Biological Forum – An International Journal **15(4): 789-798(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

A Comprehensive Review of Recent Studies on Matrix Tablets for Drug Delivery with Oral Controlled Release

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(Received: 08 February 2023; Revised: 14 March 2023; Accepted: 18 March 2023; Published: 20 April 2023)
(Published by Research Trend)

ABSTRACT: Developing oral controlled release matrix tablet with constant release rate has always been a challenge to pharmaceutical technologist. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects. Oral drug delivery has traditionally been the most popular mode of administration when compared to other options. Matrix tablets are the most common method for modifying a drug's release profile. By protecting the active ingredient from hydrolysis and degradation and reducing dose frequency, controlled release matrix tablets increase patient compliance. Hydrophobic polymer-based matrices release drugs more slowly than hydrophilic polymer-based matrices do. Diffusion or dissolving control mechanism ensures that medications are released from controlled release matrix tablets at a controlled and predictable rate. In order to create oral controlled drug delivery dosage forms, hydrophilic polymer matrix systems are commonly used due to their adaptability and capacity to provide a desired drug release profile. In this formulation polymer (The hydrophilic and hydrophobic polymers) used as release rate retardants, that's why it controls drug blood level with uniform therapeutic level and avoid fluctuation thus prevent local or systemic adverse reactions.

Keywords: Controlled release, hydrolysis, dissolution, diffusion, erosion, hydrophobic polymer, hydrophilic polymer, and kinetics of drug release.

INTRODUCTION

The most common method of medicine delivery is through oral ingestion. One of the popular and traditional oral solid dose forms are tablets. The two types of tablets are rapid release tablets and prolonged release tablets. Within 30 minutes of administration, immediate release pills release their contents, and controlled and sustained release tablets are another subcategory of extended release tablets. In contrast to continuous release tablets, which have no effect on the medication release rate, controlled release tablets release the medicine at a preset pace for a set period of time (Kohrs *et al.*, 2018). Site and receptor targeted release, prolonged release, and delayed release are further categories for controlled release tablets (Rakesh, 2018).

The development of controlled drug delivery systems was inspired by the need to make sure that patients take their prescriptions as prescribed and are successfully treated or have their illness conditions managed (Frederick *et al.*, 2019). Due to limitations in the use of conventional dosage forms, alternative dosage forms, such as sustained-release products, have been developed. Such products are available on the market only for a few drugs of these categories (Malipeddi *et al.*, 2017). In general, controlled drug delivery attempts to Patel *et al.* (2012). Sustain drug action at predetermined rate by maintaining constant and effective drug level in the body with concomitant minimization of undesirable side effects associated with saw tooth pharmacokinetic pattern. Localize the drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.

Target drug action by using carriers or chemical derivatization of drugs to a particular target. Delivering a drug at a therapeutically effective rate to a desired place, modifying GI transit time, and minimizing first pass elimination are the key problems for oral drug delivery systems. With less frequent dosing and fewer side effects, the control release dosage form improves the maintenance of an optimal and effective medication level for a longer period of time (Ravi *et al.*, 2020). Melt granulation, a quick and simple one-step process for turning tiny powders into granules, is a fascinating strategy for manufacturing CR matrix compositions. The use of a low melting point binder, which is solid at ambient temperature and melts at relatively low

temperatures (50-80°C), encourages the agglomeration of the powder. The benefits of melt granulation over other CR delivery methods have spurred interest in the method. Due to the elimination of the drying stage due to the solvent-free nature of the process, it requires less time and energy (Shailesh *et al.,* 2011). Poor bioavailability has been recorded for some drugs formulated in sustained release dosage forms. Their narrow absorption window, lower solubility at high pH values, or enzymatic degradation in the intestinal or colonic environments was the reason of decreased bioavailability (Nimker *et al.,* 2017).

In controlled release drug delivery systems (CRDDSs), an active therapeutic is incorporated in the network structure of the polymer in such a way that the drug is released in a predefined controlled manner (Arora *et al.,* 2011). In matrix devices, the drug is homogeneously dispersed in either a hydrophobic or hydrophilic polymer matrix. The release rate from matrix systems remains unaffected by thin spots, pinholes, and other similar defects, which can be a serious problem with reservoir systems (Hiremath and Saha 2008).

Matrix materials such as different grades of hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose are used. The drug release for extended duration; particularly for highly water soluble drug using a hydrophilic matrix system is restricted because of the rapid diffusion of the dissolved drug though the hydrophilic network (Patnaik *et al.,* 2015). Controlled release dosage forms have number of advantages over conventional dosage forms, such as improved patience compliance due to decrease in dosing frequencies, reduction in fluctuation in steady-state levels and therefore better control of disease, maximum utilization of drug enabling reduction in total amount of dose administered (Basanta *et al.,* 2016). More than 50% of commercially accessible drugs were found to be administered orally, according to earlier studies (Kumar *et al.,* 2012; Kumar *et al.,* 2013). A broad variety of formulations for prolonged action fall under the category of controlled release dosage forms, which offer continuous release of their active ingredients for a predetermined period of time and at a predetermined rate. Most of these formulations are intended to be taken orally. The provision of an extended duration of action and the resulting assurance of improved patient compliance are the main goals for the development of these systems (Azharuddin *et al.,* 2011). The best, most practical and recommended method of medicine administration is by oral route. Target specificity and rate-controlled release are often not provided by conventional oral medication administration. An active therapeutic is inserted into the polymer's network structure in controlled release drug delivery systems (CRDDSs) so that the drug is released in a predetermined, controlled manner (Arora *et al.,* 2011).

Controlled drug release has been attempted to achieve by following classes

A. Diffusion controlled system:

i) Reservoir type; ii) matrix type;

B. Ion exchange resin-drug complexes;

C. Osmotic pressure controlled systems.

D. pH dependent formulations;

E.Dissolution controlled system:

i) Reservoir Type ii) Matrix Type

Israel Lipowski, who worked on coated pellets, created the first oral controlled medication release delivery method in 1938. 1940 saw the development of the oral sustained release delivery system, and 1950 saw the creation of the controlled release system (Gujral *et al.,* 2018).

Matrix tablets: The "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants" is what matrix tablets are, according to one definition. The controlled medication delivery technology known as matrix tablets releases the medicine continuously. The drug substance is uniformly blended with the rate-regulating component in a matrix system, either as crystalline, amorphous, or, in a few rare instances, as a molecular dispersion (Gahlyan and Jain 2014). These release the medication through diffusion- or dissolution-controlled processes (Kumar *et al.,* 2012). The two most important conditions for a drug delivery system to qualify as innovative are the ability to convey the active ingredient to the target site for action and administer a drug at a controlled rate. To achieve this hard novelty in oral medication formulation, formulation scientists have employed a variety of strategies, including either regulating drug release in the blood to obtain the intended plasma drug concentration or combining drug distribution into a carrier system profile in time (Pandita and Sharma 2013). Drug releases may be subject to temporal and/or spatial control thanks to controlled release drug delivery systems. In order to manage the release of medications taken orally, the oral controlled release drug delivery system is the most used (Dixit *et al.,* 2013). There are numerous benefits associated with this method, including the prevention of variations in plasma drug levels, a decrease in the number of times pharmaceuticals need to be administered, an increase in drug bioavailability, an increase in patient compliance, and a reduction in drug side effects and toxicity (Kotha *et al.,* 2013). Contrarily, the traditional oral drug dosage form has a number of drawbacks, including a high tendency for fluctuations in the plasma drug level, an increase in the frequency of drug administration, a time limit on the drug's ability to act at the target site of action, and low oral bioavailability of some medications because of interactions with food or an unsuitable gut environment, such as cefotaxime Na (Arafat *et al.,* 2015).

Matrix tablets' advantages include: (Kumar *et al.,* 2013; Narasimharao *et al.,* 2011**)**

1. In the event of rupture, there is no risk of dose dumping.
2. Wide variety of sizes and forms can be produced.
3. Versatile and powerful
4. It is inexpensive.

Disadvantages of matrix tablet: (Arafat *et al.,* 2015**)**

1. Expensive preparation.

2. The rate of transit through the gut and numerous other factors, including diet, influence the release rates.
3. The square root of time affects how quickly drugs are released.
4. Due to a rise in diffusional resistance and/or a fall in effective area at the diffusion front, the release rate continuously decreases. However, using extremely slow release rates, which in many situations are identical to zero order, can result in a significant persistent effect.

Matrix tablets' limitations:

1. It is challenging to achieve zero order release.
2. After the medicine has been released, the residual matrix needs to be removed.
3. Not all medications can be mixed with a certain polymeric matrix.
4. The square root of time affects the medication release rates.

Production methods for matrix tablets

1. Sintering technique: Powder compact heated in a controlled setting at a temperature below the melting point of solid particles while under air pressure (Uhumwangho *et al.*, 2012).

2. Melt granulation: Granulation is made of mouldable binders, which melt between 50 -80 degrees Celsius. Dry granules were gathered when it was cooled to room temperature.

3. Foam granulation: Aqueous binders are added as foam, increasing the foam's surface area and improving the dispersion of water in the powder bed (Shanmugam *et al.*, 2015).

4. Freeze granulation: Granulation is made of moldable binders, which melt between 50 and 80 degrees Celsius. Dry granules were gathered when it was cooled to room temperature.

5. Direct compression: Powders or granules that are directly crushed into tablets without changing their physical characteristics.

6. Dry granulation: It comes in two varieties: roller compaction and slugging. Granules are recompressed and slugs are crushed to create granules using the slugging method. As opposed to roller compaction, this uses pressure rolls to recompress the powder.

7. Wet granulation: It entails massaging dry granule mixtures in a flammable fluid, wet sizing, drying, and then dry screening.

8. Steam granulation: Instead of using water, steam serves as the granulation's binder. It diffuses and spreads evenly throughout the granules. More surface area makes the granules rounder, which increases the pace at which drugs dissolve from granules.

Classifications for Tablets Using the Controlled Release Matrix:

It can be divided into three types depending on the above criteria.

1. Polymer used
2. Void fraction
3. Miscellaneous ways (Abdul *et al.*, 2004)

Matrix system classifications based on void fraction and porosity size:

A. Macro-porous matrices:

Drug diffusion occurs in this kind through holes that range in size from 0.1 to 1 m. The system's matrix porosity is bigger than its diffusing dimension. Drug compounds having molecular sizes less than 1 m can be used in this method.

B. **Micro-porous matrix system: (**Solano-Umaña *et al.*, 2015)

In this form, drug diffusion takes place in pores that range in size from 50 to 200 A°. Small medicinal compounds with molecular weights under 200 A° can use this method.

C. Non-porous matrices: (Zhou *et al.*, 2017**)**

Since there are no accessible pores, drug diffusion in this form occurs through network meshes instead.

Matrix systems are categorized according to the type of polymer:

1.Hydrophilic matrices
2.Biodegradable matrices
3.Hydrophobic matrices
4. Mineral matrices
5. Fat wax matrices

1. **Hydrophilic.** This matrix can be used to regulate the rate of medication release. Swellable controlled release matrices is another name for it. Water is needed by the hydrophilic matrix to initiate the release mechanism and explore a number of benefits, such as ease of fabrication and great tablet consistency. Drug and hydrophilic polymer are uniformly dispersed in matrix tablets, which serve as gelling agents. Because polymers may absorb fluid from the G.I. and create 3-D structures, the release of medication from matrix tablets is controlled. The expansion and corrosion of the gel, which regulates the release of the drug, causes the drug to be released from the gel barrier. The system's drug release kinetics are influenced by the chemistry, density, and strength of the polymers. It has been employed to control the rate at which drugs with various aqueousities are released.

Three broad categories of polymers are employed in the creation of hydrophilic matrices:

A. Cellulose derivatives, including sodium- carboxy - methylcellulose, hydroxyethylcellulose (HEC), and ethylhydroxyethylcellulose (EHEC). (NaCMC).

B. Polymers of acrylic acid: Carbopol is a polymer that is utilized in the acrylic acid category (Thakur *et al.*, 2019).

C. Non-cellulose natural or semi synthetic polymers

- Molasses, Polysaccharides of mannose
- Agar-agar, Carob Gum, Alginates,
- Galactose, Chitosan and Modified starches.

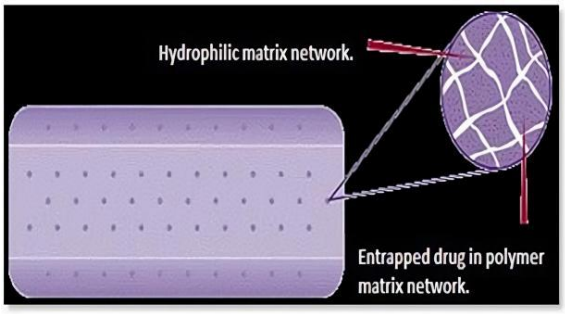

Fig. 1. Depicts a typical hydrophilic matrix tablet in cross-section.

2.Biodegradable matrices. This matrix's polymers are made up of monomers joined together by weak bonds that can break down and dissolve by enzymatic or non-enzymatic mechanisms to form oligomers and monomers that can be digested and eliminated.
Proteins, polysaccharides, aliphatic polyesters, and polyanhydrides are examples of natural polymers employed in this matrix basis (Song *et al.,* 2018).

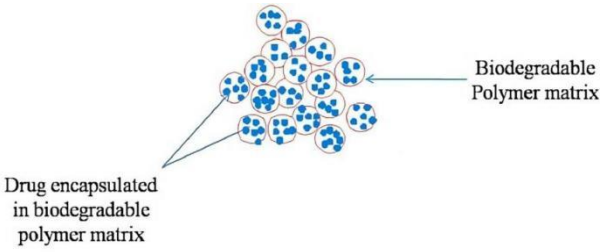

Fig. 2. Biodegradable matrices.

3. Hydrophobic matrices (Giammona and Craparo 2019). Inert or hydrophobic materials were initially proposed as matrix materials in 1959. It also goes by the name of plastic matrices. Drugs are granulated into matrix tablets utilizing hydrophobic polymers and latex or pseudo-latex. Polyethylene, polyvinyl chloride, ethyl and methyl cellulose, cellulose acetate, polystyrene, latex, and carbomers are a few examples of hydrophobic polymers. The hydrophobic matrices' rate-limiting component is insoluble in water, by maintaining drug dispersion across the matrix, controlled release by including soluble excipients in the matrix, such as lactose, the release profile of a drug can be altered in these matrices. Due to continuous molecular mobility and a limited release profile, insoluble medicines are not a good fit for hydrophobic matrix (Liechty *et al.,* 2010).

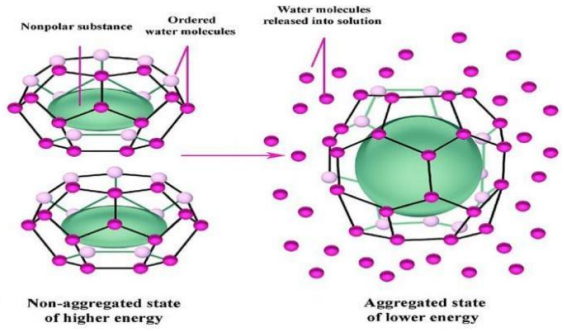

Fig. 3. Hydrophobic matrices.

4. Mineral matrices: (Inko *et al.,* 2017). Polysialates are the name for mineral polymers. Algins, which are polysaccharide & hydrophilic create viscous gum when hydrated, are one type of seaweed that contains polymers that are used in this matrix system.
5. Fat wax matrices (Teixeira *et al.,* 2020**).** It also goes by the name "lipid matrix system." Lipid waxes or other relevant materials are employed to construct the matrices in this sort of matrix system. Drug release happens via pore diffusion as well as erosion. The matrix included water-filled tubes through which drugs were dispersed in dissolving media. Surfactant incorporation in the system can also affect the pattern of release & the percentage of total active substances inside the matrix. Granules can be created from drugs and other excipients such as waxes and diluents by compacting, drying, mixing, and granulating.

Matrix tablet classification based on release mechanism:

Matrix dissolution system (Ranade *et al.,* 2011). The medication is evenly distributed in rate-limiting media, such as castor oil, carnauba wax, etc. Modifying the matrix and additives' porosity and wettability controls the rate of dissolution. The rate at which polymers dissolve can be used to calculate the medication release rate. Dissolution is the solubilisation of a solid material in a specific solvent. This stage, when liquid diffuses from solid particles, is rate-limiting (Lu *et al.,* 2011). Monoliths is another name for it. Diffusion is the migration of drug particles from one concentration to another and occurs when a polymeric membrane that is inert and insoluble in water acts as a barrier. By adjusting the drug's initial concentration, solubility, the type of polymers utilized, and the size of the inert membrane's aperture, the drug release in the diffusional matrix system may be controlled. The polymeric matrix contains a dispersion of the drug particles in the system. The drug's active components are released by diffusion from the matrix when the drug's outer layer dissolves in the dip liquid.

Classifications based on several alternative matrix construction methods include:

A. pH sensitive matrix system (Khirwadkar *et al.,* 2012). After oral administration, this kind of matrix structure can shield antigen or protein molecules from the severe acidic environment of the stomach. This kind of matrix system can employ PH-sensitive polymers like HPMC-phthalate or cellulose acetate phthalate.
An enteric coating on the solid dosage form can shield the medication in this sort of matrix system from the harsh acidic environment of the stomach. Drug molecules that are low pH sensitive can so safely enter the small intestine and colon.

B. Multilayered matrix system (Syed *et al.,* 2011). In this kind of matrix system, the drug molecules are coated with a semi-permeable polymeric substance and the matrix core is formed of hydrophilic materials. During preparation, this semi-permeable polymeric substance is used as a barrier-layer on the core's two surfaces. Barrier-layers may influence how quickly the core swells, which would reduce the amount of surface area that drug molecules would have to interact with during the release process. By changing the shape of the barrier-layer in the matrix, different drug release profiles can be achieved. The matrix's barrier layers inflate, gel, and then dissolve, controlling the drug release.

C. Floating matrix system (Gambhire *et al.,* 2007). The bulk density of the matrix in this sort of matrix system is lower than the gastric fluid in the stomach. The drug molecules may progressively release from the matrix after generating buoyancy in the stomach. Long-lasting drug release enhances the stomach residence duration and, as a result, the bioavailability of fast-acting therapeutic compounds.

A popular polymer in this kind of hydrophilic matrix system is HPMC. Its ability to act as a gelling agent is pH independent.

D. Mucoadhesive matrix system (Arora *et al.*, 2016). Ocular, respiratory, gastrointestinal, buccal, nasal, rectal, urethral, and vaginal tissues can all be targets in this type of matrix system. This kind of matrix technology can also be used on any mucosal tissue throughout the body, including the GIT.

Swellable hydrophilic polymers that can interact with the glycoproteins present in the gut's mucous layer are the materials used in this system.

Polymers used in the matrix: Both hydrophilic and hydrophobic polymers are among the most frequently used in the creation of matrix systems.

a) Hydrophilic Polymers

Sodium alginate, poly(ethylene oxide), Xanthan gum, hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), hydroxyl ethyl cellulose (HEC), and cross-linked homo polymers and co-polymers of acrylic acid

b) Hydrophobic Polymers

Wax and water-insoluble polymers are frequently used in their production.

c) **Waxes**

Low molecular weight polyethylene, carnauba wax, bees wax, candelilla wax, microcrystalline wax, ozokerite wax, and paraffin waxes.

d) Insoluble polymers

Latex dispersion comprising methacrylic ester copolymers, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, and ammonium ethacrylate co-polymers (Eudragit RL100, PO, RS100, PO).

Components to make up a matrix tablet.

These consist of:

a) Active drug
b) Matrix modifiers like wicking and channeling agents
c) Density-modifying agents (if required)
d) Matrix formers, release controlling agent(s)
e) Lubricants and flow promoters
f) Additional coatings to prolong the lag time and further slowdown drug release, etc.
g) Solubilizing agents and pH adjusters

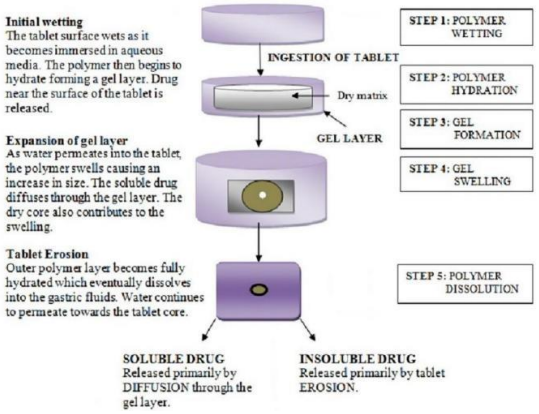

Fig. 4. Hydrophilic and hydrophobic matrix system and corresponding drug release process.

Channeling agents: These were picked because they can dissolve in the gastrointestinal tract and leach out of the formulation, leaving tortuous capillaries through which the released medication can diffuse. A solid substance that is water soluble and accepted by pharmaceuticals is more likely to be used than the drug itself as a channeling agent. Typical examples are polyols, sugars, and sodium chloride. The drug and desired released properties will determine this decision. These ingredients may make up 20–30% of the final product.

Matrix formers: As matrix formers, hydrophobic substances that are solid at room temperature and do not melt at body temperature are employed. These include microcrystalline wax, carnauba wax, cotton seed oil, soy oil, and hydrogenated vegetable oils. These waxes typically make about 20–40% of the formulation.

Solubilizes and pH modifiers: These were picked because they can dissolve in the gastrointestinal tract and leach out of the formulation, leaving tortuous capillaries through which the released medication can diffuse. A solid substance that is water soluble and accepted by pharmaceuticals is more likely to be used than the drug itself as a channeling agent. Typical examples are polyols, sugars, and sodium chloride. The drug and desired released properties will determine this decision. These ingredients may make up 20–30% of the final product.

Anti-adherent or glidants (Babu *et al.*, 2010**).** Heat produced during matrix compaction may cause wax matrix forming components to melt and adhere to punches. Talc and colloidal silicon dioxide are suitable anti adherents for dealing with the sticking. The flow of formulations on the tablet machine can be improved by these components' ability to function as glidants. According to the anti-adhesive being used, the average dosages will range from 0.5 to 1% for colloidal silicon dioxide to 4-6% for talc. If added, magnesium stearate can also function as an anti-adherent.

Methods for achieving the controlled release of medications taken orally:

A) **Dissolution Controlled Systems:**

a) 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 produced by alternating drug layers with rate-controlling coatings. 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.

b) Matrix type: The more typical kind of controlled-release dose form for dissolving. Either a drug-impregnated sphere or a drug-impregnated tablet can be used; both will slowly erode over time.

B. Diffusion Controlled System: Diffusion process essentially depicts the migration of drug molecules from a higher concentration area to a lower concentration area. This system comes in two types.

a) The reservoir type is characterized by a drug core encircled by a polymer membrane that regulates the release rate.

b) The uniform dispersion of solid medication in a polymer mixture is what defines a matrix system.

C) Bioerodible and Combination of Diffusion and Dissolution Systems:

It is distinguished by uniform drug dispersion within an erodible matrix.

Method of Preparation matrix tablet:

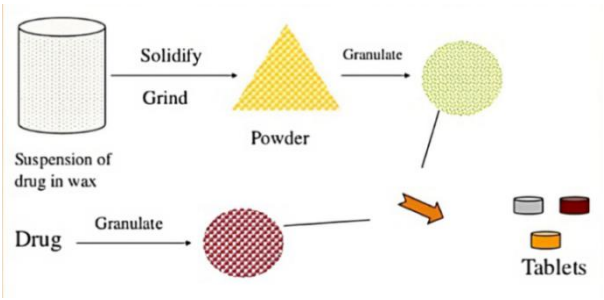

Fig. 5. Method of preparation of matrix tablet.

Basic idea behind medication release (Krishanaiah *et al.*, 2003). Drugs will diffuse in solution from a high concentration area to a low concentration area. The drug diffusion out of a system is being pushed by this concentration gradient. In a similar way, water diffuses into the system. The surrounding medium contains a lot of water; hence the system should permit water infiltration. Initially, the system's interior has less water than the medium outside.

Factors affecting drug release from matrix tablets:

1. Physicochemical factors
2. Biological factors
3. Release limiting factors

A. Physicochemical factors:

a) Dose of administration: The mass unit dose will be too high to administer for drugs that require a big dose of administration, hence they are not suited for controlled release matrix formulation. Typically, 1 g is regarded as the upper limit.

b) Ionization: Drugs that have been ionized are not suitable for controlled-release tablets. When compared to ionized drug forms, unionized drug absorption is reported to be 3–4 times higher.

c) Aqueous solubility: Medications with extremely low solubility—less than 0.01 mg/ml—are sustained by themselves, so the compound's solubility will not make it a good contender for medications that are only marginally soluble. Drug solubility in modified release systems must not go below 0.1 mg/ml. One of the best possibilities for the sustained release method is very soluble medicines.

d) Distribution coefficient: Drug molecules with high levels of hydrophilic or lipophilic have apical distribution coefficients, which result in either high or low flux into the tissues, which in turn affects absorption. Therefore, neither extreme is preferred for a controlled release mechanism.

e) Stability: Systems for delivering drugs orally are susceptible to both hydrolytic and metabolic degradation. Constant medications may be created as an extended delivery method to release the medication in the intestine. When given in an extended form, medications that have consistency in the small intestine reduce bioavailability; these medications can be adjusted to take the shape of a gastro retentive dose form.

g) Molecular mass & diffusion-coefficient: Diffusivity is the rate at which a drug spreads across a polymeric sheet and is a function of the drug's molecular mass. To disseminate throughout the matrix, the substance with a high molecular weight has a low release profile in a modified release device. The size, structure, and mass of the active pharmaceutical ingredient are what determine the diffusion co-efficient.

h) Formulation excipients. The hydrophobic diluents produce a gel with a resistant surface that reduces drug diffusion and aqueous medium infiltration. While insoluble fillers alter the diffusion rate by obstructing the tablet's surface pores, soluble fillers promote the dissolving of soluble medicines by reducing tortuosity.

By solubilizing drug particles, surfactants speed up drug release while binding agents coat drug particles and change the rheology of the gel layer, slowing down drug release.

B. Biological Factors:

a) Half-life (t1/2) (Timmins *et al.*, 2014). Tablets with a controlled release are not a good option for medications with a half-life less than 2 and greater than 8. Larger doses of the active components are needed for drugs with a shorter half-life, whereas those with a longer half-life are already prolonged.

b) Absorption: (Olivares-Morales *et al.*, 2014). Drugs that absorb slowly, inconsistently, or erratically are not ideal candidates for controlled-release tablets. Drugs taken through a specific gastro intestinal location, such as the absorption window or by carrier-mediated transport, are also not suitable candidates.

c) Metabolism (Lennernäs, 2014). Medications that are metabolically processed before being consumed have a lower bioavailability than medications with regulated release. Pro-drug is an effective treatment for these kinds of medicines. For controlled release systems, medications that have no digestive reaction are frequently used. Controlled release systems also assist in ensuring that a drug is metabolized in a specific environment because a drug's metabolism can result in it becoming inactive or converting into another active metabolite.

d) Distribution (Thombre *et al.*, 2005). Drugs with a large distributing volume (Vd) can interfere with the elimination process and are not ideal for controlled release because they are sustained in the body, such as digoxin (500l Vd) and chloroquine (15000l Vd).

e) **Protein binding**: Given that the drug stays in the body for a long period, prolonged and severe plasma protein binding increases drug half-life and variable bioavailability, making it an unsuitable candidate.

f) Therapeutic index: (Thombre *et al.*, 2005). Due to their greater safety and efficacy margin, drugs with higher therapeutic ratios are preferred. The safer the medicine is, the higher the ratio. To keep the plasma drug level within a tight therapeutic and safety range for medications with a narrow therapeutic index, release kinetics should be more precise.

g) Side effects (Badshah *et al.*, 2010). The fluctuation in plasma medication concentration is to blame. The

regulated drug release and decreased fluctuation of matrix tablets reduce negative effects.

h) Disease state (Rakesh, 2018). Disease control is improved by the controlled release delivery mechanism. For example, in rheumatoid arthritis, aspirin controlled release tablets maintain the desired plasma drug level, particularly over the course of the night, and as a result, reduce morning stiffness.

A. Release limiting factors

Polymer hydration (swelling process) (Ghori *et al.*, 2015). It is a process of polymer dispersion in the dissolving medium as well as polymer absorption and dissolution in water. The release of the medication will increase when the polymer hydrates.

Polymer composition (Körner *et al.*, 2009). Functional groups and cross-links inside a polymer's structure may interact with other molecules and different species, making the polymer non-soluble and stable. These interactions may have an impact on the pharmacokinetic characteristics of different medications.

a) Polymer viscosity (Maderuelo *et al.*, 2011). Drug dissolution will be reduced because the density of the gel surface will increase with increasing polymer viscosity. Without influencing the rate of release, the gel-forming moiety delays the primary hydration process.

b) Drug solubility (Chakraborty *et al.*, 2009). The polymeric membrane's medication release rate is directly influenced by solubility. Drug solubility and molecular weight are crucial factors in determining how quickly a drug is released from dissolution and matrix invasion. Drugs that are hydrophilic release through diffusion while those that are insoluble release through erosion.

c) Solution solubility (Timmins and Allenspach 2018). The release pattern is managed by sustaining the dissolution process and must not be impacted by factors affecting solubility parameters because all biological dissolution processes are controlled by invasion and solubilization.

d) Polymer diffusion: The process is driven by the diffusivity of tiny drug particles in matrices. Diffusivity movement is influenced by the length and scope of polymer series, chemical bonding, and polymer complexity. Particle size, viscosity, and concentration are the three variables that control release rate.

e) Particle size (Ghori *et al.*, 2015). If a substantial amount of polymer is used, particle size has no bearing on the pattern of release. When the amount of polymer is low, particle size is taken into account.

f) Viscosity (Saha *et al.*, 2001). As polymer viscosity increases, the density of the gel surface in matrices increases, which slows the process by which active compounds dissolve.

g) Polymer concentration (Ghori *et al.*, 2015). The gel's viscosity will increase with polymer content, which will also cause a decrease in the drug's diffusivity and, as a result, in the drug's release and bioavailability.

Polymer diffusional line density Fick's rules of diffusion often govern how drugs are released from a matrix. i.e.

$$JD = D\frac{dc}{dx}$$

JD = Diffusion flux
D = Diffusion coefficient
dc/dx = Gradient of concentration along axis

EVALUATION OF MATRIX TABLETS

A) Pre-compression evaluation studies on the compatibility of drug excipients Using DSC and FTIR spectra, any interactions or incompatibilities between the medication and the polymer were investigated.

1. Fourier transforms infrared spectroscopy: It is used to characterize configurations and determine whether pharmacological recipients are compatible. The samples are prepared as KBr-disk compressed at 10 tonne/nm^2 pressure after drying in a hot air oven at 500C for 2 hours. Due to chemical interactions between the medication and the polymer, there may be an additional peak or an absence of the characteristic peak (Gaikwad *et al.*, 2020).

2. Differential scanning Calorimetry: The study of the chemical interactions between active and inactive substances is conducted. The sample for analysis is placed inside perforated DSC aluminium pans, which are scanned within the predetermined temperature range. Nitrogen acted as a gas that was purged while the heating rate was maintained. The liquid nitrogen cooled the system. For this, a differential thermal analyzer is used (Ofori-Kwakye *et al.*, 2015).

3. X ray diffraction pattern: X ray diffractometry was used to analyze the medication, polymer, and their physical combination. After each step, it is executed to perform a full scan while adding up the counts for 1s-1.

4. Determination of solubility: Solubility is measured by adding a quantity of the component to the solvent that is significantly greater than its saturation solubility. Extra drug compounds stir for a few hours in each buffer before being centrifuged. Checking the solubility involves examining an aliquot of supernatant after 24 hours **(**Ofori-Kwakye *et al.*, 2015).

5. Moisture content determination: Karl-Fischer titrations and infrared drying (gravimetric and chemical, respectively) are used to determine the moisture content. The amount of weight loss that occurs while the sample is heated is used in thermo-gravimetric moisture balances to calculate moisture content. As opposed to Karl Fischer titration, this involves adding a reagent to the sample that reacts with the water to create a chemical that is not conductive (Ofori-Kwakye *et al.*, 2015).

6. Particle Size Analysis: To research sieve analysis, several sieves and agitation tools are employed. For sieve analysis and endpoint results, each approach may produce different results. Vertical oscillation, a horizontal circular motion, tapping, or any combination of these can be produced using mechanical or electro-magnetic agitation methods. Another technique is the entrainment of airborne particles.

Angle of repose

$\Theta = \tan^{-1}(h / r)$

h = height of cone

r = radius of conical base

Porosity

Porosity = Void volume/Apparent volume

Density

Apparent density = Mass /Apparent volume of occupied powder

Tapped density = Mass/Tapped volume of powder

Compressibility (Carr's) index & Hausner's ratio:

Carr's index (%) = [(Tapped density – Apparent density) × 100] /Tapped density

Hausner ratio = Tapped density / Apparent density

Post-compression evaluation

Weight uniformity:

20 pills are weighed individually using an analytical balance. The weight variation must stay within the given parameters. If more than two tablets are out of range, the test will fail.

Dimension (Hardness and thickness):

Friability:

Ten weighted pills are put into a friabilator, which rotates at 25 rpm for four minutes. The tablets were then reweighed and dedusted. It should ideally range from 0.5 to 1.0%. Calculating % friability is as follows:

$$\%\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Swelling-studies: (Simancas-Herbada *et al.,* 2020)

$$\%S = \frac{W_t - W_o}{W_o} \times 100$$

(W_t = weight after putting, and W_o = weight before putting)

Disintegration test. Six pills are placed in a fluid-filled beaker in a disintegration tester at body temperature (37ºC), and the time is recorded until no residue is left.

Dissolution. Dissolving tests are performed using the prescribed USP dissolving method under the prescribed USP Pharmacopeial conditions at a body temperature that is maintained, or 37°C, samples extracted using a syringe filter at various time intervals and tested using a designed HPLC technique or an ultraviolet-visible spectrophotometer

Analysis of dissolution data. Drug-release profile equation is used to determine the active content in a dissolving sample. Drug release patterns are evaluated utilizing a model-dependent and model-independent approach (Cascone *et al.,* 2017).

Surface-morphology. Surface morphology is used to produce scanning electron micrographs of matrix tablets before and after dissolution. Before analysis, the samples were coated with gold in an argon environment while under vacuum. With magnifications of 200X and 1000X, the scanning electron microscope (SEM) examines the sample while operating at 30 kV **(**Ahmed *et al.,* 2018**)**.

Stability studies. The manufactured matrix tablets will be exposed to accelerated stability conditions at 0, 1, 2, 3, and 6 days (40°C & 75%). Differential scanning Calorimetry (DSC) thermogram recorded after 6 months under accelerated conditions will be used to establish the product's stability.

CONCLUSIONS

Oral release of control one of the convenient, safe, and effective dosing forms is the matrix tablet. Different polymers can be used to build various sorts of controlled release systems. The numerous biological and physicochemical characteristics of the medication and excipients are necessary for the successful production of the matrix tablet system. The distinct benefits of matrix tablets make them a compelling alternative for an oral controlled medication delivery system. Many medications can be given in ways that not only increase safety and efficacy but, in some circumstances, allow for novel and more effective therapies by using matrix tablets as an oral controlled release formulation. Different matrices, polymers, and release mechanisms from the matrix tablets have been discussed in this paper.

Matrix tablets have discrete advantages which make them interesting candidate for oral controlled drug delivery system. Matrix tablets are helpful in increasing the efficiency of dose, increasing patient compliance. The problem of high cost of production, which was the disadvantage in early days, has been solved with improvement in technology. Using matrix tablet as oral controlled release formulation, many drugs, can be delivered in ways that not only improves safety and efficacy but, in some cases, permit new and more effective therapies.

FUTURE SCOPE

In many drug delivery systems that use controlled release, matrix tablets are used. Controlled release matrix tablets promote stability by shielding the active ingredient from hydrolysis and degradation and improve patient compliance by reducing dose frequency. It uses either a diffusion control mechanism or a dissolution control mechanism to release pharmaceuticals at a defined and predicted pace in a regulated way. The rate-controlling agent, which are polymers that may be hydrophilic, evenly disseminate the active substance.

Conflict of Interest. None.

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How to cite this article: Dipak P. Kardile, Pravin B. Awate, Vishwas C. Bhagat, Ratan S. Birajdar, Rajkumar V. Shete, Suchita S. Lathi, Bhagyashri R. Mathdevru, Onkar P. Pawar and Rani M. Mhetre (2023). A Comprehensive Review of Recent Studies on Matrix Tablets for Drug Delivery with Oral Controlled Release. *Biological Forum – An International Journal*, *15*(4): 789-798.