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MATRIX DRUG DELIVERY SYSTEM: A REVIEW

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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.

KEYWORDS: Matrix tablets, sustained release dosage forms.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe [in respect to Parenteral route] due to its ease of administration, patient acceptance and cost effective manufacturing process.[1]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:[2]1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. 2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. 3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Controlled drug delivery systems: Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[4] Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories. 1) Delayed release 2) Sustained release 3) Site-specific targeting 4) Receptor targeting More precisely, controlled delivery can be defined as:[5] 1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. 2) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type. 3) Provide a physiologically/therapeutically based drug release system.

Advantages of controlled drug delivery system[6]

1) Avoid patient compliance problems.

2) Employ less total drug

- Minimize or eliminate local side effects
- Minimize or eliminate systemic side effects
- Obtain less potentiating or reduction in drug activity¬ with chronic use.
- Minimize drug accumulation with chronic dosing.

3) Improved efficiency in treatment

- Cures or controls condition more promptly.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Improves bioavailability of some drugs.

E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4) Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period

may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
6) Stability problems.
7) Increased cost.
8) More rapid development of tolerance and counseling.
9) Need for additional patient education and counseling.

Factor affecting the design and performance of controlled drug delivery[4]

1. Drug properties

- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and
- Diffusivity.

2. Biological properties

- Absorption
- Metabolism
- Elimination and
- biological half life
- Dose size
- Route of administration
- Target sites
- Acute or chronic therapy
- Disease condition

Oral controlled drug delivery systems[7]

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
(ii) The anatomic and physiologic characteristics of the gastrointestinal tract and
(iii) Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Methods used to achieve controlled release of orally administered drugs[8]

A. Diffusion controlled system: Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

This system is of two types

a) Reservoir type: A core of drug surrounded by polymer membrane, which controls the release rate, characterizes reservoir devices.

b) Matrix type: Matrix system is characterized by a homogenous dispersion of solid drug in a polymer mixture.

B. Dissolution controlled systems

a) Reservoir type: Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.

b) Matrix type: The more common type of dissolution controlled dosage form. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

C. Bioerodible and combination of diffusion and dissolution systems: It is characterized by a homogeneous dispersion of drug in an erodible matrix. (a) bulk-eroding and (b) surface-eroding Bio erodible systems.

D. Methods using ion exchange: It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract.

E. Methods using osmotic pressure: It is characterized by drug surrounded by semi permeable membrane and release governed by osmotic pressure.

F. pH– Independent formulations: A buffered controlled release formulation, is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

G. Altered density formulations: Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. High-density approach Low-density approach.

Matrix tablets

One of the least complicated approaches to the manufacture of controlled 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.[9]

Drawback of conventional dosage form[10]

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.

Classification of matrix tablets

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

1. Hydrophobic Matrices (Plastic matrices)[13]

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 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.

2. Lipid Matrices[14]

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[15]

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; Hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose. B. Non cellulose natural or semi synthetic polymers: AgarAgar; 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[15]

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[15]

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 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 diffusing 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.

Method of Preparation of Matrix Tablet
A. Wet Granulation Technique[13]
- Milling and 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 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 compact at 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.[15] 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.[16]:
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:
$dM/dh = Co.\ dh - Cs/2$ …… (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:
$M = [2Cs.\ Dm.Co.t]\ 1/2$ …… (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 porousmonolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.[17, 18]

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:
$M = [Ds.\ Ca.\ p/T.\ (2Co - p.Ca)\ t]\ 1/2$ …….. (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.Ca .Co (p/T) t] ½ …….. (6)

The total porosity of the matrix can be calculated with the following equation:
p = pa + Ca / ρ + C ex / ρ ex …… (7)

Where,
p = Porosity
ρ = Drug density
Pa = 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 …….. (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

CONCLUSION

Most of drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentration of the drug on oral administration. Which can be overcome by sustained release formulations, can improve the therapeutic efficacy of drug product especially matrix controls the release of the drug from the formulation. Matrix Sustained Release formulations decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The release of the drug through such system includes dissolution controlled as well as diffusion controlled mechanisms.

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