A REVIEW ON SUSTAIN RELEASE MATRIX TABLET

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ABSTRACT

Wet granulation, direct compression, or dispersion of solid particles within solid particles within a porous matrix created by employing various polymers, such as polymethyl methacrylate (PMMA), polyglycolic acid, HPMC, etc., are the main methods used to create sustained release matrix tablets. The matrix regulates the drug's rate of release. Release inhibitors, such as HPMC, can help with sustained release, making them a key excipient in the formulation. The process involves directly compressing a mixture of the medicine, the retardant material, and the additives to create a tablet with the drug embedded in the matrix core of the retardant. Granulation may also be done before compression. The matrices employed could be mineral, hydrophilic, hydrophobic, or biodegradable in nature.Studies of in-vitro dissolution can be used to determine the medication release rate. Ambroxol HCl, nateglinide, and other medications have been created as sustained release matrix tablets. Thus, by reducing the total dose and dosage schedule, sustained release matrix tablets can provide improved patient compliance, which is very beneficial for the treatment of chronic diseases.

KEYWORDS: Sustained release, in-vitro dissolution,Polymer, Matrix tablet.

INTRODUCTION

The primary goal of the administration of drugs is the treatment of diseases. Never deliver a drug in its pure form; instead, turn it into a dosage form that will allow you to monitor the drug's onset, intensity, and overall duration of action. A controlled drug delivery system is optimal if it can administer the medication locally or systemically at a defined rate for a predetermined amount of time with the least amount of variation in plasma drug concentration, the least amount of toxicity, and the most amount of effectiveness. Currently, new and innovative drug delivery technologies are quickly replacing traditional drug dosage forms.Due to its high patient compliance, economic effectiveness, lack of sterility restrictions, flexibility in dosage form design, and ease of manufacture, oral drug delivery is the most popular and practical method of drug administration. Due to its greater potency, greater precision in dosage, ease of production, and preference for tablets as an oral dosage form, oral medication administration has historically been the most common method of drug delivery. Approximately 50% of drug products on the market are delivered orally.. There are many different types of tablets available on the market, from simple instant release formulations to complicated sustained release or modified release dose forms . The goal of a sustained release drug delivery system was to maintain plasma drug levels by slowly dispensing the medication. The sustained release drug delivery system is suited for drugs with a shorter half-life. As tablets represent the most affordable method of sustained and controlled release solid dosage forms, matrix tablets are a potential strategy for the implementation of extended-release medication therapy.The oral solid dosage forms known as matrix tablets are those in which the medication is

uniformly dissolved or disseminated inside hydrophilic or hydrophobic polymeric matrices. Sustained release dosage forms theoretically ought to release the medication by a zero-order mechanism that keeps the drug's plasma level time consistent with intravenous infusion[4]. The matrix system is a release mechanism that extends and regulates the drug's distributed or dissolved release. A well-mixed composite comprising one or more medications and a gelling agent, such as hydrophilic polymers, is referred to as a matrix. In the world of pharmaceutical technology, the introduction of the matrix tablet as a sustained release has resulted in a new breakthrough for unique drug delivery systems.The matrix tablet gradually erodes under stomach pH conditions. There are two mechanisms at work: dissolving of coated particles and zero-order erosion, which both result in a reduction in surface area. the ability to manage blood levels of active pharmacological ingredients within a specific range, above the minimal effective level and below the toxic leve.

In matrix frameworks with different systems, the drug molecule seems to be better supported for a sustained drug release profile. By distributing solid particles within a porous matrix made of hydrophilic and hydrophobic polymers, matrix tablets can be made using wet granulation or direct compression techniques.
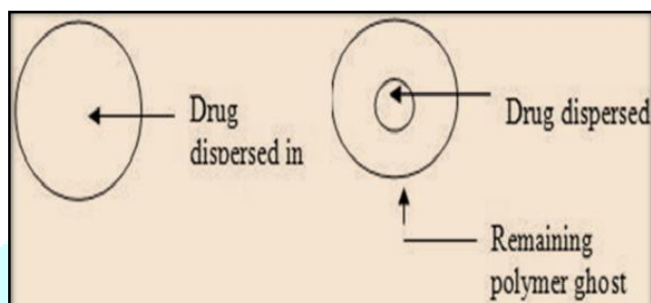

Figure 1: Drug release from a system with an inert matrix

In matrix frameworks with different systems, the drug molecule seems to have a prolonged drug release profile that is better maintained. Wet granulation or direct compression techniques can be used to create matrix tablets by dispersing solid particles within a porous matrix made of hydrophilic and hydrophobic polymers.

SUSTAINED RELEASE MATRIX TABLETS' BENEFITS INCLUDE:

I)PATIENT COMPLIANCE

Lack of compliance is typically associated with chronic diseases that require long-term therapy because the success of a drug treatment depends on the patient's ability to comply. Many elements, including understanding of the illness process, patient confidence in therapy, and comprehension of the patient in relation to a rigid treatment plan, affect patient compliance. Along with the complexity of treatment plans, the expense of treatment, and any local or systemic adverse effects from the dosage type. By using a sustained release drug delivery system, this problem can be partially resolved. [10-14]

II) LESSENING OF "SEE-SAW" VOLATILITY

When a medication is administered in a standard dose form, the drug concentration in the bloodstream and tissue compartments frequently exhibits a "seesaw" pattern. Drug kinetics, such as the rate of absorption, distribution, elimination, and dosage intervals, are a major factor in determining the sizes of these variances. [15] Since recommended dose intervals are rarely shorter than four hours, the "see-saw" pattern is more pronounced just in the case of medications with biological half-lives under four hours. The frequency of drug dosing can be significantly reduced by a well-designed sustained release drug delivery system, which can also keep the drug concentration in the bloodstream and target tissue cells constant. [16]

III)TOTAL DOSE REDUCTION

Sustained release drug delivery systems use a smaller amount of total medication to treat a disease. Reduced systemic or local side effects are seen when the complete dose of the medicine is used. Additionally, this would boost the economy. [17]

IV). CORRECTION OF TREATMENT DEFICIENCIES

Effective drug delivery to diseased tissues and organs is necessary for effective disease treatment. It is frequently essential to deliver dosages that are far higher than those that the cells need in order to reach the required therapeutically effective concentration. Unfortunately, this could have adverse immunological, toxicological, and toxicological consequences on tissue that is not the target. The acute or chronic disease condition is better managed with a sustained release dose form. [18]

V) THE ECONOMY

Due to the unique properties of these substances, sustained release solutions often have higher initial unit costs than conventional dosage forms, but more crucially, the average cost of treatment over an extended period of time may be lower.[19].

DISADVANTAGES OF SUSTAINED RELEASE MATRIX TABLETS.

• Exorbitant price.

• Frequently low systemic availability

• The demand for more patient counselling and education.

• Dose dumping. [20]

• Often poor in vivo-in vitro correlation. [21]

CHARACTERISTICS OF DRUG SUITABLE FOR SUSTAINED RELEASETABLET

The following are the optimal physicochemical and pharmacokinetic characteristics of drugs that can be categorised as extended release tablets:

1. Atomic size should be less than a thousand Dalton.

2. For pH values of 1 to pH 7.8, aqueous solvency should be more than 0.1 mg/ml.

3. A high partition coefficient is required.

4. The preferred mode of absorption is diffusion, and pH and catalysts should not have an affect on the general absorbability of all GI fragment discharge.

5. The elimination half-life should be 2 to 8 hours. [7]

6. Drugs should not be metabolised before being absorbed because this reduces their bioavailability.

7. Absolute bioavailability should be 75% or higher.

8. The discharge rate should be greater than the absorption rate constant (Ka). A significant apparent volume of distribution (Vd) is required.

9. Total clearance shouldn't be influenced by dosage. [15]

10. Therapeutic concentration (Css) should be low and smaller (Vd), and elimination rate constants are necessary for design. [3,4,5].

Polymers used in sustained release tablet

Hydrophilic and hydrophobic polymers are among the most prevalent materials utilised in the creation of matrix systems.

a) Hydrophilic Polymers, first Sodium alginate, poly(ethylene oxide), Xanthan gum, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyl ethyl cellulose (HEC), and cross-linked homopolymers and copolymers of acrylic acid. [22-24] .

b) Hydrophobic Materials Wax and water-insoluble polymers are frequently used in their formulation.

c) Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, and Chitosan are examples of natural polymers.

METHODS OF PREPARATION

 1.compression method

This technique compresses finely ground materials directly without altering the drug's physical or chemical characteristics.

2.Wet Granulation

In this procedure, weighed amounts of the medication and the polymer are combined with an adequate amount of the granulating agent. Once there is sufficient cohesion, the bulk is sieved, dried at 40°C, and maintained in a dessicator. The tablets are compressed using a tablet compression machine29 after lubricants and gliders are applied.

3. Melt Granulation

Since meltable substances serve as the liquid binding agent in melt granulation, organic solvents are not necessary. This liquid can be poured over the substrate while it is still molten and then heated to a temperature above its melting point. In the melt granulation process, many lipophilic binders, including Glyceryl Palmitostearate, are utilized. [16]

Drug characteristics that make it inappropriate for sustained-release oral dosage forms:

Specialized Drugs not absorbed well in the small intestine Vitamin B2, iron salts Quickly absorbed and eliminated (12-hour biological half-life) Phenytoin with valium need for large dose > 1 gm sulfonamide Drug with acceptable side effects and cumulative action but poor therapeutic indices Digitoxin with phenobarbital A precise dosage that is adjusted for each individual is needed. Cardiovascular glycosides, anticoagulants. [9]

CRITERIA TO BE SATISFIED FOR THE DRUGS INCORPORATION INTO SUSTAINED RELEASE DOSAGE FORM:

There are a few physicochemical factors to consider when choosing a medicine to be packaged in a sustained release dosage form, chief among which is understanding how the drug is absorbed from the gastrointestinal (G.I.) tract.

Physicochemical criteria for choosing a medicine Parameters Criteria 1000 Daltons or less for molecules In Aqueous Media For pH 1 to pH 7.8, more than 0.1 mg/ml a partition coefficient that is apparent Diffusion mechanism with high absorption Generally absorbing from every GI region pH and enzymes shouldn't have any effect on release.

Drug selection pharmacokinetic parameters: Parameters Comment Half-life of elimination: 2 to 8 hours 100% bioavailability should be at least 75% Must be the absorption rate constant (Ka)superior to the release rate apparent distribution volume (Vd) Greater Vd and MEC, greater dose will be needed Entire distance not rely on dosage Constant elimination rate necessary for design therapeutic intensity (Css) The more medicine is needed for loss among, the lower the Css and smaller the Vd. Aside from the value of MTC and MEC, toxic concentration, safer dose form . [4,10,11]

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

Half-life in biology: Intake: Metabolism: Distribution: binding of proteins: Biological half-life:

1) Biological half-life: Margin of safety An oral SR formulation's straightforward principle is to sustain therapeutic blood levels throughout time. To accomplish this, the drug must enter the bloodstream at a rate that is almost equal to its rate of elimination. The sum of all elimination activities, which typically include metabolism, urine excretion, and any other processes that permanently remove drugs from the blood stream, determines the elimination rate for each medication, which is a unique property. The ideal candidates for sustain release formulation are medications with a short half-life.Levodopa and other medications with a half-life of less than 2 hours are poor candidates for SR formulation. Drugs whose half-lives are longer than 8 hours make poor candidates for SR formulations since their effects are already long-lasting. For instance, digoxin and phenytoin.

2) Absorption: Controlling the medication release rate so that it is substantially slower than the rate of absorption is the main objective of SR products. The extreme half-life for absorption should be in the range of 3–4 hours if we assume that the majority of medications take 8–12 hours to travel through the absorptive parts of the GI tract. If not, the dosage form will leave the likely absorptive regions before the drug release is finished. Thus, to give 80–95% over this time period, corresponds to a minimum apparent absorption rate constant of 0.17–0.23h-1. Therefore, it accepts that the small intestine's entire length should absorb drugs at a fairly consistent rate.

3) Metabolism: The slow-releasing dose form's decreased bioavailability was demonstrated by Drugs that are considerably processed in the intestine's tissue or lumen prior to absorption may have lower bioavailability when taken in slow-releasing dose forms. A medication with weak water solubility can be designed in a dose form called sustain release. This can be accomplished using a variety of strategies that can be used to increase the drug's solubility following the development of a sustain release formulation. But because the drug's potential to crystallise occurs as it enters the systemic circulation, this should be avoided, and precautions should be taken to avoid it.

4) Distribution: The apparent volume of distribution has a significant impact on the drug's rate of elimination. Therefore, medications with a high apparent volume of distribution, which affects the rate of medication clearance, are thought to be poor candidates for oral SR drug delivery systems. Consider chloroquine.

5) Protein Binding: All drugs are to some extent bound to plasma and/or tissue proteins in order to produce a pharmacological response, however unbound drug concentration is more crucial than bound drug concentration. Despite the kind of dosage form, the drug's therapeutic impact is heavily influenced by protein binding. Because substantial binding to plasma lengthens the biological half-life, SR drug delivery systems are not always necessary for this class of medicine.

6) Molecular size and diffusivity: Drugs in a number of sustained release systems must diffuse across a matrix or membrane that regulates their rate of diffusion. A drug's molecular size plays a role in its ability to disperse through membranes, also known as its diffusivity (diffusion coefficient). a significant factor affecting the diffusivity's value. The diffusing species' molecular weight and size are represented by the letter "D" in polymers.

7) Safety margin: Generally speaking, a drug's therapeutic index determines how safe it is. The higher the therapeutic index value, the safer the drug. Less effective medications are typically not good choices for oral SR drug delivery. [7,12,13,14]

PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

a) Dose size: For a conventional dosage form, a single dose generally containing 500 mg to 1 g of medication is regarded as the maximum. The same standards apply to dosage forms with sustained release. compounds with huge doses that may occasionally be administered in numerous doses or packaged into liquid systems. The margin of safety, which entails administering large doses of a medication with a limited therapeutic window, is another factor to take into account.

b) Aqueous solubility, pka, and ionisation: Most drugs are weak acids or bases. Since medications in their unmodified form can pass across lipid membranes, the link between the compound's pka and the absorptive environment is crucial. It is desirable to give the drug in its unmodified form for drug permeation. Unfortunately, the more complicated

conversion to unaltered form will result in a reduction in the water solubility. The solubility of the drug in aqueous media will be equally important to delivery systems that depend on diffusion or dissolution. These dosage forms must work in a pH-changing environment, with the small intestine being more neutral and the stomach being more acidic. The effect of the release mechanism must also be outlined.

c) Partition Coefficient: As a result, the partition coefficient of medications that are oil soluble is crucial in figuring out how well they penetrate membrane barriers. Lipophilic substances with high partition coefficients are not well soluble in water and stay in the lipophilic tissue for a longer period of time. Poor bioavailability occurs when a drug has an extremely low partition coefficient, which makes it very difficult for the compound to pass through the membrane. Additionally, diffusion through polymer membranes is not exempt from the effects of partitioning. The partitioning properties of the medication heavily influence the choice of diffusion-limiting membranes.

d) Stability: Drugs taken orally are prone to both enzymatic and acid-base hydrolysis degradation. This is the preferable composition of delivery for problematic circumstances because a drug's degradation will proceed at a slower rate in the solid state. Systems that prolong delivery over the whole length of transit in the GI tract are advantageous for dose forms that are unstable in the stomach. This holds true even for systems that hold off on releasing the medication until the dosage form reaches the small intestine. When taken from a sustaining dose form, substances that are unstable in the small intestine may exhibit lower bioavailability. This is due to the small intestine's increased medication delivery and the medicines' vulnerability to degradation. [7, 8,10,12]

FORMULATION

SRDDS Diffusion Sustained System Dissolution in the Oral Form Permanent System Approach Employing the Ion Exchange Method Osmotic pressure is used Formulation Based on pH System of Alternate Density

DESIGN AND FORMULATION OF ORAL SUATAINED RELEASE DRUG DELIVERY SYSTEM12-16

Due to its versatility in dosage form, design, and patient compliance, the oral mode of administration is the most popular. However, one must here take into account the varied pHs that the dosage form would experience during its transit, gastrointestinal motility, the enzyme system, and its impact on the drug and the dosage form. The majority of oral sustained release systems generate delayed drug release to the gastrointestinal environment through diffusion, dissolution, or a combination of these two methods. Theoretically and ideally, a sustained release delivery device should release the medication by a zero-order process, producing a blood level time profile comparable to that after intravenous constant

Numerous classes of sustained drug delivery systems have been used to try to create sustained (zero-order) medication release.

1. A persistent diffusion system. I Type of reservoir. ii) Type of matrix

2. A sustained system for dissolution. I Type of reservoir. ii) Type of matrix

3. Techniques utilising ion exchange

4. Osmotic pressure-based procedures

5. formulations with no regard to pH.

6. Modified formulas for densities.

Diffusion Sustained System

Diffusion process essentially depicts the migration of drug molecules from a higher concentration area to a lower concentration area. Fick's law determines the flow of the drug J (in amount/area-time) across a membrane in the direction of decreasing concentration.

. J= - D dc/dx

D = the diffusion coefficient in both space and time. dc/dx equals the concentration change of c with distance x. In its typical form, a medication must diffuse through a membrane that is impermeable to water. The formula for the medication release rate, dm/dt, is

dm/ dt= ADKΔ C/L

Where: A = Area; K = Drug Partition Coefficient between Drug Core and Membrane. Diffusion path length = L (i.e. thickness of coat). Concentration differential across the membrane, abbreviated as c..

Reservoir Type

A drug core is enclosed in the system by a water-insoluble polymeric substance (Figure 1). Drug will interchange with the fluid surrounding the particle or tablet after partitioning into the membrane. More medication will enter the polymer, diffuse to the periphery, and interact with the media there. receptacle system

Matrix Type

solid drug is disseminated in an insoluble matrix, and drug release depends more on drug diffusion than solid disintegration. For this system, Higuchi has arrived at the proper drug release equation:

Q = Dε/ T [2 A –εCs] Cst½

Where; Q = Weight in gms of drug released per unit area of surface at time t. D stands for the drug's diffusion coefficient in the release medium. = The matrix's porosity. Cs is the drug's solubility in the release medium. T stands for the matrix's torque. A is the medication concentration in the tablet, expressed as gm/ml.

Dissolution Sustained Systems

A medicine with a slow rate of dissolution is naturally sustained, and for drugs with a high water solubility, the rate of dissolution can be slowed down with the right salt or derivative synthesis. Enteric coated dosage forms are most frequently produced using these techniques. A coating that dissolves in natural or alkaline media is used to shield the stomach from the effects of medications like aspirin. As a result, drug release from the device is inhibited until it reaches the higher pH of the intestine. Most of the time, enteric coated dosage forms are not genuinely sustaining in nature, but they do serve a useful purpose in guiding drug release to a particular spot. For molecules that are harmed by severe conditions, the same strategy might be used.conditions that can be found in the stomach.

Reservoir Type

A coating of a specific thickness is applied to the drug, and it progressively dissolves in the contents of the gastrointestinal system. A pulsed delivery can be achieved by alternating the drug layers with the rate-controlling coatings as shown in figure 1. Initial drug levels in the body can be quickly set with pulsed intervals if the outer layer of the body is releasing the bolus dosage of the drug promptly. The biological consequences may be similar even though this is not a real continuous release method. An alternate way is to deliver the medication as a collection of beads with varying coatings. In figure, this is displayed. The beads' release happens gradually because of the varying coating thicknesses. The ones that have the fewest layers will offerthe first dose. Those with thicker coatings will be able to keep medication levels steady over time. The spansule capsule operates on this basis. Acetyl salicylic acid tablets were coated with synthetic cellulose nitrate phthalate as an enteric coating agent.

Matrix Type

The most prevalent kind of sustained dissolution dose (as shown in figure 1). It can either be a drug-impregnated sphere or a drug-impregnated tablet, and both will slowly erode. Dissolution sustained pulsed delivery systems are in two different varieties.

• Single bead type device with alternating drug and rate-controlling layer

• Drug-containing beads with various dissolving coat thicknesses Due to the following benefits, hydrophilic matrix technology is the most popular drug delivery technique among sustained release formulations.

•Provide desired release profiles for a broad range of therapeutic medication categories, doses, and solubility.

•Easy and affordable manufacture using already-in-use tableting unit operation equipment.

• Strong formulation.

• Widespread acceptance by patients and regulators.

•Ease of drug release modification by level and system selection for polymeric structures

EVALUATION TEST FOR SUSTAINED RELEASE TABLETS:

Weight Variation:

Twenty tablets were weighed individually and then collectively, average weight of the tablets wascalculated.

Hardness:

Monsanto's hardness tester was used to test each batch of tablets, and average values were derived.

Friability:

The Roche friabilator, which rotates at a speed of 25 rpm for four minutes, was used to evaluate the tablets for friability.

Thickness:

A micrometre screw gauge was used to measure the thickness of the tablets. Content

Uniformity:

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

IN VITRO DISSOLUTION STUDY:

Rotating Paddles equipment is typically used to determine drug release studies. Buffer is primarily utilised as a dissolving media. The dissolution medium in which the medication is released is sampled as needed at regular intervals, and the same quantity of the medium is replaced, all while maintaining the bath's temperature at 370C. An UV spectrophotometer is used to measure the quantity of the medication emitted. The % release of a drug at a certain moment is plotted against time. Short Term Stability Investigation: The best batch underwent a short term stability study to ascertain how the in vitro release profile changed upon storage. [22,23,24]

CONCLUSION

This review paper has focused on the formulation of prolonged release matrix tablets, their advantages and disadvantages, various types of polymers, the method of preparation, and the evaluation criteria.

As opposed to their conventional equivalents, matrix tablets improve patient compliance, maintain a stable plasma drug concentration level, lessen the likelihood of toxicity, and lower the overall cost of treatment by using a once-daily drug regimen. The explanation above leads to the conclusion that matrix tablets are useful in overcoming patient non-compliance and issues associated with conventional dose forms, such as the dosage form's effectiveness in triggering desired therapeutic response. Therefore, this extended release formulation may be an appropriate formulation into which an antidiabetic medication might be integrated to produce greater pharmacological effect. This article could be helpful.

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