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Review Article

AN OVERVIEW: MATRIX TABLET AS CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

In past decade great interest got generated on replacing conventional administration of drug by delivery system which would release effective quantities from a protected supply at a controlled rate over a long period of time. An appropriately designated controlled release drug delivery system can be are major advance toward solving problems concerning targeting of a drug to a specific organ or a tissue and controlling the rate of a drug delivery to the target site. Matrix system are favoured because of their simplicity, patient compliance etc, than traditional drug delivery(TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations.

Keywords: Controlled release system, Conventional tablet, Matrix tablet, Sustained release.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form.

Oral route is considered most natural, uncomplicated, convenient and safe [in respect to Parentral route] due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[1]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as: [2]1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Controlled drug delivery systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery,

sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[4] Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release

2) Sustained release

3) Site-specific targeting

4) Receptor targeting

More precisely, controlled delivery can be defined as: [5]

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and

the rate of drug release are determined by the physiological/ therapeutic needs of the body.

Factor affecting the design and performance of controlled drug delivery: [4]

1. Drug properties

Partition coefficient

Drug stability

Protein binding

Molecular size and diffusivity

2. Biological properties

Absorption

Metabolism

Elimination and biological half life

Dose size

Route of administration

Target sites

Acute or chronic therapy

Disease condition

Advantages of controlled drug delivery system: [6]

1) Avoid patient compliance problems.

2) Employ less total drug

- Minimize or eliminate local side effects
- Minimize or eliminate systemic side effects
- Obtain less potentiating or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.

3) Improve efficiency in treatment

- Cures or controls condition more promptly.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Improves bioavailability of some drugs.
- Make use of special effects.

E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4) Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages:

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor *in vitro – in vivo* correlation.

3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

6) Stability problems.

7) Increased cost.

8) More rapid development of tolerance and counseling.

9) Need for additional patient education and counseling.

Oral controlled drug delivery systems[7]:

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed. The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

1) Development of a drug delivery system: To develop a viable oral controlled release drug

delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Methods used to achieve controlled release of orally administered drugs: [8]

A. Diffusion controlled system:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. This system is of two types:

a) Reservoir type: A core of drug surrounded by polymer membrane, which controls the release rate, characterizes reservoir devices.

b) Matrix type: Matrix system is characterized by a homogenous dispersion of solid drug in a polymer mixture.

B. Dissolution controlled systems:

a) Reservoir type: Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure no.1, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.

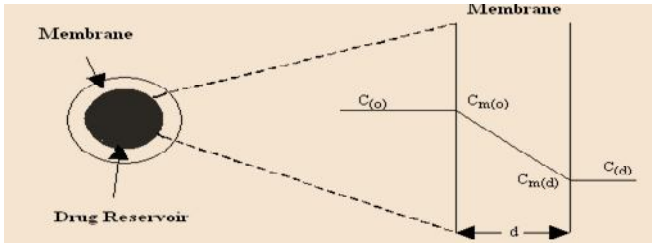

Figure 1 Schematic representation of diffusion controlled drug release reservoir system

b) Matrix type: The more common type of dissolution controlled dosage form as shown in figure .2. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

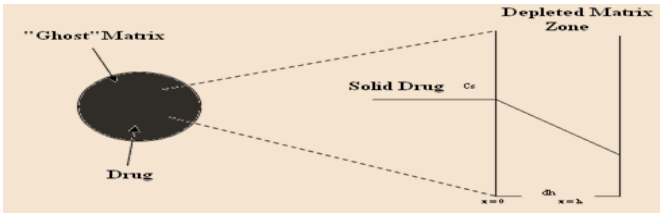

Figure 2 Schematic representation of diffusion controlled drug release matrix system

C. Bioerodible and combination of diffusion and dissolution systems: It is characterized by a homogeneous dispersion of drug in an erodible matrix. (Shown in figure.3)

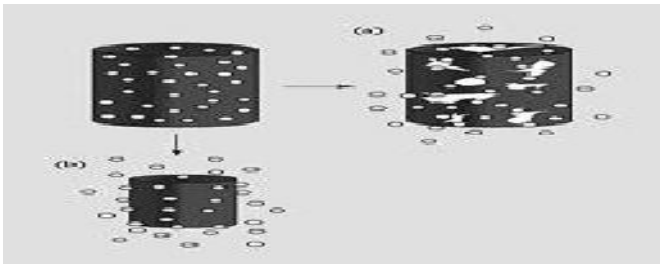

Figure 3 Drug delivery from (a) bulk-eroding and (b) surface-eroding Bio erodible systems

D. Methods using ion exchange: It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets

exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract.

E. Methods using osmotic pressure: It is characterized by drug surrounded by semi permeable membrane and release governed by osmotic pressure.

F. pH– Independent formulations: A buffered controlled release formulation as shown in figure 4, is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

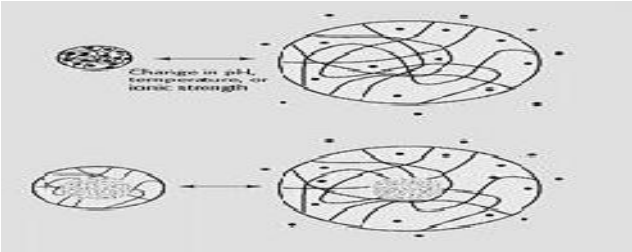

Figure 4 Drug delivery from environmentally pH sensitive release systems

G. Altered density formulations: Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High-density approach

Low-density approach

Matrix tablets*:* One of the least complicated approaches to the manufacture of controlled 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.[9]

Drawback of conventional dosage form: [10]

Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult

The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Disadvantages of matrix tablet:[11-12]

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.

Classification of matrix tablets:

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types. [13-15]

1. Hydrophobic Matrices (Plastic matrices): [13]

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 in to 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. Examples of materials that have been used as inertor hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. 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.

2. Lipid Matrices: [14]

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to

totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices: [15]

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices:[15]

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices: [15]

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix: [16-19]

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

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 m. 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.

Method of Preparation of Matrix Tablet: [20]

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.

Mechanism of drug release from matrix tablet: [21-23]

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 behaviour for the system can be mathematically described by the following equation:

dM/dh = Co. dh - Cs/2 …… (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.

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

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (2)

Where,

Dm = 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 = [Cs. Dm (2Co –Cs) t] ½ …… (3)

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

M = [2Cs.Dm.Co.t] 1/2 …… (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 = [Ds. Ca. p/T. (2Co – p.Ca) t] 1/2 …… (5)

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional path length

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

M = [2D.Ca .Co (p/T) t] ½ …….. (6)

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

p = pa + Ca/ ρ + Cex / ρex …… (7)

Where,

p = Porosity.

ρ = Drug density.

pa = Porosity due to air pockets in the matrix.

ρex = Density of the water soluble excipients.

Cex = Concentration of water soluble excipients.

For the purpose of data treatment, equation 7 can be reduced to:

M = k. t 1/2 …….. (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.

Effect of release limiting factor on drug release: [24-25]

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 accessibleplaces, 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 Ed 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 viz, i. Polymer particle size ii. Polymer viscosity iii. Polymer concentration.

i. 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.

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.

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:

$$JD = D\, dc/dx$$

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 andand 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.

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: [24, 26]

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 (t1/2). 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 controlon 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 0.17-0.23h-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 law 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

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: [24, 26]

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 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.

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 itretain 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. 27

Evaluation of Matrix Tablet [20]

A. Precompression characterization

a. Bulk Density: Bulk density of a powder is defined as the ratio of the mass of the powder and its bulk volume. For bulk density determination a weigh quantity of the powder material is introduce into a graduated measuring cylinder and volume of powder is determine.

Bulk Density = Mass of the powder/ Bulk volume

b. Granule Density: Granule density is the ratio of the mass of the granular powder and the volume occupied by the granular material together with its intraparticle spaces.

Granule density = Mass of the granular powder/ Granule volume

c. Tapped Density: For determination of the bulk density, a weigh quantity of the granular powder is introduced into a graduated measuring cylinder and is tapped mechanically either manually or using a tapping device till a constant volume is obtain.

Tapped density = Mass of the granular powder/ Tapped volume of granules

d. Compressibility Index:

$$C = 100(1 - \rho B / \rho T)$$

Where ρ B is the freely settled bulk density of the granules, and ρ T is the tapped bulk density of the granules.

A Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

e. Angle of Repose: The angle of repose is determine by allowing mass of powdered to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. The angle of repose is determined by the formula:

$$\tan\theta = h/r$$

$$\text{or} \quad \theta = \tan^{-1} h/r$$

where, θ is the angle of repose,

h is the hight of the heap of powder and

r is the radius of the base of the heap of powder.

B. Post Compression Characterization

a. Weight Variation Test: The weight of tablet is measured to ensure that a tablet contain the proper amount of drug.

1. The weight variation test is run by weighing 20 tablets individually.
2. Calculate the average weight.
3. Comparing the individual tablet weights to the average weight.
4. The tablets pass the test if not more than 2 tablets go outside the percentage limit.

Average weight of tablet allowed (mg)	Maximum % difference
130 or less	10 %
130 – 324	7.5 %
More than 324	5 %

b. Friability Test: This test evaluates ability of tablet to with abrasion and edge damage during packing, handling and shipping. Friability is measured by the help of Roche friabilator. A number of pre weigh tablet is placed in plastic chamber that revolves at 25 rpm for 100 revolutions. The tablet are then de-dusted and reweighed. The friability is calculated by the formula.

$$F = (1 - w/w^*)100$$

Where W* is the original wt. of tablet

W is the final wt. of tablet after test.

Acceptance limit of friability is : 0.5 – 1%.

c. Hardness Test: Tablet require a certain amount of hardness to with stand mechanical shock of handling in manufacture , packaging , and shipping. Hardness is measured with the help of hardness tester like:

Monsanto tester

Pfizer tester

Strong cob tester

Hardness is measured with the help of Monsanto tester. The tester consist of a barrel containing a compressed spring held between two plungers. The lower plunger is then forced against a spring by turning a threaded bolt

until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is record and the zero force reading is deducted from it .Hardness is measured in kg/ cm sq.

d. In Vitro Drug Release profile:[28]

In vitro drug release profile of matrix tablet is determine with the help of USP dissolution apparatus type 2. In general , a single matrix tablet is placed in dissolution flask which contain 900 ml dissolution medium. The flask is maintained at 37° ± 0.5° C by a constant temperature bath. The motor is adjusted to turn at the specified speed (50 rpm), and sample of the fluid are withdrawn at intervals to determine the amount of drug in the solution. Matrix tablet slowly release the drug for a prolong period of time as compare to conventional tablet.

Conclusion: By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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