International Journal of Pharma Research and Health Sciences, 2022; 10(6): 3511-20.
DOI:10.21276/ijprhs.2022.06.04
Abhinay *et al.*

CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Review article

A Comprehensive Outline on Sustained Release Matrix Tablets: A Promising Dosage Form

Abhinay*, Abneet, Madhu Bala, Ritesh Rana

Department of Pharmaceutical Sciences, Himachal Institute of Pharmaceutical Education and Research, Hamirpur, India.

ARTICLE INFO:
Received: 02 Dec 2022
Accepted: 22 Dec 2022
Published: 31 Dec 2022

Corresponding author *
Madhu Bala,
Lecturer,
Department of Pharmaceutical Sciences (Pharmaceutics),
Himachal Institute of Pharmaceutical Education and Research, India
E-mail: immadhu456@gmail.com

ABSTRACT:
Pharmaceuticals with sustained release have recently emerged as a very practical tool in medical practice, providing patients with a variety of real and perceived benefits. By eliminating fluctuations in the therapeutic concentration of the drug in the body, sustained release is also a viable method of reducing the negative side effects of medication in your body. Nowadays, there aren't many new pharmaceuticals emerging from research and development, and those that are already on the market are suffering from drug resistance owing to improper use, particularly in the case of antibiotics. Therefore, altering the operation is a suitable and optimal technique to increase the effectiveness of some drugs by slightly changing the drug distribution. By avoiding the volatility of the therapeutic concentration of the drug in the body, sustained release is also offering a promising technique to reduce the negative effects of medication. Most medications, if not formulated properly, may readily release the medication at a faster rate and are likely to produce toxic concentrations of the medication upon oral administration. The release of the medication through such a system includes both dissolution controlled as well as diffusion controlled mechanisms.

Keywords: Matrix tablets, Sustain release polymers, Patient convenience and compliance.

1. INTRODUCTION

The terms delayed release, continued action, slow release, controlled discharge, expanded release, and modified release have all been used to describe oral dosage medications with altered liberated qualities. Each drug delivery method aims to eliminate the repeated fluctuations in therapeutic drug levels that occur after conventional distribution methods [1]. Sustained release dosage formulations are designed to produce either rapid achievement of a formulation's systemic level, which maintains the medication's therapeutic range for an extended period, or sustained achievement of medication's therapeutic levels, which is released slowly (which is prolonged action).

The requirements that must be met to ensure consistent drug plasma levels are as follows: 1) The rate of absorption of drug release must be resolved by the zero-order rate of drug; and 2) The rate of drug elimination must be equal to the rate at which the drug is liberated from the maintenance dose at the required steady state levels. The definitions that follow are a collection of key words that are used to explain various modified release dose formulations.

A. Modified release dosage form

Dosage forms designed to achieve plasma and practical goals not possible with conventional preparations due to different drug liberation systems of time path and site [2].

B. Controlled release

The drug concentration varies with time after delivery and is discharged at a constant (zero order) rate.

C. Delayed release

The medication is given out after delivery, but not right away [3].

D. long term or extended release

Slow drug release is required to maintain therapeutic plasma concentrations for an extended period of time (typically 8-12 hours) [4].

E. Prolonged release

It denotes that a single dose is administered very quickly and that subsequent second or third doses are administered at irregular intervals [5].

F. Repeat the action

The delivery mechanism determines how quickly the medication is delivered, which is slow [6].

G. Receptor targeting sustained release system

Any pharmaceutical administration technique that achieves the drug's progressive release over an extended period of time is referred to as a sustained-release system.

A system is considered a controlled-release system if it is successful in maintaining constant drug levels in the target tissue or cells, regardless of whether the control is temporal, spatial, or both.

Sustained release dosage implies an initial release of the medication sufficient to deliver a therapeutic dose shortly after administration, followed by a progressive release over time.

In contrast to quick release tablets, which may need to be taken three or four times per day to achieve the same medication effect, sustained release tablets and capsules are frequently taken only once or twice per day. In a sustained release dosage form, the active ingredient that provides the desired treatment for curing a condition is typically released all at once. The leftover medicine should then be released, and the therapeutic effect should be sustained over time. The sustained release of medication boosts the maintenance of medication plasma levels as seen in Figure 1 [7].

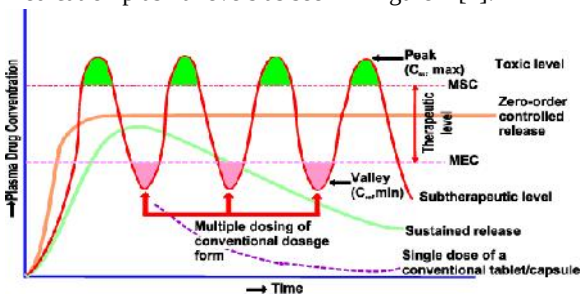

Fig1: Plasma drug concentration profile for a sustained release formulation

The goal of a sustained release drug delivery system was to gradually dispense medication while maintaining plasma drug levels. Sustained release medication delivery is appropriate for formulations with a shorter half-life. Designing innovative matrix-based formulations with extended drug release using readily available, low-cost excipients remains a hot topic. There has been a noticeable increase in interest in sustained release pharmaceutical delivery systems over the last 20 years. This is due to a variety of factors, including the prohibitive cost of developing new drug entities, the ageing of existing international patients, the discovery of new polymeric materials useful for delaying drug release, and the therapeutic effectiveness and safety improvements attained by these delivery systems.

A number of interconnected, important factors influence oral sustained release delivery systems, including the type of delivery system, the condition being treated, the patient, the length of therapy, and the properties of the medication. A sustained release System is any medication delivery method that achieves gradual drug release over a long period of time [8].

2. BENEFITS OF A CONTROLLED RELEASE DELIVERY SYSTEM

a) Local and systemic side effects are reduced: GI irritability has been reduced [9, 10].
b) Drug use has increased: With repeated doses, the overall dosage of the medication is reduced, and there is little medication absorption.
c) Enhanced therapeutic efficacy
d) Treatment has been improved.
e) Less volatility in medicine dosage results in a more consistent pharmacological response.
f) Illustration of special effects: Long-term release Aspirin provides enough medication to provide symptomatic relief to the arthritic patient upon awakening.
g) Treatment or condition management that is more rapid.
h) With continued use, there is less drug activity.
i) Techniques for achieving continuous release, which can improve the bioavailability of some medications. Medication that is susceptible to enzymatic inactivation, for example, can be protected by being enclosed in polymer systems designed for prolonged release.
j) Because of their unique properties, the initial unit cost of sustained release drugs is frequently higher than that of conventional dosage forms. However, the average cost of therapy over a longer period may be lower.

3. SUSTAINED RELEASE DOSAGE FORMS DRAWBACKS

a) It keeps the therapy from being stopped abruptly.
b) There is less room for dose adjustment.
c) The typical biological half-life was used as a model for developing these dosage forms [11].
d) They are expensive.

4. MATRIX TABLET

Because matrix tablets are the most cost-effective sustained and controlled release solid dose forms, they could be used to introduce extended-release drug therapy. Matrix tablets are oral solid dosage forms made of hydrophilic or hydrophobic polymeric matrices in which the drug is evenly dissolved or dispersed. A zero-order mechanism, in theory, should allow the drug to be released from a sustained release dosage form while maintaining the drug plasma level close to that of an intravenous infusion [12].

The matrix system, a release mechanism, prolongs and controls the drug's dispersed or dissolved release. A matrix is a well-combined mixture of one or more medications and a gelling agent made of hydrophilic polymers.

4.1 Benefits

1. Simple to make, Convenient, efficient, and economical [13, 14].
2. Has the ability to release compounds with a high molecular weight.
3. Sustained release formulations may be able to maintain higher therapeutic concentrations for longer periods of time.
4. Sustained release formulations help to keep blood concentrations low.
5. Sustained-release medications have the potential to improve patient compliance.
6. To reduce toxicity, postpone drug absorption.

7. Protect the drug from hydrolysis and other derivative changes in the gastrointestinal system to increase its stability.
8. Reduce the negative local and systemic effects.
9. Increased therapeutic value.
10. Drug accumulation is reduced with continuous dosing.
11. Drug use is less prevalent.
12. Some drugs' bioavailability is being improved.

4.2 Disadvantages

1. The leftover matrix must be removed after the medicine has been released [15].
2. Expensive planning.
3. A variety of factors, including diet and the rate at which the stomach empties, influence release rates.
4. Medication release rates are influenced by the square root of time. The diffusional resistance and/or the effective area at the diffusion front cause a continuous decrease in the release rate. However, using extremely slow-release rates, which are frequently equivalent to zero-order, may have a significant long-term effect.

5. SUSTAINED RELEASE MATRIX SYSTEM

The introduction of the matrix tablet as a sustained release in the world of pharmaceutical technology has resulted in a new breakthrough for unique drug delivery systems. In stomach acids, the matrix pill eventually deteriorates. There are two processes at work: zero-order erosion and coated particle dissolution, both of which result in a decrease in surface area. Blood levels of active pharmaceutical ingredients can be kept within a narrow range, above the minimal effective level but below the dangerous level [16].

In matrix frameworks, multiple mechanisms appear to better support the medication's extended drug release profile. By distributing solid particles inside a porous matrix made of hydrophilic materials, matrix tablets can be created using wet granulation or direct compression techniques [17, 18].

The sustained release method can be used to maintain a therapeutically effective concentration in the systemic circulation over time, improving patient compliance. SR oral dose forms such as osmotic systems, matrices containing water soluble/insoluble polymers, and membrane-controlled systems have all been developed. Extensive research has been conducted to develop SR techniques for medications that are poorly water soluble [19].

6. CLASSIFICATION OF MATRIX TABLETS

6.1. Depending on the Specific Reducing Substance Employed

6.1.1. Hydrophobic Matrices

To achieve prolonged release from an oral dosage form, the medication is combined with an inert or hydrophobic polymer and crushed into a tablet. To achieve continuous release, the drug is distributed through a network of channels that exist between compacted polymer particles. Materials such as polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate polymers and their co-polymers have been used as inert or hydrophobic matrices. The liquid's penetration into the matrix is the rate-regulating stage in these formulations. Diffusion is one possible method of medication release in these types of tablets [20].

6.1.2. Lipid Matrices

These matrices were created using lipid waxes and other materials. Drug release from these matrices occurs via erosion as well as pore diffusion. As a result, release characteristics are more sensitive to the composition of the digestive fluid than a completely insoluble polymer matrix. Carnauba wax has been used as a retardant base in conjunction with stearyl alcohol or stearic acid in a variety of long-release formulations [21].

6.1.3. Hydrophilic Matrices

Hydrophilic polymer matrix systems are frequently used in oral controlled drug delivery due to their versatility in achieving a desired drug release profile, economic effectiveness, and widespread regulatory acceptability. Medication formulation in gelatinous capsules or, more commonly, tablets with hydrophilic polymers with high gelling capacities as base excipients [22, 23].

6.1.4. Biodegradable Matrices

These are made up of polymers with monomers linked together by functional groups and backbones made up of brittle links. They are physiologically degraded or destroyed into oligomers and monomers that can be metabolized or excreted by enzymes or non-enzymatic mechanisms in neighboring living cells. Synthetic polymers such as aliphatic poly (esters) and poly anhydrides are examples, as are naturally occurring polymers such as proteins and polysaccharides22 and modified natural polymers [24].

6.1.5. Mineral Matrices

These are made up of polymers derived from various types of seaweed. One example is alginic acid, a hydrophilic carbohydrate produced by brown seaweed species (Phaeophycean) using diluted alkali [25].

6.2. Upon the Principles of Matrix Porosity [26]

6.2.1. Macro porous System

Drug diffusion occurs in these systems through holes in the matrix ranging in size from 0.1 to 1 m. This pore size is exceeded by the diffusant molecule.

6.2.2. Micro Porous System

In this type of structure, diffusion occurs primarily through pores. The range of pores in micro porous systems is 50 to 200 A°, which is slightly larger than the diffusant molecule size.

6.2.3. Non-Porous System

In non-porous systems, molecules diffuse over the network meshes due to the absence of pores. In this case, only the polymeric phase is present; the pore phase is not.

6.3. Continuous Delivery Matrix System Polymers

The following polymer varieties are utilized in sustained release matrix systems:

- Hydrophilic Polymers

Sodium alginate, poly (ethylene oxide), Xanthan gum, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl

cellulose (HPC), hydroxyl ethyl cellulose (HEC), and cross-linked homopolymers and co-polymers of acrylic acid [28].

- **Hydrophobic Materials**

Wax and water-insoluble polymers are typically used in their formulation [29].

- **Natural Polymers**

Guar Gum, Sodium Alginate, Pectin, Xanthan Gum, and Chitosan [30].

- **Biodegradable polymers**

Polyglycolic acid (PGA), polycaprolactone (PCL), polyanhydrides, and polyorthoesters are examples of polymers [31].

- **Non-biodegradable Polymers**

Cellulose acetate (CA), Polyvinyl chloride (PVC), Polyether urethane (PEU), Polydimethylsiloxane (PDS), and Ethyl cellulose (EC) [31] are examples of polyethylene vinyl acetate (PVA) [32].

7. FACTOR INFLUENCING SUSTAIN RELEASE DELIVERY SYSTEM

7.1. Physiochemical Factors

7.1.1. Partition coefficient

The partition coefficient is the ratio of the medication in an oil phase to that in an adjacent aqueous phase. Because biological membranes are lipophilic, drugs that pass through them have very high bioavailability if the drug's partition coefficient is affected. Medicines with lower partition coefficients are not suitable for oral CR drug delivery systems because they will not partition out of the lipid membrane once they enter it, whereas medications with higher partition coefficients are also not suitable for oral SR drug delivery systems [33].

7.1.2. pka, ionization, and water solubility

Most drugs must be absorbed as weak acids or bases around the delivery site [34].

7.1.3. Drug uniformity

When drugs are administered orally, they are susceptible to enzymatic and acid/base hydrolysis degradation. Extended delivery to the entire GI tract benefits drugs that degrade quickly in the stomach because it slows the rate of decomposition. If a medication is administered in an extended-release dosage form and is unstable in the small intestine, its bioavailability may be reduced. This is because more medication is transported to the small intestine, where it is more likely to be broken down [35].

7.1.4. Dose size

A popular dosage form has a maximum dose size of 500-1000 mg. This description also applies to formulations for long-acting drugs. as a precautionary measure for security. Evaluation of dosage size is critical as a gauge for the safety associated [36].

7.2. Biological Factors

7.2.1. Half-life

A medicine's half-life is a measurement of how long it remains in the body. If the chemical has a short half-life, the dosage form may contain an excessively high concentration of the medication (less than 2 hours). Drugs with an elimination half-life of at least 8 hours, on the other hand, are well handled in the body when taken in regular doses, negating the need for a sustained release drug delivery system. For the development of a pharmaceutical delivery system, the optimal drug half-life is 3-4 hours [37, 38].

7.2.3. Therapeutic Range

Low therapeutic index medications should not be included in sustained release formulations. If the body's mechanism malfunctions, dosage dumping may cause toxic effects [39].

7.2.4. Absorption

The medicine should be absorbed at a relatively constant rate along the length of the small intestine. If a medication is absorbed via active transport or is limited to a specific region of the stomach, SR preparation may be detrimental to absorption. One method of supplying chemicals with prolonged delivery mechanisms is to keep the chemicals in the stomach. The drug can then be released gradually and delivered to the absorptive area. Because the goal of developing an SR product is to have control over the delivery mechanism, the rate of release must be much slower than the rate of absorption [40].

7.2.5. Protein Binding

Drugs are all bound to plasma and tissue proteins to some degree, but the pharmacological response is determined by the drug's unbound concentration rather than its total concentration. The drug's ability to bind to proteins influences its therapeutic impact regardless of dosage form. Because significant combining to plasma prolongs half-life, sustained release drug delivery systems aren't always required in this type of medicine [41].

8. DRUG RELEASE METHOD FROM MATRIX TABLET

The medication first dissolves in the upper shell of the matrix that is accessible towards the bathing liquid before diffusing out of the matrix. The bathing fluid is still in contact with the solid drug during this process. As a result, for such a mechanism to be diffusion regulated, the rate at which drug component dissolves inside the matrix must be much quicker than the rate at which drug component dissolves outside the matrices. In order to explain this system, the following assumptions are made during the mathematical model's derivation [42-44]:

a) During drug release, a false-steady condition is maintained.
b) The average distance of drug permeation through the matrices is smaller than the dimensions of the drug particles.
c) At all times, the bathing solution offers sink conditions. The system's release behaviour may be statistically characterized by the following equation:

dM/dh = Co. dh - Cs/2 (Equation 1)

Cs = Saturated medication concentration inside the matrices.
Co = Total medication quantity in a unit volume of matrices

dh = Alteration in the width of the drug-depleted zone of the matrix

dM denotes the alterations in the quantity of medicine discharged per unit area.

Furthermore, as per theory of diffusion:

dM = (Dm. Cs / h) dt (Equation 2)

Dm denotes the diffusion variable in the matrices.

The width of the medication-depleted matrix is given by h.

dt = Time Variation

Using equations1 and 2, together with integration

M = [Cs. Dm (2Co −Cs) t] ½ (Equation 3)

Once the quantity of the substance used exceeds the saturation content, the following occurs:

M = [2Cs.Dm.Co.t] ½ (Equation 4)

In equations 3 and 4, the amount of medicine released is proportional to time squared. As a result, if a system is primarily diffusion controlled, a graph of drug discharge versus function of time should increase linearly. Drug liberation from a porous monolithic matrix is defined as the concurrent entry of neighboring liquids, breakdown of the medication, and leaking out of the substance via twisted interstitial pathways and apertures.

The release of drug from a permeable or granular medium should then regard for the amount and extent of the entrances:

M = [Ds. Ca. p/T. (2Co – p. Ca) t] ½ (Equation 5)

p = The permeability of the matrices

p = The permeability of the matrices = t

Ca is the solubility of the medication in the dissolution medium.

Ds is the dispersion coefficient in the discharging medium.

T denotes the distance traversed by diffusion.

The equation for false stable state is as follows:

M = [2D. Ca .Co (p/T) t] ½ (Equation 6)

The following equation may be used to determine the matrix's complete porosity:

p = pa + Ca/ ρ + Cex / ρex (Equation 7)

pa = Air pocket porosity in the matrix

Cex = Water-soluble excipient percentage

p = Porousness

ρ= Medication's density

ex = Water-soluble excipients' density

Equation 7 may be simplified for data processing purposes to:

M = k. t ½ (Equation 8)

In which k is constant, If the drug release from the matrix is diffusion-controlled, the amount of drug released vs the function of time will be linear. In this scenario, medication release from a uniform matrix system could be regulated by adjusting the following criteria:

- Asymmetry
- Permeability
- Initial drug content inside the matrix
- Drug solubility
- Polymer component creating the matrices

9. EFFECTS ON MEDICATION DISCHARGE FROM MATRIX SYSTEMS

9.1. Medication-related variables

9.1.1. Drug solubility

Because diffusion is determined by the concentration slope throughout the channel, that is a feature of solubility [45, 46, 47], a drug with a high solubility will release more quickly; however, drugs with low solubility (0.01 mg/ml) will frequently release only partially due to their slow solubility and matrix dissolution rates. In the matrices of insoluble medicines, polymer attrition prevails, whereas erosion and diffusion work together to govern drug release in soluble meds. Drugs having pH-dependent solubilization, particularly in the digestive system pH range, are weak matrices system options [48].

9.1.2. Dosage content

Due to the necessity for huge amounts of the matrix former and additional matrix formers, medications with large dose levels (> 500 mg) are difficult to synthesize into a matrix system (excipients). Because of the higher drug concentration and the accompanying greater accumulation slope at the distribution front, a rise in dosage form at a constant polymer level enhances medication discharge [49].

9.1.3. Molecular weight and size

The hydrophilic gel form constraint is thought to cause drugs with molecular weights greater than 5000 Dalton to diffuse poorly across hydrophilic matrices

9.1.4. The particle size and shape

Because particle size and shape of soluble medicines affect effective surface area and thus intrinsic dissolving rate, they also affect drug release.

9.2. Polymer-related variables

9.2.1. The type of polymer

The type of polymer has a significant impact on the release of the medicine from the matrix. Hydrophilic and lipophilic polymers can be used to make prolong release matrices.

9.2.2. Grade of polymer viscosity

At a fixed polymer level, the viscosity of the polymer chosen regulates matrices effectiveness by influencing the mechanical, diffusional properties of the gel surface. Higher viscosity polymers hydrate quickly and form a mechanically stable gel layer. Fast hydrating polymers form gels quickly, which reduces initial dosage disposition from matrices and increases distribution time [50, 51].

9.2.3. Polymer content

With different polymer concentrations, medication's release profile from the matrix system may change as polymer concentration increases.

9.2.4. Particle properties of polymers

Lowering particle dimensions resulted in shorter lag times and a reduced burst effect. The reasoning was based on the smaller particles expanding faster, allowing the gel barrier to form faster.

9.2.5. Polymer mixture

The combination of polymers may synergistically delay drug discharge from controlled release tablets. The molecular physical interactions of the various polymers may be the cause of this synergism.

9.3. Formulation-related variables

9.3.1. Geometry of the formulation

The dimensions and form of a matrices type tablet with diffusive plus erosional dispersion can have an impact on how rapidly the drug dissolves. To obtain the lowest possible discharge rate, tablet matrices should be as spherical as feasible.

9.3.2. Process variables

Metoprolol tartrate was allegedly released faster in direct compression formulations than in free flowing or particularly high milling processes. Enhancing the crushing strength has a considerable impact on the firmness and diameter of the tablets

9.3.4. Preparation ingredients

Reformulation investigations of potential excipient interactions in solid dosage forms are required due to the potential for these interactions to impact drug release and bioavailability. Soluble fillers improve soluble medicine dissolution by shortening the diffusional route, whereas insoluble fillers slow diffusion by obstructing the tablet's surface pores.

Table1: The medication to be produced as a sustained release matrix tablet formulation with polymer and the technique can be used [52-55]

Drugs Used	**Category**	**Method Used**	**Polymer Used**
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Venlafaxine	Anti-depressant	Wet Granulation	Beeswax, Carnauba wax
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit-RSPO
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934, EC
Minocycline	Antibiotic	Wet Granulation	HPMC-K4M, HPMC-K15M, EC
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M, K15M, K100M, E15, EC, Guar gum
Metformin HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC
Diclofenac sodium	Anti-inflammatory	Wet Granulation	Chitosan, EC, HPMCP, HPMC
Acarbose	Anti-diabetic	Direct Compression	HPMC, Eudragit
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
Ambroxol HCL	Expectorant, Mucolytic	Direct Compression	HPMC-K100M,
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100, S100
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Diethyl carbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV
Diltiazem	Ca^{+2} channel blocker	Direct Compression	HPMC-K100M, HPMC-K4M, Karaya gum, Locust bean gum, Sod.CMC
Enalapril maleate	ACE inhibitor	Direct Compression	HPMC-K100M, HPMC K4M,
Itopride HCL	Prokinetic agent	Direct Compression	HPMC-K100M, HPMC-K4M, EC
Indomethacin	Anti-inflammatory	Direct Compression	EC, HPMC
Chlorpheniramine maleate	H1 antagonist	Melt-extrusion	Xanthan gum, Chitosan
Theophylline	Respiratory depressant	Direct Compression	Carbopol-934P, HPMC-K100M, HPMC-K4M, HPMC-K15M, EC
Losartan potassium	Anti-hypertensive	Direct Compression	HPMC-K100M, HPMC-K4M, Eudragit-RSPO
Metoclopramide	Anti-emetic	Direct Compression / Wet Granulation	HPMC, CMC, EC, SSG
Miconazole	Anti-fungal	Direct Compression / Wet Granulation	Pectin, HPMC
Naproxen	Morphine antagonist	Direct Compression	HPMC-K100M, HPMC-K15M, PVP
Nicorandil	Ca+2	Wet	HPMC, CMC, EC

	channel blocker	Granulation	
Amlodipine	Anti-arrhythmic	Direct Compression	HPMC, EC
Phenytoin Na	Anti-epileptic	Wet Granulation	Tragacanth, Acacia, Guar gum, Xanthan gum
Ranitidine HCL	H2 antagonist	Direct Compression	Chitosan, Carbopol-940
Ondansetron	Anti-hypertensive	Wet Granulation	HPMC-K100M, HPMC-K4M, HPMC-K15M
Tramadol	B2 blocker	Wet Granulation	HPMC-K4M, Karaya gum, Carrageenan gum
Verapemil	Ca+2 channel blocker	Direct Compression	HPMC-K100M, HPMC-K4M, HPMC-K15M

10. VARIOUS TECHNIQUES USED FOR FORMATION

10.1. Direct Compression

In this procedure, powdered materials are crushed directly without altering the physiochemical characteristics of the medication [56].

10.2. Wet granulation

The granulating agent is mixed with weighed amounts of the drug, polymer, and both. After a certain level of cohesiveness, wet bulk screening should be performed. Using a single-punch tablet compression machine, the particles are dehydrated, screened of dried particles, then combined with lubricating agent and disintegrants to form "flowing powder" medicine [57].

10.3. Melt Granulation

This technique makes use of a substance that melts at less temperatures. Such liquid could be heated past its melting point before being dropped over a molten substrate. The melt granulation technique was used to evaluate a variety of lipophilic binders [58].

11. SUSTAINED RELEASE MATRIX TABLET EVALUATION

Until a pharmaceutical with a prolonged release may be marketed, its strength, safety, stability, and dependability must be proven in vitro and in vivo, as well as a relationship connecting these two. Several studies have been published on the standards and processes for evaluating controlled delivery formulations [59, 60, 61]:

11.1. Weight Variation

Weigh each of the twenty pills separately. Determine the total weight of these 20 pills. After that, the average pill weight was calculated.

11.2. Hardness

The hardness of tablets from each batch was measured with a Monsanto's hardness tester, and median values were calculated.

11.3. Friability test

Roche friabilator was used to determine the degree of friability of the tablets. For four minutes, it rotates at a speed of 25 rpm.

11.4. Thickness

The thickness of the tablets was measured using micrometer screw gauges.

11.5. Content Consistency

The amount of medication was determined using a UV-visible spectrophotometer and the calibration curve method.

11.6. Dissolution in vitro

The matrix tablet's release rate was determined using the USP dissolving testing apparatus II (paddle method). The dissolving test used 900 cc of solvent and a predetermined rotation per minute. At various intervals, a sample of the solution was removed from the dissolving apparatus. The equal quantity of new dispersing liquid was used to substitute the specimens. The contents were filtered using a membrane filter [62].

11.7. Medication content

An average was found after weighing ten tablets. To generate a total amount of 100 ml, an 8 mg powder was mixed in 8 ml of 0.1N NaOH prior getting diluted with phosphate buffer saline at pH 6.8. After shaking for an hour, the solution was stored for 24 hours. In a 10 ml volumetric flask, 1 ml of the stock mixture was collected and adjusted to pH 6.8 using phosphate buffer. For spectrophotometric measurements of absorbance at 379nanometer against pH 6.8 phosphate buffer, filtered solution was used as a blank. The drug content of one tablet was computed [63, 64].

12. DRUG DISSOLUTION PROFILE KINETICS MODELLING

To achieve accurate kinetic modeling of drug release, the solubility of the most effective formulation was adapted to the zero order, first order, and Higuchi models. To identify the optimal model, the strategies were utilized.

i. Percentage of total medication released versus time. (Zero order)
ii. Plot time against the accumulated percentage of medication left (First order kinetic model)
iii. The Higuchi model: cumulative proportion of medication released vs. time squared.

Zero order: Zero order kinetics may be observed in various modified discharge dose forms, especiallycontrolled or prolonged release dosage forms (those dose forms in which the drug is released in a scheduled, predetermined, and longer manner than normal).Total percentage of drug released.

First Order: This dissolving action is present in the majority of conventional dosage formulations. Several

modified release drugs, particularly those with a long release period, use this type of dissolution pattern. When the medication dissolves, a gel-like layer forms around it, presumably allowing the drug's molecules to disseminate. A linear plot depicts the log cumulative fraction of drug remaining present over time.

Higuchi model: In modified release dosage formulations, a matrix structure of some kind is frequently present. In these cases, the substance separates from the matrix. Water penetrating rate determines the drug's dissolution pattern (diffusion controlled). A cumulative plot of drug release percentages [65, 66].

13. CONCLUSION

The main topics of this review article were the sustained release matrix tablet and its various benefits and drawbacks, goals, classes, and types of polymers used in its formulation, method of preparation, various drug distribution methods, factors affecting sustained discharge system, as well as assessment of prolonged release matrix system.

Sustained release matrix tablets are popular due to their ease of preparation, scalability, and adaptability. In addition to other advantages, continuous release matrix tablets offer a once-daily dosage and a low cost. They can be used to improve dose effectiveness in order to generate the necessary therapeutic response, as well as to address issues with traditional dosage forms and patient compliance. Tablets with a sustained release matrix have the potential to quickly dominate the market.

14. REFERENCES

1. Dixit N, Maurya SD, P.S. Sagar B. Sustained release drug delivery system. Indian Journal of Research in Pharmacy and Biotechnology. 2013;1:305–10.
2. Nisargi Shah, ChintanOza, ShitalTrivedi, Nihar Shah, Shreeraj Shah, Review on Sustained Release Matrix Tablets: An Approach to Prolong the Release of Drug, JPBSR. 2015; 5(3): 315-21.
3. Chien Y. W. Novel Drug Delivery System 1992; 2: 139 – 140.
4. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003.
5. Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd Edn, Vol. 72, Marcel Dekker Inc. New York, 1996, 575.
6. Salsa T, Veiga F And Pina M.E, Drug Develop. Ind Pharm. 1997; 23: 931.
7. Banker GS, Rhodes C.T. 2009
8. Sudhahar D. Sustained release matrix technology and recent advance in matrix drug delivery system: a review. International Journal of Drug Research and Technology, 2013; 3(1):12-20.
9. Roy H, Nayak BS. Formulation and Design of Sustained Release Matrix Tablets of Lamivudine: Combination of Chitosan and HPMC. American Journal of Pharmacy and Health Research. 2017; 5: 01-10.
10. Ray Brijesh, M.M. Gupta, A Review on: Sustained Release Technology. International Journal of Therapeutics Application, 2012, Volume (8):18-23.
11. Purnachandra Reddy Guntaka, Lankalapalli S. Design and Development Of Spray Dried Telaprevir For Improving The Dissolution From Tablets. International Journal of Pharmaceutical, Chemical & Biological Sciences. Volume 7, 2017.
12. Dunn CJ, Peters D. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs. 1995; 49:721-49.
13. Zhang J, Nur A. Recent progress in sustained/controlled oral delivery of captopril: an overview. Int J Pharm Tech. 2000;194 :139–49.
14. Zalte HD, Saudagar R.B. Review on Sustained Release Matrix Tablet, Int J Pharmacy Biological Sci. 2013:3:17-29.
15. Hoffman A. Pharmacodynamics aspects of sustained release preparations. Adv Drug Delivery Rev.1998:33:185-99.
16. Munday DC, Cox PJ. Compressed xanthan and karaya gum matrices: Hydration, erosion and drug release mechanisms. Int J Pharm.2000:203:179-92.
17. Bhargava A, Rathore RPS, Tanwar YS, Gupta S, Bhaduka G. Oral sustained release dosage form, an opportunity to prolong the release of drug. Int J Adv Res Pharm Bio Sci. 2013:3:7-14.
18. Ali Alyahawi, Abdulmajed Alsaifi. Quality control assessment of different brands of ciprofloxacin 500 mg tablets in Yemen. Univ J Pharm Res. 2018; 3: 31-6.
19. Banker GS and Rhodes CT. Modern Pharmaceutics. 3rd Ed., New York: Marcel Dekker Inc; 1996: 575-609.
20. Yang Shao, Liang Li, XiangqinGu, Linlin Wang, Shirui Mao, Evaluation of chitosan anionic polymers based tablets for extended- release of highly water soluble drugs. Asian J Pharm Sci. 2015; 10: 24- 30.
21. Leon S, Susanna W and Andrew BC. Applied Biopharmaceutics and Pharmacokinetics, 5th edition McGraw-Hill's Access Pharmacy. 2004; 171-179.
22. Abdel-Rahman I, Gamal MM and El-Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J. 2009; 17: 283-8.
23. Chandran S, Laila FA and Mantha N. Design and evaluation of Ethyl Cellulose Based Matrix Tablets of Ibuprofen with pH Modulated Release Kinetics. Ind J Pharm Sci. 2008; 70: 596–602.
24. Gothi GD, Parinh BN, Patel TD, Prajapati ST, Patel DM, Patel CN, Journal of Global Pharma Technology, 2010; 2: 69-74.

25. Roy Harekrishna, Nayak Shankar Bhabani, Nandi Sisir, Poloxamer Based Urapidil Loaded Chitosan Microparticle in Approach to Improve the Mechanical Strength by Tensile Strength and Entrapment Determination. Current Drug Therapy 2022; 17: 56-69.
26. Aulton Michael. E, The Design and Manufacture of Medicines, Church Hill Living Stone Vol. 3, 2007: 483-494.
27. Basak SC, Reddy BJ, Mani KL. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. Indian Journal of Pharmaceutical Sciences. 2006; 68(5).
28. Harekrishna Roy. Formulation of Sustained Release Matrix Tablets of Metformin hydrochloride by Polyacrylate Polymer. . Int J Pharma Res Health Sci. 2015; 3: 900-6.
29. Dhat S, Aphale S, Bagul U, Tagalpallewar A, Vanshiv S, Shah N. Effect of Two Different Diluents on Release Profile of Aceclofenac from Sustained Release Matrix Tablets Using Gum Damar as Release Retardant. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3:30713
30. Kumar S, Kant S, Prashar B. A review on sustained release drug delivery system. Int J Inst Pharm life Sci. 2012:2:356-76.
31. Oyeniran Taiwo Opeyemi, Obanewa opeyemi Adegbenro. Development and characterization of direct compressed matrix mini tablets of naproxen sodium. Univ J Pharm Res. 2018; 3: 7-11.
32. Kumar N, Roy Mahasweta, Kumar B, PuriPooja, Hasan M. Formulation and Evaluation of Sustained Released Metformin HCl Tablet Using Natural Polymers. Int J Pharmacy Pharm Res. 2016:6:217-37.
33. Prajapati B, Patel R, Patel D, Shah P. Metformin hydrochloride sustained release tablet using different matrixing tablet, e-Journal of Science and Technology (e-JST). 2013:4:61-72.
34. Singh S, Virmani T, Virmani R, Kumar P, Mahlawat G. Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation. Univ J Pharm Res. 2018; 3: 60-69.
35. Singh A, Rajput DS, Gopalrao AA, Chauhan D, Mafidar R, Bhowmick M, et al. Design and characterization of sustained release matrix tablets of metformin hydrochloride using combination of hydrophilic polymers. J Drug Deliv Therap. 2018; 8: 96-101.
36. Ho WH, Lee HLV. Sustained Drug Delivery Fundamentals and Applications: Design and fabrication of oral controlled release drug delivery system. 2nd ed. Marcel Dekker Inc, New York: 1987; 373-420.
37. Dusane RA, Gaikwad PD, Bankar VH, Pawar SP. A Review on: Sustained release technology. IJRAP. 2011; 2: 1701-8.
38. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences. 3rd ed. Varghese Publishing House. Bombay: 1991: 512-19.
39. Mohammed AD, James LF, Michael HR, John EH, Rajabi-Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxy methylcellulose and Hydroxypropyl methylcellulose. Phar. Dev. Tech. 1999; 4:313-24.
40. Lachaman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese publishing house 1987.
41. Chugh I, Seth N, Rana AC. Oral sustained release drug delivery system: An overview. IRJP 2012; 3: 57-62.
42. Purnachandra Reddy Guntaka, Lankalapalli S. Solid Dispersion-A Novel Approach for Bioavailability Enhancement of Poorly Water-Soluble Drugs in Solid Oral Dosage Forms. Asian Journal of Pharmaceutical and Clinical Research. 2019 Feb 7:17-26.
43. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. Vallabh Prakashan, Delhi: 2009; 399-401.
44. Lee VHL. Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design. 2nd ed. Marcel Dekker, Inc. New York: 1987: 16-25.
45. Wani MS et al. Controlled Release System-A Review. 2008; 6. Available on www.pharmainfo.net/review. URL: http://www.pharmainfo.net/reviews/controlled-released-system-review.
46. Singh A, Rajput DS, Gopalrao AA, Chauhan D, Mafidar R, Bhowmick M, et al. Design and characterization of sustained release matrix tablets of metformin hydrochloride using combination of hydrophilic polymers. J Drug Deliv Therap. 2018; 8:96-101
47. Roy Harekrishna, Panda Sanjay Kumar, Parida Kirti Ranjan, Biswal Asim Kumar. Formulation and In-vitro Evaluation of Matrix Controlled Lamivudine Tablets. International Journal of Pharma Research and Health Sciences. 2013; 1(1): 1-7.
48. Prakashpawan. Role of natural polymers in sustained release drug delivery system: Application and recent approaches. International research journal of pharmacy, 2011; 2: 6–11.
49. Venkata DeepthiVemuri, Purnachandra Reddy Guntaka. Posaconazole-amino acid cocrystals for improving solubility and oral bioavailability while maintaining antifungal activity and low in vivo toxicity. J drug Dev Sci Tech, Volume 74, 2022.
50. A Goyal et.al. Factors influencing drug release characteristics from hydrophilic polymer matrix tablet. Asian journal of pharmaceutical and clinical research. 2009; 2: 93 – 8.
51. Hargel L, Yu A. Modified release drug products. Appl. Biopharm. Pharmacokinet. 4th ed. McGraw Hill; 1999:169–71.

52. Verma BK, Pandey S, Arya P. Tablet granulation: current scenario and recent advances. Univ J Pharm Res. 2017; 2: 34-9.
53. Patil DM, Pawar PA, Pagar RY, Ghule RS, Bairagi VA, Formulation and development of sustained release matrix tablets of lornoxicam. J Drug Delivery Therap. 2018; 8:102-6.
54. Brahmankar H, Jaiswal S. Biopharmaceutics and Pharmacokinetics A Treatise. Vallabh Prakashan; 2000:337,348–57.
55. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill. 1999; 169-71.
56. Kanke PK, Sawant P, Jadhav A, Usman MRM, A review on disintegration control matrix tablets. J of Drug Deliv Therap. 2018; 8:19-22.
57. Roy H, Nayak Bhabani S. Formulation and Design of Sustained Release Matrix Tablets of Lamivudine: Combination of Chitosan and HPMC. American Journal of Pharmacy and Health Research. 2017; 5(2): 01-10.
58. Swapna S, Choudhary DK, Revanth CH, Sai Kumar B, Ch Praveen. Design and characterization of metoprolol floating matrix tablet. Pharmaceutical & Biological Evaluations. 2017; 4: 118-26.
59. Bookya P, Raparla R, Prasad Sriramula1, Harikishan, Tarrigopula S, Sridhar V. Formulation and Evaluation of Metformin Hydrochloride Sustained-Release Oral Matrix Tablets. Asian J Pharm Clin Res. 2018: 11:342-5.
60. Roy Harekrishna, Balaiah s, Vinay Kumar T. Design and in-vitro evaluation of cefuroxime axetil floating microbeads for the treatment of acute bacterial caused chronic bronchitis. Res J Pharma Tech. 2018; 11: 2276-82.
61. Shah MuradMastoi, Azmat Ali, Hina Aslam, Khalid Niaz. Comparision of antidyslipiemic potential of 80 milligrams of Fenofibrated with 8 grams of Nigella sativa seeds daily. Univ J Pharm Res. 2017; 2: 50-2.
62. Misal R, Atish W, Aqueel S. Matrix tablets: A promising Technique for controlled drug delivery. Indo Am J Pharm Res. 2013; 3: 3791–805.
63. Hadi Md. A, Lokeswara VB, Pal N, Rao SA. Formulation and evaluation of sustained release matrix tablets of montelukast sodium. International Journal of pharmacy. 2012; 2: 574-82.
64. Roy Harekrishna, Venkateswar Rao P, Panda Sanjay Kumar, Biswal Asim Kumar, Parida Kirti Ranjan, Dash Jharana. Composite alginate hydrogel microparticulate delivery system of zidovudine hydrochloride based on counter ion induced aggregation. Int J Applied Basic Med Res. 2014; 4(Sup 1): S31-36.
65. Purnachandra Reddy Guntaka, Lankalapalli SR. Solubility and dissolution enhancement of Ivacaftor tablets by using solid dispersion technique of hot-melt extrusion-a design of experimental approach. Asian Journal of Pharmaceutical and Clinical Research. 2019 Jan 7:356-63.
66. Purnachandra Reddy G, Lankalapalli S. A comparative study of ledipasvir solid dispersion technique using spray drying and hot-melt extrusion. International Journal of Pharmaceutical Sciences and Research. 2018; 9: 5145-54.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable.