



Review Article

Formulation And Evaluation of Sustained Release Matrix Tablets – A Review

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ARTICLE INFO

Received: 24 May 2023

Accepted: 28 May 2023

Published: 04 July 2023

Keywords:

Sustained release, Techniques, Matrix tablet, Polymers

DOI:

10.5281/zenodo.8114751

ABSTRACT

Oral drug delivery is still the finest and most popular method for administering pharmaceuticals via the internal route. Sustained release is also a good option for reducing adverse effect of drugs and boosting its therapeutic potency. The fundamental ideas of sustained drug delivery system optimise a variety of factors, such as a drugs pharmaceutical, pharmacokinetic and pharmacodynamic properties in order to increase therapeutic efficacy, minimise side effects and make disease cure simple. The major goal of this review is to provide comprehensive information about sustained release dose and its benefits as well as to outline the numerous factors to consider when choosing a drug for a certain drug delivery system and techniques used in sustained release dosage forms. The review highlights the types of matrices, mechanisms involved, polymers used in matrix tablets, method of preparation and evaluation studies such as angle of repose, bulk density, tapped density, hausner's ratio, carr's index, hardness test, friability test, weight variation test, uniformity of thickness, disintegration test, in-vitro drug release, determination of drug content.

INTRODUCTION

The development of oral sustained release drug delivery systems has received more attention over the past 30 years as the cost and difficulty of selling new pharmacological entities have increased, along with the knowledge of the therapeutic benefits of prolonged drug administration. Reducing dosage, dosage frequency, and ensuring uniform drug administration are the objectives of the design of sustained release drug delivery systems. So, a

dosage form known as sustained release is the one that constantly releases medication in a planned pattern for a set amount of time, either systemically or locally to a specific target organ. (1,2)

Drug Delivery Systems

Drug delivery systems are classified into two types. (3) They are,

- I. Conventional drug delivery system
- II. Modified drug delivery system

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



I. Conventional delivery system

Conventional drug delivery is effective for the majority of the medications, but some medications have unstable or hazardous properties, a limited therapeutic window, or poor solubility problems.

⁽⁴⁾ To maintain the constant plasma levels, a method of continuous therapeutic agent administration is preferred. Sustained or controlled drug delivery system can be used to provide this continuous drug delivery as shown in figure 1. Compared to conventional systems, these administration methods have a number of benefits, including increased effectiveness, decreased toxicity, and a greater patient convenience. ⁽⁵⁾

Limitations of conventional drug delivery

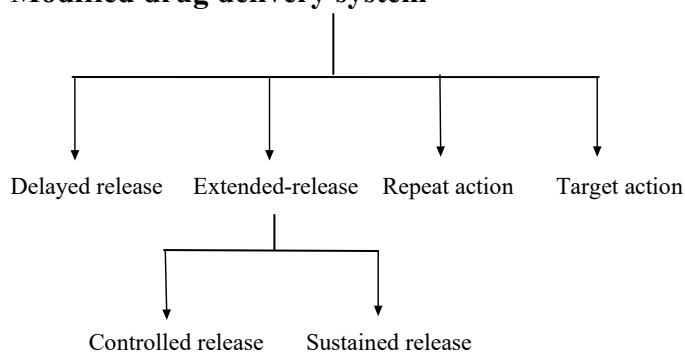
- In conventional oral dosage forms, there is little or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent administration of glossy excessive doses.
- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- When over medication occurs, drug levels changes may lead to harmful effects, particularly for drugs with low Therapeutic Index (TI).
- The physicochemical characteristics of drugs, the presence of excipients, various physiological factors like the presence or absence of food, the Ph of the gastrointestinal

tract, the gastrointestinal motility, and other factors can all have a significant impact on the rate and extent of drug absorption from conventional formulation. ⁽⁶⁾

II. Modified drug delivery system

Dosage forms can be designed to alter the drug release over a period of time after administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are frequently desired to boost the drugs stability, safety and effectiveness, to enhance the therapeutic result of drug therapy, and to boost the patient compliance and administration convenience. ⁽⁷⁾

Modified drug delivery system ^(2,8,9)



Delayed release

These dose regimens use one or more immediate release units combined into a single dosage form to deliver a medicine repeatedly and intermittently.

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at a predetermined rate and necessarily reduce the dosage frequency by two folds.

Repeat action

Typically, these dosage forms contain two single doses of medication, one for immediate release and the other for delayed release.

Target action

Drug release that aims to concentrate or isolate a drug in a specific body part, tissue, area for absorption or drug action.

Controlled release

Controlled drug delivery is the administration of medication at rate or site dictated by the needs of the body or state of the patient over certain period of time.

Sustained release

Sustained drug delivery may provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specified period time usually 8-12 hours. The basic goal of therapy is to achieve steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Sustained release implies slow release of the drug over a time period. It may or may not be controlled release.

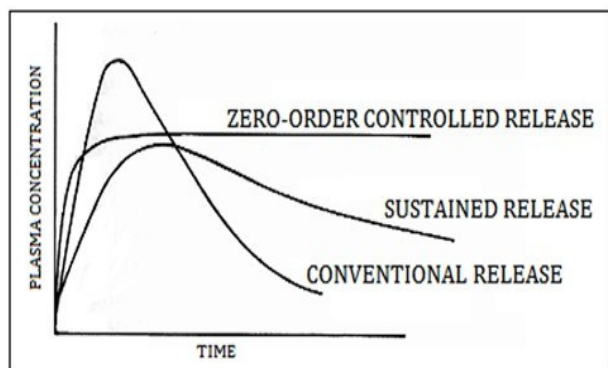


Figure 1: Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release

Advantages

- Reduction in dosing frequency.
- Reduced fluctuation in steady-state drug levels.
- Reduce side effects.
- Increased safety margin of potent drug.
- Uniform release of drug over time.
- Maximum utilization of the drug.
- Better patient compliance.
- Drug administration can be made more convenient as well.
- To extend the duration of action of the drug (8,10,11).

Disadvantages

- Cost of the formulation is high.
- Toxicity due to dose dumping.
- Increased cost.
- Reduced potential for dose adjustment.
- Poor invitro and in-vivo correlation (IVIVC).
- Requirement for additional patient education for proper medication.
- Increase potential for first pass metabolism (1,11,12).

Factors affecting the oral sustained release dosage form

A. Pharmacokinetic factors

1. Biological half-life

Biological half-lives of 2 to 8 hours are seen to be a good fit for sustained release dosage forms of medication. Drugs with an extremely short biological half-life, however, might not be a good fit for sustained release dosage forms. (13)

2. Absorption

When a medicine is absorbed by active transport, only the intestine can absorb it, hence the rate of absorption of a sustained formulation depends on the drug's release rate constant from the dosage form. (14)

3. Distribution

The overall drug elimination kinetics may be significantly influenced by the drug's distribution in tissues. Since it can be rate limiting in its equilibrium with blood and extra vascular tissue and lowers the concentration of circulating medication, the apparent volume of distribution will take on varying values depending on how the drug will be disposed of over time. In order to design sustain release products, one needs to know how drugs are used. (15)

4. Metabolism

Before changing a substance's shape, the metabolic conversion to a drug must be taken into account. An effective sustain release product can be produced as long as the location, rate, and extent of metabolism are known. (16)

B. Drug properties relevant to sustain release formulation

1. Dose size

For a traditional dosage form, a dose size of 500-1000mg is thought to be the maximum. For sustained release dose formulation, the same is valid. Given that the safety involved in administering large amounts with a limited therapeutic range is determined by the dose size. (17)

2. Ionization, PKa and aqueous solubility

The majority of medications are weak acids or bases, therefore for them to be absorbed, they must dissolve in the aqueous phase nearby the administration site before partitioning into the absorbing membrane. (18)

3. Partition coefficient

The partition coefficient has a significant impact on the drug's bioavailability. Since a drug's capacity to penetrate a biological membrane depends heavily on the partition coefficient of the drug. Low partition coefficient drugs are good candidates for sustain release formulations. Because, they will concentrate in aqueous phase. (19)

4. Drug stability

Acid-base hydrolysis and enzymatic breakdown occur, when medications are taken orally. The drug release mechanism that gives medication over an extended period of time is better in this situation if the drug is unstable in the intestine, which will have problems with low bioavailability. (20)

Drug selection for sustained release drug delivery system

The formulation of sustained release drug delivery systems, consider some criteria such as the route of administration, type of drug delivery system, what disease to be treated, the patient, the duration of treatment and the characteristic of the drug. (1) There are some physicochemical parameters pharmacokinetic parameters for the drug selection

to be formulated in sustained release dosage form as shown in the table 1&2. (3,11)

Table 1: Physicochemical Parameters For Drug Selection

Physicochemical parameter	Preferred value
Molecular weight	<1000 Daltons
Solubility	>0.1 mg/ml for pH 7.8
Partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segment
Release	Should not be influenced by pH and enzymes

Table 2: Pharmacokinetic Parameters Of Drug Selection

Pharmacokinetic Parameters	Preferred value
Elimination half-life	Preferably between 2 to 8
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution (Vd)	The larger Vd and MEC, the larger will be the required dose size
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration	The lower C _{uss} and smaller Vd loss among the dose required
Toxic concentration	Apart the values of MTC and MEC, safe the dosage form. Also suitable for drugs with very short half life

Techniques used in sustained release dosage forms

The following techniques are employed in the design and fabrication of oral sustained release dosage forms. (21,22,23)

1. Dissolution sustained release
 - Encapsulation type
 - Matrix type
2. Diffusion sustained release

Reservoir type

Matrix type

3. Ion exchange resins
4. pH-independent formulations
5. Osmotically controlled release
6. Altered density formulations

1. Dissolution sustained release

With dissolution sustained system, a medicine with a slow rate of dissolution is automatically sustained, and for drugs with a high-water solubility, one can speed up the process by forming the proper salts or derivatives. enteric coated dosage forms are most frequently produced using these techniques. Until the medication reaches the higher pH of the colon, this prevents the drug release dose form. The dissolution process at steady state was described by Noyes-Whitney equation,

$$dc/dt = KA(C_s - C) = D/h$$

Where,

dc/dt = dissolution rate

K = diffusion co-efficient

A = surface area of dissolving solid

C_s = saturation solubility of the solid

C = concentration of solute in bulk solution

H = thickness of diffusion layer

Encapsulation type

These techniques often involve coating individual medication particles with a substance that takes a while to dissolve. In order to create spansule goods, the coated particles can either be immediately compacted into tablets or put within capsules. A narrow or wide range of coated particles of different thickness can be used to achieve prolonged activity because the time needed for the coat to dissolve is depended on thickness and water solubility.

Matrix type

In those procedures, the medication is compressed with a carrier that dissolves gradually into a tablet shape. Here, the speed at which the dissolving

fluid permeates the matrix regulates the pace at which the medicine becomes available. This can be influenced by the granule surface wettability, the presence of hydrophobic additives, and the porosity of the tablet matrix.

2. Diffusion sustained release

Drug molecules travel by mechanism of diffusion from one area of higher concentration to another of lower concentration. Fick's law predicts how much drug will travel across a membrane in the direction of decreasing concentration.

Reservoir type

The drugs active ingredient is enclosed in a polymeric substance that is insoluble in water. The medication will diffuse into the fluid surrounding the particle or tablet after partitioning into the membrane as shown in figure 2

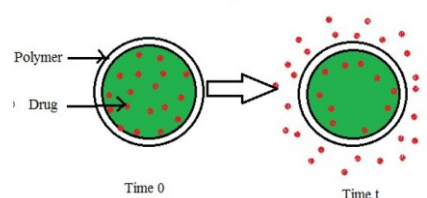


Figure 2: Representation of diffusion type reservoir system

Fick's first law of diffusion describes the diffusion process,

$$J = D dc/dx$$

Where,

J = flux of the drug across the membrane

D = diffusion coefficient

dc/dx = change in concentration c with distance x

Advantages

- Zero order delivery is possible.
- Release rate varies with polymer type.

Disadvantages

- System must be physically removed from implant sites.
- Difficult to deliver high molecular weight compounds.
- Increased cost per dosage unit.

Matrix type

A solid medication is dispersed in an insoluble matrix in this system. Not the rate of solid disintegration, but the rate of drug diffusion determines the rate of drug release. According to this hypothesis, the drug initially dissolves in the bath solution-exposed outer layer before diffusing out of the matrix as shown in figure 3.

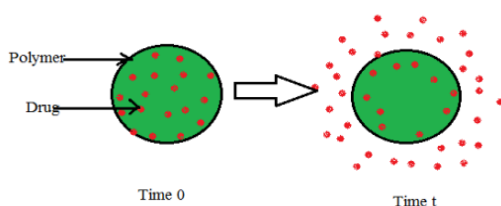


Figure 3: Schematic representation of diffusion type matrix system

The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi,

$$DQ/dt = (DAC_s/2t)^{1/2}$$

Where,

A is the total amount of drug in a device,

D is the diffusion coefficient of the drug in the polymer,

C_s is the solubility of drug in the polymer,

t is time.

Advantages

- Easier to produce than reservoir or encapsulated devices.
- Can deliver high molecular weight compounds.
- Usage of less total drug.
- Increase the stability.
- Minimize drug accumulation with chronic dosing.
- Minimizes local and systemic effects.

Disadvantages

- Cannot provide zero order release.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The release rate varies with square root of time.

- Removal of remaining matrix is necessary for implanted system.
- Not all drugs can be blended with polymeric matrix.

3. Ion exchange systems

They are cationic or anionic exchange resin salts or insoluble complexes where the exchange of bound drug ions that are often present in GI fluids causes medication release. The idea that positively or negatively charged medical compounds paired with the right resins produce insoluble poly salt resonates underlies the use of ion exchange resins to extend the effects of medications.

4. Osmotically controlled system

This device is made of a tablet that includes an osmotically active medication that is water soluble and was combined with osmotically active diluents by triacetate. When drug is stored in water, an osmotic pressure difference across the membrane causes a precise hole to form in the barrier, through which the drug is delivered. Two types of osmotically sustained systems are: Type A contains an osmotic core with drug. Type B contains the drug in flexible bag with osmotic core surroundings.

Advantages

- Zero order release rate are obtainable.
- Release of drug is independent of the environment of the system.

5. pH independent formulations

A basic or acidic medicine is combined with one or more buffering agents, then the mixture is granulated with the proper pharmaceutical excipients before being coated with GI fluid permeable film forming polymer. This formulation is known as buffered controlled release formulation. The buffering agent adjusts the fluid inside to an appropriate constant pH as GI fluid steps through the membrane, resulting in a constant rate of medication release.

6. Altered density formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastro intestinal tract. The pellets in the high-density technique must have a density greater than that of the contents of a typical stomach, or at least 1-4g/cm³. In a low-density method, globular shells that appear to be denser than stomach fluid can be employed as drug carriers for sustained release. Certain dose formulations are desirable for numerous reasons, including; ensures that the medical product is more bioavailable. This technique is typically employed when a single dose is needed throughout the course of the treatment, whether it lasts for days or weeks as is the case with infections, diabetes, or hypertension.

Matrix tablet

The most probable oral sustained-release medication delivery type has been matrix tablets. The mechanism of action of matrix tablets is to keep a steady plasma drug concentration, support the rate of drug release over time, and generate therapeutic action for a long period of time.

Active and inactive components are uniformly mixed and dispersed in the dosage form to create a matrix system. The popularity of the matrix system can be attributed to a number of variables, making it by far the most widely used oral sustained release technology. The first rule of diffusion, formulated by Fick, governs the release from the matrix type formulations. The medication is continuously released by matrix drug delivery devices. ⁽²⁴⁾

Polymers used in matrix tablet ⁽²⁵⁾

Table 3: Some Of The Types Of Polymers Used In Matrix Tablets

Polymer type	Examples
Soluble polymers	Poly ethylene glycol (PEG), Poly vinyl alcohol (PVA), Hydroxy propyl methyl cellulose (HPMC), Poly vinyl pyrrolidone (PVP).

Biodegradable polymers	Poly lactic acid (PLA), Poly caprolactone (PCL), Poly glycolic acid (PGA), Poly anhydrites, Poly orthoesters.
Non-biodegradable polymers	Poly vinyl chloride (PVC), Poly ethylene vinyl acetate (PVA), Poly dimethyl siloxane (PDS), Cellulose acetate (CA), Ethyl cellulose (EC), Poly ether urethane (PEU).
Mucoadhesive polymers	Sodium carboxy methyl cellulose, Polycarbophil, Methyl cellulose, Tragacanth, Poly acrylic acid, Pectin.
Hydrogels	Poly-hydroxyethyl methacrylate (PHEMA), Cross-linked poly vinyl alcohol (PVA), Cross-linked poly vinyl pyrrolidone (PVP), Polyacrylamide (PA), Polyethylene oxide (PEO).
Natural gums	Xantham gum, Guar gum, Karaya gum, Gum arabica

Classification of Matrix tablets

Matrix tablets can be classified as;

A) On the basis of retardant materials used

Under this category the matrix tablets are further divided into 5 types:

i. Hydrophobic matrices or Plastic matrices

Inert, hydrophobic materials were used in 1959 to create the first plastic matrices. In this procedure, the medication was first combined with a hydrophobic polymer before being compressed into a tablet. The medicine is dispersed by diffusion through a network of channels that connects tightly packed powder particles. As a result, sustained release is generated. Utilizing polyethene, poly-vinyl chloride, and acrylate polymers and their co-polymers, the hydrophobic matrices are created. Due to the water and digestive fluids included, these matrix pills are

inert by nature. Diffusion is how these matrix tablets work, and the rate-limiting stage is liquid penetration. ⁽²⁶⁾

ii. Lipid matrices

These matrices are created by using lipid waxes. These matrices allow the medication to be delivered through pore diffusion and erosion. Compared to entirely insoluble polymer matrix, the sustained release via these matrices is more sensitive to the make-up of digestive fluid. Most sustained release formulations use a retardant base made of carnauba wax, stearyl alcohol, and stearic acid. ⁽²⁷⁾

iii. Hydrophilic matrices

Due to their versatility in achieving a desired drug release profile, economic effectiveness, and wide spread regulatory acceptability, hydrophilic polymer matrix systems are often utilised in oral controlled drug delivery. The manufacture of medications in gelatinous capsules or, more often, tablets employing hydrophilic polymers with high gelling capabilities as base excipients is of special relevance in the field of controlled release. One or more medications that have been thoroughly combined with a gelling agent are said to “infect a matrix”. (Hydrophilic polymer). the term “swellable controlled release systems” is used to describe these systems the polymers used in the preparation of hydrophilic matrices are divided into following groups,

a) Cellulose derivatives

Methylcellulose 400 and 4000cps, Hydroxy ethyl cellulose; Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000and 15000cps; and Sodium carboxy methyl cellulose.

b) Non cellulose natural or semi synthetic polymers

Carob gum; Alginates; Agar-Agar; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

c) Polymers of acrylic acids

Polymers used in acrylic acid category is Carbopol 934. other hydrophilic materials used are Alginic acid, Gelatin and Natural gums. ⁽²⁸⁾

iv. Biodegradable matrices

These are composed of polymers with unstable backbone linkages made up of monomers connected to one another by functional groups. By enzymes produced by nearby live cells or by non-enzymatic processes, they are physiologically eroded or decomposed into oligomers and monomers that can be metabolised or expelled. Examples include synthetic polymers such as aliphatic polyesters and poly anhydrides, as well as natural polymers like proteins and polysaccharides, as well as modified natural polymers. ⁽²⁹⁾

v. Mineral matrices

Polymers derived from several seaweed species are present in mineral matrices. Mineral matrices include hydrophilic carbohydrates like alginic acid which may be produced from some types of brown seaweed using diluted alkali. ⁽³⁰⁾

B) On the basis of porosity of matrix: ^(31,32)

In this drug molecules diffuse across the matrix and produce sustained release. The matrix is further divided into three types;

i. Macro porous systems

This type of matrix has holes that are between 0.1 and 1m in size, which is greater than diffusant molecule size. This sort of technology allows the medicine to permeate via these pores.

ii. Micro porous systems

Permeation of drug molecules occurs through pores of size ranging from 50-200 Å.

iii. Nonporous systems

No pores exist in this system. Molecular diffusion takes place through network meshes. Whereas the polymeric phase is present, there is no pore phase.

METHODS OF PREPARATION MATRIX TABLETS

1) Wet granulation technique



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. ⁽³³⁾

2) Direct compression

Direct compression is a dry process. This technique compresses directly highly powdered materials without altering the drugs physical or chemical characteristics. This process involves only two-unit operations powder mixing and tableting. ⁽³⁴⁾

3) Melt granulation

Organic liquids are necessary in the process of melt granulation because meltable substances serve as the liquid binding agents. when elevated above its melting point, the substrate can be covered with this material when it is in molten state. The melt granulation method makes use of various lipophilic compounds, including glycerol palmitostearate. ⁽³⁵⁾

EVALUATION OF SUSTAINED RELEASE DOSAGE FORMS

Precompression parameters ^(8,36)

1. Angle of repose (Θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. It is an indication of the flow properties of the powder. The powder mixture is allowed to flow through the funnel fixed to a stand at definite height(h). It is calculated by the following formula,

$$\tan \Theta = h/r$$

Where,

Θ = angle of repose,

h = height in cm

r = radius in cm

2. Bulk density

Bulk density is defined as the mass of a powder, divided by the bulk volume. The bulk density of

powder depends primarily on particle size distribution, particle shape, and tendency of particles to adhere to one another.

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume}}$$

3. Tapped density

Set measuring cylinders to 300 taps per minute and operate for 500 taps. The tapped density is calculated by the following formula,

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{tapped volume}}$$

4. Hausner's ratio

Hausner's ratio can be calculated from the bulk and tapped density. It was given by the equation,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5. Carr's index

It is the simplest way of measurement of free flow of powder. Carr's index can be calculated from the bulk and tapped density by using the following formula,

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100$$

Post compression parameters: ^(37,38,39)

1. Hardness test

Tablets require certain amount of hardness and resistance to friability, to withstand mechanical shocks during manufacturing, packaging, and shipping. The hardness of tablet was determined by using Monsanto hardness tester. It is expressed in kg/cm².

2. Friability test

Roche friabilator is used for the measurement of friability using 20 tablets. Twenty tablets are weighed and rotated at 25 rpm for 4

minutes. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\% \text{ Friability} = \frac{(\text{Initial weight} - \text{final weight})}{\text{Initial weight}} \times 100$$

3. Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The USP allows a little variation in the weight of the tablet. The following percentage deviation in weight variation is allowed.

Table 4: Percentage Deviation In Weight Variation

Average weight of a tablet	Percentage deviation
200 mg or less	10
More than 190 mg or less than 200 mg	7.5
200 or more	5

4. Uniformity of thickness

The thickness of individual tablet may be measured with a digital vernier calliper, which permits accurate measurements and provides information on the variation between tablets.

5. Disintegration test

The process of breakdown of tablet into smaller particles is called as disintegration. The invitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. The test was carried out on 6 tablets, by placing tablet into each test tube (3 inches long and have 10 mesh screen) using the distilled water (used as disintegration medium) at a frequency of 28-32 cycle/minute and $37 \pm 2^\circ\text{C}$ and the time in seconds is taken for complete disintegration of tablet with no palatable mass remaining in the apparatus was measured in seconds.

6. In-vitro drug release studies

Drug release study is generally determined in rotating paddle apparatus. Mainly buffer is used as

dissolution medium. The temperature of the bath is maintained at 37°C and required sample of the dissolution medium in which drug released is taken at regular intervals and the same quantity of the medium is replaced. The amount of drug released is determined using an UV spectrophotometer. Drug dissolved at specified time period is plotted as percent release verses time.

7. Determination of drug content

The sample is analysed using a visible spectrometer and a standard calibration curve of the purified substance after being dissolved in an appropriate solvent, such as pH 7.4 phosphate buffer solution.

STABILITY STUDIES

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within the specified limits throughout its shelf life and recommended storage conditions.

CONCLUSION

The sustained release drug delivery system is particularly beneficial for improving patient compliance, dose efficiency, and dose safety. The formulation of an oral sustained release drug delivery system is influenced by a number of variables, including the physical-chemical characteristics of the drug, the type of delivery system, the disease being treated, the patient's condition, the length of the treatment, the presence of food, gastrointestinal motility, and the co-administration of other medication. We may conclude from the description above that the use of matrix tablets is also under control. Due to the use of these of these tablets the daily required frequency of the doses was also reduced. The price of oral sustained release drug delivery systems has

made it easier for them to replace oral conventional drug delivery system in the market.

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HOW TO CITE: Muni Raja Lakshmi K*, Naseema Shaik, Lavanya E, Venkata Rao Gadde, Formulation And Evaluation of Sustained Release Matrix Tablets – A Review, *Int. J. in Pharm. Sci.*, 2023, Vol 1, Issue 7, 170-181. <https://doi.org/10.5281/zenodo.8114751>

