

ROLE OF MATRIX TABLET IN SUSTAINED RELEASE SYSTEM**Saritadevi Gupta^{*1}, Asish Dev², Samreen Mansoori³ and Akshay Yelwe⁴**

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ABSTRACT

Many of the pharmaceutical dosage form are formulated as sustained release dosage form to retard the release of therapeutic agent such that its appearance in systematic circulation is prolonged and plasma profile is sustained in duration. Matrix system is widely used for purpose of sustained release. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to pharmaceutical technologist. matrix tablet may be formulated by wet granulation or direct compression method by dispensing solid particle with in a porous matrix formed of hydrophilic and hydrophobic polymers. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulation.

KEYWORDS: sustained released, matrix tablet, direct compression, wet granulation, hydrophilic and hydrophobic polymers.

INTRODUCTION

The matrix system is the mixture of materials with the drug, which will cause the drug to slow down. However, this system has several subcategories: hydrophobic matrices, lipid matrices, hydrophilic matrices, biodegradable matrices, and mineral matrices.^[1]

- A hydrophobic matrix is a drug mixed with a hydrophobic polymer. This causes SR because the drug, after being dissolved, will have to be released by going through channels made by the hydrophilic polymer.^[1]
- A hydrophilic matrix will go back to the matrix as discussed before where a matrix is a mixture of a drug or drugs with a gelling agent. This system is well liked because of its cost and broad regulatory acceptance. The polymers used can be broken down into categories: cellulose derivatives, non-cellulose natural and polymers of acrylic acid.^[1]
- A lipid matrix uses wax or similar materials. Drug release happens through diffusion through and erosion of, the wax and tends to be sensitive to digestive fluids.^[1]
- Biodegradable matrices are made with unstable, linked monomers that will erode by biological compounds such as enzymes and proteins.^[1]
- A mineral matrix which generally means the polymers used are obtained in seaweed.^[1]

Advantages of Matrix Tablet^[2,3]

- Easy to manufacture.
- Versatile, effective and low cost Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.
- Ex: Morning relief of arthritis through bed time dosing.

Disadvantages of Matrix Tablet^[2-3]

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Criteria For Formulation of Matrix Tablet^[11,14,15]

The ideal physicochemical and pharmacokinetic characteristics of drugs which can be formulated as extended release tablet are as follows:

- Molecular size should be below of 1000 Dalton.
- Aqueous solubility should be more than 0.1 mg/ml for pH 1 to pH 7.8.
- The partition coefficient should be high.
- Absorption mechanism should be diffusion and the general absorbability from all GI segments release should not be influenced by pH and enzymes.
- Elimination half-life should be between 2 to 8 hrs.
- Drugs should not metabolized before absorption it caused less bioavailability.
- Absolute bioavailability should be 75% or more.
- Absorption rate constant (K_a) should be higher than release rate.
- Apparent volume of distribution (V_d) should be large.
- Total clearance should not depend on dose.
- Elimination rate constant are required for design and therapeutic concentration (C_{ss}) should be low and smaller (V_d).

Drugs Those Are Unsuitable For Such Design^[11,14,15]

- Elimination half-life less than 2 hours.
- Administered in large dose.
- Therapeutics index is narrow.
- Poor water solubility.

- Long elimination half-life.
- Drugs having extensive first-pass clearance.

Matrix System

Diffusion controlled systems also known as matrix systems are very popular for sustained release formulations (Colombo *et al.* 2000). They can be divided up into different types of mechanisms by which they prolong drug release, these include reservoir matrix systems, monolithic matrix systems and osmotic pump systems.^[4]

Reservoir matrix systems

This system involves a membrane which controls the release of drugs from the matrix system. The drug will eventually diffuse through the membrane and its release is kept constant by the diffusion distance that the drug particles have to cover.^[4]

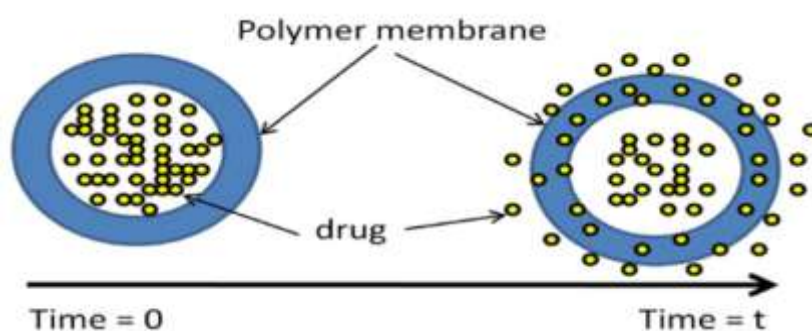


Fig. 1: Schematic representation of Reservoir matrix systems (The figure is adopted from Dash and Cudworth 1998).

Osmotic pump systems

Osmotic systems operate on osmotic pressure. They contain a core tablet that is surrounded by a semi-permeable membrane coating which has an orifice. The core tablet has two layers to it, one containing the active ingredient/drug known as the active layer and the second containing the osmotic agent which is also known as the push layer. Water enters the tablet through the semi-permeable membrane causing the drug to dissolve and suspend. The increase in osmotic pressure causes the dissolved/suspended drug to be pumped out of the delivery orifice. The rate of drug delivery can be changed by altering the size of the delivery orifice and the thickness of the semi-permeable membrane.^[4]

Monolithic matrix systems

systems involve drug to be encapsulated or dispersed in a matrix (Kim 2000). These systems can be employed by forming hydrophobic matrices.^[5] They can be divided into soluble/hydrophilic matrix systems which swell on hydration and dissolve to release drug and insoluble/hydrophobic matrix systems which release drug after being dissolved by a solvent.^[4]

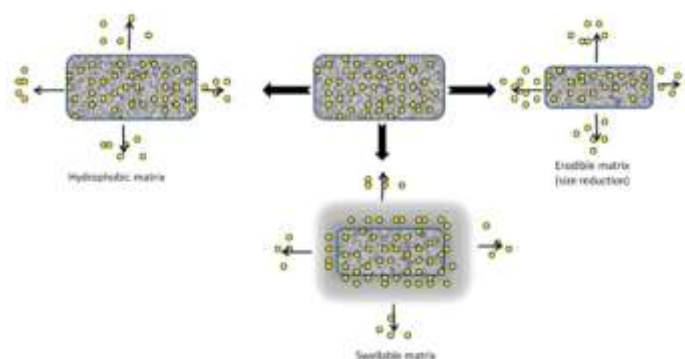


Fig. 2: Schematic representation of drug release from different types of matrix tablets.

Hydrophobic matrix systems are formulated by waxes mainly and can be suitable for drugs which have a high solubility. Wax based matrices have been investigated to ascertain the factors that would affect the release of drug. Drug release has been successfully modulated in hydrophobic matrices however, in a study conducted by Sudha and co-workers (2010) it was concluded that matrices which are based on waxes can modify release rate by increasing the amount of drug or wax concentration, as well as incorporating hydrophilic polymers which would enhance the release. Even though the hydrophobic matrix was able to modulate drug release, the processes that had to be carried out such as hot fusion and thermal treatment highlighted the length of the process that would be required to form such tablets. This can potentially be a deterrent for manufacturing companies who would prefer a more economical method of producing sustained release formulations.^[4]

Hydrophilic matrix systems tend to be more popular in tablet manufacture for controlled release drug delivery systems due to their low manufacturing cost. On contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer via diffusion or erosion of the gel eventually allowing drug to be released. There has been a lot of research into the mechanisms of drug release from

hydrophilic matrices and the critical factors that influence the release rate.^[6]

These swell able matrices have more than one 'front' as a part of its release mechanism.^[4]

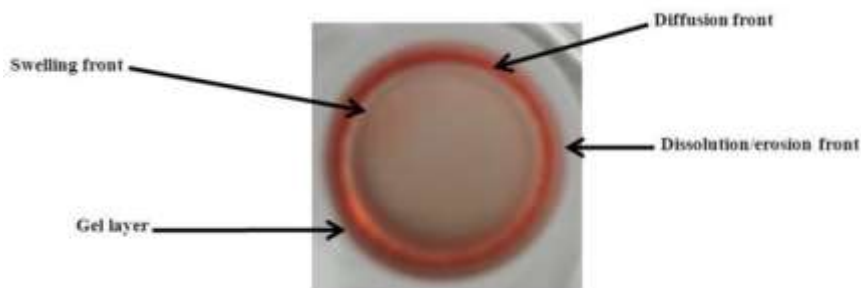


Fig 3: Different front within a matrix tablet containing colouring agent to distinguish different swelling fronts.

The area of dissolved drug and un-dissolved drug are separated by two types of “fronts” from the swollen gel region. They have a diffusion front which is located in between the swelling and erosion front. Drug release can occur by many mechanisms such as erosion, diffusion, polymer relaxation or a combination. Modulation of drug release from geo-matrix multi-layered tablets was proposed by Conti and Maggi (1996) and they found that a swellable barrier around an active core provides greater modulation for soluble drugs.^[4]

Polymers Used In Matrix Tablet^[7]

Hydrogels

Polyhydroxyethylmethacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

Soluble polymers

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

Biodegradable polymers

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

Non-biodegradable polymers

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

Mucoadhesive polymers

Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin

Natural gums

Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

Mechanism of Drug Release From Matrix Tablet^[8,9,10]

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:

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

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

$$dM/dh = C_0 \cdot dh - C_s/2 \dots\dots\dots (1)$$

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

C₀ = 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:

$$dM = (D_m \cdot C_s / h) dt \dots\dots\dots (2)$$

Where,

D_m = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 1 and equation 2 and integrating:

$$M = [C_s \cdot D_m (2C_o - C_s) t]^{1/2} \dots\dots\dots (3)$$

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

$$M = [2C_s \cdot D_m \cdot C_o \cdot t]^{1/2} \dots\dots\dots (4)$$

Equation 3 and equation 4 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:

$$M = [D_s \cdot C_a \cdot p/T \cdot (2C_o - p \cdot C_a) t]^{1/2} \dots\dots\dots (5)$$

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 path length

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

$$M = [2D \cdot C_a \cdot C_o (p/T) t]^{1/2} \dots\dots\dots (6)$$

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

$$p = p_a + C_a / \rho + C_{ex} / \rho_{ex} \dots\dots\dots (7)$$

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 7 can be reduced to:

$$M = k \cdot t^{1/2} \dots\dots\dots (8)$$

Where, k is a constant, so that 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:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

Method of preparation of matrix tablet^[7]

A. Wet Granulation Technique

- Milling and gravitational mixing of drug, polymer and excipients.
- Preparation of binder solution.
- Wet massing by addition of binder solution or granulating solvent.
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules.
- Blending with lubricant and disintegrant to produce “running powder” Compression of tablet.

B. Dry Granulation Technique

- Milling and gravitational mixing of drug, polymer and excipients.
- Compression into slugs or roll compaction.
- Milling and screening of slugs and compacted powder.
- Mixing with lubricant and disintegrant Compression of tablet.

C. Sintering Technique

- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.

- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

Effect of Release And Limiting Factor On Drug Release^[11-12]

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

- A. Polymer hydration:** It is important to study polymer hydration/swelling process 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.
- B. 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.
- C. 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.

D. 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 crystallinity of polymer.

The release of drug may be attributed to the three factors viz,

- a. Polymer particle size
- b. Polymer viscosity
- c. Polymer concentration.

a. Polymer particle size: Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

b. 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.

c. 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.

E. 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: $JD = D \frac{dc}{dx}$ Where, JD is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx .

- F. 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 δd .
- G. 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 monotonically 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.
- H. 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. *Siepmann et al.* found that release from small tablet is faster than large cylindrical tablets.
- I. Diluent's effect:** The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose 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.
- J. 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 Tablet^[11,13]

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

Biological half-life: The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. 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. Digoxin and phenytoin are the examples.

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 $0.17-0.23\text{h}^{-1}$ 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. For many compounds this is not true. 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. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.

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 Sustained-Release dosage form is,

- Drug should have low half-life (<5 hrs.)
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- 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. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

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.

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.

Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

Physicochemical Factors Influencing Release From Matrix Tablet^[11,13]

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 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.

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. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. 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 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.

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 lipidic; 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.

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.

Below table show the drug to be formulated as a matrix tablet with polymer and method used for its preparation

Drugs used	Category	Method used	Polymer used
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934, EC
Venlafexine	Anti-depressant	Wet Granulation	Beeswax, Caranuaba wax
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit-RSPO
Minocycline	Antibiotic	Wet Granulation	HPMC-K4M, HPMC-K15M, EC
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP
Metformin HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
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
Diclofenac Na	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diethylcarbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV
Diltiazem	Ca ²⁺	Direct Compression	HPMC-K100M, HPMC-

	channel blocker		K4M, Karaya gum, Locust bean gum, Sod.CMC
Enalapril meleate	ACE inhibitor	Direct Compression	HPMC-K100M, HPMC K4M,
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Indomethacin	Anti-inflammatory	Direct Compression	EC, HPMC
Chlorphenarimine meleate	H1 antagonist	Melt-extrusion	Xanthan gum, Chitoson
Itopride HCL	Prokinetic agent	Direct Compression	HPMC-K100M, HPMC-K4M, EC
Losartan potassium	Anti-hypertensive	Direct Compression	HPMC-K100M, HPMC-K4M, Eudragit-RSPO
Metoclopramide	Anti-emetic	Direct Compression / Wet Granulation	HPMC, CMC, EC, SSG
Miconazole	Anti-fungal	Direct Compression / Wet Granulation	Pectin, HPMC
Naproxen	Morphine antagonist	Direct Compression	HPMC-K100M, HPMC-K15M, PVP
Nicorandil	Ca ²⁺ channel blocker	Wet Granulation	HPMC, CMC, EC
Ondansertan	Anti-hypertensive	Wet Granulation	HPMC-K100M, HPMC-K4M, HPMC-K15M
Phenytoin Na	Anti-epileptic	Wet Granulation	Tragacanth, Acacia, Guar gum, Xanthan gum
Ranitidine HCL	H ₂ antagonist	Direct Compression	Chitoson, Carbopol-940
Theophylline	Respiratory depressant	Direct Compression	Carbopol-934P, HPMC-K100M, HPMC-K4M, HPMC-K15M, EC
Tramadol	B ₂ blocker	Wet Granulation	HPMC-K4M, Karaya gum, Carrageenan gum
Verapemil	Ca ²⁺ channel blocker	Direct Compression	HPMC-K100M, HPMC-K4M, HPMC-K15M
Amlodipine	Anti-arrhythmic	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

Evaluation of Matrix Tablet^[16,17]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations:

- **Weight Variation:** Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.
- **Hardness:** Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.
- **Friability:** The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.
- **Thickness:** The thicknesses of tablets were determined using micrometer screw gauge.

Content Uniformity: Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.

• Kinetic Studies

- **In Vitro Dissolution Study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37°C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time.
- **Stability Studies:** Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.
- **In-Vivo Methods:** Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation.

Various in-vivo evaluation methods are

1. a. Clinical response
2. b. Blood level data
3. c. Urinary excretion studies
4. d. Nutritional studies.

5. e. Toxicity studies
6. f. Radioactive tracer techniques

CONCLUSION

This review article focus on formulation of sustained released matrix tablet, their advantage, disadvantage and various polymers use to design such system. From above discussion, it can be easily concluded that sustained release formulation are more helpful in increasing the efficiency of dose as well as they are also improving the patient's compatibility. This review has elaborated various matrices, polymer and release mechanism from matrix tablet.

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