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SUSTAINED RELEASE MATRIX TYPE DRUG DELIVERY SYSTEM: REVIEW

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ABSTRACT

Nowadays pharmaceutical industries are aiming on development of sustained release formulations due to its inherent boons. Sustain release system are considered a wiser approach for the drugs with short biological half-life and which need to repeated dosing and **Matrix type drug delivery system** is a new approaches when developing an oral controlled release system. Which is providing promising way to minimize the side effects of drug and cure of the disease is achieved by preventing the fluctuation of the therapeutic concentration of the drug in the body. There are several benefits of sustained release drug delivery over conventional dosage form like improved patient compliance due to less frequent drug administration, maximum utilization of the drug, increased safety margin of potent drug, minimize the fluctuation in plasma drug concentration levels, reduction in healthcare costs and improved the therapeutic effectiveness with shorter period of treatment.

KEYWORDS: Controlled drug delivery, Sustained-release, Matrix system.

INTRODUCTION

The sustained release dosage form has achieved superior attention for oral delivery system because of more flexibility in dosage form design. The novel system of drug delivery offer a better therapeutic effectiveness of drug by providing sustained, controlled delivery and targeting the drug to desired site.[1]

Controlled Drug Delivery System (CDDS) is type of Novel Drug Delivery of System (NDDS) which offers several benefits over conventional dosage forms such as it provides improved patient compliance due to less frequent drug administration, increased safety margin of high potency of drugs due to better control of plasma levels. CDDS is helpful in

treatment of chronic condition of diseases, where patient are treated with a lot of medicine for longer period of time. which can lead to patient non-compliance. These problems are shown in drug having short biological half-life because this type of medicine must be taken several times a day. This problem can be overcome by sustained release drug delivery systems.[2] Sustained release of the drug is achieve by design of matrix system, which is control the release of the drug and providing rapid achievement of a drug plasma level that remains constant within the therapeutic range of a drug for desired period of time or delivers the drug at slow rate.[3] The matrix systems, which release the drug in continuous manner by both dissolution controlled or diffusion controlled mechanisms., The release is depends on properties of drug as well as polymeric substances. These are containing different solubility characteristics and the drug is dispersed in swellable hydrophilic substance and swellable hydrophobic materials or plastic materials. The design of matrix system may be assumed to contain two portions, one that provides the initial loading dose, and one that provides the maintenance or sustained dose.[4]

THE MAJOR DRAWBACKS RELATED WITH CONVENTIONAL DOSAGE FORMS[5,6]

- Poor patient compliance, increased probabilities of missing the dose of a drug with short half-life for which repeated administration is necessary.
- The un-avoidable fluctuations of drug concentration finely lead to under medication or over medication.
- The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.
- Recently, several advancement in drug delivery system have been developed to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery and sustaining the duration of therapeutic action.

Advantages:[7-9]

a) Therapeutic benefits

Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

b) Reduction in adverse side effects and improvement in acceptability

Drug plasma concentration levels are maintained within a narrow therapeutic window with no sharp peaks and AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

c) Improve effectiveness in treatment

Cure or control of condition more quickly and increase the bioavailability of some drugs. useful in superior treatment e.g. Aspirin is used for morning relief treatment of arthritis condition taken on bed time.

d) Patient compliance

Oral route of drug administration is the most preferable and convenient for patient and a reduction in dosing frequency enhances compliance.

e) Total dose reduction

The treatment of a disease condition, less amount of total drug is needed in sustained release drug delivery systems. And local or systemic side effects are decreased. This would also lead to superior economy.

f) Reduction in Health care cost

The total cost of treatment of the controlled release product could be comparable or lower than the instant release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.

g) Superior control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.

h) These can be made to release high molecular weight compound and less risk of dose dumping.

Disadvantages:[10,11]

a) Less flexibility in precise dose adjustment

The dose adjustment is much simpler in Conventional dosage form than controlled release dosage form e.g. tablet can be divided into two fractions. In case of controlled release dosage

forms, this appears to be much more complicated. If dosage form is fractured, the property of controlled release may get lost.

b) Patient variation

The required time period for absorption of drug release from dosage form may differ among individuals. Co-administration of other drugs, in presence or absence of food and residence time in gastrointestinal tract is different among patients.

c) Termination of therapy

After oral administration of controlled release medication does not permit quick termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if any adverse effects are observed, cannot be accommodated.

d) Poorly water soluble drug candidate is not suitable for controlled release dosage form, because poorly. Absorb in gastrointestinal tract.

e) Economic factors - High cost of manufacturing.

MATRIX SYSTEM

In matrix system the active ingredient (drug) is present as dispersion within the polymer matrix. They are formed by compression of a polymer/ drug mixture or by melting. The drug is present in matrix device; outside layer exposed to the bathing solution is first dissolved and then diffuses out of the matrix. These process continue with the interface between the bathing solution and the solid drug, moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be more rapidly than the diffusion of dissolved drug leaving the matrix. This type of oral sustained release drug delivery systems, release the drug in continuous manner, by both dissolution controlled as well as diffusion controlled mechanism.[12]

CLASSIFICATION OF MATRIX TABLETS[13-15]

A. On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types

1. Hydrophobic Matrices (Plastic matrices)

The concept of hydrophobic materials is used as matrix material was first introduced in 1959. In these methods attaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to tablet. Sustained release has given a reason is that the dissolving drug has diffused through a network of channels that sandwiched

between compacted polymer particles. Examples of Hydrophobic material where used, such as polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate- controlling step in this formulation is liquid penetration into matrix. The possibilities of drug release mechanism in these types of tablets are diffusion. Such type of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Hydrophilic Matrix Tablet

Hydrophilic polymer matrix system is universally used in oral controlled drug delivery because of their elasticity properties to attain an attractive drug release profile, cost effectiveness, and comprehensive regulatory acceptance. The formulation of the drugs in gelatinous capsules or tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. The drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablets formulation. An insufficient polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablets due to fast penetration of water. It is acceptable for formulation of water soluble drug.

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups:

i. Cellulose derivatives

Methylcellulose 400 and4000cPs, Hydroxy ethylcellulose, Hydroxy propyl methylcellulose (HPMC) 25, 100, 4000 and 15000cPs and Sodium carboxymethylcellulose.

ii. Non cellulose natural or semi synthetic polymers

Agar-Agar, Carobgum, Alginates; Molasses, Polysaccharides of mannose and galactose, Chitosan and Modified starche.

iii. Polymers of acrylic acid

Carbopol-934is the most used variety. Other hydrophilic material used for formulation of matrix tablets such as Alginic acid, Gelatin and Natural gums.

3. Lipid Matrices

These type of matrices prepared by the lipid waxes and other materials. The drug are incorporated into a melt of fats and waxes and released by leaching and or hydrolysis as well as dissolution of fats under influence of enzyme and pH changes in the gastrointestinal tract.

The addition of surface active agents to the formulation can also improve both drug release rate and the proportion of total drug that can be incorporated into a matrix. Example: Carnauba wax in combination of stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

4. Biodegradable Matrices

The biodegradable matrices made up of different monomers like to each other, through functional groups and these is unstable linkage in the backbone. They are biologically degraded or eroded into oligomers and monomers by enzymatic or non-enzymatic process that can be metabolized. Example are natural of polymers which is protein and polysaccharides, modified natural polymers, and synthetic polymers such as aliphatic poly ester or polyandries.

5. Mineral Matrices

These matrices consist of the polymer which is obtained from various kind of seaweeds. Example is Alginic acid which is a water soluble carbohydrate obtained from species of brown seaweeds (Phaephceae) by the use of dilute alkali.[16]

B. On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types

a. Macro-porous system: In this system the diffusion of drug occurs through pores of matrix, the pore size range between 0.1 to 1 µm. This pore size is larger than diffusant molecule size.

b. Micro-porous system: Diffusion is occurs through pores in this type of system. For micro porous system, pore size ranges between 50-200 A°, which is slightly larger than diffusant molecule size.

c. Non-porous system: In non- porous system have no pores and the molecules diffuse through the network like structure. In this system, only the polymeric phase exists and no pore phase is present.

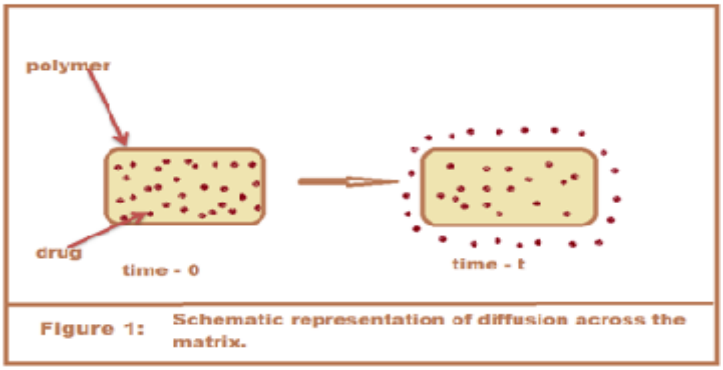

Figure 1: Schematic representation of diffusion across the matrix.

SUITABLECHARACTERISTICS FOR SUSTAINED RELEASE MATRIX DDS[16-17]

Table 1: Physicochemical properties.

Parameters	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 absorbability From all GI segments	Release Should not be influenced by pH and enzymes

Table 2: Pharmacokinetic properties.

Parameters	Comments
Elimination half-life	Between 2 to 8 hrs
Absolute bioavailability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution(Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

POLYMERS USED IN MATRIX TABLETS[18]

There are number of polymers which can be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required.

Polymers used for matrix tablets may be classified as

a) **Hydrogels Polymer:** Poly hydroxyl ethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked Polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

b) **Soluble polymer:** Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), Polviny pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC).

c) **Biodegradable polymers:** Polylactic acid (PLA), Polyglycolic acid (PGA), Poly caprolactone (PCL), Polyanhydrides, Polyorthoesters.

d) **Non-biodegradable polymers:** Polyethylene vinyl acetate (PVA), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

e) **Mucoadhesive polymers:** Polycarbophil, Sodium Carboxymethyl cellulose**,** Tragacanth, Methyl cellulose, Pectin.

f) **Natural gums:** Xanthan gum, Guar gum, Karaya gum, Gum Arabic, Locust bean gum.

EFFECT OF VARIOUS PARAMETERS ON DRUG RELEASE[19-21]

Various factor could be accounted for the mechanism of drug release from hydrophilic matrices. These factors are geometry of matrix, particle size of polymer matrix swelling index (which depend on polymer types and water control and diffusion coefficient of drug), polymer and drug concentration, chain length and as well as characteristics of drug.

I. Physicochemical factors

a. Drug solubility

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

b. Polymer hydration

It is important to study of polymer hydration / swelling process for maximum number of polymer and polymeric combinations. The most important step in polymer dissolution include absorption/adsorption of water in more accessible site, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains linkage, swelling and dispersion of polymeric chain in dissolution medium.

c. 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 crystallinity of polymer. The release of drug may be affected by two factors such as –

- **Polymer viscosity:** when molecular weight and viscosity of polymer is increasing in matrix system then increases the viscosity of gel layer and thus dissolution of drug is slow.
- **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 successful diffusion coefficient of the drug and therefore reduction in drug release.

d. 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 = diffusibility of drug molecule,

dc/dx = concentration gradient of drug molecule across a diffusion path with thickness dx.

e. Thickness of hydrodynamic diffusion layer

The drug release profile is affected by variation in thickness of hydrodynamic diffusion layer on the surface of matrix devices. As the thickness of hydrodynamic diffusion layer increases, the simultaneously magnitude of drug release value decreases.

f. Drug loading dose

The release kinetic is 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 dose virtually release rate first decreases and then increases, whereas, the release rate is increase in case of freely soluble drugs, and simultaneously the porosity of matrix upon drug depletion increases

g. Surface area

The *in-vitro* and *in-vivo* drug release is observed that it is mostly dependent on surface area of dosage form. The release of drug from small tablet is faster than large cylindrical tablets.

h. Effect of diluents

The effect of diluents or filler is depends upon the nature of diluents. The water soluble diluents like lactose cause marked increases 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 erosion rate of matrix. The reason behind is that water soluble filler in matrices simulate the water penetration into inner part of matrix, due to increase in hydrophobicity of the system, causing rapid diffusion of drug, lead to increased drug release rate.

i. Additives

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate worked on hydro soluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less significant if the excipients are insoluble like tricalcium phosphate.

II. Biological factors

a. Biological half-life

The usual goal of an oral sustained release formulation is to maintain therapeutic blood levels oven an prolonged 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 blood stream.

The compound having a short biological half- life is excellent candidates for sustained release formulation, since this can reduce dosing of drug administration. However, this is restricted for a drug with very short half-life may require a large amount of drug in each dosage form unit to maintain the therapeutic sustaining effects. The drug with half-life shorter than 2 hours are poor candidates for sustained release formulations. Compound with long half-life, more than 8 hours, are generally not preferred in sustaining forms, because there effect is already sustained.

b. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Since the reason of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release much slower than the rate of absorption. Slowly absorbed drug or the drug absorbed with a variable absorption rate is poor candidates for a sustained release system. Water soluble but poorly absorbed potent drug and these are absorbed by carrier mediated transport processes or absorbed through window are poor candidates for controlled release system.

c. 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 drug binding 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.

d. Metabolism

Drug that is significantly metabolized before absorption, either in lumen or tissue of the intestine, can show decrease bioavailability from slower releasing dosage form. Most intestinal wall enzyme systems are saturable. As the drug release is slower at these regions, small quantity of drug is existing in enzymatic process during a specific period and allowing complete drug transformation to its metabolites. Prodrug is another viable solution for enzymatic susceptible compounds.

e. Protein Binding

Protein binding of drug play an important role in its therapeutic activity of a drug depends on unbound concentration of a drug rather than total concentration. The drug which bound to some extent of a plasma and tissue proteins enhance the biological half-life of a drug. The release of this type of drug extended over a period of time and therefore no need to develop extended release formulation.

METHOD OF PREPARATION OF MATRIX TABLET[22]

Direct Compression Technique

In this process weighed the drug with all ingredient or excipients and compressed directly without changing the properties of the drug like physical and chemical properties.

Wet granulation Technique

In this method weighed the quantities of drug and polymer are mixed with sufficient volume of granulating agent. After adequate cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant to produce "running powder" tablets is compressed using a single-punch tablet compression machine.

Melt granulation Technique

In this process a substance used, which melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binder was tried by using melt-granulation technique.

Hot-Melt Extrusion Technique

In the hot-melt extrusion method, a mixture of the active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The material is transferred inside the heated barrel by a rotating screw. The material melt at elevated temperature and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimension of the die cylinders, films can also be produced from the extruder.

Evaluation of Matrix Tablets[23-24]

1) Pre Compression Parameter

i. Bulk Density (Db)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

Db = M / Vo

Where,

Db = Bulk density (gm/cc)

M = the mass of powder (g)

Vo = the bulk volume of powder (cc).

ii. Tapped density (Dt)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was tapped 100 times from constant height and tapped volume was noted. It is denoted by gm/cc and is given by,

Dt = M / Vt

Where,

Dt = Tapped density (gm/cc)

M = the mass of powder (g)

Vt = the tapped volume of powder (cc).

iii. Compressibility index

The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = = b=(v/b) X100

Table 3: Grading of powders for their flow properties according to carr's index.

S.No.	Carr's Index	Flow Properties
1.	5 -15	Excellent
2.	12 -15	Good
3.	18 -21	Fair to Passable
4.	23 -30	Poor
5.	33 -38	Very Poor
6.	>40	Very- Very Poor

iv. Hausner ratio

Hausner ratio = Tapped density/Bulk density

Value of Hausner ratio; < 1.25: good flow

>1.25: poor flow

If Hausner ratio is between 1.25 – 1.5, flow can be improved by addition of glidants.

v. Angle of repose (θ)

It is well-defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$\tan\theta = h/r$

$\theta = \tan^{-1}(h/r)$

Where,

θ = angle of repose,

h = height of pile,

r = radius of the base of the pile.

Table 4: Comparison between angles of reposes and flow property.

S.No.	Angle of repose	Flow Properties
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	>40	Very Poor

2) Post Compression Parameters

A. Thickness and diameter

The Control of physical dimension of the tablet such as thickness and diameter is necessary for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness / Crushing Strength

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was placed between moving jaw. Scale was adjusted to zero point; load was slowly increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. The crushing strength of tablet generally 4kg is considered to be minimum for acceptable tablets. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Friabilator USP EF-2. Pre weighed tablets were allowed for 100 revolutions (4min),at 25 rpm, taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

Friability = $[(W_1 – W_2)/W_1]100$

Where

W_1 = initial weight of tablet

W_2 = final weight of tablet

Acceptance limit of friability is : 0.5 – 1%.

D. Weight variation test

The weight of the tablet being made in routinely measured to ensure that a tablet contains the accurate amount of drug. The USP weight variation test were done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the following table,

Table 5: Weight variation limits.

S. No.	Average weight of tablets (mg)	Maximum % difference allowed
1.	130 or less	10
2.	130 -324	7.5
3.	324 or more	5

% Deviation = average weight – individual weight / average weight×100

E. Estimation of drug content

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was taken in media (such as water or Phosphate buffer) the drug content was determined measuring the absorbance through its wavelength. After suitable dilution by using a UV/Visible Spectrophotometer.

F. In-Vitro Drug Release profile

In-vitro drug release profile of matrix tablet is determine by using USP dissolution apparatus type 2. Generally one matrix tablet is placed in dissolution flask which contain 900 ml dissolution medium. The flask is maintained at 37º ± 0.5º C by a constant temperature bath. The motor is adjusted at the specified speed (50 or 100 rpm), and sample of the fluid are withdrawn at intervals to determine the amount of drug in the solution. Matrix tablet slowly release the drug for a prolong period of time as compare to conventional tablet.

IN-VITRODRUG RELEASE CHARACTERIZATION MODELS: MATHEMATICAL MODELS[25,26]

Zero order release kinetics

Zero order release kinetics refers to the process of constant release the drug from a drug delivery device. E.g. transdermal system, osmotic tablets, matrix tablets with low- soluble drugs and other delivery system. A zero order release would be predicted by the following equation,

$$Q_t = Q_0 + K_0 t$$

Where,

Q_t = the amount of drug release or dissolved in time‘t’.

Q_o = Initial amount of drug concentration in solution.

K_0 = Zero order rate constant.

When the data was plotted as Cumulative % drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to K_o. This model represents an ideal release profile in order to achieve the prolonged therapeutic effects.

First order release kinetics

The rate laws predicted by the different mechanism of dissolution alone or in combination, have been discussed by Higuchi model. dissolution rate in a quantitative manner was proposed by Noyes and Whitney as -

dc / dt = k (Cs – Ct)

Where,

dc /dt = the rate of change in concentration with respect to time, andk is the release rate constant.

The integrated form of the equation is:

In [Cs / (Cs – Ct)] = kt

Log C = Log C_0 – kt / 2.303

Where, C_0 is the Initial amount of drug concentration in solution.

The equation predicts a first order depend on the concentration gradient (i.e. Cs – Ct) between the static liquid layer to solid surface and the bulk liquid. Noyes and Whitney explained their dissolution data using a concept similar to that used for diffusion model. These consideration relate to condition in which there is no changes in the shape of solid during the dissolution process (i.e. the surface area remains constant). However, for pharmaceutical solid dosage form such as tablets, disintegration occurs during dissolution and surface area generated consequently varies with respect to time.

The Hixson-Crowell model defined the release from the device. There is a change in surface area of particle or tablets. It is probable to derive an equation that expresses the rate of dissolution based on the cube root of the particles.

$Q_0$1/3-Q_t1/3 =K_{HC}t

Where,

Q_t is the amount of drug released in time t

Q_0 is the initial amount of the drug in tablet and

K_{HC} is the rate constant for Hixson-Crowell rate equation.

In first order release kinetic when data was plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics.

Higuchi Model

Ideally, controlled drug-delivery systems should deliver the drug at a controlled rate over an expected duration. One of the approaches known for obtaining controlled release, hydrophilic matrix is recognized and is most widely used. In the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and contribute to the overall drug-release rate. It is recognized that drug release from hydrophilic matrices shows a typical time-dependent release profile (i.e. decreased drug release with respect to time because of increased diffusion path length). This inherent limitation leads to first-order release kinetics.

Many controlled release formulation are designed based on the principle of embedding the drug in porous matrix. Liquid penetrates into the matrix and dissolves the drug, which is then, diffuses into the liquid. Higuchi model tried to relate the drug release rate to physical constants based upon laws of diffusion. The drug release rate from both a planner surface and a sphere were considered.

Higuchi was the first to given an equation to defined the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

$$\mathbf{Q_t = [2DS' (A - 0.5S')]^{0.5} * t^{0.5}}$$

Simplifying,

$$Q_t = kH\ (t)^{0.5}$$

Where,

Q_t is the amount of drug released in time t,

D is the diffusion co-efficient,

S is the solubility of drug in the dissolution medium,

A is the drug content per cubic centimeter of matrix tablet, and kH is the release rate constant for the Higuchi model.

The release of drug from the granular matrix system involve concurrent penetration of the surrounding liquids, dissolves the drug and leaching out of the drug through pores or channel.

The volume and length of the opening in the matrix must be accounted for in the diffusion equation, leading to a second form of the Higuchi equation:

$Q = [DK/L (2A- KCs) Cst]^{0.5}$

Porosity Q, is the fraction of matrix that exists as pores or channels into surrounding liquid that can penetrate.

Tortuosity P, is introduced in equation to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest "straight-through" pores. Tortuosity tends to reduce the amount of drug release in a given time interval.

When data was plotted according to higuchi equation, i.e., cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Korsmeyer-Peppas Model

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

$At/A\infty = ktn$

Where,

k = Constant.

n = Release.

t = Time.

At and $A\infty$= Absolute cumulative amount of drug released at time't'.

This model is applicable when the drug release mechanism is not well known or when more than one type of release phenomenon could be involved.

CONCLUSION

This review article focus on problem with oral drug delivery such as fluctuation in drug plasma levels, more frequent dosing of a drug, low bioavailability. The problem of Conventional oral drug delivery overcome by design of matrix tablets. The matrix tablet is formulated by using various polymers like hydrophilic and hydrophobic polymer. The release

of drug depends on both drugs as well as, which type of polymer used in the matrix system. The sustained release matrix formulation is helpful in increasing the therapeutic efficiency of drug as well as patient compliance. The sustained release dosage form is betterment for treatment of disease in chronic condition.

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