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Review Article

AN OVERVIEW ON ORAL CONTROLLED RELEASE MATRIX TABLET

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Among the various routes of drug delivery oral route is most preferred route. But conventional dosage form offers few limitations which could be resolved by modifying the existing dosage form. Sustained and controlled drug delivery system helps in maintaince of constant plasma drug concentration and retards the release rate of drug thereby extending the duration of action. There are various formulation strategies controlled release tablets among which matrix tablet serves as an important tool. Hence the problem like poor patient compliance, multiple dosing, see-saw fluctuations can be easily minimized. Matrix tablets can be formulated by either direct compression or wet granulation method by using a variety of hydrophilic or hydrophobic polymers. The rate of drug release from the matrix is primarily governed by rate and extent of water penetration, swelling of polymer, dissolution and diffusion of drug. Thus,controlledrelease matrix tablet can offer better patient compliance and could be quite helpful in treatment of chronic diseases. The present article concentrates on oral controlled release tablets with a special emphasis on matrix tablet.

Keywords: controlled Release, Matrix Tablet and polymer.

INTRODUCTION

Oral route has been one of the most popular commonly employed routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints, flexible design of dosage forms and cost effectiveness to manufacturing process[1]. Tablets are most popular oral formulations available in market and preferred by patients and physicians alike. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. [1]

1.1. Oral controlled drug delivery system

An alternative to administration of another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations. Oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Controlled release formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduced dose and side effects and increased margin of safety for high potency drugs[2].

The term “controlled release” has been associated with those systems which release their active principle at a predetermined rate[6]. Physician can achieve certain desirable therapeutic benefit by prescribing controlled release dosage forms; since the frequency of drug administered is reduced the patient compliance gets improved. The blood level oscillation characteristic of multiple dosing of

conventional dosage form is also reduced, as a more even blood level is maintained.

Advantages:

1. Maintains therapeutic concentrations over prolonged periods.
2. Avoids the high blood concentration.
3. Reduction in toxicity by slowing drug absorption.
4. Minimize the local and systemic side effects.
5. Improvement in treatment efficacy.
6. Better drug utilization
7. Minimize drug accumulation with chronic dosing.
8. Can be made to release high molecular weight compounds.
9. Improved patient compliance.
10. Economical (Although the initial cost of treatment is high the overall treatment cost will be less due to less dosing frequency).[3]

Disadvantages:

1. The remaining matrix must be removed after the drug has been released.
2. Greater dependence on GI residence time of dosage form.
3. Increased potential for first-pass metabolism.
4. Delay in onset of drug action.[4]

1.2. Challenges in controlled release formulations:

1. Cost of formulation i.e. preparation and processing.
2. Fate of controlled release system if not biodegradable.
3. Biocompatibility.
4. Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants.
5. Dose dumping (Chewing or grinding of oral formulation by the patients).
6. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.[5,6]

1.3. Rationale for designing controlled drug delivery:

1. Reducing the frequency and quantity of dose.
2. To increase effectiveness of the drug by localization at the site of action.
3. To avoid an undesirable local action within the GIT.
4. To provide programmed and uniform drug delivery pattern.
5. To increase extend of absorption/bioavailability.
6. To extend the time of action of drug after administration.[7]

1.4 Ideal drug candidates for controlled drug delivery systems

1. It should be orally effective and stable in GIT medium.
2. Drugs with short half-lives, ideally a drug with half-life in the range of 2 – 4 H makes a good candidate for formulation into CR dosage forms.
3. The dose of the drug should be less than 0.5 g as the oral route is suitable for drugs given in dose as high as 1.0 g.eg. Metronidazole.

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4. A drug for CRDDS should have therapeutic range wide enough such that variations in the release do not result in concentration beyond the minimum toxic levels.[8]

1.5 Matrix tablets:

Matrix tablet may be defined as "oral solid dosage form in which the drug or active ingredient is homogeneously dispersed throughout the hydrophobic or hydrophilic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution controlled or diffusion controlled mechanisms (as shown in Fig 2). Usually the drug release from these matrices includes penetration of fluid, followed by dissolution of drug particles and diffusion through fluid filled pores. The diffusion of drug through a matrix is a rate limiting step. Matrix tablets serves as an important tool for oral extended- release dosage forms. They can be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers. The use of different classes of polymers in controlling the release of drugs has become the most important aspect in the formulation of matrix tablets.[9]

1.6 Polymers used in matrix tablets:

There are number of polymers which may be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required. Polymers used for matrix tablets may be classified as:

1.Hydrogels

- Polyhydroxy ethyl methyl acrylate (PHEMA)
- Cross linked polyvinyl alcohol (PVA)
- Cross linked polyvinyl pyrrolidone (PVP)
- Polyethylene oxide (PEO)
- Polyacrylamide (PA)

2. Soluble polymers

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinyl pyrrolidone (PVP)
- Hydroxypropyl methyl cellulose (HPMC)

3. Biodegradable polymers

- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Polycaprolactone (PCL)

4. Non-biodegradable polymers

- Polydimethylsiloxane (PDS)
- Polyethylene vinyl acetate (PVA)

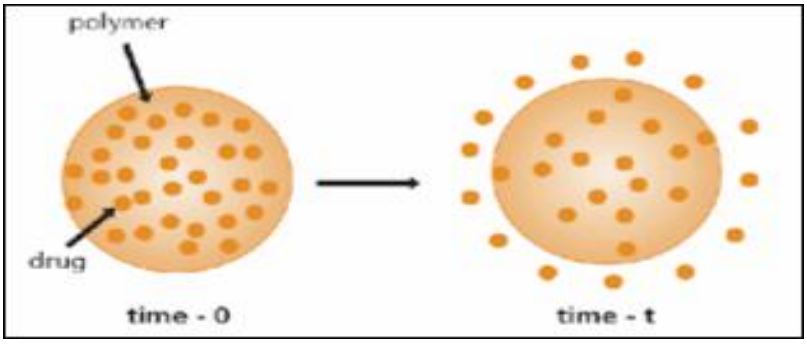

Fig 1: Drug diffusion through matrix tablet

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5. Mucoadhesive polymers

- Polycarbophil
- Sodiumcarboxy methyl cellulose
- Polyacrylic acid

6. Natural gums

- Xanthan gum
- Guar gum
- Karaya gum
- Gum Arabic
- Locust bean gum[10,11,12,13]

1.7 Classification of matrix tablets:

1) Hydrophilic matrix tablet

Hydrophilic matrix tablets may be defined as "Homogeneous dispersion of drug molecules within a skeleton of hydrophilic polymers, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, or carbopol among others, that swells upon contact with water".[14]

2) Hydrophobic matrix tablets

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. The primary rate-controlling components of hydrophobic matrix are water insoluble in nature. Examples of materials that have been used as inert or hydrophobic matrices include waxes, glycerides, polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.[15]

1.8 Mechanism of drug release from matrix tablet:

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.[16]

1.9 Bimodal Release:

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.[17]

Swellable matrix tablets are activated by water, and drug release control depends on the interaction between water, polymer and drug. Water penetration is the first step leading to polymer swelling and polymer and drug dissolution. The presence of water decreases the glassy rubbery temperature (e.g., for HPMC from 184°C to lower than 37°C), giving rise to the transformation of glassy polymer in a rubbery phase (gel layer). The enhanced mobility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The latter may add a convective contribution to the drug transport mechanism in drug delivery.[18]

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The gel layer thickness depends on the relative contributions of water penetration, chain disentanglement, and mass (polymer and drug) transfer in water. At the beginning the water penetration is more rapid than chain disentanglement and a quick build-up of gel layer thickness takes place. But when the water penetrates slowly, due to the increase of the diffusional distance, little chance in the gel thickness is obtained because water penetration and polymer disentanglement rates are similar. Thus the gel layer thickness dynamics in swellable matrix tablet shows three distinct phases:

- It increases when the penetration of water is the fastest phenomenon.
- Stays constant when the disentanglement rate is similar to the penetration.
- Decreases when the entire polymer is in the rubbery phase.[19]

1.10. Swellable matrix tablets as drug delivery systems:

Swelling controlled release systems for drug delivery are very often prepared as monoliths, i.e., matrices formed by compression of hydrophilic micro particulate powders. The amount of swellable polymers usually range from 10-30% of the total weight of the matrix. Different types of swellable matrix tablets can be prepared by the use of hydrophilic polymers, such as:

1. **Free swellable matrix tablets:** Polymers and solid drug mixed and compressed, in which swelling is unhindered.[20]
2. **Swelling restricted matrix tablets:** Their function is to alter the swelling behaviour and then the drug release. The partial coating of swellable matrix tablets containing soluble polymers with impermeable films (Cellulose acetate) created conditions for attainment of zero-order release.

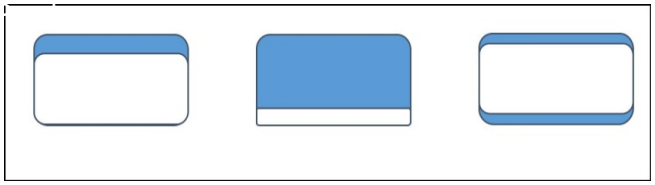

Fig.2: Swelling restricted matrix tablet (Blue colour illustrates coating with Polymer)

3. **Swelling controlled reservoir system:** Swellable polymers are used as coating for delaying or controlling the diffusion of drug from the core.[21]

1.11. Factors affecting drug release from a matrix system:

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.

2.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 crystallinity of polymer. The release of drug may be attributed to the three factors:

(A) Polymer particle size: e.g. when the content of hydroxyl propyl methylcellulose (HPMC) is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable is more important when the content of polymer is low. Results may be justified by considering that in certain areas of matrix containing low levels of HPMC led to the burst release.

(B) Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

(C) Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.[22,11,15]

3. 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= Flux of diffusion across a plane surface of unit area.

D= diffusibility of drug molecule.

dc/dx = conc. gradient of drug molecule across a diffusion path with thickness dx.

4. 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.[14,23]

5. 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 increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. [22]

6. 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.[8]

7. Diluent's effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose, mannose 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.[10]

1.12. Biological factors influencing release from matrix tablets:

Biological half-life: SR product aims to maintain therapeutic blood levels over an extended period of time. In order 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 h such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 h are also generally not used in sustaining form, since their effect is already sustained.E.g. Digoxin and phenytoin.maximum half-life for absorption should be approximately 3-4 h; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 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. 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.[25]

1. Metabolism: Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence, criteria for the drug to be used for formulating SR dosage form is:

- Drug should have short half-life (2-4 h.)
- Drug should be soluble in water
- Drug should have large therapeutic window
- Drug should be absorbed throughout the GIT

2. 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.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.[15]

3. 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.

4. 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 for this type of drug.[10,11]

5. Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with low therapeutic index are usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.[26]

1.13. Physicochemical factors influencing release from matrix tablets:

1. Dosesize: 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 0.5-1.0 g is considered maximal for a conventional dosage form. This also holds true 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.[12]

2. 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. 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 pH and 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.[13]

3. 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 having lipophilic nature; 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 it retain 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. [26]

4. Stability: Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form 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.[22]

1.14. Evaluation of controlled release matrix tablets:

Before marketing a controlled release product it is necessary to assure the strength, safety, stability and reliability of the product by performing *in vitro* and *in vivo* analysis and correlation between the two.

1.15. *In vitro* Evaluation:

For solid oral controlled release dosage forms, drug release characterisation is the most important among various *in vitro* tests because the *in vivo* absorption is determined by the release kinetics of the dosage forms. Avalidated *in vitro* dissolution test can serve the purposes of

- Providing necessary quality and process control
- Determining stability of the relevant release characteristics of the product
- Facilitating certain regulatory determinations and judgments concerning minor formulation changes, change in site of manufacture

However the dissolution rate of a specific dosage is essentially arbitrary parameter that may vary with the dissolution methodology, such as type of apparatus, medium, agitation, etc. The key elements during the dissolution evaluation include:

- Reproducibility of the method
- Maintenance of sink condition
- Dissolution profile with a narrow limit on 1-h specification to assure lack of dose dumping
- At least 75% of drug released at the last sampling interval to assure complete release.[27]

Commonly used USP dissolution methods are recommended for determination of drug release from oral controlled release dosage forms are;

(I) USP apparatus I (basket method): Preferred for capsules and dosage forms that tend to float or disintegrate slowly.

(II) USP apparatus II (Paddle method): Preferred for tablets.

(III) USP apparatus III (Bio-Dis dissolution method, or modified disintegration): Useful for bead type dosage form.

(IV) USP apparatus IV (Flow-through cell method): For insoluble drugs.[18]

1.16. *In vivo* performance evaluation:

Once the satisfactory *In vitro* profile is achieved, it becomes necessary to conduct *in vivo* evaluation and establish an *in vitro* - *in vivo* correlation. The various *in vivo* evaluation methods are:-

- Clinical response
- Blood level data
- Urinary excretion studies
- Nutritional studies[24]

CONCLUSION : It is concluded that, Oral controlled Release tablets provide the drug release in a modified form than their counterparts. It is an effective to ascertain the therapeutic goals with maximum patient compliance. However, accurate adjustment of various physicochemical parameters is necessary. Matrix tablet is helpful in overcoming the problems associated with conventional dosage form. Apart from various advantages associated with it cost effectiveness and once daily dose are the key benefits associated with it. Due to its key benefits and better patient compliance it can easily lead the market by replacing its counterparts.

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