Recent Approaches of Matrix Release Tablet in NDDS System

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ABSTRACT

The purpose of this analysis is to categorize matrix tablets according to the kind of polymer they are made of as well as the rate at which they release their contents. When it came to medicinal applications, the matrix system was the very first oral extended release platform ever developed. The utilization of matrix tablets enables the modification of drug release characteristics. They are highly favored for this kind of treatment because of the benefits they give for the patient in terms of better adherence to the treatment, more stable medication levels, decreased dose and bad effects, and a bigger safety margin for highly potent medications. Because of their versatility in delivering a desired drug release profile, cheap cost, and general regulatory acceptability, hydrophilic polymer matrix systems are frequently used in oral controlled drug delivery dosage forms. Because of the rapid diffusion of the dissolved medication via the hydrophilic gel network, the use of hydrophilic matrix alone for delayed drug release is not possible for medicines that are very water soluble. It is now generally accepted that the formulation of such drugs requires the use of matrix systems that incorporate hydrophobic polymers. It would appear that the most successful strategy would be to create a formulation for oral controlled release by employing matrix tablets.

Keywords - NDDS, Matrix tablet, Polymers, Excipients.

I. INTRODUCTION

When it comes to administering medication, taking it by mouth has always been the most popular practice[1]. This is due to the fact that the design of the dose form for the gastrointestinal route allows for more creative freedom than does the creation of dose forms for any other route. Oral administration accounts for over half of all medications now available on the market. Tablets are the most common delivery method for pharmaceuticals. To hasten the transport of the medication into the patient's bloodstream, conventional drug delivery systems, as the name of this type of system suggests, make use of tried-and-true methods. When using these fast release formulations, both the absorption of the drug and the beginning of the accompanying pharmacodynamic effects take place very quickly [1-3]. The pharmaceutical industry faces a number of critical challenges, one of which is the development of a method of medicine delivery that is not only reliable but also efficient. As a result, it is essential to locate the pharmacological characteristics and administration strategy that are the most efficient. When it comes to the administration of pharmaceuticals in the form of oral consumables, matrix tablets are a helpful way for ensuring a slow and consistent release of the medication.
The oral sustained release system is the most common, desirable, and preferred route of administration for therapeutic drugs with systemic effects. This is because it improves patient compliance and treatment efficacy. The tablet matrix is composed of both hydrophilic polymers and hydrophobic lipids[4]. This combination was chosen so that the rate of medication release may be controlled and maintained. At the moment, a significant amount of cash is being allocated toward research and development on matrix sustained formulations [4]. This includes matrix tablets that contain hydrogels. Because they are chemically inert, affordable, widely recognized by regulators, and adaptable in terms of providing for the optimum drug release profile [5, 6], matrix systems that incorporate hydrophobic lipids are popular in the field of controlled drug delivery. As the difficulty and expense of bringing new medicinal agents to the market have continued to rise, more effort and resources have been allocated to the study and development of modified release drug delivery systems. Using a controlled release matrix method, a medicine can be administered either topically or systemically [7, 8].

The polymers that are employed in the creation of systems are the name given to these types of devices. The polymers that are employed in the creation of hydrophilic matrices can be broken down into three distinct categories: A. Cellulose derivatives, such as methylcellulose 400 and 4000cPs and hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000, and 15000cPs; and sodium carboxymethylcellulose. B. Other polymers. B. Non-cellulose natural or semi-synthetic polymers, such as agar-agar, carob gum, alginites, molasses, polysaccharides containing mannose and galactose, chitosan, and modified starches. C. Modified starches. Polymers of acrylic acid, specifically Carbopol-934, which is the most common type[15].

II. CLASSIFICATION OF MATRIX TABLETS

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic matrices): In the year 1959, the idea of employing hydrophobic or inert materials as matrix materials was presented for the very first time. To achieve prolonged release from an oral dosage form using this technique, the medication is first combined with an inert or hydrophobic polymer, and then the resulting tablet is subjected to compression. The dissolving drug has moved through a network of channels that exist between the compressed polymer particles, which is the cause of the sustained release that has been formed as a result of this process. The following are some examples of materials that have been employed in inert applications[13].

2. Lipid Matrices: These matrices were created using lipid waxes and other components that are linked to them. Both pore diffusion and erosion contribute to the process of drug release from matrices of this kind. Because of this, the properties of the release are more sensitive to the composition of the digestive fluid than they are to the fully insoluble polymer matrix. Carnauba wax, when combined with stearyl alcohol or stearic acid, has been used as a retardant base in a number of formulations for prolonged release[14].

3. Hydrophilic Matrices: 1. Hydrophilic polymer matrix systems are frequently utilized in oral controlled drug delivery because to the flexibility they provide to produce a desirable drug release profile, the cost effectiveness they offer, and the widespread regulatory acceptance they enjoy. In the realm of controlled release, one area of particular interest is the formulation of pharmaceuticals in gelatinous capsules or, more frequently, in tablets, employing hydrophilic polymers with high gelling capabilities as base excipients. This method uses hydrophilic polymers as base excipients. A matrix is a well-mixed compound of one or more pharmaceuticals with a gelling agent, often known as a hydrophilic polymer. Swellable controlled release systems are the name given to these types of devices. The polymers that are employed in the creation of hydrophilic matrices can be divided down into three distinct categories: A. Cellulose derivatives, such as methylcellulose 400 and 4000cPs and hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000, and 15000cPs; and sodium carboxymethylcellulose. B. Other polymers. B. Non-cellulose natural or semi-synthetic polymers, such as agar-agar, carob gum, alginites, molasses, polysaccharides containing mannose and galactose, chitosan, and modified starches. C. Modified starches. Polymers of acrylic acid, specifically Carbopol-934, which is the most common type[15].

4. Biodegradable Matrices: These are the polymers that are composed of monomers that are functionally coupled to one another and have a linkage in the backbone that is unstable. They undergo an enzymatic or nonenzymatic process that breaks them down into oligomers and monomers that can then be metabolized or eliminated from the body, respectively. This process is known as biological degradation or erosion. Natural polymers such as proteins and polysaccharides are two examples of natural polymers. Modified natural polymers and synthetic polymers such as aliphatic poly
(esters) and poly anhydrides are two examples of synthetic polymers.[16]

5. Mineral Matrices: These are made up of polymers that are extracted from a wide variety of seaweeds. For instance, alginic acid is a hydrophilic carbohydrate that may be produced from certain species of brown seaweeds (Phaeophyceae) by treating them with diluted alkali.[17]

**Fig: 1 Classification of matrix tablets**

*Polymers used in matrix tablets*

**Hydrophobic matrix formers**

Hydrophobic matrix materials are large-molecular-weight water-insoluble polymers that can be used in the production of prolonged release dosage forms. The following are some examples of hydrophobic matrix formers:

- Polyethylene
- Polyvinyl chloride
- Ethylecellulose, and
- Acrylate copolymers

The swelling of the particles and the diffusion of the medication through a network of channels that are present between the compacted polymer particles are what cause the sustained release of the drug. The pace at which liquid is introduced into the matrix serves as the rate-controlling step in these formulations.[18]

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Examples of lipid matrix formers include

- Carnauba wax in combination with stearic acid,
- Glycerol dibehenate
- Glycerol tristearate
- Tripalmitin
- Trymysterin, and
- Hard Fats

Lipid matrices are inert, non-eroding and non-dissolving systems that achieve drug release prolongation through the creation of a hydrophobic domains in the tablet. These domains not only slow down the hydration of the tablet but they also control the rate of dissolution and release of the drug into the aqueous.[20]

**Hydrophilic matrix formers**

As a result of their user-friendliness, cost-effectiveness, and widespread regulatory acceptance, hydrophilic matrix formers are the materials of their kind that see the greatest amount of use. They are typically hydrophilic polymers that are made up of a high number of molecules and have a high gelling capacity. They expand and gel when they come into contact with water, which results in the creation of a moving barrier that regulates the rate at which the medicine is released. As a result of this characteristic, people also refer to them as swelling controlled release systems.[23][24].

Polymers used in the preparation of hydrophilic matrices are divided in to three broad groups:[25]

1. Cellulose derivatives, such as methylcellulose, hydroxypropylcellulose, Hypromellose, and Sodium carboxymethylcellulose.
2. Non cellulose natural or semi synthetic polymers such as Agar-Agar; Carob gum; Alginates; Xanthan gum, Pectin, Chitosan and Modified starches.
3. Polymers of acrylic acid, such as Carbomer 934

**Biodegradable matrix**

The last category of matrix forming materials are a special group of polymers that are biologically degraded or eroded by enzymes to generate simple metabolites that are eliminated through the usual processes. These polymers may be natural polymers such as proteins and polysaccharides, semi-synthetic polymers or fully synthetic systems, such as the well-known aliphatic poly (esters) and poly anhydrides.

**Factor Affecting Drug Release Matrix[27]**

The majority of the time, the controlled release systems that are utilized for DES are constructed as matrix systems or reservoir kinds. These types of controlled release systems are easier to design while still being effective and programmable to release the medication at the rate that is desired. According to Yang and Burt (2006), these systems are difficult to discover, define, and bring under control because they produce significant and dynamic concentration gradients across tissues. The release kinetics of such systems are impacted by the whole of the ingredients from which the DES is synthesized as well as the process settings under which it is coated. It has the ability to independently and mutually regulate the drug's release rate. When constructing and experimenting with CR systems, it is vital to do in-depth research on each element, as each of these factors might separately have a significant impact on the release kinetics of the system. When researching the kinetics of drug release for a particular system, it is important to keep in mind not only the drug release rate but also a wide variety of other biological characteristics at the same time. Transport of drug via diffusion-convection, biological features of tissue and artery...
ultrastructure, hydrodynamic conditions at the implantation site, and the design of the stent all play a significant role in significantly modulating the release rate and the ultimate biological response to drug-eluting stents[28].

### Table 1: Factors affecting drug release

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Possible effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic properties of drug</strong></td>
<td></td>
<td></td>
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<tr>
<td>Drug hydrophobicity/hydrophilicity</td>
<td>Affects aqueous solubility, protein binding, tissue retention characteristics and local drug concentrations</td>
<td>Creel et al. (2000)</td>
</tr>
<tr>
<td>Diffusion/dissolution characteristics</td>
<td>Affects release kinetics</td>
<td>Kamath et al. (2006)</td>
</tr>
<tr>
<td>Solubility in polymer</td>
<td>Affects release kinetics</td>
<td>Venkatraman et al. (2007)</td>
</tr>
<tr>
<td>Solubility in release media</td>
<td>With higher solubility, higher drug release rate</td>
<td>Ranade et al. (2005)</td>
</tr>
<tr>
<td><strong>Properties of rate controlling polymer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For biodegradable polymers – initial molecular weight, co-polymer ratio, absorption rate and time period, pH of dissolution medium</td>
<td>Affects degradation behavior and time</td>
<td>Shameem et al. (1999) Miyajima et al. (1999)</td>
</tr>
<tr>
<td><strong>Processing Parameters</strong></td>
<td></td>
<td></td>
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<tr>
<td>Properties of solvent (BP, thermal history)</td>
<td>Residual solvent effects, merging of coating layers, thus influencing release kinetics</td>
<td>Saylor (2006)</td>
</tr>
<tr>
<td>Solvent evaporation rate Phase diagram of ternary system (drug-polymer-solvent)</td>
<td></td>
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<tr>
<td><strong>Coating Design</strong></td>
<td></td>
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<tr>
<td>Drug to polymer ratio</td>
<td>Effect on drug carrying capacity of polymer and drug elution rate</td>
<td>Kamath et al. (2006)</td>
</tr>
<tr>
<td>Drug (initial solid phase) concentration and distribution inside the matrix</td>
<td>Describes initial burst effect and dissolution mechanism</td>
<td>Balakrishnan et al. (2007) Kamath et al. (2006)</td>
</tr>
<tr>
<td>Microstructure of coating (spatial variation in physical and chemical composition)</td>
<td>Exhibits process conditions and eventual effect on drug delivery kinetics</td>
<td>Prabhu (2004)</td>
</tr>
<tr>
<td>Top layer (drug free) thickness and hydrophobicity of polymer</td>
<td>Regulates drug kinetic behavior lowering diffusion phenomena</td>
<td>Leon et al. (2003)</td>
</tr>
</tbody>
</table>
Adantages of oral controlled release matrix tablets[29][30]

Oral controlled release matrix tablets offer several advantages in drug delivery systems. Here are some of the key advantages:

1. Improved drug efficacy: Matrix tablets provide sustained release of the drug, maintaining therapeutic levels in the body for an extended period. This controlled release profile enhances drug efficacy by optimizing drug concentration and minimizing fluctuations, ensuring a more consistent therapeutic effect.

2. Reduced dosing frequency: With oral controlled release matrix tablets, the dosing frequency can often be reduced compared to immediate-release formulations. This improves patient compliance by reducing the number of daily administrations and simplifying medication schedules.

3. Enhanced patient convenience: Matrix tablets eliminate the need for frequent dosing and reduce the chances of missed doses. Patients can benefit from the convenience of taking medication less frequently, which can improve treatment adherence and overall patient satisfaction.

4. Improved safety profile: Controlled release matrix tablets can help reduce adverse effects associated with fluctuating drug concentrations. By maintaining a consistent drug level within the therapeutic window, the incidence and severity of side effects can be minimized.

5. Steady-state plasma levels: Matrix tablets provide a sustained release of the drug, which leads to the attainment of steady-state plasma levels. This allows for more predictable drug exposure, making it easier to achieve the desired therapeutic effect.

6. Lower peak-to-trough fluctuations: The controlled release profile of matrix tablets helps to minimize peak-to-trough fluctuations in drug plasma concentrations. This results in a smoother drug release profile, reducing the occurrence of drug concentration-related side effects and improving patient tolerability.

7. Extended duration of action: Matrix tablets can be designed to release drugs over a prolonged period, extending the duration of action. This is particularly beneficial for drugs with short half-lives or those requiring continuous therapeutic coverage.

8. Improved bioavailability: In some cases, controlled release matrix tablets can enhance drug bioavailability by optimizing drug absorption. This can be achieved by utilizing excipients that modify drug release, permeability enhancers, or targeting specific absorption sites in the gastrointestinal tract.

9. Reduced frequency of administration-related variability: By reducing the number of daily administrations, matrix tablets help to minimize variability associated with administration times. This can be especially important for drugs with narrow therapeutic windows or those requiring precise dosing intervals.

10. Flexibility in formulation design: Controlled release matrix tablets offer flexibility in formulation design, allowing for customization of drug release kinetics. This enables tailoring of the release profile to meet specific therapeutic needs, including immediate release, delayed release, or pulsatile release.

Disadvantages of oral controlled release matrix tablets[31][32]

Oral controlled matrix release tablets, also known as extended-release tablets, offer several advantages over immediate-release formulations. However, they also have certain disadvantages. Here are some disadvantages of oral controlled matrix release tablets:

1. Slow onset of action: The extended-release formulation is designed to release the drug gradually over time, which can result in a delayed onset of action compared to immediate-release tablets. This can be a disadvantage when immediate relief or quick therapeutic effects are required.

2. Limited flexibility in dosage adjustment: Extended-release tablets typically come in fixed strengths, and it may be difficult to adjust the dosage according to individual patient needs. Immediate-release tablets offer more flexibility in dosage adjustment since they can be easily split or crushed.

3. Increased risk of dose dumping: Dose dumping refers to the rapid release of the entire drug content from the tablet, leading to an overdose. In certain cases, if the controlled-release mechanism is compromised (e.g., due to tablet damage or inappropriate storage conditions), it may result in the sudden release of the entire drug dose, potentially causing adverse effects.

4. Higher cost: Extended-release formulations often involve complex manufacturing processes, which can make them more expensive compared to immediate-release tablets. This increased cost may affect
affordability and accessibility, particularly in healthcare systems with limited resources.

5. Limited suitability for certain drugs: Not all drugs are suitable for controlled-release formulations. Some drugs have a narrow therapeutic index, meaning they require precise and immediate dosing to maintain their therapeutic effect. In such cases, immediate-release formulations may be preferred over extended-release tablets.

**Biological Factor:**

- Biological half-life:
- Absorption:
- Metabolism:
- Distribution:
- Protein binding:
- Margin of safety:

1) **Biological half-life:** The simple theory of an oral SR formulation is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter into the blood circulation at almost the same rate at which it is eliminated. Each drug has its own characteristic related to elimination rate, which is the sum of all elimination processes, generally include metabolism, urinary excretion and all the process that permanently remove drug from the blood stream.

2) **Absorption:** The goal of forming a SR product is to control the release rate of drug is much slower than the rate of absorption. If we presume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the extreme half-life for absorption should be in the region of 3-4 hours; otherwise, the dosage form will pass out of the probable absorptive regions before drug release is complete.

Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. So, it accepts that the absorption of drug should occur at a relatively uniform rate over the entire length of small intestine. If a drug is absorbed by active transport or transport is restricted to a specific region of intestine, SR preparation may be disadvantageous to absorption. 3) **Metabolism:** Decrease bioavailability from slow releasing dosage form shown by Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slow releasing dosage form. A drug which having poor water solubility can be formulated in Sustain release dosage form. For this, various techniques which are available for enhancing the solubility of the drug after the enhancing the solubility Sustain Release formulation is possible. But during this crystallization of the drug is possible when the drug is entering into the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

4) **Distribution:** The rate of elimination of drug is mainly depends upon the apparent volume of distribution. So drugs with high apparent volume of distribution, influence the rate of elimination of the drug, this drugs are consider to be a poor candidate for oral SR drug delivery system. E.g. Chloroquine

5) **Protein Binding:** To achieve pharmacological response unbound drug concentration is important rather than bound drug concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug which shows a main role in its therapeutic effect in spite of the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

6) **Molecular size and diffusivity:** In several sustained release systems Drug must diffuse through a rate controlling membranes or matrix. Ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a role of its molecular size. An important influence upon the value of the diffusivity. ‘D’ in polymers is the molecular size for molecular weight of the diffusing species.

7) **Margin of safety:** Safety of drug generally depends upon the therapeutic index, Larger the value of therapeutic index of a drug safer is the drug. Drugs having less therapeutic index are generally poor candidates for oral SR drug delivery system.

**III. METHODS OF PREPARATION OF MATRIX TABLETS[33][34]**

**Direct Compression**

In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

**Wet Granulation**

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrant to produce “running powder”tablets are compressed using a single-punch tablet compression machine.

**Melt Granulation**

In this process use of a substance, which melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using melt granulation technique.

**IV. EVALUATION PARAMETER[35]**

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study etc.

**Weight variation test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.
Uniformity of weight

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg. Weight control is based on a sample of 20 tablets.

Dimensions

The dimensions (diameter and thickness) were then determined to within ± 0.01 mm by using digital vernier calipers. Thickness of the tablets was determined using a vernier caliper.

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Hardness of the tablets was determined using a hardness testing apparatus (Monsanto Type). A tablet hardness of about 5-6 kg/cm2 is considered adequate for mechanical stability.

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of tablets is dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w. 10% Friability = (W0-W)/ W0 x 100

V. CONCLUSION

This article’s focus has been on the formulation of sustained-release matrix tablets. These matrix tablets can both boost your dose and be of assistance. Because of the utilization of these tablets, the daily needed frequency of the dose has also been decreased, which contributes to the control of the costs associated with the production of matrix tablets, which are also under control. Matrix pills of the medication contain a controlled release and a number of different factors and mechanisms. The mechanistic model has been discussed, and it has been determined that HPMC polymers are widely used in all polymers due to the specific characteristic matrix tablets are the economical dosage forms that improved the patients' compliance, reduced dose frequency, minimum plasma fluctuation, and increased the bioavailability of the drug. Patients who require a steady delivery of the medication over an extended period of time can benefit from the usage of this system in their medical care.

REFERENCES


