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REVIEW ARTICLE

Matrix tablet- simplest method of sustaining drug action

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ABSTRACT

Matrix tablet were designed to achieve the sustained released of drug from dosage form. Sustained release of drug is required to prolong the duration of action of drug, thus reducing the dosing frequency. Matrix tablet were designed first in sustained release dosage forms. Matrix tablet offers least manufacturing cost among other sustained release formulations. Matrix tablet are designed by dispersing drug in hydrophobic or hydrophilic polymer. The release of drug from such system may be dissolution or diffusion controlled or both. Various type of factor and method of manufacturing affect the drug release from tablet matrix. Matrix tablet are widely used due to simplicity of formulation and easiest in use. The basic rationale of matrix tablet is to optimize the biopharmaceutical pharmacokinetics and pharmacodynamics properties of drug in dosage form in such a way that it utility maximized and side effects are reduced to cure disease.

Key words: Sustained released, Matrix tablet, pharmacokinetics and pharmacodynamics.

INTRODUCTION:

Oral route for administration of drug in sustained release dosage form is oldest and convenient because of lowest cost of therapy and ease of administration[1]. 50% products available are administered orally[2]. The goal of any dosage form is to delivered drug as proper site in body to achieve therapeutic effect. Sustained release dosage forms are developed to achieve the uniform drug plasma level with minimal side effect with reduced dosing frequency. The two aspects of drug delivery are spatial placement and temporal drug delivery [3]. First one relates to targeting a drug to specific organ or tissue while second one relates to release of drug from its delivery system controlled release drug is advanced towards these steps. Sustained released, Prolong release, modified release, extended release are different delivery system which prolog the drug action in body [4].

Advantage of prolong release over convenient dosage form include uniform blood level of drug and better patient compliance[5]. Matrix system is widely used to achieve the sustained release of drug from its dosage form. A matrix is defined as dispersion or dissolution of drug in a hydrophobic or hydrophilic polymer to retard the release of drug from the matrix[6].

ADVANTAGE: [7, 8]

Prolong drug action include many advantage over convenient;

- Reduced dosing frequency the inconvenient
- Uniform drug plasma level
- Maximum utilization of incorporated drug
- Improvement in treatment efficiency
- Local and systemic Side effects are minimized
- Ability to provide spatial effects e.g. Morning relief of arthritis through bed time dosing

DISADVANTAGE: [9, 10]

- Higher cost of manufacturing.
- Increase potential for hepatic first-pass metabolism
- Onset of action of drug is delayed
- presence of food in stomach affects the drug release rate
- Prolong duration of action cannot be greater than GI transit time.
- Poor in vivo-in vitro correlation.

PROPERTIES OF DRUG TO BE USED IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM:

1. BIOLOGICAL CHARACTERISTICS: [11, 12, 13]

Biological half life:

The drug with sort half life needed to prolong their release for longer duration of action. So sustained release formulation required to maintain therapeutic blood level for extended time period. Drugs biological half life is estimated by elimination rate i.e. some of metabolism and excretion by any route. However, drug with vary sort

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half life may required excessive large amount of drug in each dosing unit, evolving formulation limitations. The drug with biological half life 2-8 hours are generally used for sustained release formulation development.

Absorption:

Absorption of drug is manly affected by solubility of drug. Since the purpose of developing sustained release drug delivery system is to place control on release rate of drug from drug delivery system, it is necessary that release rate must slow than absorption rate. Compounds with better absorption rate will be suitable for sustained release drug delivery system due to limit of gastro intestinal tract transit time; 8-12 hours. Drug with slow absorption rate, are poor candidate for sustained drug delivery system.

Distribution:

Drug elimination mainly depends on metabolism and distribution of it in tissue. Distribution is result of binding of drug to tissue and protein in blood. Apparent volume of distribution is another term to explain the magnitude of distribution. There is no need for sustained release formulation of drug with excessive protein binding

Metabolism:

Lumen or tissue of intestine significantly metabolized drug before absorption thus decreases bioavailability conversion into product of such enzyme susceptible drug is another viable solution.

2. PHYSICOCHEMICLE CHARACTERISTIC[14, 15]:

Dose size:

A single dose of 0.5-1.0 gm is considered maximal for conventional dosage form via oral route. Sustained release formulation may contains higher dose but not too much to cause swallowing problem. Large dosing size can some time giving in multiple amounts. Narrow therapeutic range drug also considered for their safety margin.

Aqueous Solubility:

Very low soluble drug are inherently sustained because there bioavailability is limited by dissolution of drug. Drug with 0.1mg/ml solubility or more, may required for sustained release drug delivery system. Mechanism to be employed in sustained drug delivery system for absorption as diffusion will be poor choice for slightly soluble drugs because driving force is concentration gradient in solution.

Partition coefficient:

Drugs have to cross biological membrane to appear in blood. Since biological membranes are lipoidal in nature, Thus drug must have posses some lipophillicity in nature. Thus drug have a balance in lipophillicity and hydrophillicity to solublise in aqueous solution of intestine and to cross lipoidal barrier of intestine. Partition coefficient is ratio of the fraction of drug in an oil phase top that of an aqueous phase when mixed with each other.

Stability:

Oral route is subjected to acid base hydrolysis and enzymatic degradation. Degradation is reduced by solid state formulation like tablet and capsule. Drug which are unstable in stomach delayed release formulation are beneficial. Drugs which are unstable at intestinal pH may reduce their bioavailability.

CLASSIFICATION OF MATRIX TABLET[15, 16, 17]:

On the basis of retardant material used:

The most common retardant/polymer use to achieved oral sustained drug delivery via matrix tablet are as fallows-

Hydrophilic type matrix tablet:

Such type system consists of rate controlling materials which are water soluble and/or swellable matrix is dispersion of one or more drug in the hydrophilic polymer. Commonly use hydrophilic polymer are; e.g.

- Nonionic soluble cellulose ether, such as HPMC (e.g. MethocelK100M, K4M, K15M, K100M), Hydroxypropyl cellulose (Klucel GXF, MXF), Hydroxyl ethyl cellulose (Natrosol).
- Nonionic homopolymer of ethylene oxide e.g. polyethylene oxide (MW-100000-8000000), poly OX WSRN12K.
- Water soluble natural gum of polysaccharide e.g. xanthum gum, alginate, locust bean gum.
- Insoluble water swellable high molecular weight homopolymer e.g. carbopol
- Polyvinyl acetate and povidone mixture e.g. kollidone SR
- Cross-linked high amylase starch.
- Ionic methycrylate copolymer (e.g. eudragit<30D).

Hydrophobic type matrix tablet:

Oldest matrix type system for oral sustained drug delivery was hydrophobic type. The concept first introduced in 1959 for premarin tablets. Drug was mixed with inert or hydrophobic polymer to compress into tablet. Sustained release of drug is due to diffusion of dissolved drug from compacted polymer via channel between particles.eg

- Fatty acid, fatty acid ester, mono,-di and triglycerides of fatty acids; fatty alcohols, waxes of synthetic and natural origin as well as hydrophobic polymers like stearic acid, lauryl,cetyl or cetosteryl alcohol, carnauba wax, bees wax, candelilla wax, microcrystalline wax.

• Insoluble polymer includes fine powders of ammoniomethycrylate copolymer (Eudragit RL100, RS 100), ethyl cellulose, cellulose acetate, cellulose acetate butyrate.

Lipid type matrix tablet:

Lipid waxes and related materials are used for matrixing process. Pore diffusion and erosion both are way of drug diffusion. Release charecterstics are more sensitive to composition of gastric fluid than insoluble polymer matrix. e.g.

• carnauba wax with stearyl alcohol or stearic acid used as base.

Biodegradable type matrix tablet:

These are polymer those monomers are linked to one another through unstable functional group in their back bone. These functional group are degraded by enzyme in GI tract e.g.

• Natural polysaccharide such as protein and polysaccharide,

• Modified natural polymer,

• Synthetic polymer such as aliphatic polyester and polyanhydrides.

Mineral type matrix tablet:

Such type polymers are obtained from species of sea weeds, e.g. alginic acid which is hydrophilic carbohydrate extracted from brown sea weed (Phaephyceae) by dilute alkali.

On the basis of porosity[18, 19]:

Matrix system can also be classified on the basis of porous nature of matrices

Macro-porous system:

Drug diffusion occurs through the pores of matrix. Size of pore range from 0.1-1mum

Micro-porous system:

Drug diffusion in such system occurs essentially through pores ranging in size 50-200A.

Non-porous system:

Such systems have no pores, so molecule diffuses through network meshes. In this only polymeric phase exists.

DESIGNING OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM[20, 21, 22]:

Oral controlled release systems are mostly solid and based on dissolution, diffusion or both. Depending on drug release, these system can be;

1. Dissolution controlled release systems:

Easiest system to design. Drug of choice is one which has inherently slow dissolution or high aqueous dissolution rate and solubility. Highly aqueous soluble drug shows challenge in controlling their dissolution rate. Dissolution controlled release is obtained by matrixing drug in an insoluble polymer or by coating with them. Diffusion of drug across the insoluble polymer is rate controlling step. Dissolution rate (dm/dt) can be given by equation;

$dm/dt = ADs/h$ ……(1)

where,

s- Aqueous solubility of drug

A- Surface area of the dissolving drug

D- Diffusivity of the drug

h- Thickness of the boundary layer.

These systems are two types:

(a)Matrix or monolith dissolution controlled system:

In this system, drug is homogeneously dispersed in rate controlling medium. Rate controlling media employs waxes such as beeswax, carnauba wax, which controlled dissolution fluid penetration to control the drug release from matrix tablet. First order release kinetics is followed by drug release from matrices.

(b)Reservoir dissolution controlled system:

In this system, drug particles are coated or encapsulated by insoluble material like, cellulose and polyethylene glycol. Solubility and thickness of coating determine the dissolution rate. Dissolved drug diffuses from the polymeric membrane.

2. Diffusion controlled release systems:

In this system, rate limiting step is diffusion of dissolved drug through polymeric membrane. As the diffusional path length increases with time, the drug release rate never can be zero-order. Diffusion controlled system are manufactured either by encapsulating the drug particle or by dispersing drug in the polymeric matrix. Drug passes into solution by partitioning itself through polymer.

Rate of drug release (dm/dt) is given by following equation;

$Dm/dt = ADK\Delta C/l$ ……(1)

Where,

A- Area of diffusion,

D- Diffusion coefficient of drug,

K- Partition coefficient of drug between the drug core and membrane,

l- Diffusional path length, and

ΔC- Concentration difference across the membrane.

The two different type of diffusion controlled drug delivery system are,

(a)Reservoir type:

Drug particles are coated or encapsulated by one or more insoluble polymer like, cellulose and propylene glycol. Insoluble polymer encases the water soluble drug. The drug partitions itself into polymeric membrane and gets exchanged with surrounding fluid.

(b)Matrix type:

Water soluble drug is dispersed into insoluble matrix, thus release of drug depends on rate of drug diffusion, not on dissolution rate of solid drug.

3. Dissolution and diffusion controlled release systems:

In this type system, the drug is encased in a partially soluble polymeric membrane. Thus pores are created due to partial dissolution of membrane. Pore permits entry of water into core drug to dissolve it, and allow diffusion of dissolved drug into fluid medium.

4. Ion exchange resins controlled release system: ion exchange resins are water insoluble polymer carrying ionisable functional group. The resins used in formulation posses two properties i.e. taste masking and controlled release system. Prolong exposure of drug to ion exchange resins results in irreversible complex formation between drug and resins. Resin bound drug is exchanged when appropriate ion are in contact with ion exchange resin groups. Rate of drug release depends on the area, length of diffusional pathway and the amount of cross linked polymer resin moiety.

5. pH dependent system: drug formulations are exposed to different pH in the gastrointestinal tract. The drug release from sustained formulation may be pH dependent, since most of drugs are either weak acid or weak base and soluble at particular pH. Buffer could be added to the formulations to maintain the constant pH to reduce the rate of drug release from the formulations eg salt of citric acid, phosphoric acid, or tartaric acid to propylene glycol 4000 to retard the rate of drug release.

MECHANISM OF DRUG RELEASE FROM MATRIX TABLET[23, 24, 25]:

The drug present in outermost layer of tablet, exposing to fluid is dissolved first and diffuse in fluid. This process continues on the interface between fluid and outermost surface of tablet drug. The rate of drug dissolution in matrix must be much faster than diffusion rate of dissolved drug leaving the matrix.

Equations derived to express drug release involve the following assumptions;

- A pseudo-steady state is maintained during drug release.
- Sink condition is provided by bathing solution at all time.

Release rate (dM/dh) of drug from matrix system can be described mathematically as,

$dM/dh = Co.dh - Cs/2$ .....(1)

Where,

dM – change in the amount of drug release 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 unit volume of matrix,

Cs – saturated concentration of drug within the matrix.

According to diffusion theory,

$dM = (Dm.Cs/h)\, dt$ .....(2)

Where,

Dm – Diffusion coefficient in matrix,

h – Thickness of drug depleted matrix,

dt – Change in time.

By combining equations (1) and (2)

$M = [Cs.Dm\ (2Co-Cs)t]^{1/2}$ .....(3)

At a time drug is much higher than saturation concentration; then

$M = [2Cs.Dm.Co.t]^{1/2}$.....(4)

Equation (3) and (4) relates the amount of drug release to the square-root of time. So that ,if system is diffusion controlled then the plot of drug release vs. square-root of time will be straight line. For the drug release into solution volume and length of porous matrix must be accounted,

$M = [Ds.Ca.p/T.(2Co-pCa)t]^{1/2}$.....(5)

Where,

P – Porosity of matrix,

t – Tortuosity,

Ca – Solubility of drug in release medium,

Ds – Diffusion coefficient of drug in release medium,

T – Diffusional path length.

For pseudo-steady state,

$M = [2D.Ca.Co\ (p/T)\ t]^{1/2}$.....(6)

The total porosity of matrix can be calculated by equation-

$P = pa + Ca/\rho + Cex/\rho ex$.....(7)

Where,

P – Porosity,

ρ - Drug density,

pa – Porosity in matrix,

ρex – Density of water soluble excipients,

Cex – concentration of water soluble excipients.

For further data treatment, equation (7) can be written as,

$M = K.t1/2$ .....(8)

Where, K is constant.

If the drug release from matrix is diffusion controlled, plot of drug release vs. square-root of time will be linear. In this case, the drug release can be controlled by various parameters;

- Initial concentration of drug in matrix.
- Porosity.
- Tortuosity.
- Polymer system forming matrix.
- Solubility of the drug.

CONCLUSION:

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the drug therapy as well as they are also improving the patient's compatibility. The problem of complexity of sustained-release formulation is also overcome by making tablet by simple compression using tableting technology. Using matrix tablet as oral controlled release formulation, many drugs, can be delivered in ways that not only improves safety and efficacy but, in some cases, permit new and more effective therapies. This review has elaborated simplicity of matrix tablet, designing of matrix tablet and release mechanism of drug from the matrix tablets.

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