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MATRIX TABLETS: A TOOL OF CONTROLLED DRUG DELIVERY

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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. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target sites. The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Matrix type drug delivery systems are an interesting and promising option when developing an oral controlled release system. This review focuses on the progress made in the design of controlled release dosage forms employing various types of matrices as carriers for the active ingredients.

Key Words: Controlled drug delivery, Matrices, Oral controlled release system, Matrix tablets.

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parentral 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 Parentral 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 unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.
4) 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) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

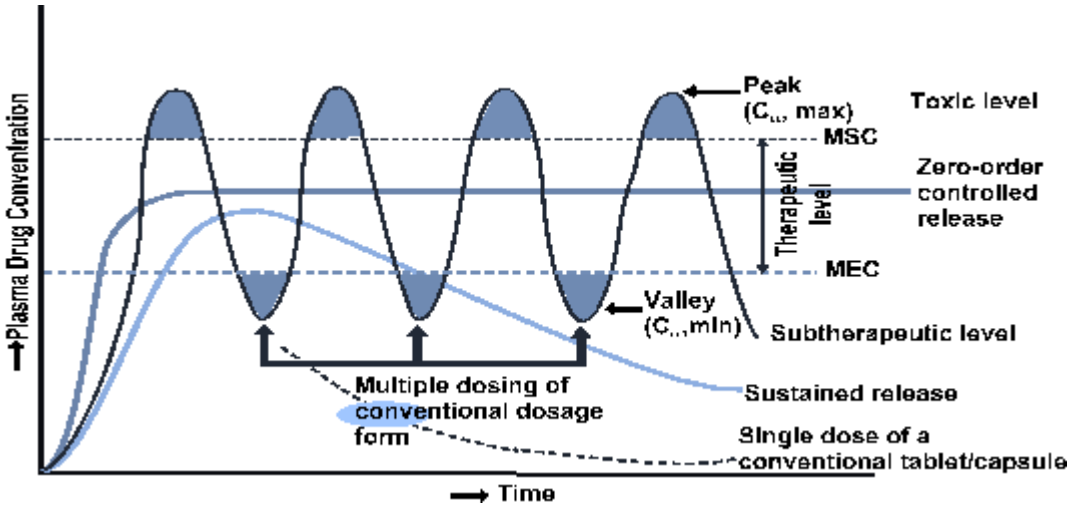

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

Rationale of Controlled Drug Delivery: [5, 6]

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more a design property of a rate controlled dosage form, and less, or not at all, a property of the molecule's inherent

kinetic properties. Thus optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug.

The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. The dose and dosing interval can be modified in case of conventional dosage forms. However, therapeutic window of plasma concentration below which no therapeutic effect is exhibited and above which undesirable effects are manifested. Therapeutic index is the prime parameter for development of a controlled delivery system of a particular drug candidate.

Factors 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

Advantages of Controlled Drug Delivery System: [6]

1) Avoid patient compliance problems.
2) Employ less total drug
    1. Minimize or eliminate local side effects
    2. Minimize or eliminate systemic side effects
    3. Obtain less potentiating or reduction in drug activity with chronic use.
    4. Minimize drug accumulation with chronic dosing.
3) Improve efficiency in treatment

1. Cures or controls condition more promptly.
2. Improves control of condition i.e., reduced fluctuation in drug level.
3. Improves bioavailability of some drugs.
4. Make use of special effects, 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.

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 as shown in figure no.2, 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.

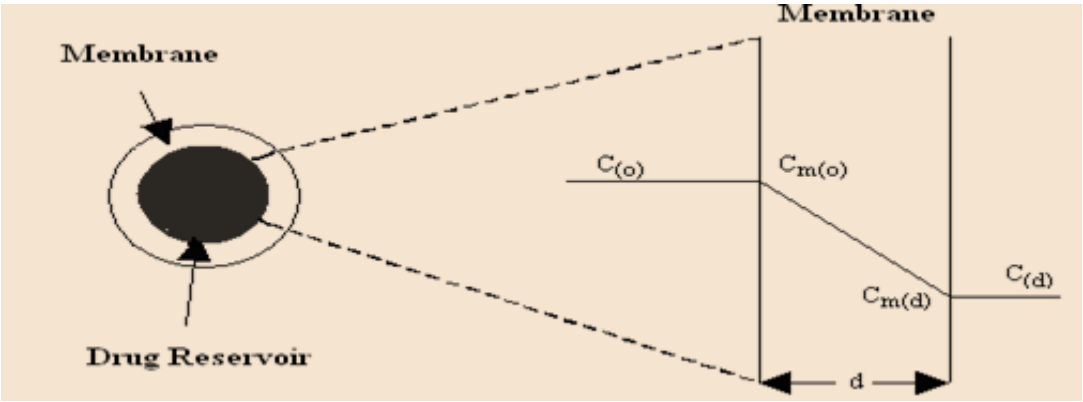

Figure 2: Schematic representation of diffusion controlled drug release reservoir system.

b) **Matrix type:**

The more common type of dissolution controlled dosage form as shown in figure .3. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

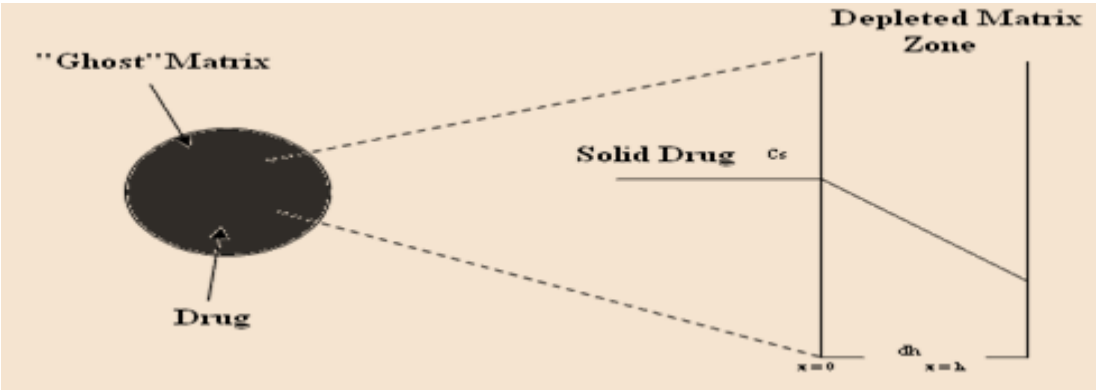

Figure 3: Schematic representation of diffusion controlled drug release matrix system.

C. **Bioerodible and Combination of Diffusion and Dissolution Systems:**

It is characterized by a homogeneous dispersion of drug in an erodible matrix. (Shown in figure.4)

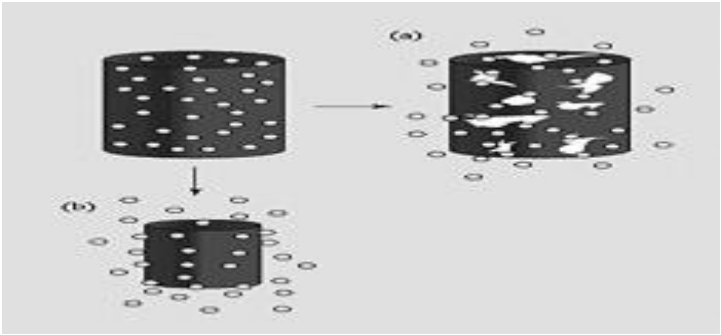

Figure 4: Drug delivery from (a) bulk-eroding and (b) surface-eroding Bio erodible systems.

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 as shown in figure 5, 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.

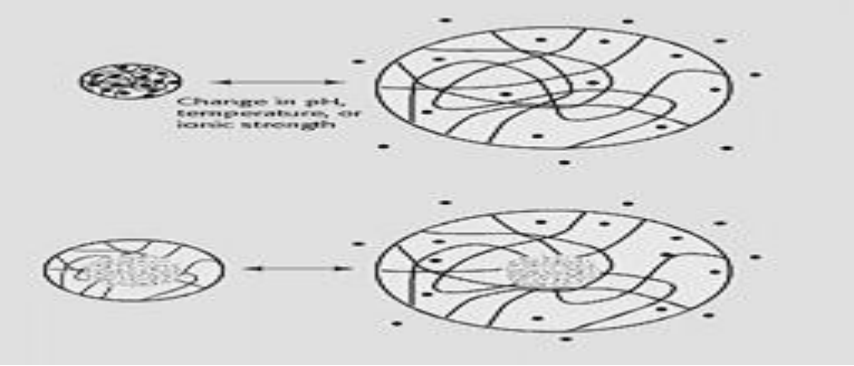

Figure 5: Drug delivery from environmentally pH sensitive release systems.

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] Examples of Retardant Materials used to formulate matrix tablet are shown in Table 1.

Table 1: Examples of Two Classes of Retardant Material used to Formulate Matrix Tablet

Sr No.	Matrix Characteristics	Material
1	Insoluble, Inert	Polyethylene, Polyvinyl chloride, Ethyl Cellulose
2	Insoluble, Erodible	Carnauba wax, Stearic acid, Polyethylene glycol

CLASSIFICATION OF MATRIX TABLETS: [10]

A: On the basis of polymer used

i) Hydrophilic matrix tablet:

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tabulated by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behaviour from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

Cellulose derivatives

- Hydroxyethylcellulose,
- Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps,
- Sodium carboxy methyl cellulose and
- Methyl cellulose 400 and 4000 cps.

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

- Polymer which is used in acrylic acid category is Carbopol 934.

Other hydrophilic materials

- Alginic acid,
- Gelatin and
- Natural gums.

ii) **Fat-wax matrix tablet:**

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminute for controlled-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GIT. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

iii) **Plastic matrix tablet (hydrophobic matrices):**

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Controlled release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminute or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses.

For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

iv) **Bio-degradable matrices:**

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymatic process into olegomers and monomers that can be metabolised or excreted.

Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

v) **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.

MATRIX SYSTEM CAN ALSO BE CLASSIFIED ACCORDING TO THEIR POROSITY AND CONSEQUENTLY AS FOLLOWS

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 diffusing 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.

POLYMERS USED IN THE MATRIX: [11]

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

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.

Hydrophobic Polymers:

This usually includes waxes and water insoluble polymers in their formulation.

Waxes: carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

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.

DRUG RELEASE FROM MATRIX: [12]

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:

$$DM/Dh = Co.\ Dh - Cs/2 \quad (1)$$

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:

$$DM = (Dm.\ Cs / h).Dt \quad (2)$$

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:

$$M = [Cs.\ Dm.\ (2Co - Cs).\ t]\ ½ \quad (3)$$

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

$$M = [2Cs.\ Dm.\ Co.\ t]\ ½ \quad (4)$$

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:

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

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:

$$M = [2D.Ca\ .Co\ (p/T)\ t]\ ½ \quad (6)$$

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

$$p = pa + Ca/\ \rho + Cex/\ \rho ex \quad (7)$$

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:

$$M = k.\ t\ ½ \quad (8)$$

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 of the drug.

COMPONENTS OF MATRIX TABLETS: [11]

These include:

- Active drug
- Release controlling agent(s): matrix formers
- Matrix Modifiers, such as channelling agents and wicking agents
- Solubilizers and pH modifiers
- Lubricants and flow aid
- Supplementary coatings to extend lag time further reduce drug release etc.
- Density modifiers (if required)

Matrix formers:

Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers.

These include hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20-40% of the formulation.

Channelling agents:

These are chosen to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used.

Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

Solubilizers and pH modifiers:

It is often necessary to enhance the dissolution of drug. This may be achieved by the inclusion of solubilising agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

Anti adherent or glidants:

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These materials also can act as glidants and improve the flow of formulations on the tablet machine.

The typical amounts used will depend on the anti adherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an anti adherent.

BASIC PRINCIPLE OF DRUG RELEASE: [11]

In solution, drug diffusion will occur from a region of high concentration to the region of low concentration. This concentration gradient is the driving force for the drug diffusion, out of a system. Water diffuses into the system in analogous manner. There is an abundance of water in the surrounding medium and system should allow water penetration. The inside of the system has low water content initially than the surrounding medium.

Factors Affecting Drug Release from Matrix Tablets: [12]

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

Advantages of Matrix Tablets: [5, 13]

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.

Limitations of Matrix Tablets: [5, 13]

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.

CONCLUSION:

In conclusion, 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.

REFERENCES:

1. Chalo CSL, Robinson JR, Lee VHL. Sustained Release Drug Delivery Systems. Remington's Pharmaceutical Sciences. 17th ed. Mack; 1995.
2. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics a Treatise. 1st ed. New Delhi: Vallabh Prakashan; 1995.
3. Chein YW. Noval Drug Delivery Systems. 2nd ed., New York: Marcel Dekker; 1992:1-42.
4. Jain NK. Pharmaceutical Product Development. 1st ed., New Delhi: CBS Publishers and Distributors; 2006:419-424.
5. Vyas SP, Khar RK. Controlled Drug Delivery Concepts and Advances. 1st ed., New Delhi: Vallabh Prakashan; 2010:1-12.
6. Robinson JR, Lee VHL. Controlled Drug Delivery: Fundamentals and Applications. 2nd ed., New York: Marcel Dekker; 1987: 253-260.
7. Lalla JK. Introduction to Controlled Release and Oral Controlled Drug Delivery System. The Eastern Pharmacist 1991; 45: 25-28.
8. Jantzen GM, Robinson JR. Morden Pharmaceutics. 4th ed., New York: Marcel Dekker; 1996:492-520.
9. Modi SA, Gaikwad PD, Bankar VH, Pawar SP. Sustained Release Drug Delivery System: A Review, Int J Pharma. Res Dev 2011; 2; 12: 147-160.
10. Lieberman HA, Lachman L, Schwartz JB., Pharmaceutical Dosage Forms: Tablets, Volume 3, 2nd ed., 199-287.
11. Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd ed., Churchill livingstone; 2005: 296-298.

12. Wise DL. Handbook of Pharmaceutical Controlled Release Technology. 1st ed., New York: Marcel Dekker, Inc; 2005: 5-24.
13. Kamboj S, Gupta GD. Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms, 2009; 7(6).www.pharmainfo.net/review.