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A REVIEW ON MATRIX DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is the most convenient route of drug administration. So far so many oral dosage forms have been developed to improve the patient compliance. The drugs with less half life are eliminated from the body with in short period of time. Such drugs are needed to be administered frequently to get the required plasma drug levels. The increased dose frequency may reduce the patient compliance. This difficulty can be avoided by formulating the drugs as matrix type sustained release drug delivery systems.[1]

KEYWORDS: Matrix tablets, sustained release dosage forms.

INTRODUCTION

Sustained Release dosage forms are most convenient dosage forms to improve the bioavailability of drugs. These dosage forms delay the release of drug by matrix formation there by allow the drug to get solubility and absorption completely from intestinal mucosa. These dosage forms are prepared by using rate retarding polymers which form network like matrix upon hydration.[2] The drugs which are sensitive to gastric environment can also be protected by formulating as matrix type dosage forms because of their ability to withstand the acidic environment. To get a successful sustained release product, the drug must be released from the dosage form at a predetermined rate and dissolve in the gastrointestinal fluids.[5]

The formulations of sustained-release drug delivery systems wish to achieve desired release rates, decrease the number of daily administrations, improve compliance and minimize side-effects. Among all the formulations of sustained release, matrix tablets are useful because of many advantages.[3]

ADVANTAGES OF MATRIX TABLETS[4]

- Easy to manufacture
- Versatile, effective and low cost Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

Ex: Morning relief of arthritis through bed time dosing.[11]

DISADVANTAGES OF MATRIX TABLETS[6]

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.[11]

CLASSIFICATION OF MATRIX TABLETS.[7,8]

On the Basis of Retardant Material Used: Matrix tablets can be divided into 5 types:

1. Hydrophobic Matrices
2. Lipid Matrices
3. Hydrophilic Matrices
4. Biodegradable Matrices
5. Mineral Matrices

1. Hydrophobic Matrices (Plastic matrices)
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 inertor 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.[8]

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. 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.[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. 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.[9]

A. Cellulose derivatives
Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.[9]

B. Non cellulose natural or semi synthetic polymers
Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.[2]

C. Polymers of acrylic acid
Carbopol-934, the most used variety.[9]

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 non enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.[10]

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. On the Basis of Porosity of Matrix:Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous 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 diffusingmolecules 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.

Method of Preparation of Matrix Tablet
A. Wet Granulation Technique[13]
Milling and gravitational mixing of drug, polymer and excipients. Preparation of binder solution. Wet massing by addition of binder solution or granulating solvent. Screening of wet mass. Drying of the wet granules. Screening of dry granules. Blending with lubricant and disintegrant to produce "running powder" Compression of tablet.

B. Dry Granulation Technique[14]
Milling and gravitational mixing of drug, polymer and excipients. Compression into slugs or roll compaction. Milling and screening of slugs and compacted powder. Mixing with lubricant and disintegrant Compression of tablet.

C. Sintering Technique[15]

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compactat a temperature below the melting point of the solid constituents in a controlled. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

MECHANISM OF DRUG RELEASE FROM MATRIX TABLETS[14]

1. Diffusion controlled

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,

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

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

$$dM/dh = C_o . dh - Cs/2 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

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:

$$dM = (Dm. C_s / h) dt \quad \ldots\ldots\ldots\ldots\ldots (2)$$

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:

$$M = [C_s . Dm (2C_o - C_s) t]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

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

$$M = [2C_s.Dm.C_o.t]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

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:

$$M = [D_s . Ca . p/T . (2C_o - p.C_a) t]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots (5)$$

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 = Diffusional path length

For pseudo steady state, the equation can be written as:

$$M = [2D.C_a .C_o (p/T) t]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

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

$$p = p_a + C_a/ \rho + C_{ex} / \rho_{ex} \quad \ldots\ldots\ldots\ldots\ldots (7)$$

Where,

p = Porosity

ρ = Drug density

p_a = Porosity due to air pockets in the matrix

ρ_{ex} = Density of the water soluble excipients

C_{ex} = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k . t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots (8)$$

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. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

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

2. by Swelling[14,15]

In some systems there is anomalous release of the active ingredient. In these systems release is primarily by diffusion. Sometimes the ER polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution. A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodible matrix[16]

1) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix.

2) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

3) Upon contact with water the drug dissolves and diffuses out of the device.

4) With increasing water content, the diffusion coefficient of the drug increase substantially.

5) In the case of a poorly water-soluble drug, dissolved and undissolved drug coexist within the polymer matrix.

6) Finally, the polymer itself dissolves. The penetration of the medium into the matrix is accompanied by the formation of a series of fronts which later disappear along the process of matrix dissolution.

Factors affecting Drug Release from Matrix Tablets

PHYSICOCHEMICAL FACTORS

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 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.[21]

Ionization, pka and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Compounds with very low solubility.[20]

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. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and itretain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.[22]

Biological factors

Biological half-life
Absorption
Metabolism
Distribution
Protein binding
Margin of safety

Biological half-life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t^{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.[25]

Absorption

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs 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.[17,18] Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h to give 80-95% over this time period.

Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-

administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.[21]

Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasingshould be cautious for the prevention of the sameDosage form.[19] Hence criteria for the drug to be used for formulating Sustained-Release dosage form is[21],

- Drug should have law half-life (<5 hrs.)
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- Drug should be absorbed throughout the GIT

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented.[20]

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.[24]

Protein Binding

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required.[22]

Margin of safety

As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rate.[20]

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