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Review on Matrix Tablets as Sustained Release

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ABSTRACT

Among all drug delivery system, oral drug delivery is the most preferred route of administration of various drug. Sustained release products provide advantage over conventional dosage form by optimizing biopharmaceutics, pharmacokinetics and pharmacokinetics properties of drug. Thus, sustained release formulation provides important way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Sustained Release is also providing promising way to decrease the side effect of drug bye drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The release of the drug through such system includes both dissolutions controlled as well as diffusion-controlled mechanism, most of drugs, if not formulated properly, may readily the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. This article contains the basic information regarding sustained release formulation and also the different types of the same Key words: Matrix tablets, Sustain release polymers, Patient convenience and compliance.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other route[1].The terms Sustained release ,prolonged release, modified release, extended release or depot formulations are used to identify drug delivery system that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.[1]

The oral route of administration for sustained release system has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery system 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 drug.

Sustain release system include any drug delivery system that achieves slow release of drug over an extended period of time.[1]

DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS

1. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

2. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur.

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

4. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.[5]

ADVANTAGES OF SRDDS

Following are some advantages of SRDDS.

Clinical Advantages 9,10,11,12 [5]

I. Reduction in frequency of drug administration

II. Improved patient compliance

III. Reduction in drug level fluctuation in blood

IV. Reduction in total drug usage when compared with conventional therapy

V. Reduction in drug accumulation with chronic therapy

VI. Reduction in drug toxicity (local/systemic)

VII. Stabilization of medical condition (because of more uniform drug levels)

VIII. Improvement in bioavailability of some drugs because of spatial control IX. Economical to the health care providers and the patient Commercial advantages [17]

Commercial Advantages|13|[5]

I. Product life-cycle extension

II. Product differentiation

III. Market expansion

IV. Patent extension

DISADVANTAGES OF SRDDS,15,16,17) [5]

Following are some disadvantages of SRDDS:

I. Delay in onset of drug action.

II. Possibility of dose dumping in the case of a poor formulation strategy.

III. Increased potential for first pass metabolism

IV. Greater dependence on GI residence time of dosage form.

V. Possibility of less accurate dose adjustment in some cases. VI. Cost per unit dose is higher when compared with conventional doses.

VI. Not all drugs are suitable for formulating into ER dosage form.

VII. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass

metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

VIII. Poor In vitro In vivo correlation.

IX. Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersentivity reactions.

X. Reduced potential for dose adjustment of drugs normally administered in varying strength.

IDEAL PROPERTIESOF Drug Suitable of Srdds[18][5]

I. It should be effectively absorbed by oral route and stable in gastro-intestinal (GI) fluid.

II. Drugs that have short half-lives (2-4 hrs) are ideal drug candidate for formulation into SR dosage forms e.g.Captopril, Salbutamol sulphate.

III. The dose of drug should not be less than 0.5gm and maximum dose of drug for designing SRDDS is 1.0 gm e.g Metronidazole.

IV. The therapeutic range of the drug should be high in SRDDS for drug should have wide therapeutic range enough such that variation in the release does not result in concentration beyond the minimum toxic levels.

Challenges of Srrds 19,20[5]

Dose dumping

This can greatly increase the concentration of a drug in the body and there by produce adverse effects or even drug induced toxicity. Dose dumping means the relatively large quantity of medication in a sustained release formulation is slowly released. If the dose dumping can leads 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 case of conventional dosage forms, the dose adjustments are much simple e.g., tablet can be divided into two portions. In case of sustained release dosage forms, this can appear to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor in-vitro-in-vivo correlation

sustained release dosage form, theIn rate of drug release is slowly reduced to achieve drug release possibly over a large region of gastrointestinal tract. Hence it is so called as 'Absorption window' becomes important and give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

Patient variation

The time period required for absorption of drug released from the dosage form may vary among individuals. The coadministration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Criteria For Selection of Srdds [22,21] [5]

Following is the criteria of SRDDS;

Desirable half-life

The half-life time of a drug in the body has a residence time of index. Drug has a short half-life time in the dosage form may contain a large quantity of the drug. The drugs have elimination half-life of eight hours are sufficiently sustained in the body.

High therapeutic index

In the sustained release formulation drugs with low therapeutic index are unsuitable for incorporation. Dose dumping may occur due to the system fails in the body that leads to fatalities. e.g Digitoxin.

Small dose

In the conventional dosage form, if the dose of a drug is high then its suitability as a candidate for sustained release is seriously undetermined. This is important because the size of a unit dose sustained release formulation would become larger, to administer without difficulty.

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physicochemical factor [5]

Dose size

In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form.

Ionization, pka and aqueous solubility

Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Low soluble Compounds (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

Partition Coefficient

To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefor the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability.

Stability

The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms

that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.

Biological factor [5]

Half-life

The half-life of a drug is an index of its residence time in the body. If the drug has short half life(less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage from and Sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system.

Therapeutic index

If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty.

Absorption window: Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the absorption window'. These candidates are also not suitable for SRDDS.

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.

Candidates for oral SR drug delivery system.

Concentration dependency on transfer of drug: Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidates for oral SR delivery system .It should be of first order kinetics.

Terminology: [1]

Controlled and sustained Release, both has been used in inconsistent and confusing manner. Both represent separate delivery process. SR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both [27,28].

Modified Release Drug Product: The term modified release drug product is used to describe products that alter the timing or the rate of release of the drug substance.

Extended-Release Dosage Forms: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release(conventional)dosage Examples of extended-release dosage forms include controlled-release, sustained release and long-acting drug products.

Sustained release: It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a predetermined rate.

Controlled Release: It includes any drug delivery system from which the drug is delivered at a predetermined rate over a prolonged period of time

Delayed Release Dosage Form: A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration Example: Enteric coated dosage forms.

Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended-release characteristic.

Repeat Action Dosage Forms: It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a later time.

Prolonged Action Dosage Forms: It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period of time.

Classification of SR Formulation

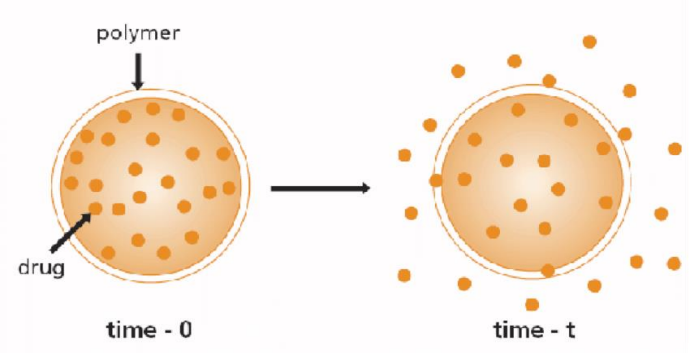
The most common methods used to achieve sustained release of orally administered drugs are as follows:

Diffusion systems [2]

Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized reservoir devices and matrix devices.

a) Reservoir Device

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. It is also possible to use polymer coatings to achieve sustained release. For this purpose, the polymer itself should not dissolve, but rather should allow the drug to diffusion through the polymer membrane to the outside, in the case of oral drug delivery, into the gastrointestinal tract.



i) Matrix Devices

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion ate of dissolved drug leaving the matrix.

i) Dissolution systems

It seems inherently obvious that a drug with a slow dissolution rate will demonstrate sustaining properties, since the release of drug will be limited by the rate of dissolution. This being true, sustained-release preparation of drugs could be made by decreasing their rate of

dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

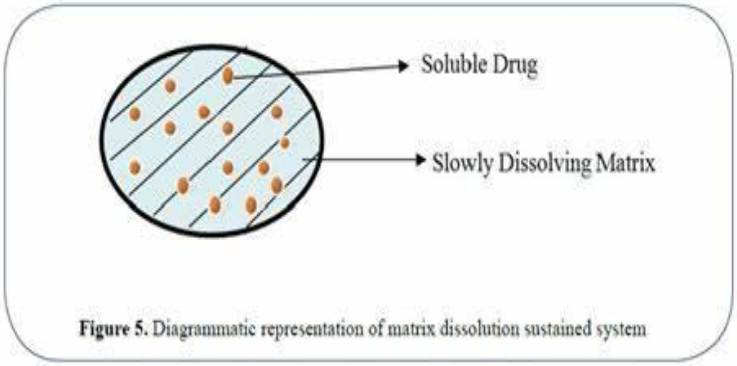
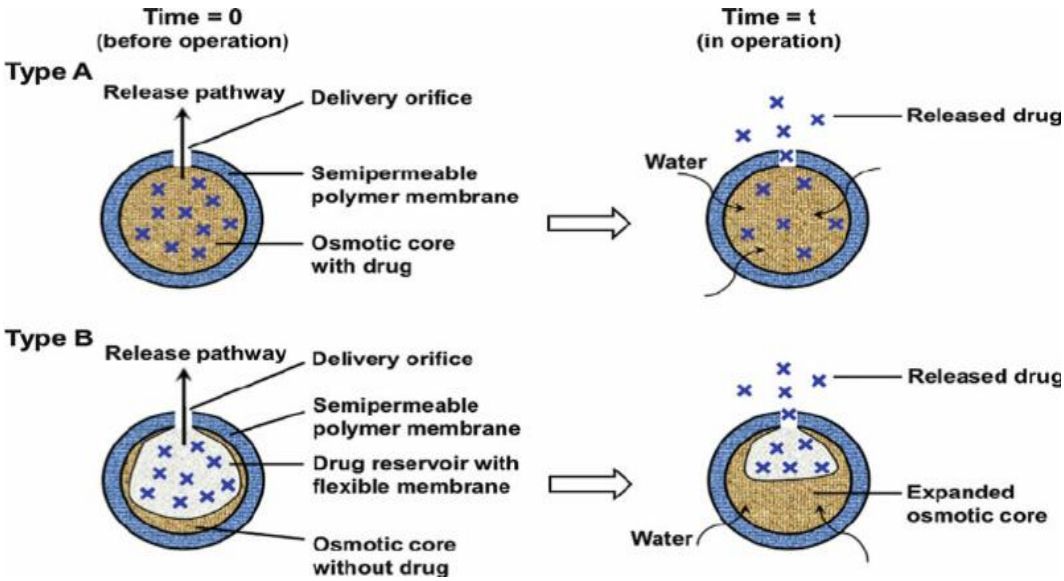


Figure 5. Diagrammatic representation of matrix dissolution sustained system

ii) Osmotic system

Osmotic pressure is employed as the driving force to generate a constant release of drug. Consider semipermeable membrane that is permeable to water, but not to drug. When this device is exposed to water or anybody fluid, Water will flow into the to water will flow into the tablet owing to the osmotic pressure difference.

These systems generally appear in two different forms. The first contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device.



Lon-exchange resins

Ion-exchange systems generally use resins cross-linked composed of water-insoluble polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

Resin drug+ X resin X + drug

Conversely,

Resin drug + Y resin - = Y + drug

The free drug diffuses out of the resin. The drug resin complex is prepared either by repeated exposure of the resin to the drug in chromatography column, or by prolonged contact in solution.

Swelling and expansion systems

Conventional hydrogels swell slowly upon contact with water due to their small pore size, which usually ranges in the nanometres and ombrometer scale. However, if the hydrogel has a pore size of more than 100 um, swelling is much faster and may lead to a large increase in size. Swelling ratios of over 100 can be achieved. These swollen systems become too large to pass through the pylorus and thus may be retained in the stomach even after housekeeper wave, provided they have a sufficiently high mechanical strength to withstand the peristaltic movement in the antrum of the stomach.

Floating systems

If the dosage form has a lower density than the gastric fluids, it will float on a top of the stomach content, allowing for an increased time span to release the drug before the system is emptied out into small intestine. The gastric fluid has a density of approximately Igm/cm³. If the density of the dosage form is lower than that, it will float on the gastric fluids. These systems require the presence of sufficient fluid in the stomach and the presence of food as discussed above. Several types of low-density ingle-unit dosage forms (tablets) and multiple-unit dosage forms (pellets) have been developed. If a dosage form has density of larger than approximately 2.5gm/cm³, it will sink to the bottom of the stomach and pellets may be trapped in the folds of the gastric wall.

Bio adhesive or Mucoadhesive systems

It has also been suggested to use bio adhesive or mucoadhesive polymers such as polyacrylic acid and chitosan to achieve gastric retention. The basic idea here is that the mucoadhesive or bio adhesive polymers leads to the dosage forms sticking on to the mucus of the gastric wall. Whilst the bio adhesive or mucoadhesive approach is a sensible one for buccal or sublingual formulations, due to rapid turnover of the mucus in the stomach, for gastroprotective systems this approach is not as straightforward. Finally magnetic materials may be added to the dosage forms. These systems can then be held in place by an external magnate, but this approach requires a precise positioning of the external magnate and is not likely to have a high patient compliance.

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types [29-31] [1]

1**. Hydrophobic Matrices (Plastic matrices**) [29]: The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in toa tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2**. Lipid Matrices** [30]: These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for re+ tardant base for many sustained release formulations.

3**. Hydrophilic Matrices [31**]: Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high

gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy ethyl cellulose; Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.

B. Non cellulose natural or semi synthetic 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, Gelatine and Natural gums

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. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminated sustained-release granulations. 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.

4**. Biodegradable Matrices [32]:**

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural

polymers such as proteins and polysaccharides; modified natural polymers: synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. **Mineral Matrices** [33]: These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophycean) by the use of dilute alkali.

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