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REVIEW ARTICLE

A COMPREHENSIVE REVIEW ON SUSTAINED RELEASE MATRIX TABLETS: A PROMISING DOSAGE FORM

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ABSTRACT

Oral ingestion is most convenient and commonly employed route of drug delivery due to its ease of administration, least aseptic and flexibility in the design of dosage form. The objective of the study was to explore the necessity, advantages and various techniques of extended release matrix tablet to get a constant drug delivery rate and reproducible kinetics for advance delivery. 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. Matrix controls the free rate of drug. Matrix tablets can be formulated by either direct compression or wet granulation method by using a variety of hydrophilic or hydrophobic polymers. 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.

Keywords: Controlled release, extended release, *in-vitro* dissolution, matrix tablet, polymers.

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INTRODUCTION

Drugs are administered with a main aim of treatment of the diseases. Drugs are never administered in their pure form but are converted in a suitable dosage forms so that its onset and intensity of action as well as total duration of action can be checked¹. 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 production². 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. Tablet accessibility in market ranges from generally straight

forward immediate release formulation to complex sustained release or modified release dosage forms³.

Sustained release drug delivery system was meant to discharge the medication in a delayed rate to keep up plasma drug levels. The medications having shorter half life are appropriate for the sustained release drug delivery system. 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 solid dosage forms. Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices. Hypothetically, sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion⁴.

Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release has given a new breakthrough for novel drug delivery system in the field of

Pharmaceutical technology. Under gastric pH conditions, matrix tablet slowly erodes. Two mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles. 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 level⁵.

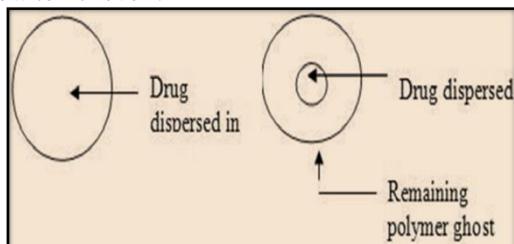


Figure 1: Release of drug dispersed in an inert matrix system

The drug molecule appears better supported sustained drug release profile in matrix frameworks by distinctive systems. Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers⁶⁻⁹.

Advantages of Sustained Release Matrix Tablets

i) Patient compliance

Lack of compliance is mainly seen with chronic disease which required long term treatment, as achievement of medication treatment relies upon the patient capacity to agree with the medication treatment. Patient compliance is affected by a many factors, like knowledge of ailment process, patient confidence in treatment, and understanding of patient related to a strict treatment plan. In addition to the difficulty of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This issue can be set out to some degree by administering sustained release drug delivery system¹⁰⁻¹⁴.

ii) Reduced 'see-saw' fluctuation

Drug concentration in the systemic circulation and tissue compartments show 'see saw' pattern frequently when the drug administration in conventional dosage form. The sizes of these variances fundamentally rely upon drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals¹⁵. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well-designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain a steady drug concentration in blood circulation and target tissue cells¹⁶.

iii) Total dose reduction

To treat an ailing condition less measure of aggregate drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy¹⁷.

iv). Improvement of deficiency in treatment

Ideal treatment of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those

required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition¹⁸.

v). Economy

The initial unit cost of sustained release products is typically more than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less¹⁹.

Disadvantages of sustained release matrix tablets

- Highly expensive.
- Often poor systemic availability.
- Need for additional patient education and counseling.
- Dose dumping²⁰.
- Often poor *in vivo-in vitro* correlation²¹.

Characteristics of Drug Suitable for sustained Release Tablet

The ideal physicochemical and pharmacokinetic qualities of medications which can be defined as extended release tablet are as per the following:

1. Atomic size ought to be beneath of 1000 Dalton.
2. Aqueous solvency ought to be in excess of 0.1 mg/ml for pH 1 to pH 7.8.
3. The partition coefficient ought to be high⁵.
4. Absorption mechanism ought to be diffusion and the general absorbability from all GI fragments discharge ought not to be impacted by pH and catalysts.
5. Elimination half-life ought to be between 2 to 8 hrs⁷.
6. Drugs ought not to metabolize before absorption it cause less bioavailability.
7. Absolute bioavailability ought to be at least 75% or more.
8. Absorption rate constant (Ka) ought to be higher than discharge rate. Apparent volume of distribution (Vd) ought to be substantial.
9. Total clearance ought not to rely upon dosage¹⁵.
10. Elimination rate constant are required for design and therapeutic concentration (C_{ss}) ought to be low and smaller (Vd)^{3,4,5}.

Polymers used in sustained release tablet

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

a) Hydrophilic Polymers

Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and copolymers of acrylic acid²²⁻²⁴.

b) Hydrophobic Polymers

This usually includes waxes and water insoluble polymers in their formulation²⁵.

c) Natural polymers

Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan²⁵.

d) Biodegradable polymers

Poly(lactic acid) (PLA), Poly(glycolic acid) (PGA), Polycaprolactone (PCL), Poly(anhydrides), Poly(orthoesters)²⁶.

e) Non-biodegradable polymers

Poly(ethylene vinyl acetate) (PVA), Poly(dimethylsiloxane) (PDS), Poly(ether urethane) (PEU), Poly(vinyl chloride) (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)²⁷.

METHODS OF PREPARATION**1. Direct Compression**

In this method, finely powdered materials are compressed directly without changing the physical and chemical properties of the drug²⁸.

2. Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of the granulating agent. After enough cohesiveness was obtained, the mass is sieved and dried at 40°C and kept in a desiccator. Lubricants and Glidants are added and the tablets are compressed using a tablet compression machine²⁹.

3. Melt Granulation

In melt granulation, meltable substance act as liquid binding agent and hence does not require the use of organic solvents. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Various lipophilic binders such as Glyceryl Palmitostearate are used in melt granulation technique¹⁶.

CLASSIFICATION OF MATRIX TABLETS**A. On the Basis of Retardant Material Used****1. Hydrophobic Matrices (Plastic matrices)**

In the hydrophobic matrix tablets, the active drug is dispersed in a tablet within a porous skeletal structure by direct compression of the drug with plastic materials. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles²¹. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, poly(vinyl 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 fluid³⁰.

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.

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. Hydrophilic matrix may be formulated by a wet granulation of the drug and hydrophilic matrix materials or by direct compression of the blended mixture of active ingredient and certain hydrophilic carriers¹⁷.

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. When immersed in fluid the drug release is controlled by a gel diffusion barrier that is formed and tablet erosion³¹.

4. Fat- wax matrix tablet

The strategies include in addition of drug into fat wax. The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. Granules are showered which get hard in air, mixing in a aqueous fluid media with or without the surfactant and dried by spray drying strategy. A suspension of drug and melted fat wax are solidify by utilizing fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. In this type of matrix tablet, drug is discharged by straining and hydrolysis mechanism.

5. Mineral Matrices

Mineral matrices can be set up by utilizing polymers which are acquired from different types of sea weeds. Examples includes Alginate acid which is a hydrophilic sugar. The polymers obtained from different species of seaweeds are used to prepare mineral matrices. Alginate acid, a hydrophilic carbohydrate obtained from brown seaweeds (Phaeophyceae) by the use of dilute alkali³².

B. On the basis of porosity of matrix**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 size⁶.

2. Micro porous System

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50-200 \AA , which is slightly larger than diffusant molecules size⁸.

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 present⁶⁻⁹.

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 molecules¹⁸.

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 system²⁶.

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 time¹⁸. 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 gut²⁷.

FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS

A. Physicochemical factors

Dose size

In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. Drugs with a large dose size (> 500mg) are difficult to formulate into a matrix system because of the requirements of high amounts of the polymer as well as other matrix formers (excipients). Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems³³.

Drug solubility

Polymer erosion is more predominant in the case of the matrix with insoluble drugs, while with soluble drugs a combination of diffusion and erosion determine the release of the drug. Diffusion of the drug depends upon the concentration gradient across the medium which is a function of solubility thus a drug with high solubility shows faster release while poorly water soluble drugs (< 0.01 mg/ml) often result in the incomplete release because of their poor solubility and dissolution rate in the matrix¹². Drugs that exhibit pH-dependent solubility particularly in gastrointestinal pH range are poor candidate for matrix system³⁴.

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. 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 on the release process must be defined³⁵.

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 body⁷. 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. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration³⁶.

B. Biological factors

Biological half-life

Therapeutic compounds with short half-life are generally an excellent candidate for SR formulation, as this can reduce dosing frequency. The usual goal of an oral sustained release tablet 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.

In general, drugs with half-life shorter than 2 hr are poor candidates for sustained release preparation. Compounds with long half-lives, more than 8 hr are also generally not used in sustained form, since their effect is already sustained³⁷.

Absorption

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. 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 absorption²⁷.

EVALUATION PARAMETERS FOR EXTENDED RELEASE MATRIX TABLET

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 tablet⁸⁻¹¹.

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. The tablets to be considered of good quality if loss in weight is less than 0.8%¹⁹.

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 particular²⁶.

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 drug¹⁹⁻²³.

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 drugs¹⁸.

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. So, this extend release formulation can be a suitable formulation which an antidiabetic drug which can be incorporated and better pharmacological action can be achieved. This article may be beneficial for many researcher interested to work on the matrix tablets.

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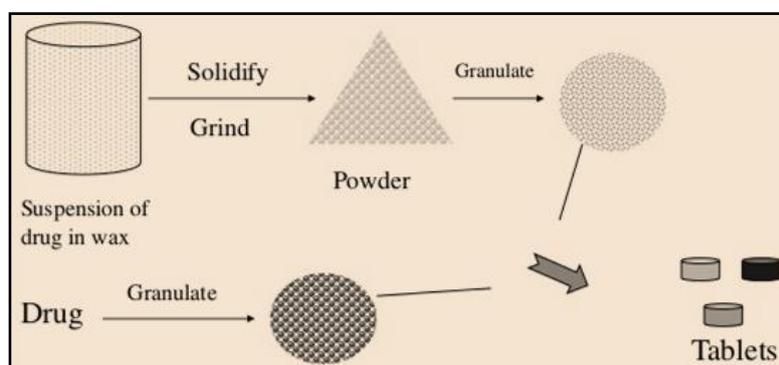


Figure 2: Preparation of matrix tablets