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A REVIEW ON: MATRIX DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is very appreciated and spacious route of a drug administration. Oral route of administration has been used for both conventional and novel drug delivery system. In the modern era, sustained release dosage form is defeating the use of conventional dosage form. The sustained release tablet provides uniform release of drug over a long period of time. Controlled release dosage form covers a wide range of prolonged action formulation which provides continuous release of their active ingredient at a predetermined rate and time. Sustained or controlled drug delivery system is to reduce the frequency of dosing or to increase the effectiveness of drug by localization at the site of action, reducing dose required, providing continuous drug delivery, reduce incidence of adverse effect and maintain drug concentration in system. This review focus on in-depth knowledge of matrix drug delivery system

KEYWORDS: Matrix tablet, Sustained release matrix.

INTRODUCTION

Oral Drug Delivery System

The oral route is the most commonly used route for the administration of drugs. Oral route is the most eldest and suitable route for the administration of therapeutic agents because of low cost of treatment and ease of administration leads to higher level of patient compliance. Almost 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the major route for drug delivery. Tablets are the most commonly and widely used dosage form. [1]

Oral drug delivery is the most extensively utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been discovered 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 Parenteral route] due to its ease of administration, patient acceptance and cost effective manufacturing process.

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: Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. 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 transform method of medication and provide a number of therapeutic benefits.

Oral route is the most convenient route of drug administration. So far so many oral dosage forms have been developed to improve the patient compliance. The drugs with less half life are eliminated from the body with in short period of time. Such drugs are needed to be administered frequently to get the required plasma drug levels. The increased dose frequency may reduce the patient compliance. This difficulty can be avoided by formulating the drugs as matrix type sustained release drug delivery systems. [2]

Oral route is very appreciated and spacious route of a drug administration. Oral route of administration has been used for both conventional and novel drug delivery system. In the modern era, sustained release dosage form is defeating the use of conventional dosage form. The sustained release tablet provides uniform release of drug over a long period of time. Controlled release dosage form covers a wide range of prolonged action formulation which provides continuous release of their active ingredient at a predetermined rate and time. Sustained or controlled drug delivery system is to reduce the frequency of dosing or to increase the effectiveness of drug by localization at the site of action, reducing dose required, providing continuous drug delivery, reduce incidence of adverse effect and maintain drug concentration in system. [3]

Matrix Drug Delivery System

These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. [4]

Introduction of matrix tablet as sustained release (SR) has given a new innovation for novel drug delivery system 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. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[5]

Matrix systems are broadly used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.[6]

Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at sequentially increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer. The drug is dispersed in the polymer matrix either by blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain, mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum.[7]

In this sense, the term "matrix" indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation.[8]

Advantages of Matrix Tablet

- Easy to manufacture
- Usage of less total drug.
- Reduce the local and systemic side effects.
- Flexible, effective and low cost
- Reduce the toxicity by slowing drug absorption.
- Progress in treatment efficacy.
- Decrease drug accumulation with chronic dosing.
- The use of sustain release formulations avoids the high blood concentration.
- Development of the ability to provide special effects.
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Sustain release formulations have the potential to improve the patient compliance.
- Enhancement the bioavailability of some drugs. [9]

Disadvantages of Matrix Tablet

- Not all drugs can be blended with a given polymeric matrix.
- The remaining matrix must be removed after the drug has been released.
- Attainment of zero order release is difficult.
- The drug release rates vary with the square root of time.

Classification of Matrix Tablet

Lipid matrix system

These matrices prepared by the lipid waxes and related materials. In this system the active compound is contained in a hydrophobic matrix that rests intact during drug release. Release depends on an aqueous medium dissolving the channeling agent, which leaks out of the compact, so forming a porous matrix of tortuous capillaries. The active agent dissolve in the aqueous medium and, by way of the water filled capillaries, diffuses out of the matrix.

Mineral Matrices

These contain of polymers which are found from various species of seaweeds. Example is Alginic acid which is a

hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

Hydrophilic Matrices

These transfer systems are also called swell able – soluble matrices. The systems are capable of swelling, followed by gel formation, erosion and dissolution in aqueous media. The hydrophilic colloid components swell to form a hydrated matrix layer when contact with water. This controls the additional diffusion of water into the matrix. Diffusion of the drug through the hydrated matrix layer controls its rate of release. The outer hydrated matrix Layer will erode as it convert more dilute. The rate of erosion depends on the nature of colloid.

Insoluble polymer matrix systems

In this system drug is surrounded in an inert polymer which is not soluble in the gastrointestinal fluids. The release rate hang on on drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles. The release rate of a drug from an inert matrix can be changed by changes in the porosity and tortuosity of the matrix. The pore forming hydrophilic salts or solutes will have a major influence on drug release. [10]

Biodegradable Matrices

These systems are involved 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 non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. [11]

Sustained Release Matrix Tablet

The aim of any drug delivery system is to offer a therapeutic amount of drug to the appropriate site in the body to reach punctually and then maintain the wanted drug concentration i.e. the drug-delivery system should deliver drug at a rate spoken by the needs of the body over a specified period of treatment. The two most important aspects of drug-delivery are spatial placement and time-based 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 suitably designed controlled-release drug-delivery system can be a major advance near solving these two problems.[12]

The Significant role of novel drug delivery system that improve the therapeutic effectiveness of combined drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The design of oral sustained release delivery systems is exposed to several consistent variables of significant importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system contains any drug delivery systems that reaches slow release of drug over prolong period of time. Matrix tablets are careful to be the commercially possible sustained action dosage forms that involve the least processing variables, develop the straight facilities and quarter large doses of drug. There rests an interest in developing novel formulations that allow for sustained the drug release using readily available, cheap excipient by matrix based formulation. During the last two periods there has been notable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the upgrading in therapeutic efficiency and safety achieved by these delivery systems. Now a day the technology of sustained release is also being applied to veterinary products also. [13]

Problems of Conventional Drug Delivery

- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The obvious fluctuations of drug concentration may lead to under medication or over medication.
- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which regular administration is necessary.
- 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.[14]

Advantages of Sustained Release Dosage Form

- Total dose reduction: To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By dropping the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.
- Improvement of deficiency in treatment: Finest therapy of a disease needs an effective transfer of active drugs to the tissues, organs that need treatment. Very frequently doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This inappropriately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.
- Reduced 'see-saw' fluctuation: Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The amounts of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less

than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain in a steady drug concentration in blood circulation and target tissue cells.

- Patient compliance: Absence of compliance is mainly observed with chronic disease which vital long term treatment, as achievement of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the charge of therapy and local or systemic side effect of the dosage form. This problematic can be determined to some amount by administering sustained release drug delivery system.
- Economy: The early unit cost of sustained release products is frequently greater than that of conventional dosage form because of the special nature of these compounds but significantly average cost of treatment over an prolong period of time may be less.[15]

Disadvantages of Sustained Release Dosage Form

- Dose dumping: Dose dumping may arise with broken formulation
- Reduced probable for dose adjustment
- Cost is more than conventional dosage form
- Increase probable for first pass metabolism
- For proper medication patient teaching is necessary
- Possible reduction in systemic availability
- Poor in vivo and in vitro correlations. [16,17]

Polymers Used In Matrix Tablet

Hydrogels

- Cross-linked Polyvinyl Pyrrolidone (PVP)
- Polyethylene oxide (PEO), Polyacrylamide (PA)
- Cross-linked Polyvinyl Alcohol (PVA)
- Poly Hydroxy Ethyle Methylacrylate (PHEMA)

Soluble polymer

- Hydroxypropyl methyl cellulose (HPMC)
- Polyvinyl Pyrrolidone (PVP)
- Polyvinyl Alcohol (PVA)
- Polyethylene Glycol (PEG)

Biodegradable polymer

- Polycaprolactone (PCL)
- Polyglycolic acid (PGA)
- Polyanhydrides
- Polylactic acid (PLA)
- Polyorthoesters.[18]

Non-biodegradable polymer

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

Mucoadhesive polymer

- Tragacanth
- Polyacrylic acid
- Sodium carboxymethyl cellulose
- Polycarbophil
- Methyl cellulose, Pectin.[19]

Natural gum

- Karaya gum
- Guar gum
- Xanthan gum
- Locust bean gum.[20]

Components of Matrix Tablet

These include

- Active drug
- Release controlling agent(s): matrix formers
- Matrix Modifiers, such as channeling agents and wicking agents
- Solubilizers and pH modifiers
- Lubricants and flow aid
- Supplementary coatings to extend lag time further reduce drug release etc.

Matrix formers

Hydrophobic ingredients that are solid at room temperature and do not melt at body temperature are used as matrix formers. These contain hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20-40% of the formulation.

Channeling agents

These are selected to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channeling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

Solubilizers and pH modifiers

It is frequently essential to enhance the dissolution of drug. This may be reached by the inclusion of solubilizing agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channeling agent.

Anti adherent or Guidant's

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These ingredients also can act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the anti-adherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an anti adherent. [21]

Methods of Preparation of Matrix Tablet

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.

Melt granulation Technique

- Wax is melted in porcelain dish on a water bath maintained at constant temperature.
- The Drug was gradually added to the molten wax with continuous stirring.
- The molten mixture was allowed to cool and solidified at room temperature.
- The solidified mass was pulverized in mortar and sieved through a screen.
- The granules passed through sieve were mixed with Glidant and compressed into a tablet with 10 mm deep concave punch using single punch tablet machine.

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.

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. [22]

Mechanism of Drug Release from Matrix Tablet

Drug in the external layer showing to the bathing solution is dissolved first and then diffuses out of the matrix. This procedure continues with the interface between the bathing solution and the solid drug moving near 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. 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.[23,24]

Effect of Release Limiting Factor On Drug Release
The mechanical analysis of controlled release of drug tells that partition coefficient; diffusivity; diffusional path thickness and other system parameters show various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

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.

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.

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.

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 might 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.

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.

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.

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.

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.

Additives
The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble 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 tri calcium phosphate.[25,26]

Biological Factors Influencing Release From Matrix Tablet
Biological half-life, Absorption, Metabolism, Distribution, Protein binding, Margin of safety.

Biological half-life
The normal goal of an oral SR product is to keep therapeutic blood levels over an extended period of time. To accomplish this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively designated by the half-life (t1/2). Each drug has its specific 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 overall, 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 aim 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 accept 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; then, 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 expressively 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 important 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 tell 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.[27,28]

Physicochemical Factors Influencing Release From Matrix Tablet

Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In common, 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 need 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 favorably permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Bestowing 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 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. Additionally, 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 topic to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the chosen 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 representative example of such drug.[29,30]

Formulated Matrix Tablet With Polymer And Method Used For Its Preparation.[31]

Table 1: Formulated matrix tablet with polymer and method used for its preparation.

Drugs used	Category	Polymer used	Method used
Ondansertan	Anti-hypertensive	HPMC-K100M, HPMC-K4M, HPMC-K15M	Wet Granulation
Nicorandil	Ca^{+2} channel blocker	HPMC, CMC, EC	Wet Granulation
Naproxen	Morphine antagonist	HPMC-K100M,HPMC K15M, PVP	Direct Compression
Miconazole	Anti-fungal	Pectin, HPMC	Direct Compression / Wet Granulation
Metoclopromide	Anti-emetic	HPMC, CMC, EC, SSG	Direct Compression / Wet Granulation
Losartan potassium	Anti-hypertensive	HPMC-K100M, HPMC-K4M, Eudragit-RSPO	Direct Compression
Itopride HCL	Prokinetic agent	HPMC-K100M, HPMC-K4M, EC	Direct Compression
Chlorphenarimine maleate	H1 antagonist	Xanthan gum,Chitoson	Melt-extrusion
Indomethacin	Anti-inflammatory	EC, HPMC	Direct Compression
Flutamide	Anti-androgen	HPMC-K4M, Sod.CMC, Guar gum,Xanthan gum	Direct Compression
Enalpril maleate	ACE inhibitor	HPMC-K100M,HPMC K4M,	Direct Compression
Diltiazem	Ca^{+2} channel blocker	HPMC-K100M, HPMC-K4M, Karaya gum, Locust bean gum, Sod.CMC	Direct Compression
Diethylcarbamazepine citrate	Anti-filarial	Guar gum, HPMC-E15LV	Wet Granulation
Diclofenac Na	Anti-inflammatory	Chitoson, EC, HPMCP, HPMC	Wet Granulation
Aspirin	Anti-inflammatory	EC, Eudragit-RS100, S100	Direct Compression
Ambroxol HCL	Expectorent, Mucolytic	HPMC-K100M,	Direct Compression
Aceclofenac	Anti-inflammatory	HPMC-K4M,K15M, K100M,E15,EC, Guar Gum	Wet Granulation
Acarbose	Anti-diabetic	HPMC, Eudragit	Direct Compression
Furosemide	Anti-diuretic	Guar gum, Pectin, Xanthan gum	Direct Compression
Propranolol HCL	Beta-adrenergic blocker	Locust bean gum, HPMC	Wet Granulation
Metformin HCL	Anti-diabetic	HPMC-K100M, EC	Direct Compression
Minocycline	Antibiotic	HPMC-K4M, HPMC-K15M, EC	Wet Granulation
Alfuzosin	Alfa-adrenergic Agonist	HPMC-K15M, Eudragit-RSPO	Direct Compression
Ibuprofen	Anti-inflammatory	EC, CAP	Wet Granulation
Domperidone	Anti-emetic	HPMC-K4M, Carbopol-934	Wet Granulation
Zidovudine	Anti-viral	HPMC-K4M, Carbopol-934, EC	Direct Compression

Rationale of Developing Sustained Release Matrix Devices

- To decrease inter and intrasubject variability.
- To reduce the fluctuations in plasma level.
- To decrease the frequency of dosing.
- To prolong the duration of action of the drug.
- To increase drug utilization. [32]

Drug Release Kinetics From Sustained Release Matrix System - Model Fitting Of The Dissolution Data

Every time a new solid dosage form is established or produced, it is essential to confirm that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, currently, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t). Some analytical definitions of the Q(t) function are generally used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models. Different models expressing drug release kinetics were given in Table

Zero order kinetics

$$Q_1 = Q_0 + K_0 t$$

Where Q_1 is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution (most times, Q_0=0) and K_0 is the zero order release constant.

$f_t = K_0 t$

Where $f_t = 1-(W_t/W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

Use: This relation can be used to define the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics
Kinetic equation for the first order release is as follows
$Log\ Q_t = log\ Q_0 + K_1t/2.303$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model
$f_t = K_H\ t^{1/2}$

Where KH is the Higuchi dissolution constant treated former a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to define the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

Hixson–Crowell model
Hixson and Crowell (1931) identifying that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_S t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in plane that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

Drug Release Kinetics
Table 2: Drug Release Kinetics.[33]

Kinetic Model	**Relation**	**Systems Following the Model**
First order	$\ln Q_t = \ln Q_o + K_t$ (release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations
Hixson-Crowell	Wo 1/3 – Wt 1/3 = Kst	Erodible isometric matrices
f_t = fraction of dose release at time 't'; K_H, K_o, and K_s = release rate constants characteristic to respective models; Q_o = the drug amounts remaining to be released at zero hour; Q_t = the drug amounts remaining to be released at time 't'; W_o = initial amount of drug present in the matrix; W_t = amount of drug released at time 't'.		

CONCLUSION

From the discussion, it can be concluded that matrix tablets, developed by using a rational combination of polymers can successfully applied to sustain the release of the drug. Sustaining the release of the drug may be helpful in increasing the efficiency of the drug as well as they are also useful to improve patient's compliance. The systems are economic since these are developed by using

the commonly available polymers. These systems are especially useful in case of the patients who need a constant delivery of drug for a longer period of time.

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REFERENCES

1. Loyd V, Allen Jr, Nicholas G, Popvich, Howard C, Ansel. Ansel's Pharmaceutical dosage forms and drug delivery system. 8th ed., 2010; 260-263.
2. Yie W. chein , Yie. Novel Drug Delivery System, 1992.
3. Remington.the Science and practice of pharmacy, 20th ed., Lippincott Williams & Wilkins, 2002.
4. ME Aulton. "Pharmaceutics" The Science of dosage form design, 2nd ed., Churchill Livingstone, 2002.
5. Joshep R Robinson, Vincet H Lee. Controlled drug delivery, 2nd ed., Marcel Dekker, 1987; 4-15.
6. Altaf AS, Friend DR, MASRx and COSRx Sustained-release technology in modified release drug delivery technology, Marcell Dekker Inc., New York, 2003.
7. Vidyadhara S, Rao PR, Prasad JA. Indian J.Pharm Sci, 2004; 66: 188-192.
8. Reddy KR, Mutalik S, Reddy S. AAPS Pharm. Sci. Tech, 2003; 4: 1-9.
9. Mohammed AD, James LF, Michael HR, John EH.et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxy methylcellulose and Hydroxypropyl methyl cellulose. Phar. Dev. Tech, 1999; 4: 313-324.
10. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind. Pharm, 1999; 25: 493-501.
11. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd ed, Vol. 72, Marcel Dekker Inc. New York, 1996; 575.
12. Salsa T, Veiga F and Pina M.E, Drug Develop. Ind. Pharm, 1997; 23: 931.
13. Jantzen GM, Robinson JR, Sustained and controlled release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd, Revised and Expanded, Drugs and the Pharmaceutical Sciences, vol 72, Marcell Dekker, Inc. New York, 1995; 575-609.
14. H Bechgaard, G H Nielson. Controlled release multiple units and single unit dosage; Drug Dev. & Ind. Pharm, 1978; 4(1): 53-67.
15. Alford N Martin, Patrick J. Sinko. Martin's Physical pharmacy and pharmaceutical sciences, 2006.
16. L. Lachman, HA Lieberman, Joseph L Kanig. The theory and practice of Industrial pharmacy, 3rd ed., Verghesh publishing house, 1990; 346.
17. Sayed I. Abdel-Rahman, Gamal MM, El-Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets, Saudi Pharmaceutical Journal, 2009; 17: 283-288.
18. Chandran S, Laila FA and Mantha N, Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with ph modulated release kinetics. Indian Journal of Pharmaceutical Sciences, September-October, 2008.
19. Gothi GD, Parinh BN, Patel TD, Prajapati ST, Patel DM, Patel CN, Journal of Global Pharma Technology, 2010; 2(2): 69-74.
20. Basak SC, Reddy JBM, and Lucas Mani KP.Indian Journal of Pharmaceutical Sciences, September-October 2006.
21. Varshosaz J, Tavakoli N and Kheirolahi. AAPS PharmSciTech, 2006; 7(1).
22. Raghvengra Rao NG, Gandhi S, and Patel T. International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(1).
23. Shivhare UD, Adhao ND, Dr. Bhusari KP, et al.International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(2).
24. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Ist ed., vallabh prakashan, 2002; 156-189.
25. Borguist P, Korner A, Larsson A. A model for the drug release from a polymeric matrix tablets-effect of swelling and dissolution, J Controlled Release, 2006; 113: 216-225.
26. Nishihata T, Tahara K, Yamamoto K. Overall mechanisms behind matrix sustained release (SR) tablets prepared with hydroxypropyl cellulose. J Controlled Release, 1995; 35: 59-66.
27. Siepmann J, Peppas NA. HPMC matrices for controlled drug delivery: new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics, Pharm Research, 2000; 16: 1748-1756.
28. Brahmankar HA, Jaiswal SB. Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000; 348-357-337.
29. Wani MS. Controlled Release System- A Review, 2008; 6(1).
30. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed., McGraw Hill, 1999; 169-171.
31. ICH Guideline on Stability study, 2005.
32. Nandita GD, Sudip KD. Controlled-release of oral dosage forms, Formulation, Fill and Finish, 2003; 10-16.
33. M. Ravindrakullai R and Kopparam M. Pharmaceutical applications of natural gums, mucilages and pectins - A Review. International Journal of Pharmaceutical and chemical sciences, 2013; 2(3).