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Review Article

Formulation Aspects With an Comparative Influence of Different Parameters Over Matrix Tablet

Jadhav A. S.*, Tarkase K.N.

P.D.V.V.P.F's College of Pharmacy, Vilad Ghat, Ahmednagar (M.S.), India

ABSTRACT

An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug towards specific organ or a tissue and controlling the rate of drug delivery to the target tissue. Matrix tablet is an interesting option when developing as oral controlled release formulation. The Present study focus on oral controlled release dosage forms and types of various polymers used to formulate Matrix Tablets.The use of polymer in controlling the release of drug has become important in the formulation of pharmaceuticals.

Keywords: Polymer, Therapeutic , Matrices , Diffusion ,Erosion ,Dissolution etc.

INTRODUCTION

Tablets offer safe end convenient method of active pharmaceutical ingredients administration with excellent physicochemical stability and accurate dosing. The term modified release dosage form is used to describe products that alter the timing and rate of drug release of drug substance.Controlled delivery system: Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time.

For an oral delivery of a drug :

1) Conventional Release dosage form: Designed to release the for an specified period of time.:i.e. not more than 6-8 Hrs

2) Extended release dosage Form: Extended release products are designed to release their medication in a controlled manner at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.

3) Delayed release dosage form: Delayed release products are designed to release their medication in basic environment over the intestine. Enteric/delayed release coatings consist

Author for CorrespondenceE.Mail: mr.asjadhav@rediffmail.com

of pH sensitive polymers, which means the coating remains intact in the acidic environment of the stomach and then solubilizes in the more alkaline environment of the small intestine.

Extended Vs Conventional Forms:

Extended release tablets & capsules = take once or twice daily Conventional forms = 3 to 4 times daily to achieve same therapeutic effect.

For non oral rate-controlled DDSs = 24 hours for most trans dermal patches to months to years

Drawbacks Associated with Conventional Dosage Forms:

1 Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. Typical peak valley plasma concentration –time profile is obtained which makes attainment of steady-state condition difficult.

Fluctuation in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic Index (TT) whenever over medication occurs.

Advantage of controlled release drug delivery system.

1) Therapeutic advantage: Reduction in drug plasma level fluctuation ;maintenance of steady plasma level of the drug over a prolonged time period.

2) Reduction in adverse side effects & improvement in tolerability : Drug plasma levels are maintained with in a narrow window with no sharp peaks & with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage forms.

3) Patient comfort and compliances: Oral Drug delivery is the most common and convenience for patients and a reduction in dosing frequency enhances compliance.

4) Reduction in healthcare cost: The total cost of the controlled release product could be comparable or lower than the immediate release product. With reduction in side effects, the overall expenses in disease management also would be reduced.

5) Avoid night time dosing: It is also good for patient to avoid night time dosing

Mechanism aspects of Oral drug delivery formulation

1.Dissolution : 1.Matrix 2.Encapsulation

2.Diffusion : 1.Matrix 2.Reservoir

3.Combination of both dissolution & diffusion.

4. Osmotically controlled

Classification of Matrix tablet[5,18] on the basis of retardant material used:

1) Hydrophobic Matrices (Plastic material): Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted particles. The possible mechanism of drug release in such type of tablet is by diffusion. Example of material that has been used as inert or hydrophobic matrices are Polyethylene, Polyvinyl chloride, Ethyl cellulose etc.

2) Lipid Matrices:These matrices are prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Ex. Of polymer used are Carnuba wax etc.

3) Hydrophilic Matrices:Formulation of tablet by using the polymer having high gelling capacity These system are called as 'swell able controlled release system' Ex. Cellulose derivatives HPMC , Methyl cellulose, Sodiumcarboxy methyl cellulose. Polyethylene glycol, polyvinyl alcohol,

4) Biodegradable Matrices:They are biologically degraded or eroded by enzymes generated by surrounding living cell or by nonenzymatic process in to olegomers & monomers that can be metabolized or excreted. Ex.Synthetic polymers such as aliphatic polyesters .i.e. Polyglycolic acid(PGA) , Polylactic acid (PLA), Polyortho esters.

5) Natural Gums: Ex. Xanthan gum ,guar gum , Locuast bean gum.

(A)On the Basis of Porosity of Matrices:[5,18]

Matrix can also be classified on the basis of Porosity :

1) Macroporous System : In such type of systems the diffusion of drug occurs through pores of matrix having size range 0.1 to 1 μm

2) Microporous System: For microporous system , pore size ranges between 50 – 100 Å

3) Non-porous System: Non-porous system has no pores and the molecules diffuses through the network meshs.

Advantages of Matrix Tablets

1)Easy to manufacture

2) Versatile, effective and low cost

3) Can be made to release high molecular weight compounds.

4) Reduce in drug blood levels fluctuations.

5) Frequency in reduction of dosing.

6) Reduces in adverse side effects associate with excess of drug In the body.

7) More uniform drug effect.

8) Improvement in treatment efficacy.

9) uses of less total drug.

10) Improve the bioavailability of some drug.

11) Improvement of the ability to provide special effects.

Drug Release From Matrix Tablet:[5,7,12]

i.e. Hydrophillic Matrix: After oral administration and exposure to aqueous medium , the polymer in hydrophilic matrix tablet quickly hydrates on the surfaces and forms a gel layer around the tablet.the outermost layer of gelled polymer reaches a dilution point where it no longer has structural integrity and the polymer is finally disentages and leaves the surface of the matrix. This phenomenon is referred to as erosion.

Drug release from the hydrophilic matrices ,takes place via.

1) Diffusion of water soluble drugs through the hydrated gel layer.

2) Diffusion and erosion of insoluble drug.

3) A combination of above.

Diffusion controlled matrix system: In diffusion controlled extended release system the transport by diffusion of dissolved drugs in pored filled with gastric or intestinal fluid in a solid phase is the release controlling process Depending on the part of release unit in which the drug diffusion is taking place, diffusion controlled release systems are divided into

1) Matrix system

2) Reservoir system

In the Matrix systems diffusion occurs in pores located within the bulk of the release unit, and in reservoir system diffusion takes placein a thin water insoluble film or membrane often about 5-20 μm thick which surrounds the release unit.

Drug is released from a diffusion controlled release unit in two steps

1) The liquid that surrounds the dosage form penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.

2) The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released .

Dissolution controlled release system:

In dissolution controlled extended release system the rate of dissolution in the gastrointestinal juices of the drug or another ingredient is the release controlling process. It is obvious that a

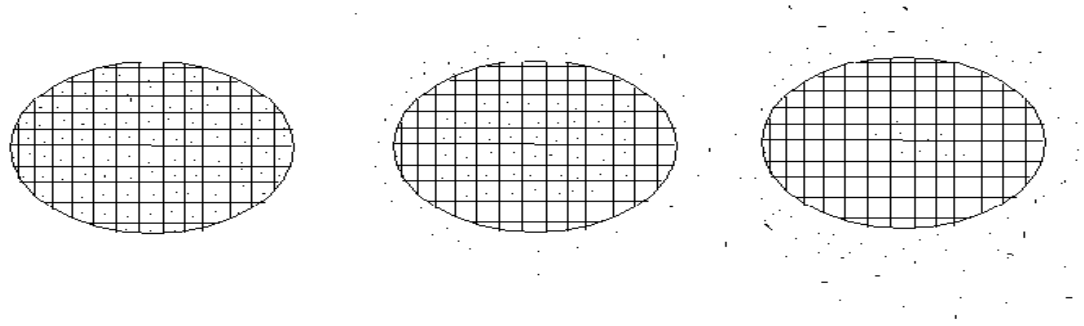

Fig 1: Diffusion control matrix system

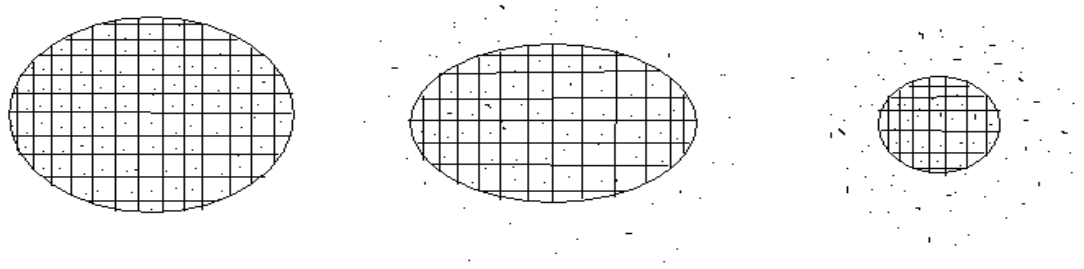

Fig 2 : Dissolution control release system (Following surface errosion)

sparingly water soluble drug can form a preparation of a dissolution controlled extended release type. A reduced drug solubility can be accomplished by preparing poorly water soluble salts or derivatives of the drug. An alternative means to achieve extended release based on the dissolution is to incorporate the drug in a slowly dissolving carrier. Dissolution controlled extended release can also be obtained by covering dug particle with a slow dissolving coating.

The release of this drug from such units occurs in two steps:

1) The liquid that surrounds the release unit dissolves the coating .

2) The solid drug is exposed to the liquid and subsequently dissolves.

Erosion controlled release system: In erosion controlled release system the rate of release is controlled byerosion of a matrix in which the drug is dispersed. Then matrix isnormally tablet i.e. matrix is formed by tabletting operations, and systemcan thus be described as a single unit system .The erosion in its simplestform can be described as a continuous liberation of matrix

material from the surface of the tablet i.e. the surface erosion. The consequences will becontinuous reduction in the tablet weight during the course of therelease process.(as shown in the fig 2). Drug release from an erosion system can thus be described in two steps:

1)Matrix material in which drug is dissolved or dispersed , is liberated from the surface of the tablet.

2)The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

Release limiting parameters [18]:

1) Drug Solubility – Hydrophilic or hydrophobic and molecular weight of drug molecule are important determinants in the release of drug form swelling and erosion controlled polymeric matrices.

2) Polymer hydration – The most important step in polymer dissolution include absorption of water in more accessible places , rupture of polymer –polymer linkages with the simultaneous forming of water polymer linkages , separation of polymeric chains , swelling and finally dispersion of polymeric chain in dissolution medium

3) Polymer viscosity- Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. The greater the viscosity of the gel , the more resistant the gel is to dilution and erosion,thus controlling drug dissolution.

4) Polymer concentration- An increase in polymer concentration causes an increase in the viscosity of gel as well as formation of gel layer with a longer diffusion path.

5) Surface area and Volume – Both the in vivo and in vitro rate of drug release are observed to be dependent on Surface area of the dosage form.

6) Diluents effect – The effect of diluents or fillers depends upon the nature of diluents. Water soluble diluents like lactose cause marked increase in drug release rate end 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. Because water soluble fillers 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.

7) Additive - The effect of adding non polymeric excipients to a polymeric matrix has been increases in the release rate of hydro soluble active principles. These increases in release rate

would be marked if the excipient are soluble like lactose and less important if the excipient are insoluble like dicalcium phosphate .

Biological Factors Influencing Release of drug From Tablet:

1) Absorption - The purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential. absorptive regions before drug release is complete. 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.

2) 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

3) 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 Sustained-Release dosage form is,

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

4) Biological Half Life- The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). 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.

5) 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.

6) 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.

Evaluation of Matrix Tablet:[3,7,10,11,12,15,16]

1) Characterization of Tablets

a) Hardness- For each formulation, the hardness of 10 tablet was determined

b) Friability- Friability is the measure of tablet strength, this test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablet to the distance of 6 inch in each revolution. A sample of pre weighted (20)tablets

Was placed in Roche friabilator which was then operated for 100 revolations. The tablet then dedusted & reweighted. A loss in weight of less than 1% is generally accepted.

c) Weight Variation- To find out weight variation 20 tablets of each formulation were weighted individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find out the deviation in weight. The test was performed according to the official method.

d) Content Uniformity- studies are performed by carrying individual assay of each tablet and % drug in tablet is determined and according to the official monograph results are checked.

2) Swelling Index- Polymeric studies are mainly been performed under swelling Index. Where the total % wt increased of the tablet by keeping it in petri dish containing dissolution medium for a specified period i.e. upto 1 Hr.

$$SI = \frac{\text{Final wt. - Initial wt.}}{\text{Final wt.}} \times 100$$

3) In Vitro Drug Release studies- The invitro drug release studies are been performed over USP -|| (type 2) apparatus. the dissolution medium and RPM are been kept as per specified in the monographic specification.

4) Scanning electron microscopy- Tablet samples were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet.

Key attributes for a successful ER hydrophilic matrix include :

1. Fast hydration of surface polymer and gel formation (to prevent burst release of soluble to highly soluble drugs)
2. Uniform distribution of polymer in the drug matrix.(to give consistent swelling /erosion intra and inter tablet batch)
3. Sufficient polymer concentration on the tablet surface as well as inside the tablet to prevent pre mature tablet disintegration (extremely crucial to prevent dose dumping)
4. Smaller particle size of polymer (in order to have uniform distribution within the tablet and also to hydrate faster due to high surface area)

Drugs can be formulated under matrix tablet :

Propranolol (Anti-hypertensive)

Venlafexin (Anti-Depressant)

Minocycline (Anti-biotic)

Ibuprofen (Anti-inflammatory)

Metformin (Anti -diabetic)

Aceclofenac (Anti -inflammatory)

Aspirin (Anti- inflammatory)

Enaprilmeleate (ACE inhibitor)

Indomethacin (Anti-inflammatory)

Metopralol (Anti-hypertensive)

Losertan Potassium (Anti-hypertensive)

Tramadol (Anti-Hypertensive)

Amlodipine (Anti- arrythmatic)

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