Review Article

Matrix Tablets: An Approach towards Oral Extended Release Drug Delivery

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ABSTRACT

The oral route is the most frequently used route for the administration of drugs. Many of the pharmaceutical dosage form are formulated as sustained release dosage form to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its plasma profile is sustained in duration. Tablets offer the lowest cost approach to sustained and controlled release dosage forms. Matrix tablets serves as an important tool for oral extended- release dosage forms. Hence, problems like patient compliance, drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels, associated with their counterparts, the conventional dosage forms were solved. Oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Extended-release drug-delivery system reduces the dosing frequency of certain drugs by releasing the drug slowly over an extended period of time Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers. The use of different classes of polymers in controlling the release of drugs has become the most important aspect in the formulation of matrix tablets. The drug release in matrix drug delivery systems by both dissolution-controlled as well as diffusion controlled mechanisms.

Keywords: Direct compression, extended-release, hydrophilic and hydrophobic polymers, matrix tablets, wet granulation.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration i.e. the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. The two most important aspects of drug-delivery are spatial placement and temporal delivery of a drug. Spatial placement relates to the targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled-release drug-delivery system can be a major advance towards solving these two problems [1].

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance [2]. Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery [3-5]. Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release products results in relatively rapid drug absorption

and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administration of another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations In recent years, pharmaceutical industries and academic laboratories have been focused on establishment of novel drug delivery system/modified release/sustained release or the controlled-release drug delivery system rather investigation and development of new drug due to investigation cost of a new drug [6-9].

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as 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". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision [10]. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression [11-14].

Advantages offered by matrix tablets: [15-16]

1) Maintains therapeutic concentrations over prolonged periods.
2) Avoids the high blood concentration.
3) Reduction in toxicity by slowing drug absorption.
4) Minimize the local and systemic side effects.
5) Improvement in treatment efficacy.
6) Better drug utilization.
7) Minimize drug accumulation with chronic dosing.
8) Can be made to release high molecular weight compounds.
9) Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
10) Reduction in health care cost.
11) Usage of less total drug.
12) Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
13) Improved patient compliance.

Disadvantages of Matrix Tablets: [15-16]

1) The remaining matrix must be removed after the drug has been released.
2) Greater dependence on GI residence time of dosage form.
3) Increased potential for first-pass metabolism.

4) Delay in onset of drug action.
5) Release rates are affected by food and the rate transit through the gut.
6) Release rate continuously diminishes due to increased diffusional resistance and decrease in effective area at the diffusion front.

Polymers used in matrix tablets:

There are number of polymers which may be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required [17]. Polymers used for matrix tablets may be classified as:

A) Hydrogels:
1. Poly-hydroxyethyle methylacrylate (PHEMA)
2. Cross-linked polyvinyl alcohol (PVA)
3. Cross-linked Polyvinyl pyrrolidone (PVP)
4. Polyethylene oxide (PEO)
5. Polyacrylamide (PA)

B) Soluble polymers:
1. Polyethylene glycol (PEG)
2. Polyvinyl alcohol (PVA)
3. Polyvinyl pyrrolidone (PVP)
4. Hydroxypropyl methyl cellulose (HPMC)

C) Biodegradable polymers:
1. Polylactic acid (PLA)
2. Polyglycolic acid (PGA)
3. Polycaprolactone (PCL)
4. Polyanhydrides
5. Polyorthoesters

D) Non-biodegradable polymers:
1. Polyethylene vinyl acetate (PVA)
2. Polydimethyl siloxane (PDS)
3. Polyether urethane (PEU)
4. Polyvinyl chloride (PVC)
5. Cellulose acetate (CA)
6. Ethyl cellulose (EC)

E) Mucoadhesive polymers:
1. Polycarbophil,
2. Sodium Carboxymethyl cellulose
3. Polyacrylic acid
4. Tragacanth
5. Methyl cellulose
6. Pectin

F) Natural gums:
1. Xanthan gum
2. Guar gum
3. Karaya gum
4. Gum Arabic
5. Locust bean gum

Suitable Drug Candidate for Extended Release Drug Delivery System (ERDDS):

The drugs that have to be formulated as extended-release matrix tablet should meet following parameters [19].

1. It should be orally effective and stable in GIT medium.
2. Drugs that have short half-lives, ideally a drug with half life in the range of 2 – 4 hrs makes a good candidate for formulation into ER dosage forms eg. Losartan, Theophylline, Captopril & Salbutamol sulphate.
3. The dose of the drug should be less than 0.5g as the oral route is suitable for drugs given in dose as high as 1.0g.eg. Metronidazole.
4. Therapeutic range of the drug must be high.
5. A drug for ERDDS should have therapeutic range wide enough such that variations in the release do not result in concentration beyond the minimum toxic levels.

Matrix Formulations of active drugs are irrational, in case of;

1. Large doses
2. Long biological half-lives
3. Very potent drugs
4. Irratic absorbed drugs
5. Drugs which do not show relationship between blood levels and biological activity

Types of matrix tablets

On the basis of type of polymer/release rate retardant used matrix tablets may be divided into two types.

Hydrophilic matrix tablets:

Hydrophilic matrix systems are presently one of the most interesting drug delivery systems. They are most widely used to control the release rate of drugs because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Hydrophilic matrix tablets may be defined as "Homogeneous dispersion of drug molecules within a skeleton of hydrophilic polymers, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, or carbopol among others, that swells upon contact with water". These systems are called swellable-controlled release systems [22].

Apart from swelling and diffusion mechanisms polymer dissolution is another important mechanism that can modulate the drug delivery rate. Swelling or dissolution can be the predominant factors for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms [21]. The release rate observed is possibly the zero-order release. Most commercial hydrophilic matrices are obtained by compression. Thus, the basic operations involved in the preparation of the matrices are the same as those used to prepare conventional tablets, such as mixing and compressing the components. Granulation prior to mixing and the coating of matrix tablets are complementary operations widely used to manufacture matrix tablets. As well as the drug and the release-limiting polymer, other excipients are usually added as diluents, lubricants and anti-adhearents. The polymers used in the preparation of hydrophilic matrices are divided in to two broad groups [20].

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs and sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar, carbo gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches.

Hydrophobic matrix tablets:

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. The primary rate-controlling components of hydrophobic matrix are water insoluble in nature. Examples of materials that have been used as inert or hydrophobic matrices include waxes, glycerides, polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers [22-23].

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. [21] As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetics. Hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release [25-26]. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk in case of hydrophilic matrix tablets [20].

On the basis of porosity of matrix: [20-22, 26-28]

Matrix tablets may also be classified on the basis of the porosity of the matrix system used in the formulation.

1) Macro porous Systems: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2) Micro porous System: Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3) Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Mechanism of drug release from the matrix tablets: [32-33]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process

continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

1) A pseudo-steady state is maintained during drug release.
2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
3) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

$$dM/dh = C_0 . dh - C_s/2 \quad \text{..... (i)}$$

Where, dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

C_0 = Total amount of drug in a unit volume of matrix.

C_s = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

$$dM = (D_m . C_s / h) dt \quad \text{..... (ii)}$$

Where, D_m = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix.

dt = Change in time.

By combining equation (i) and equation (ii) and integrating:

$$M = [C_s . D_m (2C_0 - C_s) t]^{1/2} \quad \text{..... (iii)}$$

When the amount of drug is in excess of the saturation concentration then:

$$M = [2C_s.Dm.C_0.t]^{1/2} \quad \text{..... (iv)}$$

Equation (iii) and eq. (iv) relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [D_s.C_a.p/T. (2C_o - p.C_a) t]^{1/2} \quad \text{..... (v)}$$

Where, p = Porosity of the matrix

t = Tortuosity

C_a = solubility of the drug in the release medium

D_s = Diffusion coefficient in the release medium.

T = Diffusional pathlength

For pseudo steady state, the equation can be written as:

$$M = [2D.C_a .C_0(p/T)t]^{1/2} \quad \text{.....(vi)}$$

The total porosity of the matrix can be calculated with the following equation:

$$p = p_a + C_a/ \rho + C_{ex}/\rho_{ex} \quad \text{..... (vii)}$$

Where, p = Porosity

ρ = Drug density

p_a = Porosity due to air pockets in the matrix

ρ_{ex} = Density of the water soluble excipients

C_{ex} = Concentration of water soluble excipients

For the purpose of data treatment, equation (vii) can be reduced to:

$$\mathbf{M = k.\ t^{1/2}} \quad \text{……(vii)}$$

Where, k = constant.

So the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

1) Initial concentration of drug in the matrix
2) Porosity
3) Tortuosity
4) Polymer system forming the matrix
5) Solubility of the drug

Bimodal Release: [34-35]

In some systems there is anomalous release of the active ingredient. In these systems release is primarily by diffusion. Sometimes the ER polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution. A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodible matrix:

1) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix.
2) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.
3) Upon contact with water the drug dissolves and diffuses out of the device.
4) With increasing water content, the diffusion coefficient of the drug increase substantially.
5) In the case of a poorly water-soluble drug, dissolved and undissolved drug coexist within the polymer matrix.
6) Finally, the polymer itself dissolves.

The penetration of the medium into the matrix is accompanied by the formation of a series of fronts (Fig. 1) which later disappear along the process of matrix dissolution. The following fronts have been defined with regard to anomalous release systems:

1) The swelling front. With the entry of water into the matrix, the polymer passes from the crystalline state to a hydrated or gelified state. This front is thus seen separating the crystalline state (glassy region) from the hydrated or gelified one (rubbery region).

– The rubbery zone is characterized by being the one into which more solvent has entered and hence the vitreous transition temperature (T_g) at 37^0 C of the polymer is lower than the experimental temperature.

– The glassy region is the one into which the least solvent has entered and hence its T_g is higher than the experimental temperature.

2) The erosion front or dissolution front: This separates the gelified zone from the matrix of the solvent.
3) Diffusion front (solid drug–drug solution boundary): This is located between the swelling and erosion fronts and it separates the zone of the gelified matrix containing the drug dissolved in the medium from the

zone of the matrix containing the undissolved solid drug.

A fourth front movement has been recently described by Ferrero et al.: the penetration front (dry glassy / glassy hydrated polymer interface), showing that the solvent concentration is never zero beyond the glassy/rubbery interface. Thus, the mechanisms by which drugs are released are complex and involve different processes: the entry of the aqueous medium into the matrix, swelling of the matrix, dissolution of the drug in the medium, diffusion of the drug through the gel layer, and erosion of the swelled matrix. Unlike systems formed by non-biodegradable polymers, in which release is controlled by diffusion of the drug through the gel layer, obtaining first-order release kinetics, in systems comprising biodegradable polymers – in particular hydrophilic systems – the control of drug release is exerted by the entry of water into the matrix system. This entry of water produces the swelling of the polymer or the matrix dissolution [36].

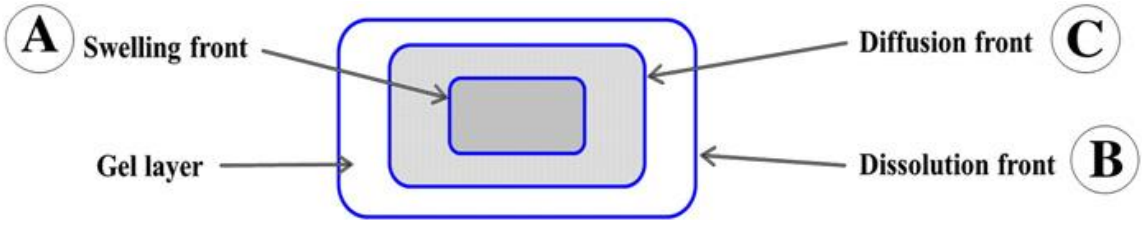

Figure 1: Scheme of the Hydrophilic Matrix after Entry of the Dissolution Medium.

With regard to swelling matrix systems, alternate models have been proposed to describe the diffusion, swelling and dissolution processes occurring with into the system and these phenomena lead to drug release. The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gums do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices. In 1985, Peppas introduced a semi-empirical equation describing the drug release behaviour from anomalous-release, hydrophilic matrix systems:

$$Q = k.\, t^{n} \quad \text{(ix)}$$

Where, Q = Fraction of drug release in time (t)

t = Time

k = Rate constant (incorporates characteristics of polymer system and drug)

n = Diffusional exponent

In order to describe relaxational transport, then modified equation (ix) in order to account for relaxational transport:

$$Q = k_1 . t^{n} + k_2 . t^{2n} \quad \text{(x)}$$

Where, k_1 = Fickian diffusion constant k_2 = Relaxational mechanism constant

If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and equation (x) is transformed to:

$$Q = k_1 . t^{0.5} + k_2 . t \quad \text{(xi)}$$

The first term of this equation accounts for diffusional phenomena, while the second term of this equation accounts for polymer erosion. The value of n is indicative of the drug release mechanism [36].

Effect of release limiting factors on drug release: [37-39]

1. Polymer hydration: Polymer hydration or swelling process is studied for the maximum number of polymers and polymeric combinations. The more

important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

2. Drug solubility: Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.
3. Solution solubility: In view of *in-vivo* (biological) sink condition maintained actively by hem perfusion, it is logical that all the *in-vitro* drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of *in-vitro* drug release profile with *in-vivo* drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.
4. Polymer diffusivity: The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion, E_d has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors:

i) Polymer particle size: e.g. When the content of hydroxyl propyl methylcellulose (HPMC) is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable is more important when the content of polymer is low. Results may be justified (Malamataris) by considering that in certain areas of matrix containing low levels of HPMC led to the burst release.

ii) Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii) Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

5. Thickness of polymer diffusional path: The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

   $$\mathbf{J_D = D\ dc/dx}$$

   Where, J_D = Flux of diffusion across a plane surface of unit area.
   D = diffusibility of drug molecule.
   dc/dx = is conc. gradient of drug molecule across a diffusion path with thickness dx.
6. Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer, δ_d.
7. Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the

relative release rate first decreases and then increases, whereas, absolute release rate increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs, another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

8. Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in-vitro* and *in-vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.
9. Diluent's effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose, mannose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.
10. Additives: The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

Biological factors influencing release from matrix tablets: [34-36]

1. Biological half-life: SR product aims to maintain therapeutic blood levels over an extended period of time. In order to achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. E.g. Digoxin and phenytoin.
2. Absorption: Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 to give 80-95% over this time period. Hence, it assumes that the absorption of the 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 limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One

method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect.

3. Metabolism: Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence, criteria for the drug to be used for formulating SR dosage form is:

i) Drug should have short half-life (2-4 hrs.).
ii) Drug should be soluble in water.
iii) Drug should have large therapeutic window.
iv) Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form.

4. Distribution: Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.
5. Protein Binding: The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless 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. Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with low therapeutic index are usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.
7. Physicochemical factors influencing release from matrix tablets: [37-39]
8. Dose size: For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds true for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.
9. Ionization, *pka* and aqueous solubility: Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.
10. Partition Coefficient: When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are having lipophilic nature; therefore the partition coefficient of oil-soluble drugs becomes important in determining the

effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

11. Stability: Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug.

Marketed formulations of sustained-release matrix tablets: [40]

List of various drugs which can be formulated as a matrix tablet with polymer and method used or its preparation are shown in **(Table 1)**.

DRUGS USED	CATEGORY	METHOD USED	POLYMER USED
Acarbose	Anti-diabetic	Direct Compression	HPMC, Eudragit
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Ambroxol HCL	Expectorent, Mucolytic	Direct Compression	HPMC-K100M,
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100, S100
Amlodipine	Anti-arrythmatic	Direct Compression	HPMC, EC
Albuterol	Anti-asthmatic	Direct Compression/Wet Granulation	HPMC-K100M, HPMC-K4M, HPMC-K15M,EC,XANTHAN GUM,GAUR GUM
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit-RSPO
Chlorphenarimine meleate	H1 antagonist	Melt-extrusion	Xanthan gum,Chitoson
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Diclofenac Na	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diethylcarbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV
Diltiazem	Ca+2 channel blocker	Direct Compression	HPMC-K100M, HPMC-K4M, Karaya gum, Locust bean gum, Sod.CMC
Enalpril meleate	ACE inhibitor	Direct Compression	HPMC-K100M,HPMC K4M,
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin,

			Xanthan gum
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP

CONCLUSION

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

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