

A REVIEW ON CONTROLLED RELEASE MATRIX TABLET

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Article Info: Received 01 August 2020; Accepted 10 September 2020

DOI: <https://doi.org/10.32553/ijmbs.v4i9.1401>

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Conflict of interest: No conflict of interest.

Abstract

Oral route is the most convenient route of drug administration. So far so many oral dosage forms have been developed to improve the patient compliance. The drugs with less half life are eliminated from the body with in short period of time. 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. This review highlights the types of matrices, mechanisms involved and evaluation studies.

Keywords: Controlled release, matrix tablet, Polymer, Diffusion

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]

An ideal controlled drug delivery system is that which delivers the drug at a specific rate locally or systemically for a specified period of time with minimum fluctuation in plasma drug concentration, reduced toxicity and maximum efficiency. In present scenario conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Oral drug delivery is the most preferred and convenient route of drug administration due to high patient compliance, cost- effectiveness, least sterility constraints, flexibility in the design of dosage form and ease of production^[2]. Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery as a result of more prominent strength, precision in dose, production ease, and formulation of tablets is favoured oral dosage form.

Oral Controlled Drug Delivery Systems^[3,4]

Oral controlled release drug delivery is a system that provides 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 .

Classification of Oral Controlled Release Systems^[4,5]

Among all routes of administration, the oral route has been most popular and successful. Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution- Controlled release
 - a. Encapsulation dissolution control
 - b. Matrix dissolution control
2. Diffusion-Controlled release
 - a. Reservoir devices
 - b. Matrix devices
3. Combination of Dissolution and Diffusion systems.
4. Ion Exchange System.
5. Osmotic Pressure System.
6. pH-Independent System.
7. Altered Density System.

Diffusion Controlled Systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types (or) subclass of diffusional systems are recognized.

➤ **Reservoir devices Diffusion control and**

➤ **Matrix devices.**

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. Matrix tablets is a promising approach for the establishment of extended release drug therapy as tablets offer the lowest cost approach to sustained and controlled release and sustained release solid dosage forms.^[6]

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 ^[7]. These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level ^[8].

Criteria of drug to be met to formulate sustained/controlled release dosage forms: ^[9,10]

- a) Desirable half-life.
- b) High therapeutic index.
- c) Small dose.
- d) Desirable absorption and solubility characteristics.
- e) Desirable absorption window.
- f) First past clearance.

(a) Desirable half-life:

The half-life of a drug is an index of its residence time in the body. If the drug have a short half-life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage form, and sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

(b) High therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

(c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undermined. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

(d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such Compounds into sustained release formulations is therefore unrealistic and may reduce overall absorption efficiency.

(e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an Absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage forms are unsuitable.

(f) First pass clearance:

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms ^[9,10]

Classification of matrixtablets

**A) On the Basis of Retardant Material Used:
Matrix tablets can be divided in to 5 types.**

1. Hydrophobic Matrices (Plastic matrices)

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers .The rate- controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become

inert in the presence of water and gastrointestinal fluid.^[11]

2. *Lipid Matrices*

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.^[12]

3. *Hydrophilic Matrices*

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. In fact a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

A. *Cellulose derivatives:*

Methylcellulose 400 and 4000 cps, Hydroxy ethylcellulose, Hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000 cps; and Sodium carboxymethyl-cellulose.

B. *Non Cellulose derivatives*

Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches. Polymers of acrylic acid: Carbopol-934, the most used variety.

4. *Biodegradable Matrices:*

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 Natural polymer such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. *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 (Phaeophyceae) by the use of dilute alkali^[13]

B) *On the Basis of Porosity of Matrix:*

Matrix tablets can be divided in to 3 types.

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 diffusant 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 diffusant 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.^[14,15]

C) *On the basis of the way of matrix preparations*

1. *Floating matrix system*

In this type of matrix system, the bulk density of the matrix is lower than the gastric fluid in the stomach. After creating buoyancy in the stomach, the release of drug molecules from the matrix can occur slowly, which prolongs gastric residence time and thereby increases the bioavailability of fast release drug molecules.^[16]

2. *pH sensitive matrix system*

In this type of matrix system, an enteric coating of the matrix system can provide protection for the drug from the harsh acidic media of the stomach. Thus, low pH sensitive drug molecules can reach the small intestine and colon safely. This matrix system works by releasing the enteric coated drug at a specifically high pH value in the GIT, where drug absorption can occur in the right location. PH sensitive polymers such as HPMC- phthalate or cellulose acetate phthalate can be used in this type of matrix system.^[17]

3. *Mucoadhesive matrix system*

Mucoadhesive matrix systems are designed to enable prolonged retention in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability. In this type of matrix system, the release of the drug is controlled over a period of time. The targeted tissues can be gastrointestinal, buccal, ocular, nasal, respiratory, rectal, urethral and vaginal tissues. In addition, this type of matrix system can be applied to any mucosal tissue in the body. The used materials in this system are swellable hydrophilic polymers which can interact with the glycoproteins being available in the mucous layer of the gut.^[18]

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).^[19]

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.^[20]

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.^[21,22]

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.^[23]

Method of Preparation of Matrix Tablet**A. Wet Granulation Technique^[24]**

- Milling and 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^[25]

- Milling and 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^[26]

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. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering. 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 TABLETS^[27]**1. Diffusion controlled**

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 behavior 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:

$$M = [Cs. Dm (2Co - Cs) t]^{1/2} \quad (3)$$

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

$$M = [2Cs. Dm.Co.t]^{1/2} \quad (4)$$

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:

$$M = [Ds. Ca. p/T. (2Co - p.Ca) t]^{1/2} \quad (5)$$

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 = Diffusional path length

For pseudo steady state, the equation can be written as:

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

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

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

Where,

p = Porosity

ρ = Drug density

Pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

C ex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k. t^{1/2} \quad (8)$$

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

EVALUATION PARAMETERS FOR EXTEND RELEASE MATRIX TABLET^[28]

Thickness and Diameter

Thickness and diameter of tablets are determined using Vernier Caliper.

Hardness of the Tablet

Tablet hardness has been characterized as, "the force required breaking a tablet in a diametric compression test". For every formulation, the hardness of three tablets is examined utilizing Monsanto hardness analyzer; end point is recognized by breaking the tablet.

Friability

Twenty tablets are weighed and placed in friabilator. The chamber is rotated for 4 minutes at a speed of 25 rpm. The tablets are removed from the chamber and weighed again. Loss in weight indicates friability. Tablets to be considered good quality if loss weight loss is less than 0.8%.

Weight variation test

This is an important process which comes under quality control test as per standard in one batch all tablet ought to be in uniform weight. Twenty tablets are weighed to determine the average weight and compared with single tablet weight. The percentage weight variation is computed according to Indian Pharmacopoeial particular.

Determination of drug content

The drug content of is determined by dissolving in a suitable solvent like pH 7.4 phosphate buffer solution and sample are analyzed with the visible spectrophotometer and standard calibration curve of the pure drug.

In-vitro Dissolution Testing

In vitro dissolution testing is a vital instrument for assessment of the best formulation. The test is carried out to measure the amount of time required for certain percentage of drug to go into the solution under the specific test conditions. Rotating paddle type and rotating basket type apparatus can be used as per pharmacopoeial standards or as mentioned in monograph of particular drug. Dissolution testing is likewise used to characterize the biopharmaceutical attributes and to distinguish conceivable hazard, for example, potential nourishment impacts on bioavailability or interaction with different drugs.

Conclusion:

The focus of this review article has been on the formulation of extended release matrix tablets, benefits and drawback, various types of polymers, technique of preparation and assessment parameters.

As compared to conventional counterparts matrix tablets offer better patient compliance, maintains constant plasma drug concentration level, reduces chances of toxicity and once a day drug therapy reduces overall cost of treatment. Above discussion ends up on the conclusion that matrix tablets are helpful to overcome the patient incompliance and effectiveness of dosage form in evoking desired therapeutic response related problems linked with conventional dosage forms.

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