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SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. This article contains the basic information regarding sustained-release formulation and also the different types of the same.

INTRODUCTION

These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.[1,2]

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. 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. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface. [3, 4]

Introduction of matrix tablet as sustained release (SR) has given a new break through 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. [5-7]

The major Drawbacks Associated with Conventional Dosage Forms are

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration-time profile is obtained

which makes attainment of steady-state condition difficult.

- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.
- Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity or targeting the delivery of drug to a tissue.[8, 9]

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) [10]

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 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.

2. Lipid Matrices[11]

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.

3. Hydrophilic Matrices[12]

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, Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

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[12]

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[12]

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.

(b) On the Basis of Porosity of Matrix: [13-16]

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Nonporous systems can be identified:

1. 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.

2. 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.

3. 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.

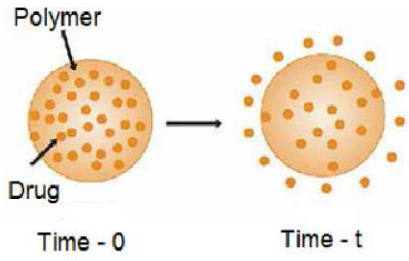

Figure 1 Schematic representation of diffusion across the Matrix

EFFECT OF VARIOUS PARAMETERS ON DRUG RELEASE[17, 18]

Drug release kinetics may be affected by many factors such as polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, drug distribution inside the matrix, drug/polymer ratio and system geometry (cylinder, sphere).

A. Drug solubility:

Water solubility of drug and molecular size is another important factor which is considered in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of water soluble drugs occurs by dissolution in infiltrating medium and the release of poorly water soluble drug are occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

B. Polymer hydration

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linkings with the simultaneous forming of water-polymer linkings, separation of polymeric chains, swelling and

finally dispersion of polymeric chain in dissolution medium.

C. Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer. The release of drug may be attributed to the mainly two factors-

- **Polymer viscosity:** Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution.
- **Polymer concentration:** An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release.

D. Thickness of polymer diffusional path:

The controlled release of a drug from matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$JD = D\, dc/dx$$

Where,

JD = flux of diffusion across a plane surface of unit area

D = is diffusibility of drug molecule,

dc/dx = is concentration gradient of drug molecule across a diffusion path with thickness dx.

E. Thickness of hydrodynamic diffusion layer:

The drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. As the thickness of hydrodynamic diffusion layer increases, the magnitude of drug release value decreases.

F. Drug loading dose:

The release kinetics is significantly affected by loading dose of drug. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically

increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading.

G. Surface area:

Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. The release of drug from small tablet is faster than large cylindrical tablets.

H. Effect of diluent:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

I. Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.[3, 10, 16]

➢ **POLYMERS USED IN THE MATRIX[19]**

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.

- **FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS[20]**

1. Swelling characteristics of polymers
2. Polymer erosion
3. Drug loading
4. Drug solubility

- **ADVANTAGES OF MATRIX TABLETS[21]**

1. Easy to manufacture.
2. Versatile and effective
3. It has low cost.
4. Can be made to release high molecular weight compounds.
5. Suitable for both non degradable and degradable systems.
6. No danger of dose dumping in case of rupture.
7. Can be fabricated in a wide range of sizes and shapes.

- **DISADVATAGES OF MATRIX TABLETS[22]**

1. The remaining matrix must be removed after the drug has been released.
2. The drug release rates vary with the square root of time.
3. Achievement of zero order release is difficult.
4. Not all drugs can be blended with a given polymeric matrix.
5. Water soluble drugs have a tendency to burst from the system.
6. Poor *in vitro – in vivo* correlation.
7. Possibility of dose dumping due to food, physiologic or formulation variables.
8. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
9. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
10. Stability problems.
11. Increased cost.
12. More rapid development of tolerance and counselling.
13. Need for additional patient education and counselling.

- **CRITERIA TO BE MET BY DRUG PROPOSED TO BE FORMULATED IN SUSTAINED RELEASE DOSAGE FORMS.[23,24]**

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 e.g. 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 undetermined. 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.

➢ **DRUG RELEASE FROM MATRIX[25]**

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 toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release;

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

c) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$\boldsymbol{DM/Dh}$ **= Co. Dh - Cs/2----- (1)**

Where,

DM = Change in the amount of drug released per unit area

Dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h).Dt----- (2)

Where,

dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

Dt = Change in time By combining equation 1 and equation 2 and integrating:

M = [Cs. Dm. (2Co−Cs). t] ½------ (3)

When the amount of drug is in excess of the saturation concentration, then:

M = [2Cs. Dm. Co. t] ½----- (4)

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the

openings must be accounted for in the drug release from a porous or granular matrix:

M = [Ds.Ca.p/T. (2Co – p.Ca) t] ½------ (5)

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusion path length for pseudo steady state, the equation can be written as:

M = [2D.Ca .Co (p/T) t] ½------ (6)

The total porosity of the matrix can be calculated with the following equation:

p = pa + Ca/ ρ + Cex / ρex------ (7)

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients For the purpose of data treatment, equation 7 can be reduced to:

M = k. t ½------ (8)

Where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled.

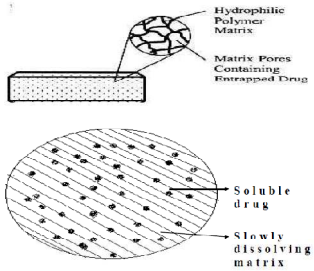

Figure 2 Drug arrangements in matrix tablet[28]

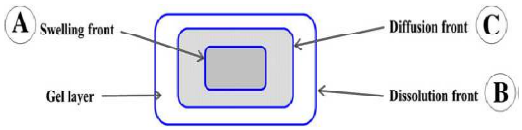

Figure 3 Scheme of the hydrophilic matrix after entry of the dissolution medium.[28]

A. The swelling front. With the entry of water into the matrix, the polymer passes from the crystalline state to a hydrated or gelified state.
B. The erosion front or dissolution front: This separates the gelified zone from the matrix of the solvent.
C. Diffusion front (solid drug–drug solution boundary): This is located between the swelling and erosion fronts and it separates the zone of the gelified matrix containing the drug dissolved in the

medium from the zone of the matrix containing the undissolved solid drug.

EVALUATION OF SUSTAINED RELEASE TABLETS: [26, 27]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

1. *In-Vitro* Methods

These are:-

a. Beaker method

b. Rotating disc method

c. Rotating Bottle method

d. Rotating Basket method

e. Stationary Basket Method

f. Oscillating tube method

g. Dialysis method

h. USP dissolution method.

2. *In–Vivo* Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are:-

a. Clinical response

b. Blood level data

c. Urinary excretion studies

d. Nutritional studies.

e. Toxicity studies

f. Radioactive tracer techniques

3. Stability Studies:

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. A sustained release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the sustained release product useless. The in-vitro and in-vivo release rates of sustained release product may be altered by atmospheric or accelerated conditions such as temperature & humidity. The stability programmes of a sustained release product include storage at both nominal and accelerated conditions such as temperature & humidity to ensure that the product will withstand these conditions.

***In vitro- In vivo* Correlations:** [24, 25]

The requirement of establishing good *in vitro - in vivo* correlation in the development of sustained release delivery systems is self-evident. To make a meaningful in-vitro in-vivo correlation one has to consider not only the pharmaceutical aspect of sustained release drug delivery system but also the biopharmaceutics and pharmacokinetics of the therapeutic agent in the body after its release from the drug delivery system and also the pharmacodynamics of therapeutic agent at the site of drug action. A simple in vitro-in vitro relationship can be established by conducting in-vitro and in-vivo evaluations of a potential drug delivery system simultaneously to study and compare the mechanism and rate profiles of sustained drug release. When the in-vivo drug release mechanism is proven to be in good agreement with that observed in the in-vitro drug release studies, then in-vitro in-vivo correlation factor is derived. For capsule type drug delivery system the factor can be represented as:

(Q/t) *In-vivo*

Q= (Q/t) *In-vitro*

Where,

Q/t = Rate of release

'Q' values are dependent profiles of drug delivery systems. Upon the sites of administration and environmental conditions to which the animals are exposed during treatment (study).

The above relationship can be used for optimization of sustained release Levy has classified *In-vivo-In-vitro* correlation in to:

A. Pharmacological correlations based on clinical observations;
B. Semi-quantitative correlations based on blood levels or urinary excretion data;
C. Quantitative correlation arising from absorption kinetics. While most of the published correlations are of semi-quantitative nature, the most valuable are those based on absorption kinetics.

Bioavailability Testing: [26]

Bioavailability is generally defined as the rate and extent of absorption of unchanged drug from its site of application to the general circulation. Bioavailability is defined in terms of a specific drug moiety, usually active therapeutic entity, which may be the unchanged drug or as with prodrug, for instance, a metabolite. In contrast, the term "absorption" often refers to net transport of drug related mass from its site of

application into the body. Hence, a compound may be completely absorbed but only partially bioavailable as would occur, when low bioavailability is caused by incomplete absorption. Pharmaceutical optimization of the dosage form may be warranted to improve absorption characteristics of the drug and thereby also its bioavailability. Bioavailability studies are ordinarily single dose comparisons of tested drug product in normal adults in a fasting state. A crossover design, in which all subjects receive both, the product and reference material on different days, is preferred. Guidelines for clinical testing have been published for multiple dose studies. Correlation of pharmacological activity or clinical evidence of therapeutic effectiveness with bioavailability may be necessary to validate the single significance of sustained release claims. While single dose studies are usually sufficient to establish the validity of sustained release dosage form design; multiple dose studies are required to establish optimum dosing regimen. They are also required when difference may exist in the rate but not the extent of absorption. When there is excessive subject-to subject variation or when the observed blood levels after a single dose are too low to be measured accurately. A sufficient number of doses must be administered to attain steady state blood levels. According to an extensive study of sustained release Theophylline products; for example, encapsulated forms showed less peaking during multiple dosing and therefore better control of blood level within the desired limits.

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. Preparatory procedures easily allow adaptation of release kinetics to delivery needs. This suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose

administration etc. So matrix tablets can overcome the above problems of conventional oral drug delivery.

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