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Review Article

SUSTAINED RELEASE MATRIX TECHNOLOGY AND RECENT ADVANCE IN MATRIX DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. 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 pharmacodynamics 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 (matrix) 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 utilisation of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. The basic goal of sustained release is provide promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body and increase patient compliance by reducing frequency of dose.

Keywords: Sustained-release, Matrix tablet, Patient compliance.

INTRODUCTION

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. The design of oral 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.[4] 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. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug.[2] There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipients by matrix based formulations.[3]

The Following are the Rationale of Developing SR Matrix DDS

- To extend the duration of action of the drug
- To reduce the frequency of dosing
- To minimize the fluctuations in plasma level
- Improved drug utilization
- Less adverse effects

Advantages of SR Matrix DDS

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:
  · Maximizing availability with minimum dose
  · Minimize or eliminate local side effects
  · Minimize or eliminate systemic side effects
  · Minimize drug accumulation with chronic dosing
- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
  · Cure or control condition more promptly
  · Improve control of condition
  · Improve bioavailability of some drugs
  · Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.
- Economy.

Disadvantages of SR matrix DDS

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in vitro and in vivo correlations.

Characteristics That Makes Drugs Suitable For Sustained Release Matrix DDS[4-5]

Biological characteristics

Biological Half-Life

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage

form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. 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 much slower than the rate of absorption. If we assume that the transits time of most drugs and devices in the absorptive areas of the GI 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. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 hours^{-1} to give 80-95% over this time period. The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining system.

Distribution

The distribution of drugs into tissue can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. One aspect of this distribution is binding of drug to tissue and proteins in blood. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. For design of sustained/controlled release products one would like to have as much information on drug disposition as possible but, in reality, decisions are usually based on only a few pharmacokinetic parameter, one of which is the apparent volume of distribution.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

Physicochemical characteristics[5-6]

Dose Size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 gm is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in administration of large amounts of a drug with narrow therapeutic range.

Aqueous Solubility

Compounds with very low solubility (less than 0.01mg/ml) are inherently sustained, since there release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.[9]

Partition Coefficient

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil-soluble drugs becomes important in determining

the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility.[9]

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transits in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compound that is unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation.[6]

Protein Binding

It is well known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part recirculated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if high degree of drug binding occurs. There are, however, other drug – protein interaction that have bearing on drug performance.

Classification of SR Formulation[4-6]

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

Diffusion systems

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 Devices

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.

b) 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.

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.

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 any body fluid, 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.

Ion-exchange resins

Ion-exchange systems generally use resins composed of water-insoluble cross-linked 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 a 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 nanometers and low-micrometer scale. However if the hydrogel has a pore size of more than 100 μm, 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 1gm/cm^3. 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/cm^3, it will sink to the bottom of the stomach and pellets may be trapped in the folds of the gastric wall.

Bioadhesive or Mucoadhesive systems

It has also been suggested to use bioadhesive or mucoadhesive polymers such as polyacrylic acid and chitosen to achieve gastric retention. The basic idea here is that the mucoadhesive or bioadhesive polymers leads to the dosage forms sticking on to the mucus of the gastric wall. Whilst the bioadhesive or mucoadhesive approach is a sensible one for buccal or sublingual formulations, due to rapid turnover of the mucus in the stomach, for gastroretentive 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.

Matrix systems

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant materials and additives to form a tablet in which drug is embedded in matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression.

Types of Matrix

Hydrophobic Matrices

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 to a 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.

Lipid Matrices

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 retardant base for many sustained release formulation.

Hydrophilic Matrices

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,

- *Cellulose derivatives*
  Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.
- *Non cellulose natural or semi synthetic polymers:*
  Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, chitosan and modified starches.

Biodegradable Matrices

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 nonenzymetic 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.

Mineral Matrices

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 (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types.

- *Macro porous systems*
  In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. This pore size is larger than diffusant molecule size.
- *Micro porous system*
  Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.
- *Non-porous system*
  Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

MASRX and COSRX Sustained-Release Technology

Masrx Technology

The objective is to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASRx). The tablets were designed to hydrate completely into the tablet core. In the process, the tablet core expanded and released the drug in a sustained-release manner.

COSRx Technology

Formulations base on constant sustained-release matrix (COSRx) technology can also be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low- or high-viscosity guar gum can be use. The formulation involves a guar-gum-base tablet and a combination of water-soluble and water-insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelations of the guar gum/drug core. As the hydration a progress, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly zero-order drug release

following a programmed period of delayed drug release.

Drug Release Mechanism From SR MATRIX DDS[3, 4]

Zero Order Kinetics

A zero order release would be predicted by the following equation,

$Q_t - Q_0 = K_0t$

Where, Q_t = Amount of drug release dissolved in time't'.

Q_o = Initial amount of drug concentration in solution.

K_0t = Zero order rate constant.

When the data was plotted as cumulative % drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to K_o. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First Order Kinetics

A first order release would be predicted by the following equation

$\text{Log } Q_t = \text{Log } Q_o - K_1t/2.303$

Where, Q_t = Amount of drug released in time't'.

Q_o = Initial amount of drug concentration in solution.

K_1t = First order rate constant.

When data was plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi's Model

Drug release from the matrix device by diffusion has been described by Higuchi's Diffusion equation

$f_t = Q = \sqrt{D\delta/\tau}\ (2C - \delta Cs)Cst$

Where, Q = Amount of drug released in time't'.

D = Diffusion coefficient of the drug in the matrix.

Cs = Solubility of the drug in the matrix.

δ= Porosity of matrix.

τ= Tortuosity.

t = Time (h).

The equation may be simplified then equation becomes;

$f_t = Q = K_H X t^{1/2}$

Where, K_H = Higuchi dissolution constant.

When data was plotted according to this equation, i.e., cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Peppas Korsmeyer Equation

In 1983 Korsmeyer *et al*. (Korsmeyer *et al.*, 1983) developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$A_t/A_\infty = kt^n$

Where, k = Constant.

n = Release.

t = Time.

A_t and A_∞= Absolutecumulative amount of drug released at time't'.

This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

Hixon-Crowell Equation

Drug released from the matrix device by diffusion has been described by Hixon-Crowell diffusion equation;

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

Where, W0 = Initial amount of drug.

W_t = Remaining amount of drug.

t = Time.

? = Constant (Kappa).

This expression applies to pharmaceutical dosage form such as tablets where the dissolution occurs in planes that are parallel to drug surface if tablet dimensions diminish proportionally in such manner that the initial geometrical form keeps constant all the time.

Pharmacokinetics and Pharmacodynamics Consideration

To achieve controlled drug delivery, it is desirable to have a zero-order drug input. Under steady state, rate in = rate out then

$R_0 = CssCL$

This equation shows that the input rate of a controlled release is determined solely by steady state concentration and plasma clearance, $t_{1/2}$, a common pharmacokinetic parameter is not directly

needed to determine the input rate. However, it does play a role in determining the benefits of formulating a drug into controlled-release dosage form. Usually drugs of $t_{1/2}$ more than 8 hours are not suitable candidates for controlled or sustained release dosage forms because they do not provide benefits over conventional dosage forms. In addition, $t_{1/2}$ may be useful in determining the dosing interval of controlled release dosage forms. Similarly, volume of distribution is not major consideration in designing controlled-release delivery systems, although often a larger volume of distribution requires a higher drug load to achieve therapeutic blood level. However, there may not exist a direct correlation between pharmacokinetics and pharmacodynamics of a drug. In other words, it may be difficult to predict the effect of a drug based only on pharmacokinetics data. As a result, a PK/PD model required to obtained a rational design of a controlled-release dosage form. Typically a graded response can be represented by

$E = PC + E_0$

Where, P is the proportionality constant, C is the plasma concentration, and E_0 is the base line effect. In some cases, a more satisfactory relationship is obtained by using,

$E = P \log C + E_0$

In fact, in most cases, the relationship is much more complex than simple linear one, and sometimes it can be represented only by an expression closely related to enzyme kinetics,

$E = E_0 + (E_{max} C^n) / (E^n_{50}) + C^n$

Table 1: Different drugs and polymers used in sustained-release MATRIX tablets

Drug	Polymer
Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC), Ethyl Cellulose (EC)
Ibuprofen	Ethyl cellulose, Cellulose acetate phthallate
Metoprolol succinate	HPMC K100M, Xanthan gum
Ambroxol Hydrochloride	HPMC
Tramadol Hydrochloride	Xanthan gum, Guar gum.
Tramadol Hydrochloride	Carrageenan gum, Karaya gum, HPMC K15 .
Aceclofenac	Carbopol 971P, Carbopol

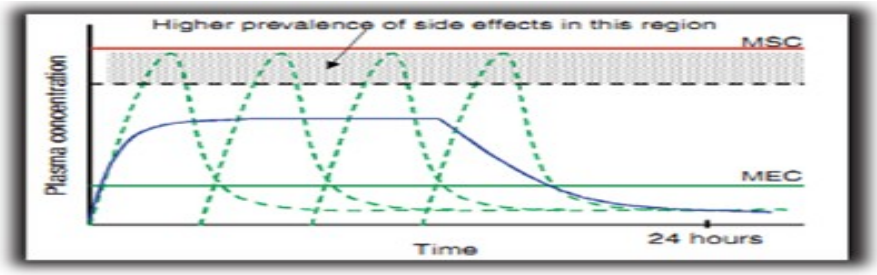

Figure 1. Plasma drug concentration profiles for conventional tablet formulation, sustained release formulation and a zero order controlled release formulation.

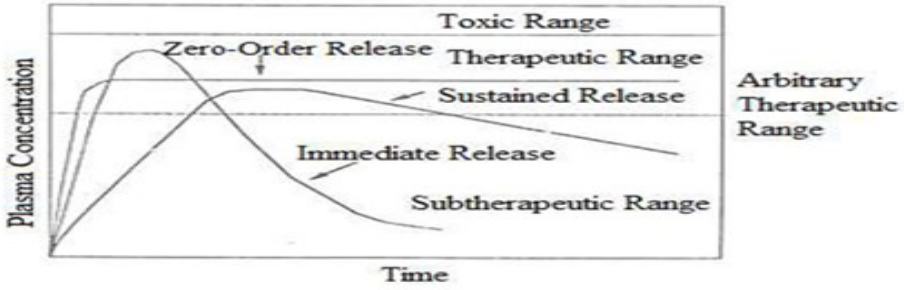

Figure 2. Drug level vs. time profile showing the relationship between sustained release and conventional release.

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