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Review Article

A REVIEW ON EXTENDED RELEASE MATRIX TABLET

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ABSTRACT

Purpose: The aim of the study was to explore the necessity, advantages and different techniques of extended release matrix tablet to achieve continuous delivery of drugs at predictable rate and reproducible kinetics for a preterm delivery and provide a therapeutic amount of a drug to the proper site of the body to achieve promptly and then maintain the desired drug concentration.

Approach: Different types of extended release matrix tablet have been explained briefly along with the various formulation which mainly by wet granulation or direct compression method or by dispersion of solid particle within a porous matrix formed by using different polymers like HPMC, guar gum, xanthan gum, pectin, chitosan etc.

Finding: The matrix controls the release rate of drug. Release retardants like HPMC can aid in extended release and thus they form core excipient of the formulation. The matrices used may be hydrophilic, hydrophobic, mineral, or biodegradable types. The drug release rate can be studied by in vitro dissolution studies. Some drugs that have been formulated as extended release matrix tablets are Ambroxol HCl, Clarithromycin, Indomethacin etc.

Conclusion: The extended release matrix tablets can assure better patient compliance through reduction in total dose and dosage regimen, which can be great help to treat chronic diseases. This review highlights the types of matrices, mechanisms involved and evaluation studies.

Key words: *Extended release, Polymer, in vitro dissolution, Matrix tablet.*

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Introduction

The design of extended release matrix tablet should be aimed to achieve continuous delivery of drugs at predictable rate and reproducible kinetics for a pre term delivery and prolong the therapeutic blood or tissue levels of the drug. The ideal extended release drug delivery system should have the advantage of single dose for complete duration of treatment and it should deliver the active drug directly at specific target.[1] Extended release tablets are provided to release their active ingredients in controlled and pre-determined rate to achieve and maintain optimum therapeutic blood levels of drug. Therefore by this technology can provide better control of plasma drug levels over longer periods of time and less frequent dosing, improve the patient compliance.[2]

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Characteristics of Drug Suitable for Extended Release Tablet [3, 4, 5]

The ideal physicochemical and pharmacokinetic characteristics of drugs which can be formulated as extended release tablet are as follows:

a) Molecular size should be below of 1000 Dalton.

b) Aqueous solubility should be more than 0.1 mg/ml for pH 1 to pH 7.8.
c) The partition coefficient should be high.
d) Absorption mechanism should be diffusion and the general absorbability from all GI segments release should not be influenced by pH and enzymes.
e) Elimination half-life should be between 2 to 8 hrs.
f) Drugs should not metabolized before absorption it caused less bioavailability.
g) Absolute bioavailability should be 75% or more.
h) Absorption rate constant (Ka) should be higher than release rate.
i) Apparent volume of distribution (Vd) should be large.
j) Total clearance should not depend on dose.
k) Elimination rate constant are required for design and therapeutic concentration (Css) should be low and smaller (Vd).

Drugs those are Unsuitable for Such Design: [3, 4, 5]

- Elimination half-life less than 2 hours.
- Administered in large dose.
- Therapeutics index is narrow.
- Poor water solubility.
- Long elimination half-life.
- Drugs having extensive first-pass clearance.

Advantages of Extended Release Matrix Tablet

1. Reduce dosage frequency.
2. Reduce fluctuation in circulating drug level.
3. Increase patient compliance.
4. Avoidance of night time dosing.
5. More uniform effect.
6. Reduction in GI irritation and dose related side effects.[6, 7, 8]

Disadvantages of Extended Release Matrix Tablet

- Highly expensive.
- Often poor invivo-invitro correlation.
- Dose dumping.
- Often poor systemic availability.
- Need for additional patient education and counseling.[9,10]

Approaches to Achieve Extended Release Matrix Tablet: [11, 12, 13]

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. The fundamental principle in design of extended release tablet are to slowing down of absorption, bio transformation and excretion rate respectively.

Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release.

1) Diffusion controlled release system.
2) Dissolution controlled release system.
3) Ion exchange resin drug complex.
4) Swelling controlled release.

Mechanism:

A matrix system consists of active and inactive ingredients, which are homogeneously dispersed and mixed in the dosage form. According to the materials used, the matrix systems have different mechanisms toward the controlled action. The release from matrix type formulations is governed by Fick's first law of diffusion.[14]

Types of matrix systems:

There are two types of matrix systems which are as follows

1. Slowly Eroding Matrix:

It consists of materials or polymers which erode over a period of time such as waxes, glycerides, stearic acid, cellulosic materials etc. The Portion of drug intended to have extended action is combined with lipid or cellulosic material and then granulated. Untreated drug granulated both mixed.[14]

2. Inert plastic Matrix:

The rate controlling release ingredients of hydrophilic matrix are polymers which act by swelling when it contact with aqueous solution and form a gel layer on the surface of the system.[14] Swelling or dissolution can be the effective factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.[15]

❖ Limitations of Matrix System

Matrix systems have lack of flexibility in adjusting to constantly change dose levels as needed by clinical

study outcome. Therefore new dosage strength is necessary. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix based technologies such as bilayer tablets are required.[16]

Different methods adopted based on type of matrix system used in ER tablet formulation:

A) Hydrophilic Matrix System:

At first drug granulated with inert, insoluble matrix polymers. Granules are compressed by direct compression technique. The formulated matrix tablet shows slowly releasing of API from the inert plastic matrix by leaching of body fluids and followed by the diffusion system.Inert insoluble polymers such as polyethylene, polyvinylacetate, polystyrene, polyamide or polymethacrylate.[16]

B) Fat-wax Matrix Tablet:

The methods involve in incorporation of drug into fat wax. Granules are sprayed congealing in air, blending in an aqueous media with or without the surfactant and dried by spray drying technique. A suspension of drug and melted fat wax are solidified by using fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. In this type of matrix tablet, drug is released by leaching and hydrolysis mechanism.[16]

C) Hydrophobic Matrix Tablet:

The method involve in preparation of hydrophobic matrix tablet is direct compression of drug with plastic materials and also can be granulated to desired particle size to facilitate mixing with the drug particle.[16]

D) Biodegradable Matrix Tablet:

It can be prepared by using polymers which comprised of monomers linked to each other by functional groups and have unstable linkage in the backbone. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.[16]

E) Mineral Matrix Tablet:

Mineral matrices can be prepared by using polymers which are obtained from various species of seaweeds. Example: Alginic acid which is a hydrophilic carbohydrate.[16]

POLYMERS USED IN MATRIX TABLET:

- Hydrogels: Poly hydroxyl ethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA).
- Soluble polymers: Poly ethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP).
- Biodegradable polymers: Polylactic acid, Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides etc.
- Non-biodegradable polymers: Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC).
- Mucoadhesive polymers: Polycarbophil, Sodium carboxy methyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum etc.[17,18,19,20]

Evaluation Parameters for Extended Release Matrix Tablets:

The extended release matrix tablets are to be evaluated like the routine checks for the tablets such as average weight, thickness, hardness, weight variation etc. The main parameter required to be monitored while formulating an extended release matrix tablets is in vitro release of the drug and that is in turn demonstrated by dissolution profile.[21,22,23]

General Aspects of Dissolution Test

In vitro dissolution testing is an important tool for evaluation of the best formulation. Dissolution testing is also utilized to define the biopharmaceutical characteristics and to identify possible risk such as potential food effects on bioavailability or interaction with other drugs. For extended release matrix tablet, to achieve special pharmacokinetic profiles, the major considerations should be done on solubility characteristics (sink) and physiological environment specification.[24]

Test medium

An aqueous test medium is preferred as dissolution medium but always needs adjustment by adding additives like enzyme, salt and surfactant.[24]

pH of test medium

In quality control usually one pH-level is used for dissolution testing. Exception are only made for extended release formulation by using different pH-levels.[24]

Apparatus

The types of apparatus used for ER-formulations are the paddle and the basket method respectively. In addition, the flow-through cell; the reciprocating cylinder and other dissolution model are used in testing of ER-formulations.[24]

Agitation

Several rotation speeds are specified in the various Pharmacopoeias. For basket / paddle 50-100 (150) rpm are described in the European Pharmacopeia, whereas 100 rpm for basket and 50-75 rpm for paddle are recommended by the FDA.[24]

Sinker

By few exception like Japan's pharmacopeia, there is no exact specifications regarding sinkers are established. Flexibility should be applied and justification of choice should be given.[24]

Test Duration

At least 80% dissolution should be achieved within the test period. Test duration to the dosage interval is justified when time axis in vitro and in vivo are in a 1:1 relationship. If the dissolution reached below of 80%, it may be accepted, in case, the test duration was at least 24hours.[24]

Setting of Specification

For ER formulation, The Federation International Pharmaceutique (FIP)- Guideline and European Pharmacopeia recommended at least 3.

Specification points as follows:

a) After 1-2 hours / 20-30 % to provide assurance against premature drug release.

b) Round 50 % to define dissolution pattern.

c) At least 80 % to ensure almost quantitative release. (FIP: < 80 % be justified / at least 24 hours)[24]

CONCLUSION:

The focus of this review article has been on the formulation of extended release matrix tablets, advantages and disadvantage, types of polymers used, method of preparation and evaluation parameters. 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.

List of various drugs which can be formulated as anextended release matrixtablet with polymer and its preparation:

DRUGS	CATEGORY	METHOD USED	POLYMER USED
Ambroxol Hcl	Secretolytic agent	Direct compression	Methocel K15MCR,
		Wet granulation	PVP K[30].25 Pectin, Guar gum.[26]
Diclofenac Sodium	Anti-inflammatory	Direct compression	Chitosan, Ethyl cellulose HPMC, Xanthan gum.[27]
Metformin Hydrochloride	Anti-diabetic	Direct compression	HPMC(K4M),HPMC (K100M) and Xanthan gum.[28]
Cefpodoxime	Antibiotic	Direct compression	HPMC (K100), HPMC (K4M), Xanthan gum.[29]
Risperidone	Antipsychotic	Direct compression	HPMC(Methocel K15M CR) Avicel 102.[30]
Lamivudine	Antiviral	Direct compression	Guar gum, Tragacanth gum PEG-6000.[31]
Isoniazide	Anti-tubercular	Wet granulation	HPMC K200M, Ethyl cellulose.[32]
Terbutaline Sulphate	bronchodilator	Wet granulation	HibiscuERosa-sinensis, Microcrystalline cellulose, Magnesium stearate.[33]
Indomethacin	Anti-inflammatory	Wet granulation	Xanthan gum, Guar gum.[34]
Cefixime trihydrate	antibiotic	Wet granulation	Tamarind Gum, Carnauba wax, HPMC, MCC, PVP K30.[35]
Propranolol hydrochloride	Antidysrhythmics	Wet granulation	native dextran, hydroxypropyl methylcellulose (HPMC).[36]

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