IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
February 2021 Vol.:20, Issue:3

A Review on Sustained Release Matrix Type Drug Delivery System

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 03 January 2021
Revised: 23 January 2021
Accepted: 12 February 2021

HUMAN JOURNALS
www.ijppr.humanjournals.com

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

ABSTRACT

Oral ingestion is the 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 tablets to get a constant drug delivery rate and reproducible kinetics for advance delivery. This article highlights advantages, disadvantages, rationale for development, polymers used in sustained delivery, methods of preparation, classification of matrix tablets and evaluation of matrix tablets. The extended-release matrix tablets can assure better patient compliance through a reduction in total dose and dosage regimen, which can be a great help to treat chronic diseases.

INTRODUCTION:

Drugs are administered with the main aim of treatment of the diseases. Drugs are never administered in their pure form but are converted into suitable dosage forms so that their onset and intensity of the action as well as the total duration of action can be checked. An ideal controlled drug delivery system is that which delivers the drug at a specific rate locally or systemically for a specified period with minimum fluctuation in plasma drug concentration, reduced toxicity, and maximum efficiency. In the present scenario, conventional dosage forms of drugs are rapidly being replaced by new and 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. 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 favored oral dosage form. Tablet accessibility in the market ranges from generally straightforward immediate release formulation to complex sustained release or modified release dosage forms (Prathiba V *et al.,* 2008).

A sustained release drug delivery system was meant to discharge the medication at a delayed rate to keep up plasma drug levels. The medications having a shorter half-life are appropriate for the sustained release drug delivery system. Matrix tablets are 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 infusion.

The matrix system is the release system that 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. The introduction of matrix tablets as sustained-release has given a breakthrough for novel drug delivery systems in the field of Pharmaceutical technology. Under gastric pH conditions, the 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 is the ability to control active pharmaceutical ingredient's blood levels in a narrow range, above the minimum effective level, and below the toxic level (Rohini Diwedi *et al.,* 2012).

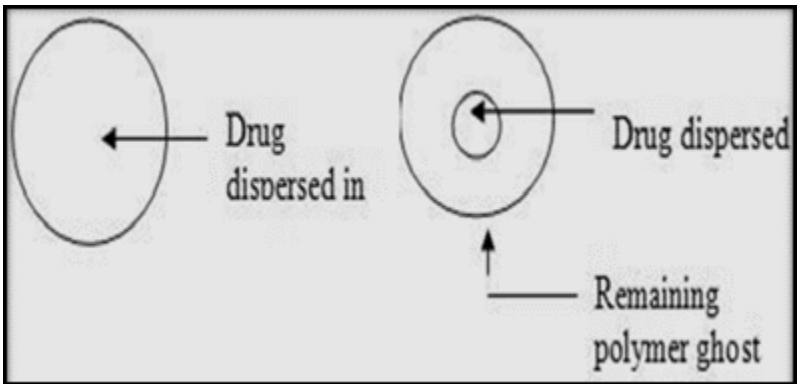

Figure No. 1: Release of drug dispersed in an inert matrix system

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 polymers (Prakhar Agarwal *et al.,* 2018).

1.1 Advantages

1. The frequency of drug administration is reduced. Patient compliance can be improved.

2. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced (Mayur Karvekar *et al.,* 2017).

3. The total amount of drug administered can be reduced, thus: Maximizing availability witha minimum dose. Minimize or eliminate local side effects. Minimize or eliminate systemic side effects. Minimize drug accumulation with chronic dosing.

4. 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 a prolonged period may be less (Prakhar Agarwal *et al.,* 2018).

1.2 Disadvantages

1. Cost of single unit higher than conventional dosage forms.

2. Toxicity due to dose dumping.

3. Unpredictable and often poor *in vitro-in vivo* correlation.

4. Risk of side effects or toxicity upon rapid release of the contained drug (mechanical failure, chewing or masticating, alcohol intake).

5. Increased potential for first-pass clearance (Sarika S. Lokhande *et al.,* 2019).

6. Need for additional patient education and counseling.

1.3 Rationale for Developing Sustained Release Matrix Drug Delivery System

a. To extend the duration of action of the drug.

b. To reduce the frequency of dosing.

c. To minimize the fluctuations in plasma level.

d. Improved drug utilization.

e. Less adverse effects.

f. The frequency of drug administration is reduced (Dixit Navin*et al.*, 2013).

1.4 Criteria of the drug to be met to formulate sustained release dosage forms:

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.

g) More bioavailability

a) Desirable half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has a short half-life(less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, the drug with an elimination half-life of eight hours or more is

sufficiently sustained in the body, when administered in conventional dosage form, and a sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have a half-life of three to four hours (Jaimini Manish *et al.*, 2012).

b) High therapeutic index:

Drugs with a 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 undetermined. This is chiefly because the size of a unit dose sustained-release formulation would become too big, to administer without difficulty (Pogula M *et al.*, 2010).

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 (Patnaik AN *et al.*, 2013).

e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of the 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 (Sivaramu Kambampati *et al.*, 2013).

f) First pass clearance:

In a sustained drug delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in the case of drugs undergoing extensive hepatic first-pass metabolism, when administered in sustained release form (Rakesh Roshan Mali *et al.*, 2015).

g) More bioavailability:

Absolute bioavailability ought to be at least 75% or more.

2. POLYMERS USED IN SUSTAINED RELEASE MATRIX DRUG DELIVERY SYSTEMS:

The polymers most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers (Prakhar Agarwal *et al.*, 2018).

a) Hydrophilic Polymers

Hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross-linked homopolymers and copolymers of acrylic acid (Misa R*et al.*, 2013).

b) Hydrophobic Polymers

This usually includes waxes and water-insoluble polymers in their formulation.

c) Natural polymers

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

d) Biodegradable polymers

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.

e) Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethylcellulose (EC).

2.1 Characteristics of an ideal polymer:

1. It should be versatile and possess a wide range of mechanical, physical, chemical properties.

2. It should be non-toxic and have good mechanical strength and should be easily administered.

3. It should be inexpensive and easy to fabricate.

4. It should be inert to host tissue and compatible with the environment (Kamboj S *et al.*, 2013).

2.2 Criteria for polymer selection:

1. The polymer should be soluble and easy to synthesise.

2. It should have finite molecular weight.

3. It should be compatible with the biological environment.

4. It should be biodegradable.

5. It should provide good drug-polymer linkage (Mayur Karvekar *et al.*, 2017).

3. METHODS OF PREPARATION:

1. Direct Compression:

In this method, finely powdered materials are compressed directly without changing the physical and chemical properties of the drug (Kumar Sunil *et al.*, 2018).

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 machine (Chauhan MJ *et al.*, 2012).

3. Melt Granulation:

In melt granulation, meltable substance act as a 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 the melt granulation technique (Dusane AR*et al.*, 2011).

4. CLASSIFICATION OF MATRIX TABLETS:

A. based on 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 because 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, ethylcellulose, 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 (Karna S *et al.*, 2015).

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. 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 as a retardant base for many sustained-release formulations (Sampath Kumar KP *et al.*, 2012).

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. The hydrophilic matrix may be formulated by wet granulation of the drug and hydrophilic matrix materials or by direct compression of the blended mixture of the active ingredient and certain hydrophilic carriers (Harnish Patel *et al.*, 2011).

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients are 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 erosion.

4. Mineral Matrices:

Mineral matrices can be set up by utilizing polymers that are acquired from different types of seaweeds. Examples include Alginic acid which is a hydrophilic sugar. The polymers obtained from different species of seaweeds are used to prepare mineral matrices. Alginic acid, a hydrophilic carbohydrate obtained from brown seaweeds (Phaeophyceae) by the use of dilute alkali (Sarika Pundir *et al.*, 2013).

B. based on the porosity of the matrix

1. Macroporous Systems:

In such systems, the diffusion of the drug occurs through pores of the matrix, which are of size range 0.1 to 1 μm. This pore size is larger than the diffusion molecule size (Harris Shoaib M *et al.*, 2006).

2. Microporous System:

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50-200 A°, which is slightly larger than diffusing 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.

C. based on 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?

2. pH-sensitive matrix system:

In this type of matrix system, an enteric coating of the matrix system can protect 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 (Diwedi RO *et al.*, 2012).

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 some time. The targeted tissues can be gastrointestinal, buccal, ocular, nasal, respiratory, rectal, urethral, and vaginal tissues. Also, 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.

5. FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS:

A. Physicochemical factors

i) 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 sizes can sometimes be given in multiple amounts or formulated into liquid systems (Kumar S*et al.*, 2012).

ii) Drug solubility:

Polymer erosion is more predominates in the case of the matrix with insoluble drugs, while with soluble drugs a combination of diffusion and erosion determines 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 incomplete release because of their poor solubility and dissolution rate in the matrix. Drugs that exhibit pH-dependent solubility particularly in the gastrointestinal pH range are a poor candidate for the matrix system.

iii) 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 Phone the release process must be defined.

iv) 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**7** Compounds which are lipophilic having high partition coefficient are poorly aqueous soluble and it retains in the lipophilic tissue for the longer time. In the case of compounds with a 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 penetration.

B. Biological factors

i) Biological half-life:

Therapeutic compounds with a short half-life are generally are an excellent candidate for sustained release 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. To achieve this, the drug must enter the circulation at approximately the same rate at which it is eliminated (Kar RK *et al.*, 2009).

In general, drugs with a 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 sustaining form, since their effect is already sustained (Patel KK *et al.*, 2012).

ii) Absorption:

Absorption of the drug should occur at a relatively uniform rate over the entire length of the small intestine. If a drug is absorbed by active transport or transport is limited to a specific region of the 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 an SR product is to place the control on the delivery system, the rate of release must be much slower than the rate of absorption.

6. EVALUATION TEST FOR SUSTAINED RELEASE TABLETS:

a) Weight Variation: Twenty tablets were weighed individually and then collectively, the average weight of the tablets was calculated and compared with a single tablet weight. The percentage weight variation is computed according to Indian Pharmacopoeia.

b) Hardness: Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.

c) Friability: The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.

d) Thickness: The thicknesses of tablets were determined using vernier calipers.

e) Determination of drug content: The drug content is determined by dissolving in a suitable solvent like pH 7.4 phosphate buffer solution and samples are analyzed with the UV-visible spectrophotometer and standard calibration curve of the pure drug.

f) *In-vitro* Dissolution Study: *In-vitro* dissolution testing is a vital instrument for the assessment of the best formulation. The test is carried out to measure the amount of time required for a certain percentage of the 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 the monograph of a particular drug.

7. CONCLUSION:

The focus of this review article has been on the formulation of extended-release matrix tablets, benefits, and drawbacks, various types of polymers, method of preparation, and evaluation parameters. As compared to conventional counterparts, matrix tablets offer better patient compliance, maintains constant plasma drug concentration levels, reduces chances of toxicity, and once a day drug therapy reduces the overall cost of treatment. By the above discussion, it can be easily concluded that sustained-release formulations help increase the efficiency of the dose as well as they are also improving the patient's compatibility.

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