process, patient confidence, understanding of patient about treatment plan and adherence to treatment schedule. This problem can be solved by administering sustained release drug delivery systems [5].
2) **Reduced plasma level fluctuations-** Drug level in blood plasma fluctuates and shows see-saw pattern in case of conventional delivery system. The magnitudes of these fluctuations are affected by drug kinetics such as absorption, distribution, elimination and dosing intervals. A well designed sustained release drug delivery system reduce the frequency of drug dosing maintains steady drug concentration in blood and target tissue cells [6].
3) **Total dose reduction-**To treat a diseased state less amount of drug is required in case of sustained drug delivery systems. By reducing the total amount of

drug, decrease in side effects are observed [7].

4) **Improved deficiency in treatment**- Ideal treatment of disease requires effective distribution of drug to the tissues, organs that need treatment. Very often doses in excess amount are required in order to achieve the therapeutically effective concentration. This may lead to toxicological, undesirable effects in non-target cells. A sustained release dosage form leads to better management of acute or chronic diseases [8].
5) **Economy**- The average cost of treatment over a prolong period of time may be less [9].

Disadvantages of sustained release tablets [10, 11]:

1. Highly expensive.
2. Need for additional patient counselling and education.
3. Dose dumping
4. Often poor *in vivo-in vitro*
5. Correlation it does not allow for quick end to therapy.

Drugs unsuitable for sustained release tablets:

a) Not well absorbed in lower intestine e.g. riboflavin and ferrous salt
b) Having short biological half-life (<1 hr) e.g. Penicillin G [12].
c) Long biological half- life (>12hrs) e.g. diazepam and phenytoin
d) Large dose required e.g. >1gm sulphonamide.
e) Cumulative action and desirable side effects with low therapeutics index e.g. digitoxin [13].

Characteristics of Drug Suitable for sustained release tablets

The ideal physiochemical and pharmacokinetic properties for drug suitable for sustained release tablets are:

Table 1: Physiochemical Properties for drug selection

Parameters	Criteria
Molecular size	<1000Daltons
Aqueous solubility	More than 0.1 mg/ml for pH 1 to 7.8
Apparent Partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from G.I. segments	Release should not be affected by pH and enzymes

Table 2: Pharmacokinetic Properties for drug selection

Parameters	Criteria
Elimination half-life	Between 2 to 8 hrs
Absolute bioavailability	Should be 75 % or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution(Vd)	Larger Vd and MEC,larger dose required
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration(Css)	Lower Cs and Vd, less amt. of drug required
Toxic concentration	Apart the value of MTC and MEC safer the dosage form

1- Diffusion sustained system

Diffusion is a process of movement of drug molecules from a region of high concentration to a region of low concentration. The flux of drug J across a membrane in the direction of decreasing concentration is given by fick's law14.

J= -D dc/dx

D= diffusion coefficient in area /time Dc/dx= change in concentration 'c' with distance 'x'

1.1) Diffusion reservoir system

In this system, a water insoluble polymer covers a core of drug. Drug partitions into the membrane and get exchanged with surrounding fluid15.

1.2) Diffusion matrix system

A drug is distributed into insoluble matrix. Composite of a drug or more drugs with gelling agent i.e. hydrophilic polymers. Matrix system is mostly used for prolonged and controlled release of drugs17. The release rate can be given by –

Release rate = AD/L = (C1-C2) A=Area

D= diffusion coefficient L=diffusion path length

C1= drug concentration in core

C2= drug concentration in surrounding medium

drug in GI medium by incorporating the drug into insoluble polymer and coating the drugs with polymers of varying thickness. The two types of dissolution sustained systems are:

2.1) Soluble matrix system

Drug is dispersed in a rate controlling medium. The rate of dissolution is controlled by:

- Decreasing wettability of tablet
- Changingfluid penetration by changing porosity

Slow dissolution rate of polymer

Types of diffusion matrix tablets a) Hydrophilic matrix tablet

These are also called swellable systems as they use polymers (HPMC, alginates) which swell in contact with aqueous solution and a Soluble reservoir system.

2.2) gel layer is formed on the surface. The drug

release is controlled by a gel diffusion barrier and erosion [18].

b) Hydrophobic Matrices (Plastic Matrix tablet)

The active drug is dispersed in a tablet with porous skeletal structure, prepared by direct compression of drug with plastic material

e.g. polyethylene, PVC. Such types of tablets become inert in presence of water and gastrointestinal fluid [19].

c) Lipid matrix tablets

These matrices are prepared by lipid waxes

e.g. carnauba wax with stearyl alcohol. Drug release occurs through pore diffusion or erosion.

d) Mineral matrices

It involves polymers obtained from seaweeds like alginic acid.

2) Dissolution Sustained systems Dissolution-

controlled release can be obtained by slowing the dissolution rate of Drug is coated or encased with erodible coat of varying thickness which slowly dissolves in contact with GI fluid.

3) Method using Ion exchange

It is based on formulation of a drug-resin complex. The drug in this complex is exchanged in GI tract and released when there is excess of Na+ and Cl-. In this system, an insoluble cross linked polymer is used20.

4) Method using Osmotic pressure

A semi permeable membrane with orifice 0.4mm surround the drug core and osmotically active substances to allow water to enter the tablet. When exposed to GI fluids, water flows under influence of osmotic force and drug is release.

5) pH dependent formulations

This system is designed for acid-labile drugs or drugs irritating GIT mucosa or drugs for intestinal targeted delivery. Iinvolves coating the drug core with combination of intestinal insoluble porous polymer (ethyl cellulose) and intestinal soluble polymer (HPMC). The polymer not dissolved in stomach pH but dissolves at intestinal Ph [21].

6) Altered density formulations

The residence time of drug in GIT can be increased by altering the density of drug particles22.

6.1) High density approach

The density of GI fluid is about 1.4g/cc so drug particles having density greater than GI fluid are used for this purpose. Iron oxide and barium sulfate is used [23].

6.2) Low density approach

These pellets have density lower than GI fluids and tends to float in gastric juices for an extended period of time. Example- drug with hydrogel like HPMC that swell and its density gets lower than 1.

Factors affecting sustained release tablets

A) Physiochemical Factors

1) Dose size

Maximum dose considered maximal for sustained release dosage forms is 0.5-1g [17].

Compounds having large dosing size can sometimes be given in multiple amounts or formulated into liquid systems.

2) Ionization, pKa and aqueous solubility Most drugs are weak acids or bases and for a drug to cross lipid membrane it should be in unchanged form, therefore pKa of drug is important. Delivery systems depending on diffusion or dissolution will depend on solubility of drug in aqueous media [11].

3) Partition coefficient

The drug must cross biological membranes to produce a therapeutic effect. Drugs which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and retards in tissues. It is difficult to penetrate lipid membranes for drugs having low partition coefficient and results in poor bioavailability. The choice of diffusion- limiting membranes depends on partitioning characteristics of drug [7].

4) Stability

The drug which are orally administered are subjected to both hydrolysis and enzymatic degradation. Compounds that are unstable in small intestine shows low bioavailability when administered from sustaining dosage form [9].

B) Biological factors

1) Absorption

The release rate of drug must be slower than
rate of absorption. If a drug is absorbed by active transport or transports to specific region of intestine, sustained release preparation may be disadvantageous8.

2) Metabolism

Drugs are metabolized before absorption, thus decreases bioavailability. The release of drug is at slower rate, less metabolism of drug before absorption [12].

3) Biological half-life

For a drug to be a suitable choice for sustained release must have a short-life [18].

4) Margin of safety

Drugs that have large therapeutic index are suitable for sustained release formulations [18].

Evaluation Test for sustained release tablets

Thickness and Diameter

Micrometer screw gauge is used for determining thickness and diameter of tablets [19].

Weight Variation

Average weight of twenty tablets is calculated and compared with weight of one tablet. It is an important aspect for quality control as all tablets must be of uniform weight in one batch.

Hardness test

Monsanto hardness tester is used to determine hardness of tablets [20].

Friability

Roche friabilator is used to determine friability of tablets at 25rpm for 4 min [8].

Content uniformity

The uniformity of drug content is determined by dissolving tablet in a suitable solvent of pH 7.4 phosphate buffer and analyzing sample in UV spectrophotometer [14].

***In-vitro* dissolution test**

Rotating Paddle apparatus is generally used to determine drug release. The amount of drug released in dissolution media is determined using UV spectrophotometer at specific time periods. A graph of percent release of drug versus time is plotted [9].

***In-vivo* methods**

After achieving desired in-vitro results, *in- vitro in-vivo* correlation becomes important.

Various in-vivo evaluation techniques employed are:

- Clinical response
- Blood level data
- Urinary excretion
- Toxicity studies

Table 3: List of Marketed Sustained release formulations

BRAND NAME	DRUG	MANUFACTURER
A-Fenac SR	Diclofenac sodium	ACME laboratories Ltd.
Anafelx SR	Naproxen sodium	ACI Limited
Anril SR	Nitroglycerine	Square Pharmaceutical Ltd.
Arofil SR	Theophylline	Incepta Pharmaceuticals Ltd.
Bucod SR	Butamitrate citrate	Sharif Pharmaceuticals Ltd.
Cardizem SR	Diltiazem HCl	Drug International Ltd.
Dia M SR	Metformin HCl	Medimet Pharmaceuticals Ltd.
Lithin SR	Lithium Carbonate	Albion laboratories Ltd.
Sultion SR	Salbutamol	Square Pharmaceutical Ltd.
Zybex SR	Bupropion HCl	Beximco Pharmaceutical Ltd.
Ofuran SR	Nitrofurantoin	Pacific Pharmaceutical Ltd.

Conclusion

This review article focuses on the formulation of sustainedrelease tablets and the efficacy of the dosage form in producing the desired therapeutic response, as well as problems associated with traditional dosage forms. The Sustained release tablets have been very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. The design of Sustained release tablets depends on various factors like, physicochemical properties of drug. From the above discussion, we can conclude that Sustained release tablets is replacing oral conventional drug delivery system.

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