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MATRIX TABLET: AN APPROACH TOWARDS EXTENDED RELEASE OF DRUG DELIVERY

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ABSTRACT
For many past decade oral route administration is most frequent used process as per it is most conventional process for patient and economically cheaper as compare to other administrational process. Matrix tablet offer an important tool for oral extended- release dosage form. Hence matrix system are favoured because of its simplicity, patient compliances etc. The problems like drug targeting, local side effect, frequency administration and fluctuation in blood concentration level can be solved. Oral extended release drug delivery system become very important approach for those drugs which are having slow half life and high dose frequency. Matrix tablet are mainly formulated either by wet or direct compression method using polymers like Poly Methyl Methacrylate (PMMA), Polyglycolic acid, HPMC and many more. The Matrix may be use for hydrophilic, hydrophobic, mineral or biodegradable types. Most of the 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.

KEYWORDS: matrix tablet, extended release, polymers.

INTRODUCTION
Noval drug delivery system now a days is rapidly replacing convential dosage form which provide proper therapeutic dosage form to perticular body to achive the desired drug concentration over specific period of treatment. There are generally two important aspects of drug delivery system i.e**. Spatial placement** and **Temporal delivery of drug.** In spatial placement generally targeted to specific organ/ tissue while on the another side temporal controls the rate of drug delivery to target tissue. Oral route is most compatible form of administration because of its lower price & ease of administration. Tablets are most oldest method for easy administration of drug.[1]

In recent year pharmaceutical industries & academic laborties are generally focusing to create noval drug delivery of drug/ sustained release/ controlled release of drug. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. They generally have prolong & control release of drug that dissolved/ dispered. [2-3]Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants".[4] 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.

Many sustained release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of sustained release systems for poorly water soluble drugs.[5]

Reason for selection of API as model drug[6]
- BCS class II drug it is low soluble in water and highly permeable and it is necessary to sustain the drug release.
- Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
- There is generally less risk of dose dumping.
- Less inter and intra subject variability.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.

- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
- Transport of drug is independent of gastric emptying.

Advantages of Matrix Tablet[7-8]

- 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.

Disadvantages of Matrix Tablet[9-10]

- 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.
- Unpredictable and often poor *in vitro-in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Increased potential for first-pass metabolism.
- Delay in onset of drug action.
- Need for additional patient education and counseling

Polymer use in Matrix Tablet[11-12]

A) Hydrogels

1. Poly-hydroxyethyle methylacrylate (PHEMA)
2. Cross-linked polyvinyl alcohol (PVA)
3. Cross-linked Polyvinyl pyrrolidone (PVP)
4. Polyethylene oxide (PEO)
5. Polyacrylamide (PA)

B) Soluble polymers

1. Polyethylene glycol (PEG)
2. Polyvinyl alcohol (PVA)
3. Polyvinyl pyrrolidone (PVP)
4. Hydroxypropyl methyl cellulose (HPMC)

C) Biodegradable polymers

1. Polylactic acid (PLA)
2. Polyglycolic acid (PGA)
3. Polycaprolactone (PCL)
4. Polyanhydrides
5. Polyorthoesters

D) Non-biodegradable polymers

1. Polyethylene vinyl acetate (PVA)
2. Polydimethyl siloxane (PDS)
3. Polyether urethane (PEU)
4. Polyvinyl chloride (PVC)
5. Cellulose acetate (CA)
6. Ethyl cellulose (EC)

E) Mucoadhesive polymers

1. Polycarbophil,
2. Sodium Carboxymethyl cellulose
3. Polyacrylic acid
4. Tragacanth
5. Methyl cellulose
6. Pectin

F) Natural gums

1. Xanthan gum
2. Guar gum
3. Karaya gum
4. Gum Arabic

Classification of Matrix Tablet

1. **On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types**[13-15]

- **Hydrophobic Matrix (Plastic Matrices)**[13]**:** In 1959 hydrophobic / inert materials was use as a matrix material. In this method oral dosage form are mixed with hydrophobic polymer & then it is compressed to form tablet. Sustained release form by dissolving drugs are diffused through network of channels that exist between polymers particles. Some examples that used as hydrophobic matrixs include Polyethylene, polyvinyle chlorides, ethyle cellulose & acrylate polymers & their copolymers. These types of matrixs tablets become inert in presences of water & gastrointestinal fluid.
- **Lipid Matrices**[14]**:** These type of matrices are prepared by lipid wax & related materials. In these matrices both pore diffusion & erosion drug release can occur. Carnauba Wax in combination with Steric acid are used in Sustained Release formulation.
- **Hydrophilic Matrices**[15]**:** They are mainly used in oral controlled drug delivery system because of its flexibility obtain desirable drug release , cost effective & regulation acceptances.

Polymers used in hydrophilic matrix are divided into 2 group

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.

- **Biodegradable Matrix[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.

- **Mineral Matrix[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.

2. On the basis of porosity of Matrix[16-19]: Matrix system is classified according to porosity and consequently microporous, macroporus and non-porous system.

- **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.

- **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.

- **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 preparation of Matrix Tablet[20]

a. Wet Granulation Technique

- 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

- 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: 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 environment under atmospheric pressure. 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 Tablet:[21-23] Drug outside the layer are first dissolve in bathing solution and then diffuse out of the matrix. This process continues interferences between bathing solution and solid drug move towards interior. This follow diffusion controlled process in which rate of dissolution of drug particles with matrix must be faster then diffusion rate of dissolved drug.

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 behavior for this system can be mathematically describe by 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 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] 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 + Cex / ρex …… (7)

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.

Biological Factors influencing release from Matrix Tablet[24-25]

- Biological Half life
- Absorption
- Metabolism
- Distribution
- Protein Binding
- Margin of safty

Biological half-life: The main goal of oral sustain product is to maintain therapeutic blood level over extended period of time. To achieve this goal drug must enter in systemic circulation approximately at similar rate at which it is eliminated. The elimination rate can be describe quantitatively by 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 good for Sustained Release formulation as it can reduce dosing frequency. 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.

Absorption: The main purpose of forming SR (sustained release) product is to place at delivery system it is necessary that the rate of release is much slower than 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. 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.

Metabolism: Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, they show decrease in bioavability from releasing of dosage. Hences drugs that can be used for formulation of SR doage form are:

- 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

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.

Protein Binding : Pharmacological response of a drug depend on the unbound drug concentration rather then total concentration all the drugs binds to plasma or tissue protein. Protein binding play a very important role in the dosage form theraputical effect as per extensive binding increases half life of the drug.

Below table show the drug to be formulated as a matrix tablet with polymer and method used for its preparation

DRUG USED	CATEGORY	METHOD USED	POLYMER USED
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934, EC
Venlafexine	Anti-depressant	Wet Granulation	Beeswax, Caranuaba wax
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit-RSPO
Minocycline	Antibiotic	Wet Granulation	HPMC-K4M, HPMC-K15M, EC
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP
Metformin HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
Acarbose	Anti-diabetic	Direct Compression	HPMC, Eudragit
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Ambroxol HCL	Expectorent, Mucolytic	Direct Compression	HPMC-K100M,
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100
Diclofenac Na	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP,
Diethylcarbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV

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 rates.

Physiochemical factors influencing release from Matrix Tablet[24-25]

- Dosage size
- Stability
- Partition Cofficient
- Ionization, pka, and aqueous solubility

Dosage Size : Drug which are orally administrated there is upper limit to bulk the size of dosage form. In general consideration, a single dose of 0.5-1.0gm is taken as maximum for conventional dosage form. Compound that have large dosing size can be given in multiple formulation. Another consideration is large drugs with narrow therapeutic range.

Ionization, pka and aqueous solubility: drugs are generally weakly acidic or basic in nature. While on the another hand drugs with unchanged form they are permeates across the lipid membrane and it is important relationship between the pka compound and absorptive environment. Drugs which are in unchanged form are generally having advantages of drug permeation 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 (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Partition coefficient: Drugs which are administrated to GI tract for producing therapeutic effect it must cross various biological membrane. Generally these membrane are lipidic in nature therefore solubility of drug is important to determine the effect of membrane barrier penetration. Compound that are lipophilic in nature have poor aqueous solubility and it retain in lipophilic tissue for longer period of time. While on the another hand compound with lower partition coefficient are difficult to penetrate which result the poor bioavability. The choice of diffusion-limiting membranes is mainly depend on the partitioning characteristics of the drug.

Stability: Drugs which are orally administrated can be hydrolysis and enzymatic degradation can be done in both acidic and basic compound. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.

Effect of release limiting factor on Drug release[24-26]
The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

a. 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 linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

b. Drug solubility: Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

c. Solution solubility: In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

d. 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 crystallanity of polymer. The release of drug may be attributed to the three factors viz,

i. Polymer particle size
ii. ii. Polymer viscosity
iii. iii. Polymer concentration.

e. Thickness of polymer diffusional path: The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion

JD = D dc/dx

Where, JD is 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.

f. Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

g. Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. 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.

h. Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

i. Diluent's effect: 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.

j. 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.

CONCLUSION

This review article has been on the formulation of extended-release matrix tablets, advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

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