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IMPACT OF MATRIX TABLETS AS A SUSTAINED RELEASE TABLET IN NOVEL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The goal of the Novel Drug Delivery System is to deliver a therapeutic amount of drug to the appropriate site in the body quickly and then maintain the desired drug concentration. For drugs to reach their intended target with minimal or no side effects. To reduce drug degradation and loss. Over the last decade, there has been a lot of interest in replacing traditional drug administration with a delivery system that would release effective quantities from a protected supply at a controlled rate over a long period of time. Sustained drug release formulations are extremely beneficial in the treatment of chronic diseases. Matrix tablets have been the most common forms of sustained drug release forms administered orally. Matrix tablets work by maintaining a constant plasma drug concentration, sustaining the rate of drug release over time, and producing therapeutic action for an extended period of time. Extended release is important in formulations with a short half-life and a high dosing frequency. The matrix regulates the drug's rate of release. Fire retardants such as hydroxy propyl methyl cellulose (HPMC), polyglycolic acid, and poly methyl methacrylate are employed. The drug is embedded in the retardant's matrix core. The matrices used may be hydrophobic, biodegradable, or mineral in nature.

KEYWORDS: Novel Drug, sustained release, matrix tablet, polymers, drug administration.

INTRODUCTION

Approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects are referred to as novel drug delivery systems (NDDS). NDDS is a drug delivery system that differs from traditional drug delivery systems. NDDS is a combination of advanced technique and new dosage forms that outperform traditional dosage forms.[1] The goal of the Novel Drug Delivery System is to deliver a therapeutic amount of drug to the appropriate site in the body quickly and then maintain the desired drug concentration. For drugs to reach their intended target with minimal or no side effects. To reduce drug degradation and loss. To increase the drug's bioavailability and the fraction of the drug absorbed at the required site.[2]

These are the types of controlled drug delivery systems that release the drug continuously through both dissolution and diffusion controlled mechanisms. To regulate the release of drugs with varying degrees of solubility. The drug is dispersed in swellable hydrophilic substances, and it is insoluble.[3]

Direct compression of a blend of drug, retardant material, and additives to form a tablet in which the drug is embedded in a retardant matrix is one of the least complicated approaches to the manufacture of sustained release dosage forms. Alternatively, the drug and retardant mixture could be granulated before compression.[4] Both hydrophilic and hydrophobic polymers are commonly used in the preparation of matrix systems. Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide), and cross-linked homopolymers and copolymers of Acrylic acid are examples of commonly available hydrophilic polymers.[5] It is typically supplied in micronized form because small particle size is critical for the rapid formation of gelatinous layer on tablet surface matrix of rigid non-swellable hydrophobic or plastic materials.[6]

The introduction of matrix tablets as sustained release (SR) has provided a new breakthrough in the field of pharmaceutical technology for novel drug delivery systems (NDDS). It excludes complex manufacturing procedures such as coating and pelletization, and the

drug release rate from the dosage form is primarily controlled by the type and proportion of polymer used in the preparations. A hydrophilic polymer matrix is commonly used in the formulation of an SR dosage form.[7,8]

Because of the increased complexity and expense associated with the marketing of new drug entities, there has been a greater emphasis on the development of sustained release or controlled release drug delivery systems.[9] Matrix systems are commonly used for long-term release. It is the release system that controls and prolongs the release of the dissolved or dispersed drug.[10] A matrix, in fact, is defined as a well-mixed composite of one or more drugs and a gelling agent, such as hydrophilic polymers.[11] The sustained release method can achieve therapeutically effective concentrations in the systemic circulation over an extended period of time, resulting in improved patient compliance. There are numerous SR oral dosage forms available.[12,13]

History

There are three time periods in the history of controlled release technology. From 1950 to 1970, there was a period of sustained drug release. From 1970 to 1990, the needs of control drug delivery were determined. The modern era of controlled release technology after 1990.[14]

Increase bioavailability with ideal DDS properties

- Provide controlled drug delivery
- Transport the drugs intact to the site of action while avoiding non-diseased tissue.
- Maintain stability and delivery under various physiological variables.
- Simple to use, safe, and dependable Medically optimal and cost-effective[15]

Ideal Drug Delivery system

In ideal drug delivery system, firstly it should deliver drug at a rate determined by the body's needs over the course of treatment. Secondly, it should only direct the active entity to the site of action.[16] This is accomplished through the development of new modified drug release dosage forms. Benefits of the right dose, at the right time, in the right place. Industrial-Efficient use of costly ingredients, resulting in lower production costs. Social benefits to patients include improved therapy, compliance, and quality of life.[17]

Terminology Used in the NDDS Dosage forms

Dosage forms with controlled action provide a longer duration of drug release with predictability and reproducibility in drug release kinetics i.e., the drug is released in a controlled manner. Sustained Action; Sustained action dosage forms initially release a sufficient amount of drug to produce the desired pharmacological effect and then periodically release the remaining fraction of drug to prolong their presence in systemic circulation and sustain their duration of action.[18,19]

Actions Provided by DDS System

Site specific action

Dosage forms with site specific action directly deliver the drug to the desired site of action, improving treatment efficacy. Timed release action; a drug that is released in small amounts over night, typically in the gastrointestinal tract. It refers to something that occurs gradually over time, such as a medication that gradually releases a drug over time. Time released medication includes sleeping pills that gradually release the active drug ingredients throughout the night. Aspirin, for example, irritates the GI tract.[20]

Extended Release Action

The pills are designed in such a way that the drugs are released gradually over time. This has the advantage of requiring fewer pills. It also implies that side effects may be reduced because drug levels in the body are more consistent in extended formulation.[21] For example, phenytoin delayed-release tablets are enteric coated to delay release of the medication until the Tablet has passed through the stomach to prevent the drug from being destroyed or inactivated by gastric juices or when it may irritate the gastric mucosa. for example (develproex sodium).[22]

Controlled Release Action

Many of the first controlled-release systems sought a delivery profile that would result in a high blood level of the drug over a long period of time. Traditional drug delivery systems cause the drug level in the blood to rise after each administration of the drug and then fall until the next administration.[23] The key point with traditional drug administration is that the agent's blood level should be maintained between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.[24]

Sustained Release Drug

Drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after a single dose administration." The therapy's primary goal to maintain a therapeutically effective and non-toxic blood level for an extended period of time. Also known as prolonged-release (PR), slow-release (SR), sustained action (SA), prolonged action (PA), or extended-release (ER).[25,26]

Advantages	Disadvantages
• Reduced drug blood level fluctuations, resulting in better disease management. • Reduced dosing frequency. • Improved patient comfort and compliance. • Reduction of adverse effects (both systemic and local), particularly in patients who are sensitive to potent drugs. • Cost-cutting in health-care services. • Increased treatment efficiency. • Cuts nursing and hospitalisation time. • Maximum bioavailability at a low dose. • Reduce drug accumulation by using chronic dosing. • Treat or control the condition more quickly. • Use special effects, such as Arthritis Treatment • Constant blood levels achieve the desired effect and maintain it for the intended time period. • Drugs that are susceptible to enzymatic inactivation or bacterial decomposition can be protected by encapsulation in an SR-compatible polymer system.	•The administration of a sustained release medication dose does not allow for the immediate termination of therapy. •When significant adverse effects are observed during therapy, immediate changes in the drug cannot be accommodated. Because the dosage form design is fixed. • The physician has less flexibility in adjusting the dosage regimen. •Sustained release dosage forms are created for the general population, based on the average biologic half-life. As a result, disease states that change drug disposition, significant patient variation, and so on are not accommodated. •Many sustained release dosage forms require more expensive processes and equipment. •Dose dumping Unpredictable and poor in vitro and in vivo relationship. •GI residence time influences and limits effective drug release time period. •More patient education is required. • Very short half life drugs or very long half life drugs are poor for candidates for sustained release dosage forms.

Sustained Release Design Form of Administration

The primary goal of dosage form design is to optimise medication delivery in order to achieve therapeutic effect control in the face of uncertain fluctuation in the vivo environment in which drug release occurs. Control of drug action via formulation also implies controlling bioavailability to reduce drug absorption rates. Curve of plasma concentration versus time.[27]

The concept of sustained release formulation can be divided into two parts.

Release rate consideration

In conventional dosage form, Kr>Ka; in this case, drug release from dosage form is not a rate limiting step. The above criteria, i.e. (Kr>Ka), apply in the case of immediate release, whereas in the case of non-immediate release (Kr<Ka), i.e. release is a rate limiting step.As a result, the effort for developing S.R.F must be focused primarily on changing the release rate. The rate of drug removal in the dosage form should be independent of time. The rate of release should adhere to zero order kinetics.[28]

$$\text{Rate in} = \text{rate out} = KeVd = Kr$$

Where Cd = total elimination and Ke = total elimination (first order kinetics).
Vd denotes the total volume of distribution.
Cd denotes the desired drug concentration.

Dose consideration

To achieve the therapeutic level and sustain it for a given period of time, the dosage form generally consists of two parts: a) the initial (primary) dose and b) the maintenance dose.

a) There can be an initial (primary) dose for the total dose 'W '.

$$W = Di + Dm$$

In a system where the therapeutic dose release follows a zero order process for a specified time period.

$$W = Di + K0\ r.\ Td$$

Td = time desired for sustained release from one dose.[29,30]

b) The maintenance dose

If maintenance dose starts to release the drug in period of dosing t=O then,

$$W = Di + K0\ r\ Td - K0\ r\ Tp$$

Tp = time of peak drug level. However a constant drug can be obtained by suitable combination of Di & Dm that release the drug by first order process, then

$$W = Di + (Ke\ Cd / Kr)\ Vd$$

Sustained action, prolonged action, controlled release, extended action, and time release dosage formed are terms used to describe drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after a single dose is administered. In the case of injectable dosage forms, this period may vary from days to months; however, in the case of orally administered forms, this period is measured in hours and is critically dependent on the dosage form's residence time in the GI tract. In some cases, drug therapy can be controlled by taking advantage of advantageous drug interactions that affect drug disposition and elimination. For example, probenicid inhibits penicillin excretion, thereby prolonging its blood level.[31,32]

Drug Therapy Versus Sustained Action

A repeat-action tablet is distinguished from its sustained-release product by the slow controlled release of the drug, which results in a plasma concentration time curve that does not resemble that of a sustained release product.[33] A repeat action tablet typically contains two

doses of drug, the first of which is released immediately after oral administration to provide a repeat onset of therapeutic response. The release of the second dose is usually delayed by an enteric coat. As a result, when the enteric coat surrounding the second dose is breached by intestinal fluid, the second dose is immediately released.[34,35]

Influencing Factors for Matrix Tablets

The release rate from the SR is influenced by two major factors. They are as follows: 1.Physicochemical elements 2. Biological elements

Physicochemical Factors	Biological Factors
Aqueous solubility	Absorption
Partition coefficient (K [O/W])	Distribution
Drug pKa and ionization at physiological Ph	Metabolism
Drug stability	Biological half-life/duration of action
Protein binding	Margin of safety/therapeutic index
Dose size	
Molecular weight and diffusivity	

Physicochemical Factors

Dose size

The bulk size of the dose to be administered has an upper limit for orally administered systems. For a conventional dosage form, a single dose of 0.5-1.0g is considered maximal. This is also true for the sustained release dosage form.[36] Compounds that necessitate a large dosing size can sometimes be administered in multiple doses or formulated into liquid systems. Another factor to consider is the margin of safety involved in administering a large dose of a drug with a narrow therapeutic range.[37]

Ionization, pka and aqueous solubility

The majority of drugs are weak acids or bases. Because the unchanged form of a drug preferentially permeates lipid membranes, it is critical to understand the relationship between the compound's pka and the absorptive environment. It is advantageous for drug permeation to present the drug in its original form. Unfortunately, the situation is complicated further by the fact that conversion to unchanged form reduces the drug's aqueous solubility.[38]

Diffusion or dissolution-based delivery systems will also be dependent on the drug's solubility in aqueous media. The effect of pH the release process must be defined in an environment of changing pH, with the stomach being acidic and the small intestine being more neutral. The majority of drugs are weak acids or bases. Because the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the Compounds with very low solubility (0.01mg/ml) are inherently sustained, because their release in the GI tract over the time course of a dosage form is limited by drug dissolution. As a result, compound solubility will be poor choices for slightly soluble drugs, because the driving force for diffusion, which is the drug's concentration in solution, will be low.[39]

Partition coefficient

When a drug is administered to the GI tract, it must cross a number of biological membranes in order to have a therapeutic effect elsewhere in the body. It is common to think about because these membranes are lipidic, the partition. The oil-soluble drug coefficient becomes significant in determining the membrane barrier's effectiveness penetration. Compounds that are lipophilic in nature and have High partition coefficients are insoluble in water. keep in lipophilic tissue for a longer period of time in the event of drug.[40]

Stability

Orally administered drugs can be affected by both acid-base reactions. Enzymatic degradation and hydrolysis Drugs in solid state will degrade at a slower rate as a result, This is the preferred delivery composition for problem cases. In the case of dosage forms that are unstable in the stomach, systems that extend delivery across the entire course of transit in the digestive tract are advantageous this is also true for systems that wait until the dosage form reaches the small intestine.[41] Compounds that are unstable in the small intestine may cause problems. When administered, show decreased bioavailability from a long-term dosage form This is due to the fact that more drugs are being produced. Delivered in the small intestine and thus susceptible to degradation. Propentheline and probanthine are two compounds a typical example of such a drug.[42]

Biological Factors

Biological half-life

The typical goal of an oral SR product is to maintain therapeutic blood levels over time. To accomplish this, the drug must enter the circulation at roughly the same rate as it is eliminated. The half-life (t1/2) quantitatively describes the elimination rate. Each drug has its own unique elimination rate, which is the sum of all elimination processes, such as metabolism, urinary excretion, and all other processes that permanently remove the drug from the bloodstream. Therapeutic compounds with a short half-life are ideal candidates for SR formulation because they can reduce dosing

frequency[43] Drugs with half-lives less than 2 hours, such as furosemide or levodopa, are generally poor candidates for SR preparation. Compounds with extended half-lives, greater than 8 hours are also generally not used in sustaining form, since their effect is already sustained.[44]

Absorption

Because the goal of developing an SR product is to exert control over the delivery system, the rate of release must be specified is significantly slower than the rate of absorption Let us suppose most drugs' transit times in the GI absorptive areas The maximum half-life for absorption is approximately 8-12 hours should be 3-4 hours; otherwise, the device will fail pass through the potential absorptive regions prior to drug administration. The release has been completed[45] As a result, corresponds to a minimum apparentn 0.17-0.23h-1 absorption rate constant for 80-95 percent over this time frame.[46] As a result, it is assumed that the absorption of the drug should occur at a fairly uniform rate throughout the entire the length of the small intestine. This is not true for many compounds. If a drug is absorbed via active transport or is restricted to a specific region of the intestine, SR preparation may be detrimental to absorption. One approach to providing sustaining mechanisms of delivery for compounds is to keep them within the stomach. This allows for the drug's slow release, which then travels to the absorptive site. These methods were developed in response to the observation that co-administration results in a sustaining effect. One such effort is to create a low density pellet or capsule. Bio adhesive materials are another approach.[47]

Metabolism

Drugs that are significantly metabolised before absorption, either in the lumen or in the tissue of the intestine, may have lower bioavailability when administered in a slower-releasing dosage form. As a result, the drug to be used in the formulation of Sustained-Release dosage form must have a legal half-life (5 hours). The drug should be water soluble.[48] The therapeutic window of the drug should be expanded. The drug should be absorbed all the way through the GIT. Even poorly water soluble drugs can be formulated in SR dosage form. To achieve this, the drug's solubility should be increased using the appropriate system before it is formulated in the SR dosage form. However, during this time, the drug is crystallising, which occurs as the drug enters the body.[49]

Distribution

Drugs with a high apparent volume of distribution, which influence the rate of drug elimination, and are ineffective Chloroquine is a candidate for an oral SR drug delivery system.

Classification of Matrix Tablets

Hydrophobic Matrices

The drug is mixed with an inert or hydrophobic polymer and compressed into a tablet in this method of obtaining sustained release from an oral dosage form. The dissolving drug has diffused through a network of channels that exist between compacted polymer particles, resulting in sustained release. Polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate polymers and their copolymers are examples of materials that have been used as inert or hydrophobic matrices. Liquid penetration into the matrix is the rate-controlling step in these formulations. Diffusion is one possible mechanism for drug release in these types of tablets. In the presence of water and gastrointestinal fluid, such matrix tablets become inert.[50]

Lipid Matrices

Lipid waxes and related materials are used to create these matrices. Drug release from such matrices occurs via pore diffusion as well as erosion. As a result, release characteristics are more sensitive to digestive fluid composition than to completely insoluble polymer matrix. For many sustained release formulations, carnauba wax in combination with stearyl alcohol or stearic acid has been used as a retardant base.[51]

Biodegradable Matrices

These are polymers made up of monomers linked together by functional groups and with an unstable linkage in the backbone. They are biologically degraded or eroded into oligomers and monomers that can be metabolised or excreted by enzymes produced by surrounding living cells or by non-enzymatic processes. Natural polymers such as proteins and polysaccharides are examples, as are modified natural polymers and synthetic polymers such as aliphatic poly (esters) and poly anhydrides.[52]

Hydrophilic Matrices

Because of their flexibility in achieving a desirable drug release profile, cost effectiveness, and broad regulatory acceptance, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery. In the field of controlled release, the formulation of drugs in gelatinous capsules or, more commonly, tablets using hydrophilic polymers with high gelling capacities as base excipients is of particular interest. In fact, a matrix is defined as a mixed composite of one or more drugs and a gelling agent (hydrophilic polymer). These are known as swellable controlled release systems.[53]

Mineral Matrices

These are made up of polymers derived from various seaweed species. Alginic acid, for example, is a hydrophilic carbohydrate extracted from brown seaweeds (Phaephyceae) using dilute alkali.[54]

Polymers Used in Matrix Tablet

Biodegradable polymers

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.[55]

Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).[56]

Soluble polymers

Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).[57]

Hydrogels polymers

Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).[58]

Table showing the drug to be formulated as a matrix tablet with polymer and method used for its preparation.

Drug Used	Method Used	Polymer Used
Zidovudine	Direct Compression	HPMC-K4M, Carbopol-934, EC
Domperidone	Wet Granulation	HPMC-K4M, Carbopol-934
Alfuzosin	Direct Compression	HPMC-K15M, Eudragit-RSPO
Minocycline	Wet Granulation	HPMC-K4M, HPMC-K15M, EC
Ibuprofen	Wet Granulation	EC, CAP[59]
Metformin HCL	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Wet Granulation	Locust bean gum, HPMC
Furosemide	Direct Compression	Guar gum, Pectin, Xanthan gum
Acarbose	Direct Compression	HPMC, Eudragit
Aceclofenac	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Ambroxol HCL	Direct Compression	HPMC-K100M[60]
, Aspirin	Direct Compression	EC, Eudragit-RS100, S100
Diclofenac Na	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diethylcarbamazepine citrate	Wet Granulation	Guar gum, HPMC-E15LV
Naproxen Morphine	Direct Compression	HPMC-K100M, HPMC-K15M, PVP
Nicorandil	Wet Granulation	HPMC, CMC, EC[61]
Ondansertan	Wet Granulation	HPMC-K100M, HPMC-K4M, HPMCK15M
Phenytoin	Wet Granulation	Tragacanth, Acacia, Guar gum, Xanthan gum
Ranitidine HCL	Direct Compression	Chitoson, Carbopol-940 [62]
Theophylline	Direct Compression	Carbopol-934P, HPMC-K100M, HPMCK4M, HPMC-K15M, EC
Tramadol	Wet Granulation	HPMC-K4M, Karaya gum, Carrageenam gum
Verapemil	Direct Compression	HPMC-K100M, HPMC-K4M, HPMCK15M
Amlodipine	Direct Compression	HPMC, EC [63,64]

CONCLUSION

Based on the foregoing discussion, it is easy to conclude that sustained-release formulations aid in increasing dose efficiency while also improving patient compatibility. Furthermore, all of this comes at a reasonable price. The dosage form is simple to optimise and very useful in the case of antibiotics, where irrational use may result in resistance. The above article's review is primarily concerned with the formulation and application of the SRDDS. It concludes that the use of matrix tablets was extremely beneficial in overcoming the patient compliance issues associated with conventional dosage forms. The cost of manufacturing matrix tablets is also under control. The daily required frequency of the doses was also reduced as a result of the use of these tablets.

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