Recent Research in Science and Technology 2013, 5(4): 36-45
ISSN: 2076-5061
Available Online: http://recent-science.com/

An overview: Matrix tablets as sustained release.

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Abstract

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered multiple doses and therefore have several disadvantages. The primary benefit of a sustained release dosage form compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Introduction of Matrix tablet as Sustained release has given a new break through for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controlls the release of 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. Numerous sustained release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has been recently focused on the designed of sustained release systems for poorly water soluble drugs.

Keywords: Matrix tablets, Sustained release, Novel drug delivery system.

INTRODUCTION

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile sustained in duration. The onset of its pharmacological action is often delayed and the duration of its therapeutic effect is sustained[1].

The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and cross-linked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.[2-4]

Received: July 10, 2013; Revised: Aug 18, 2013; Accepted: Sept 25, 2013.

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OBJECTIVES[5]

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate sustain release system for in order to achieve even plasma concentration profile up to 24 hrs. Reason for the selection of -API as a model drug,

- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to sustain the drug release.
- Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
- Less risk of dose dumping.
- Less inter and intra subject variability.
- High degree of dispersion in the digestive tract thus minimizing

the risk of high local drug concentrations.

- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
- Transport of drug is independent of gastric emptying.

Drawbacks of Conventional Dosage Forms[6]

1. Increased chances of missing the dose of a drug with short halflife for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. 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.

The following are the rationale of developing SR[7-9]

- To extend the duration of action of the drug.
- To reduce the frequency of dosing.
- To minimize the fluctuations in plasma level.
- Improved drug utilization.
- Less adverse effects.

Advantages of Sustained Release Matrix Tablet[10,11]

- 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 of the ability to provide special effects.
  Ex: Morning relief of arthritis through bed time dosing.

Disadvantages of Sustained Release Matrix Tablet

1. The remaining matrix must be removed after the drug has been released.
2. High cost of preparation.
3. The release rates are affected by various factors such as, food and the rate transit through the gut.
4. 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.

Terminology[12, 13]

Modified release delivery systems may be divided conveniently in to four categories.

A. Delayed release

B. Sustained release

1) Controlled release

2) Extended release

C. Site specific targeting

D. Receptor targeting

Delayed Release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained release

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release and improvement in the therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature or both of drug release in the body or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

Controlled Release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time

Extended Release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

DESIGN AND FORMULATION OF ORAL SUATAINED RELEASE DRUG DELIVERY SYSTEM[12-16]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.

Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system

1. Diffusion sustained system.
    i) Reservoir type.
    ii) Matrix type
2. Dissolution sustained system.
    i) Reservoir type.
    ii) Matrix type
3. Methods using Ion-exchange.
4. Methods using osmotic pressure.
5. pH independent formulations.
6. Altered density formulations.

Diffusion Sustained System

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx

Where;
D = diffusion coefficient in area/ time
dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane. The drug release rate dm/ dt is given by

dm/ dt= ADKΔ C/L

Where;
A = Area; K = Partition coefficient of drug between the membrane and drug core.
L= Diffusion path length (i.e. thickness of coat).
Δc= Concentration difference across the membrane.

Reservoir Type

In the system, a water insoluble polymeric material encases a core of drug (Figure 1). Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

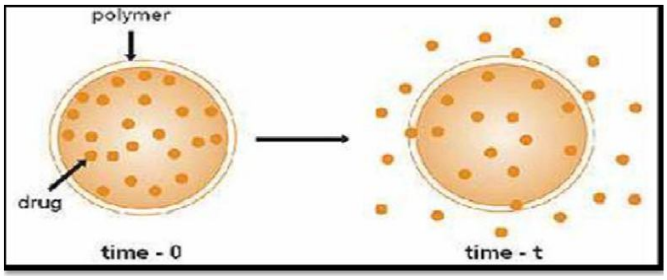

Fig1. Schematic representation of diffusion sustained drug release: reservoir system

Matrix Type

A solid drug is dispersed in an insoluble matrix (Figure 2) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Higuchi has derived the appropriate equation for drug release for this system:

Q = Dε/ T [2 A –εCs] Cst½

Where;
Q = Weight in gms of drug released per unit area of surface at time t.
D = Diffusion coefficient of drug in the release medium.
ε = Porosity of the matrix.
Cs = Solubility of drug in release medium.
T= Tortuosity of the matrix.
A = Concentration of drug in the tablet, as gm/ml.

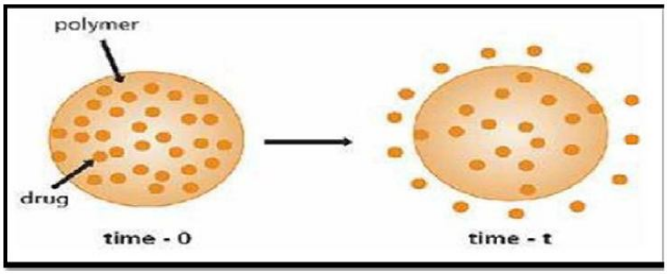

Fig 2. Schematic representation of diffusion sustained drug release: matrix system

Dissolution Sustained Systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

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 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. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

Matrix Type

The more common type of dissolution sustained 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. Two types of dissolution sustained pulsed delivery systems

- Single bead type device with alternating drug and rate-controlling layer.
- Beads containing drug with differing thickness of dissolving coats. Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages:
- Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
- Simple and cost effective manufacturing using existing tableting unit operation equipment.
- Robust formulation.
- Broad regulatory and patient acceptance.
- Ease of drug release modulation through level and choice of polymeric systems and function coatings.

Methods Using Ion Exchange

It is based on the formation of drug resin complex formed when aionic 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.

Anion Exchangers: $Resin^+ - Drug^- + Cl^-$ goes to $Resin^+ - Cl^- + Drug^-$
Cation Exchangers: $Resin^- Drug^+ + Na^+$ goes to $Resin^- - Na^+ + Drug^+$

These systems generally utilize resin compounds of water insoluble cross linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by micro encapsulation process.

Methods Using Osmotic Pressure

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are

- Type A contains an osmotic core with drug.
- Type B contains the drug in flexible bag with osmotic core surrounding.

pH– Independent Formulations

The gastrointestinal tract has some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

Altered Density Formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug content is released, it would have limited utility. To this end,

several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High Density Approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4 gm/cm^3.

Low Density Approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

Classification of matrix tablets

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types [17-19]

Hydrophobic Matrices (Plastic matrices)

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 inert or 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.

Lipid Matrices

These matrices are 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.

Hydrophilic Matrices

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. Infact 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.

Biodegradable Matrices

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 non-enzymatic 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.

Mineral Matrices

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[20-23]

Matrix system can also be classified according to their porosity and consequently.

Macro porous Systems

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

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.

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.

POLYMERS USED IN MATRIX TABLET[24]

Hydrogels

Polyhydroxyethylemethylacrylate (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.

Basic principle of drug release [25]

In solution, drug diffusion will occur from a region of high concentration to the region of low concentration. This concentration gradient is the driving force for the drug diffusion, out of a system. Water diffuses into the system in analogous manner. There is an abundance of water in the surrounding medium and system should allow water penetration. The inside of the system has low water content initially than the surrounding medium.

Drug release from matrix [26]

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:

$$DM/Dh = Co.\ Dh - Cs/2 \quad \ldots\ldots\ldots (1)$$

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:

$$DM = (Dm.\ Cs / h).Dt \quad \ldots\ldots\ldots (2)$$

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:

$$M = [Cs.\ Dm.\ (2Co - Cs).\ t]^{1/2} \quad \ldots\ldots\ldots (3)$$

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

$$M = [2Cs.\ Dm.\ Co.\ t]^{1/2} \quad \ldots\ldots\ldots (4)$$

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:

$$M = [Ds.Ca.p/T.\ (2Co - p.Ca)\ t]^{1/2} \quad \ldots\ldots\ldots (5)$$

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 = Diffusion path length

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

$$M = [2D.Ca\ .Co\ (p/T)\ t]^{1/2} \quad \ldots\ldots\ldots (6)$$

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

$$p = pa + Ca/\rho + Cex/\rho ex \quad \ldots\ldots\ldots (7)$$

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:

$$M = k.\ t^{1/2} \quad \ldots\ldots\ldots (8)$$

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.

Components of matrix tablets [25]

These include:

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

Effect of release limiting factor on drug release [9,14]

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.

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.

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 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

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 propanolol 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.

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.

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.

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.

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.

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 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[8,14,27,28]

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

Biological Half-Life

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-lives are excellent candidates for sustained release preparations since, this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. Since the purpose of forming a sustained-release 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 transits time of most drugs and devices 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. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23/ hrs to give 80-95% over this time period. The absorption rate constant is an apparent rate constant and should in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining system.

Distribution

The distribution of drugs into tissue can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. One aspect of this distribution is binding of drug to tissue and proteins in blood. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. For design of sustained/controlled release products one would like to have as much information on drug disposition as possible but, in reality, decisions are usually based on only a few pharmacokinetic parameter, one of which is the apparent volume of distribution.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete

conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

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: [13,28-30]

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 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 they 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 most largely depend on the partitioning characteristics of the drug.

Stability

Orally administered drugs can be subjected 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 drug 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 are delivered in the small intestine and hence, are subjected to degradation. Propentheline and probanthine are representative example of such drug.

Evaluation Parameters for Extended Release Tablets[31-34]

To design a tablet and later monitor its quality, quantitative evaluation and assessment are done on the basis of its physical, chemical and pharmacokinetic properties. The tablets made are evaluated for the routine checks for the tablets such as average weight, thickness, hardness, weight variation etc. The main parameter required to be monitored while formulating an extended release tablets is *in vitro* release of the drug and that is in turn demonstrated by dissolution profile.

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