Review Article

A Brief Review on Sustained Release Matrix Type Drug Delivery System

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ABSTRACT

Purpose: A review on sustained release drug delivery using polymer matrix with emphasis on its contemporary usage and future trends.

Approach: An introduction to sustained release drug delivery system (SR DDS), followed by its rationale, advantages, disadvantages, criteria of a drug to be met to formulate sustained release formulations, classification of matrix tablets, classification of polymers, its mechanism and recent advancements.

Finding: Recent studies indicate that sustained delivery for a very long period, in terms of months is possible using suitable polymer matrices. Also, challenging drug candidates such as proteins are now successfully delivered as sustained release dosage forms.

Conclusion: Sustained release DDS, since 1940s has evolved in different types of dosage forms for sustained effect but future scope will be to treat chronic diseases providing sustained effect.

Keywords: Sustained release, Polymers, Recent advancements.

INTRODUCTION

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/treatment of the disease is achieved[1]. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.

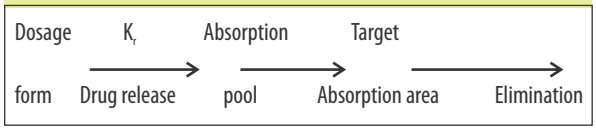
Oral sustained release (SR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamics properties of drugs in such a way that it reduce dosing frequency to an extent that once daily dose is sufficient for penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion[2]. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene

oxide) and cross-linked homopolymers and copolymers of acrylic acid[3].

Principle of Sustained Release Drug Delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme in figure 1.

Fig.1: Schematic representation of the kinetics of sustained release DDS.



The absorption pool represents a solution of the drug at the site of absorption, K_r, K_a and K_e - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that $K_r >>>> K_a$. For non-immediate release dosage forms, $K_r << K_a$ i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

$$K_{r^o} = \text{Rate In} = \text{Rate Out} = K_e C_d V_d$$

Where, K_r: Zero-order rate constant for drug release-Amount/time, K_e: First-order rate constant for overall drug elimination-time, C_d: Desired drug level in the body – Amount/volume, and V_d: Volume space in which the drug is distributed in litre[4].

The Following are the Rationale of Developing SR Matrix DDS

a. To extend the duration of action of the drug.

b. To reduce the frequency of dosing.

c. To minimize the fluctuations in plasma level.

d. Improved drug utilization.

f. Less adverse effects[5].

Advantages of SR Matrix DDS

1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient as well.
4. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
5. 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 reduce.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
7. 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 effect. Minimize drug accumulation with chronic dosing.
8. 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.
9. Economy.

Disadvantages of SR Matrix DDS

1. Probability of dose dumping.
2. Reduced potential for dose adjustment.
3. Cost of single unit higher than conventional dosage forms.
4. Increase potential for first pass metabolism.
5. Requirement for additional patient education for proper medication.
6. Decreased systemic availability in comparison to immediate release conventional dosage forms.
7. Poor *in vitro* and *in vivo* correlation[6].

Criteria of drug to be met to formulate sustained release dosage forms:

a) Desirable half-life.

b) High therapeutic index.

c) Small dose.

d) Desirable absorption and solubility characteristics.

e) Desirable absorption window.

f) First past clearance.

(a) Desirable half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has a 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 eight hours or more are sufficiently sustained 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 three to four hours.

(b) High 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, leading to fatalities eg. Digitoxin.

(c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undermined. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

(d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such Compounds into sustained release formulations is therefore unrealistic and may reduce overall absorption efficiency.

(e) Desirable 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'. Drugs exhibiting an Absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage forms are unsuitable.

(f) First pass clearance:

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms[7,8].

CLASSIFICATION OF MATRIX TABLETS

(a) On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic 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 .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[9].

2. 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[10].

3. Hydrophilic Matrices

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. In fact a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

A. Cellulose derivatives:

Methylcellulose 400 and 4000 cps, Hydroxyethyl-cellulose, Hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000 cps; and Sodium carboxymethyl- 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: Carbopol-934, the most used variety.

4. 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.

5. 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[11].

(b) 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[12,13].

POLYMERS USED IN THE MATRIX

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

(A) Hydrophilic Polymers: Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

(B) Hydrophobic Polymers: This usually includes waxes and water insoluble polymers in their formulation.

(C) Waxes: Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

(D) Insoluble polymers: ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers[14].

Characteristics of an ideal polymer

- It should be versatile and possess a wide range of mechanical, physical, chemical properties.
- It should be non-toxic and have good mechanical strength and should be easily administered.

- It should be inexpensive and easy to fabricate.
- It should be inert to host tissue and compatible with environment.

Criteria followed in polymer selection

- The polymer should be soluble and easy to synthesis.
- It should have finite molecular weight.
- It should be compatible with biological environment.
- It should be biodegradable.
- It should provide good drug polymer linkage.

General mechanism of drug release from polymer

- There are three primary mechanisms by which active agents can be released from a delivery system namely,

Diffusion

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues its rate normally decreases with this type of system since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.[15]

Degradation

Biodegradable polymer degrades within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system.

Swelling

They are initially dry and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.[16]

Drug release mechanism of sustained release drug delivery systems.

1. Zero Order Kinetics

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

$$Q_t - Q_o = K_o t$$

Where,

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

Q_o = Initial amount of drug concentration in solution.

$K_o t$ = 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 Ko. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

2. First Order Kinetics

A first order release would be predicted by the following equation

$$\text{Log } Q_t = \log Q_o - K_1 \frac{t}{2.303}$$

Where,

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

Q_o = Initial amount of drug concentration in solution.

$K_1 t$ = 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.

3. Higuchi's Model

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

$$f_t = Q = A\sqrt{(D\,(2C - C_s)\,C_s t)}$$

Where,

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

D = Diffusion coefficient of the drug in the matrix.

C_s = Solubility of the drug in the matrix.

A= Porosity of matrix.

t= Tortuosity.

t = Time (h).

4. 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).

$$M_t/M_\infty = Kt^n$$

Where,

K = Constant.

n = Release.

t = Time.

M_t and = Absolute cumulative 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.

5. Hixon-Crowell Equation:

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

$$W_0^{1/3} - W_t^{1/3} = Kt$$

Where,

W_0 = Initial amount of drug.

Wt = Remaining amount of drug.

t = Time.

K = 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[17].

Novel trends in Sustained release drug delivery systems.

For orally administered dosage forms, sustained drug action is achieved by affecting the rate at which the drug is released from the dosage form and or by slowing the transit time of dosage form through the gastrointestinal tract.

Single Unit Dosage Forms:

This refers to diffusion controlled system where the therapeutic agent is evenly distributed (Dispersed /dissolved) throughout the solid matrix. This system can be classified as follows: Complex reservoir system or coated tablets or multi-layered system

Hydrophobic/Swellable tablets

Optimum alkaloid such as morphine salts homogenized with its salt and fatty acid or any ethylene vinyl acetate copolymer (hydrophobic filler) and then compressed into tablets.

Semisolid matrix systems

In this system drug is incorporated in an oily "semisolid" hydrophobic carrier, and finally mass is typically filled into a gelatin capsule to prepare dosage form.

Ion exchange resins

The system is composed of a core tablet surrounded by a semipermeable membrane coating having a 0.4mm diameter hole produced by laser beam. The tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery

aperture in tablet coating. E.g. Glucotrol XL (glipizide) tablets (Pfizer), Covera – HS ® (verapamil HCl) tabs. (Searle)[18,19,]

Multiple Unit Dosage Forms

It represents a mixture of the dosage form, the source of which may either be homogenous or heterogeneous. The various forms which are available are multitablet system. Small spheroids compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug release characteristics. They them may be placed in gelatin capsule shells to provide the desired pattern of drug release Coated Beads, granules & microsphere In these systems, the drug is distributed on to beads, pellets, granules, or other particulate systems. Using conventional pan coating or air suspension coating, a solution of the drug substance is placed on small inert nonpareil seeds or beads made of sugar and starch or on microcrystalline cellulose spheres. Pellets prepared by coating inert drug pellet with film forming polymers. The drug release depends upon coating composition of polymers and amount of coatings. Microencapsulation is a process by which solids, liquids, or even gases may be enclosed in microscopic particles by formation of thin coatings of wall material around the substance. It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites[20].

Protein Drug Eluting Cardiovascular Stents: Protein-eluting cardiovascular stents represent another potential application of protein sustained-release technology. The chemical drugs used on current drug eluting stents, although prevent after-stenting restenosis; inhibit healing of the blood vessel endothelium damaged by stent installation. The delayed endothelium recovery causes incident bleeding and thrombus forming. Several proteins have been found effective to suppress vascular smooth muscle .proliferation and to stimulate vessel endothelium recovery when directly introduced to the stenting site. However, loading these proteins onto stents resulted in ineffectiveness. In these work, stents precoated with a layer of hydrophobic polymer was impregnated in a protein solution to adsorb proteins on the polymer surface. However, adsorbing proteins on hydrophobic polymer surfaces is a known cause for protein denaturing In addition, only limited amount of proteins can be adsorbed on a stent surface (<20 µg/stent)[21].

Sustained release injectable formulations: Development of Sustained release injectable has

Table 1: Examples of Various SR DDS Approaches.[23]

Type of device	Product name	Active ingredient	Route	Manufacturer
Diffusion (reservoir)	Estraderm	Estradiol	Transdermal	Alza/Novartis
	Norplant	Levonorgestrel	Sub-dermal implant	Wyeth-Ayerst Laboratory
	Ocusert	Pilocarpine	Ocular	Alza
	Progestasert	Progesterone	Intrauterine	Alza
Diffusion(matrix)	Nitro-Dur	Nitroglycerine	Transdermal	Key Pharmaceutical
	Nitrodisc	Nitroglycerine	Transdermal	Searle
Mixed(matrixreservoir)	Catapress-TTS	Clonidine	Transdermal	Alza/BoehingerIngelheim
Hydro Dynamically	MedoparCR	Levodopa and Benserazide	Oral tablet	Roche
Ion exchange	Colestid	Colestipol	Oral tablet or Granules	Upjohn
Coating	Compazin	Prochlorperazine	Oral capsules	Smith Kline Beecham
Nanocrystal Technology	Rapamune	Sirolimus	Oral tablet	Elan/Wyefh-Ayerst Laboratory
Osmotic pumps	Calan SR	Verapamil	Oral tablet	Alza/G. D. Searle

occurred in the past few years. This was brought into existence to prolong the effect of drug at targeted site. This advancement also offers reducing dosing frequency, maximizing the efficacy–dose relationship, decreasing adverse side effects and enhancing patient compliance. This system also leads to alleviation of pain during administration and reducing costing of parenteral drug treatment. Safety issues relating to an injectable sustained-release system cannot be overlooked. Premature termination of treatment in case of drug toxicity can be extremely difficult for most of the parenteral sustained-release systems once administered. The adverse response of local tissues to the drug and/or the system on prolonged exposure can be clinically alarming. In recent years, the research in parenteral sustained-release technologies has been fuelled mainly by the advent of novel carriers. The growth of injectable sustained-release products in the pharmaceutical marketplace is also evidenced by the increasing number of products that have been granted regulatory approval during the last 5 years[21]. Table 1 gives examples of various SR DDS.

CONCLUSION

Despite all advancements made within the field of oral drug delivery, sustained release matrix tablets are popular due to their ease in preparation, scale-up and versatility. Many new systems are still emerging. But the marketability and feasibility of each new formulation has to be assessed carefully before launching a new product.

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