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A Review: Sustained Release Matrix Drug Delivery System.

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ABSTRACT

Oral drug delivery systems most preferred option of administration for various drugs. Sustained release drug delivery system is the novel drug delivery system. The terms Sustained release, prolonged release, modified release, extended release or depot formulation are used to identified 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. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetics, and pharmacodynamic properties of a drug in such a way that it's utility is maximized, side effects are reduced and cure of the disease condition is achieved. Sustained release drug delivery is improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the of the drug, improved therapy and shorter treatment period.

Keywords: Sustained release drug delivery system, Matrix tablet, Patient compliance, etc.

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INTRODUCTION

The oral route is most popular route for the administration of various drugs. The ease of administration leads to high levels of patient compliance, and flexible design of dosage form. The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug concentration. [8] Sustained release system include any drug delivery systems that achieves slow release of drug over an extended of time. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulation that allows for sustained the drug release using readily available, inexpensive excipients by matrix based formulation. [5]

The Following are the Rationale of Developing SR Matrix DDS:

- To extend the duration of action of the drug
- To reduce the dose frequency
- To minimize the fluctuation in plasma level
- Improved drug utilization
- Less adverse effects

Advantages of SR Matrix DDS:

Sustained release drug delivery systems have numerous advantages listed below:

- The frequency of drug administration is reduced.
- Patient's compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood levels oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood levels peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variation due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus
  - Maximizing availability with minimum dose.
  - Minimize or eliminate systemic side effects.

- Minimize drug accumulation with chronic dosing

- Safety margins of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients.
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improve control of condition
- Improve bioavailability of some drug
- Make use of special effects.
- eg. Sustained release aspirin for morning relief of arthritis by dosing before bed-time.
- Economy. In comparison with conventional dosage forms, the average cost of treatment over an extended period, may be less economy, also may results from a decreasing in nursing time and hospitalization.

Disadvantages of SR Matrix DDS:

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Patients' variation.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.

Limitations

- The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of Bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- The dosage form should be administered with a minimum of glass full of water (200-250 ml).
- The drugs, which are absorbed throughout gastro-intestinal tract, which undergo first pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.

- Some drugs present in the floating system causes irritation to gastric mucosa.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms.

Some physicochemical parameters for selecting of drug to be formulated in a sustained release dosage form which mainly include the knowledge on the absorption mechanism of the drug from the gastro intestinal (GI.) tract.

Table 1: Physicochemical parameters for drug selection

Parameter	Criteria
Molecular size	< 1000 Daltons
Aqueous solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorptivity from all GI segment	Release should not be influenced by pH and enzymes

Table 2: Pharmacokinetics parameters for drug selection

Parameter	Criteria
Elimination half life	Between 2 to 4 hrs
Absolute bioavailability	Should 75 % or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution	Larger Vd and MEC
A total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration	The lower Css and smaller Vd
Toxic concentration	Apart the value of MTC and MEC safer the dosage form

Biological factors influencing release from matrix tablet:

Biological half-life

The simple theory of an oral SR formulation is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter into the blood circulation at almost the same rate at which it is eliminated. Each drug has its own characteristic related to elimination rate, which is the sum of all elimination processes, generally include metabolism, urinary excretion and all the process that permanently remove drug from the blood stream. Drugs with short half life are best candidate for Sustain release formulation. Drugs which having shorter half life less than 2 hours such as levodopa are poor candidates for SR Formulation. Drugs which having longer half life more than 8 hours are also poor candidate in SR formulation, since their effect is already sustained.

Examples: Digoxin, Phenytoin.

Absorption

The goal of forming a SR product is to control the release rate of drug is much slower than the rate of absorption. If we presume that the transit time of most drugs in the absorptive areas of the GI

tract is about 8-12 hours, the extreme half-life for absorption should be in the region of 3-4 hours; otherwise, the dosage form will pass out of the probable 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. So, it accepts that the absorption of drug should occur at a relatively uniform rate over the entire length of small intestine. If a drug is absorbed by active transport or transport is restricted to a specific region of intestine, SR preparation may be disadvantageous to absorption.

Metabolism

Decrease bioavailability from slow releasing dosage form shown by Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slow releasing dosage form. a drug which having poor water solubility can be formulated in Sustain release dosage form. For this, various techniques which are available for enhancing the solubility of the drug after the enhancing the solubility Sustain Release formulation is possible.

Distribution

The rate of elimination of drug is mainly depends upon the apparent volume of distribution. So drugs with high apparent volume of distribution, influence the rate of elimination of the drug, this drugs are consider to be a poor candidate for oral Sustained Release drug delivery system.

E.g. Chloroquine

Protein Binding

To achieve pharmacological response unbound drug concentration is important rather than bound drug concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug which shows a main role in its therapeutic effect in spite of 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.

Molecular size and diffusivity

In several sustained release systems Drug must diffuse through a rate controlling membranes or matrix. Ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a role of its molecular size. An important influence upon the value of the diffusivity. 'D' in polymers is the molecular size for molecular weight of the diffusing species

Margin of safety

Safety of drug generally depends upon the therapeutic index, Larger the value of therapeutic index of a drug safer is the drug. Drugs having less therapeutic index are generally poor candidates for oral SR drug delivery system.

EFFECT OF VARIOUS PARAMETERS ON DRUG RELEASE:[3,7]

Drug release kinetics may be affected by many factors such as polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, drug distribution inside the matrix, drug/polymer ratio and system geometry (cylinder, sphere).

Drug solubility:

Water solubility of drug and molecular size is another important factor which is considered in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of water soluble drugs occurs by dissolution in infiltrating medium and the release of poorly water soluble drug are occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

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's with the simultaneous forming of water-polymer linking's, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

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 whena 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 crystallinity of polymer. The release of drug may be attributed to the mainly two factors-

Polymer viscosity:

Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows 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 diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release.

Thickness of polymer diffusional path:

The controlled release of a drug from matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$JD = D\ dc/dx$$

Where, JD = 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:

The drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. As the thickness of hydrodynamic diffusion layer increases, the magnitude of drug release value decreases.

Drug loading dose:

The release kinetics is significantly affected by loading dose of drug. 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.

Surface area:

Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. The release of drug from small tablet is faster than large cylindrical tablets.

Effect of diluent:

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.

POLYMERS USED IN THE MATRIX

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

Hydrophilic Polymers:

Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

Hydrophobic Polymers:

This usually includes waxes and water insoluble polymers in their formulation.

Waxes:

Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

Insoluble polymers:

Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

Sustained drug release has been attempted to be achieved with various classes as follows[5,9]

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.

1. 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 Ficks law.

$$J = - D \, dc/dx.$$

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

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

$$dm/dt = ADK\Delta C/L$$

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.

i) Reservoir Type

In the system, a water insoluble polymeric material encases a core of drug (Figure 4.). 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.

ii) Matrix Type

A Solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution the portion of the drug which has dissolved in the polymercoat diffuses through an unstirred film of liquid into the surrounding fluid.

2. 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.

i) 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, 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. The maintenance of drug levels at late times will be achieved from those with thicker coating.

ii) Matrix Type:

These are common type of dissolution sustained dosage form. 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

3. Methods Using Ion Exchange

It is based on the formation of drug resin complex formed when anionic 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 release rate can be further sustained by coating the drug resin complex by microencapsulation process.

4. 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.

5. pH– Independent Formulations

The gastrointestinal tract present some unusual features forthe oral route of drug administration with relatively brief transit time through the gastrointestinal tract. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. 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.

6. Altered Density Formulation:

it is reasonable to expect that unless a delivery systems remains in the vicinity of the absorption site until most, if not all of its drug content is released. Several approaches have been developed to prolong the residence time of drug delivery system in GI.

High Density Approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

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.

MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEMS

The release of drug starting controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

Dissolution Controlled Systems

A drug with slow dissolution rate can demonstrate sustaining properties, since the discharge of the drug will be limited by the rate of dissolution. In principle, it would appear possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water - soluble. Coating the drug with a gradually dissolving material – encapsulation dissolution Incorporating the drug keen on a tablet with a slowly dissolving carrier matrix dissolution manage (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution method can be considered diffusion-layer-controlled. The rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate determining step. The dissolution method at steady-state is described by the Noyes-Whitney equation

Where,

dC / dt = dissolution rate

D = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)

Co = saturation solubility of the solid

C = concentration of solute in the bulk solution

A = Surface area

h = Diffusion layer thickness

Equation predict that the rate of release can be constant only if the following parameters are assumed constant

- **Surface area**

- **Diffusional coefficient**
- **Diffusion layer thickness**

Diffusional controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Generally, this barrier is an insoluble polymer. Commonly, two types or subclasses of diffusion systems are accepted reservoir devices and matrix devices. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusion resistance and a decrease in effective diffusion area as the release proceeds.

CLASSIFICATION OF MATRIX TABLETS [3,7,10]

(a)On the Basis of Retardant Material Used

Hydrophobic Matrices (Plastic matrices)

The concept of using hydrophobic or inert materials as matrix materials was First introduced in 1959. In this method Of obtaining sustained release from an or all 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 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. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled

release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

A. Cellulose derivatives

Methylcellulose400 and 4000cPs, Hydroxyethyl cellulose, Hydroxy propyl methyl cellulose (HPMC) 25,100, 4000 and 15000cPs; and Sodium carboxymethyl cellulose.

B. Non cellulose natural or semi synthetic polymers

Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid

Carbopol-934, the most used variety.

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 nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly(esters) and poly anhydrides.

Mineral Matrices

These consist of polymers which are obtained from various species of sea weeds. 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

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

1. Macro porous Systems

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

2. Micro porous System

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

3. Non-porous System

Non-porous systems have no pores and the molecules diffuse through the network meshes.

In this case, only the polymeric phase exists and no pore phase is present

KINETICS OF DRUG RELEASE:[6,10]

The *in- vitro* release profile obtained for all the formulation were plotted in modes of data treatments as follows;

1. A cumulative percent drug released versus time (zero order kinetic model)
2. Log cumulative percent drug remaining versus time (first order kinetic model).
3. A cumulative percent drug release versus the square root of time (Higuchi' s model).
4. A log cumulative percent drug released versus log time (Peppas model).

Zero Order Kinetics:

A Zero order release would be predicted by the following equation,

Qt- Q0 = K°t

Where,

Qt= Amount of drug release dissolved in time 't'

Co= Initial amount of drug concentration in solution.

K°t= Zero order rate constant.

When the data were plotted as cumulative % drug release versus time, if the plot is linear then data obeys zero order kinetics with slope equal to Ko. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.8

2.First Order Kinetics:

A first order release would be predicted by the following equation

Log Qt = Log Qo – K1t/2.303

Where,

Qt= Amount of drug released in time 't'

Co= Initial amount of drug concentration in solution.

K1t = first order rate constant.

When data were plotted as log cumulative % drug remaining versus time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.8

3. Higuchi's Model :

Drug release from the matrix device by diffusion has been described by Higuchi's diffusion equation

Ft=Q= VD5/T (2C-5Cs) Cst

Where,

Q= Amount of drug release dissolved in time 't'

Co= diffusion coefficient of drug in the release matrix.

Cs= Solubility of the drug in the matrix.

5 = porosity of matrix.

t= Tortuosity

T = Time (h).

The equation may be simplified then the equation becomes,

Ft=Q=KhX t1/2

Where,

KH= Higuchi dissolution constant

When data were plotted according to this equation, i.e. cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.[8]

4. Pappas Korsmeyer Equation:

In 1983 Korsmeyer et al. (Korsmeyer et al., 1983) developed a simple, semi-empirical model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

At/Ao=kt/n

Where,

K= Constant

N= Release

T= Time

At and Ao= Absolute cumulative amount of drug released at times.

Thisis used when the release mechanism is not well known or when more than one type of a release phenomenon could be involved.8

5. Hixson – Crowell Equation:

A drug released from the matrix device by diffusion has been described by Hixson- Crowell diffusion equation;

WO1/3-Wt1/3= ?t

Where,

WO= Initial amount of drug.

Wt = Remaining amount of drug.

T= Time.

? = constant (kappa).

This expression applies to pharmaceutical dosage form such as tablets where, the dissolution occurs in planes that are parallel to drug surface if tablet dimensions diminish proportionally in such manner that the initial geometrical from keeps constant all the time.

MASRX and COSRX Sustained-Release Technology [7,5,]

1. MASRx Technology

The objective is to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASRx). The tablets were designed to hydrate completely into the tablet core. In the process, the tablet core expanded and released the drug in a sustained release manner.

2.COSRx Technology

Formulations base on constant sustained-release matrix (COSRx) technology can also be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low- or high-viscosity guar gum can be used. The formulation involves a guar-gum-base tablet and a combination of water-soluble and water insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelations of the guar gum/drug core. As the hydration a progress, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly zero-order drug release following a programmed period of delayed drug release.

EVALUATION PARAMETERS OF SUSTAINED RELEASE MATRIX DRUG DELIVERY SYSTEM [5,6,9,10]

Sustained release product must be to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two.

Evaluation parameter have discussed as given below

1. *In-Vitro* Methods

a. Beaker method

b. Rotating disc method

c. Rotating Bottle method

d. Rotating Basket method

e. Stationary Basket Method

f. Oscillating tube method

g. Dialysis method

h. USP dissolution method.

2. *In–Vivo* Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in vivo correlation. The various in-vivo evaluation methods are

a. Clinical response

b. Blood level data

c. Urinary excretion studies

d. Nutritional studies

e. Toxicity studies

f. Radioactive tracer technique

3. Stability Studies

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. A sustained release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. The in-vitro and in-vivo release rates of sustained release product may be altered by atmospheric or accelerated conditions such as temperature & humidity.

The stability programmes of a sustained release product include storage at both nominal and accelerated conditions such as temperature & humidity to ensure that the product will withstand these conditions.

BIOAVAILABILITY TESTING

Bioavailability is defined in terms of a specific drug moiety, usually active therapeutic entity, which may be the unchanged drug or as with prodrug, for instance, a metabolite. In contrast, the term "absorption" often refers to net transport of drug related mass from its site of application into the body. Pharmaceutical optimization of the dosage form may be warranted to improve absorption characteristics of the drug and thereby also its bioavailability. Bioavailability studies are ordinarily single dose comparisons of tested drug product in normal adults in a fasting state. While single dose studies are usually sufficient to establish the validity of sustained release dosage form design; multiple dose studies are required to establish optimum dosing regimen.

CONCLUSION

There are several reasons for attractiveness of sustained release drug delivery system, provides

increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they Are also improving the patient's compatibility matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. Preparatory procedures easily allow adaptation Of release kinetics to delivery needs. This suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. So matrix tablets can overcome the above problems of conventional oral drug delivery.

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