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SUSTAINED RELEASE MATRIX TYPE DRUG DELIVERY SYSTEMS; A REVIEW

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Abstract

The purpose of writing this review on sustained release matrix type drug delivery systems as novel drug delivery system is to compile the recent literature with special focus on maintain the desired concentration at the site with specificity. Oral sustained release products provide advantage over conventional dosages forms by optimizing bio-pharmaceutics ,pharmacokinetics properties of drug in such way that it reduced dose frequency to an extent that once daily doses sufficient for penetration, polymer swelling, drug dissolution ,drug diffusion and matrix erosion sustained release matrix tablet is formulated mainly by wet granulation or direct compression or by dispersion of solid particles within a porous matrix formed by using polymer like polymethyl methacrylate (PMMA),polyglycoilic acid ,HPMC can be used in sustained release and thus formed core excipient of the formulation.sustainrd release is also provided promising way to decrease side effect of drug by preventing the fluctuation of the therapeutic concentration of drug in the body. This review article describe the basic information regarding sustained release formulation ,its advantage ,disadvantage, selection of drug for sustained release formulation ,mechanism of release, different type, and factor involved in oral sustained release dosages form design.

Keywords: matrix system, controlled drug release, polymers,

Introduction

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new novel Drug delivery systems. Amongst, these the controlled release/sustained release dosages form have become extremely popular in modern therapeutic Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablets as sustained release has given new breakthrough for novel drug delivery system in the field of pharmaceutical technology[1,2]. Matrix system are flavored because of their simplicity, patient compliance etc., than traditional drug delivery (TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc[3]. Developing oral sustained release matrix tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist[4,5]. Most of highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers are mainly used for formulating matrix system formulation of highly water soluble drugs[6].drug release through matrix system is by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion[7]. Highly water soluble drugs like metoprolol tartrate, ditiazem,

tramolol; ranitidine has been formulated as sustained release matrix tablets[8]. Tablets having the lowest cost approach to sustained and controlled release dosage forms. Matrix tablets serves as an important tool for oral extended- release dosage forms. Hence, problems like patient compliance, drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels, associated with their counterparts, the conventional dosage forms were solved[9,10]. Effective modified-release systems produce constant plasma levels of drugs and minimize the risk of reaching peaks above clinically tolerable levels; hence, modified- release systems can achieve reproducible and predict- able release rates, Oral controlled release drug delivery[11] is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action[12,13,14]. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework necessary for the successful development of oral drug delivery systems[15].

(i) Physicochemical, pharmacokinetic and pharmacodynamics characteristics of the drug
(ii) The anatomic and physiologic characteristics of the gastrointestinal tract and
(iii) Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.
The main areas of potential challenge in the development of oral controlled drug delivery systems are

- **Development of a drug delivery system**:
  To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment[16]
- **Modulation of gastrointestinal transit time**:
  To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose[17].
- **Minimization of hepatic first pass elimination**:
  If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.[18,19,20]

Advantages of Matrix Tablets.[21,22.]

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- No risk of dose dumping.

Disadvantages of Matrix Tablet[23,24,25,26]

- 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.
- The release rates are affected by various factors such as, food and the rate transit through the gut.

CLASSIFICATION OF MATRIX TABLETS:[27,28]

1. Hydrophobic Matrices (Plastic matrices) formation.

The concept of using hydrophobic or inert materials as Matrix materials was first introduced in 1959 [29]. In this method of obtaining sustained release from an oral dosages form, drug is mixed with an inert or hydrophobic polymer and then compressed in to tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channel that exist between compacted polymer particles. Examples of material that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers[30,31]. The rate controlling step in these formulation is liquid

penetration into matrix .the possible mechanism of release of drug in such type of tablets is diffusion. Such type of matrix tablet become inert in the presences of water and gastrointestinal fluid [32].

2. 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 [33].

3. Hydrophilic Matrices

Hydrophilic polymer matrix systems are mainly 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 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,[34,35]

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

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

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

4. 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; Synthetic Polymers such as aliphatic poly (esters) and poly anhydrides. [36,37]

5. 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[38].

Ideal properties of drug suitable for SRDDS [39,40,41]

I. It should be effectively absorbed by oral route and stable in gastro-intestinal (GI) fluid.

II. Drugs that have short half-lives (2-4 hrs) are ideal drug candidate for formulation into SR dosage forms e.g. Captopril, Salbutamol sulphate.

III. The dose of drug should not be less than 0.5gm and maximum dose of drug for designing SRDDS is 1.0 gm. e.g. Metronidazole.

IV. The therapeutic range of the drug should be high in SRDDS for drug should have wide therapeutic range enough such that variation in the release does not result in concentration beyond the minimum toxic levels.

Polymers used in sustained release tablet [42,43,44]

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

a) **Hydrophilic Polymers** –this is usually include 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
b) **Hydrophobic Polymers** -This usually includes waxes and water insoluble polymers in their formulation
c) **Natural polymers** -Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan.

EFFECT OF VARIOUS PARAMETERS ON DRUG RELEASE [45,46]

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

A. 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 [47].

B. 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 linkings with the simultaneous forming of water- polymer linkings, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium. [48,49]

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 Ed has been acquired by the diffusant is dependent on length polymer chain segment, cross linking and cristallinity of polymer .the release of drug may be attributed to the mainly two factor

1) Polymer viscosity- if the increasing the viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution.[50]

2) Polymer concentration – if the increase in polymer concentration therefore increases in the viscosity of gel as well as formulation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore slows in drug release.[51]

D. Thickness of polymer diffusional path:[52]

The controlled release of a drug from matrix type polymeric drug delivery system is essentially governed by ficks 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 thinkess dx

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. [53]

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.[54,55]

Surface area: [56,57]

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: [58,59]

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. 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 systems, causing rapid diffusion of drug, leads to increase drug release.

Terminology: [59,60, 61,]

Controlled and sustained Release, both has been used in inconsistent and confusing manner. Both represent separate delivery process. SR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both.

Modified Release Drug Product:

The term modified release drug product is used to describe products that alter the timing or the rate of release of the drug substance.

Extended Release Dosage Forms:

A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional)dosage form Examples of extended-release dosage forms include controlled-release, sustained release and long-acting drug products

Sustained release:

It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a pre- determined rate.

Controlled Release:

It includes any drug delivery system from which the drug is delivered at a pre- determined rate over a prolonged period of time

Delayed Release Dosage Form:

A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration Example: Enteric coated dosage forms.

Targeted-release drug products:

A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended- release characteristics.

Repeat Action Dosage Forms:

It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a later

Pharmacokinetic parameters for drug selection. [62,63]

Elimination half-life-between 2 to 8 hrs
Absolute bioavailability -should be 75 percentage or more

Absorption rate constant (Ka) -must be higher than release rate.

Apparent volume of distribution (Vd)-Larger Vd and MEC, Larger will be required dose.
Total clearance -not depend on dose.
Elimination rate constant-required for design.
Therapeutic concentration- the lower Css and smaller Vd, less amount of drug required.

Toxic concentration-apart the value MTC and d MEC safer the dosage form.

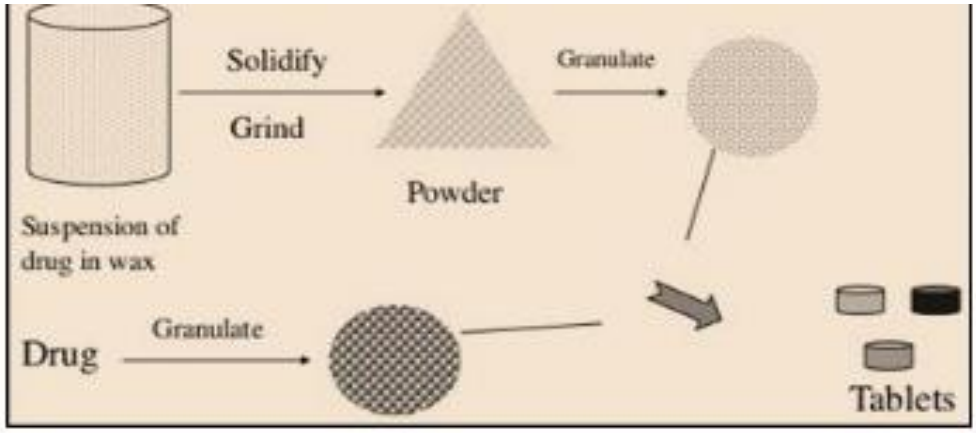

FIG 1. PREPARTION OF MATRIX TABLETS SHOWN IN fig

METHODS OF PREPARATION [64,65,66]

Direct Compression

In this method, finely powdered materials are compressed directly without changing the physical and chemical properties of the drug**.**

Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of the granulating agent. After enough cohesiveness was obtained, the mass is sieved and dried at 40°C and kept in a desiccator. Lubricants and Glidants are added and the tablets are compressed using a tablet compression machine.

Melt Granulation

In melt granulation, meltable substance act as liquid binding agent and hence does not require the use of organic solvents. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Various lipophilic binders such as Glyceryl Palmitostearate are used in melt granulation technique.

Formulation of SRDDS [66,67,69]

There are number of formulation are considered in following figure number **2**

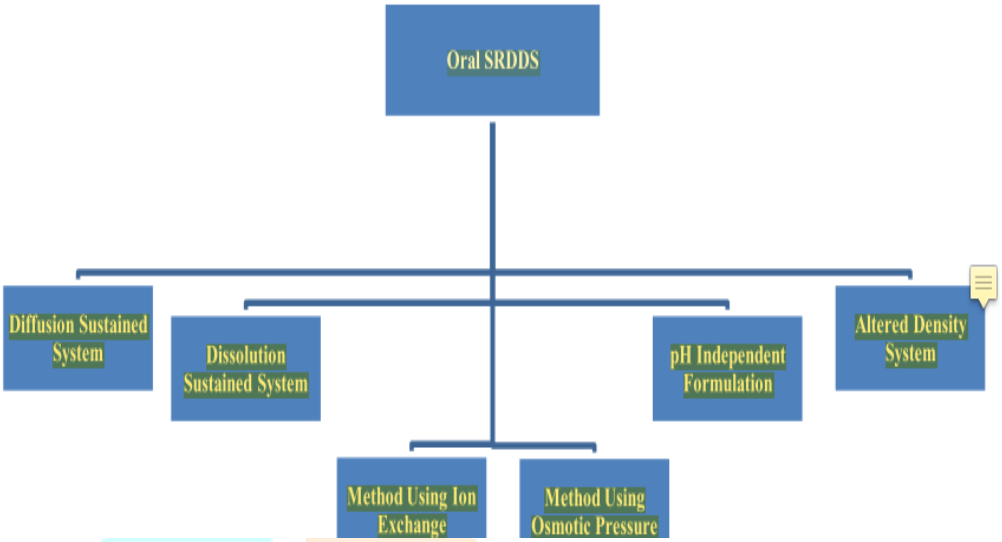

Figure 2:- Showing Different types of Oral SRDDS

Drug complexes [71,72]

The principal advantage of preparing drug derivatives for sustained release is those materials can be formulated into diverse dosage forms. This approach has proven effective in the development of injectable depot forms, in which release profiles are not subject to the variability characteristics of the gastrointestinal tract. Sensitivity to in vivo variables is a definite disadvantage of per orally administered forms; in vivo studies may not consistently support sustained release claim

Encapsulated slow release granules [73, 74,75]

The first significant marketed sustained release dosage forms were encapsulated mixed slow release beads, to which was applied the barrier principles of controlling drug release, based on model D. For low milligram potency formulations, nonpareil seeds are initially coated with an adhesive followed by powdered drug, and the pellets are dried. This step is repeated until the desired amount of drug has been applied. The resultant granules are subsequently coated with a mixture of solid hydroxylated lipids such as hydrogenated castor oil or glyceryltrihydroxystearate mixed with modified celluloses. The thickness of the barrier was regulated by the no. of applied coatings to obtain the desired release characteristics. The original formulation utilized glycerol monosterate bees wax compositions, which tended to be physically unstable, showing altered showing altered release pattern on aging.

Tableted slow release granulation [74,75]

Compression of time release granulations into tablets is an alternate to encapsulation. Such tablets should be designed to disintegrate in to stomach so as to stimulate the administration of a capsule form having the advantage associated with sustained release encapsulations, while retaining the advantage of the tablet dosage forms. Three examples, each utilizing a different process, illustrate this type of formulation. The first is a tableted mixed release granulation in which binders with different retardant properties are used to prepare three different granulations, which are color coated for identification, blended & tableted. This first is a conventional non sustained release granulation prepared using gelatin as a binder, the uses vinyl acetate, and the third uses shellac

as binders. Drug release is controlled by erosion of the granulation in intestinal fluid the vinyl acetate granulation disintegrates at a faster rate than the shellac granulation.

Controlled release technology [75,76]

Controlled release dosage forms are designed to release drug in vivo according to predictable rates that can be verified by a vitro measurements. Of the many approaches to formulation of sustained release medication, those fabricated as insoluble matrix tablets come closest to realization of this objective, since release of water soluble drug from this forms should be independent of in vivo variable. Controlled release technology implies a quantitative understanding of the physicochemical mechanism of drug availability to the extent that the dosage forms release rate can be specified. Potential developments & new approaches to oral controlled release drug delivery include hydrodynamic pressure controlled systems, intragastric floating tablets, transmucosal tablets, and micro porous membrane coated tablets.

Continuous release systems [77,78]

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow:

- Diffusion controlled release systems
- Dissolution controlled release systems
- Dissolution and diffusion controlled release systems
- Ion exchange resin- drug complexes
- pH-independent formulation

Diffusion controlled release systems [79,80]

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusions controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation:

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

Where, A = Area

D = Diffusion coefficient

K = Partition coefficient of the drug between the drug core and the membrane

L = Diffusion path length and

C = Concentration difference across the membrane

In order to o achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero- order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.

The two types of diffusion-controlled release are:

The two types of diffusion-controlled release are:

I. Matrix diffusion controlled systems

II. Reservoir devices

Dissolution- and diffusion controlled release systems [80,81]

The drug present in such system may be the one:

I. Having high aqueous solubility and dissolution rate

II. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

III. That produces slow dissolving forms, when it comes in contact with GI fluids

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by following equation:

$dm/dt = ADS/h$

Where,

A = Surface area of the dissolving particle or tablet

D = Diffusivity of the drug S = Aqueous solubility of the drug

h = Thickness of the boundary layer

The two types of dissolution-controlled release are

I. Matrix (or monolith) dissolution controlled systems

II. Reservoir dissolution controlled systems Dissolution and diffusion controlled release systems

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the systems.

Ion exchange resin-drug complexes [82,83]

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain.

Ph-independent formulation [84,85]

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent granulating agent excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release.

Osmotic pressure controlled systems [86,87]

A semi permeable membrane is placed around the tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet core. Two types of osmotic pressure controlled systems are:

I. Type 1 contains an osmotic core with drug

II. Type 2 contains the drug in flexible bag with osmotic core surrounding

By optimizing formulation and processing factor, it is possible to develop osmotic system to deliver the drug of diverse nature at pre-programmed rate.

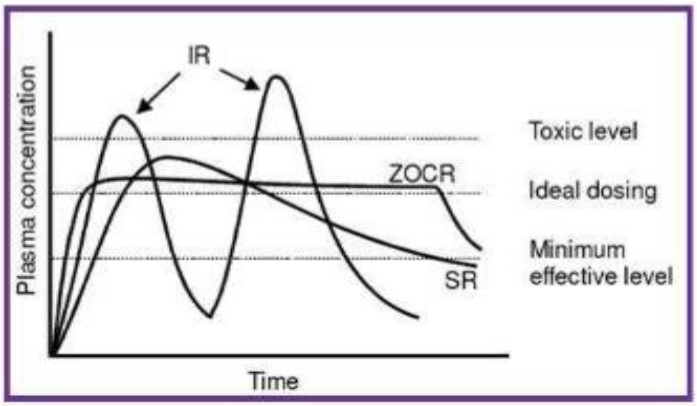

Fig no 3

Characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

EVALUATION PARAMETERS FOR EXTEND RELEASE MATRIX TABLET [88,89,90]

Thickness and Diameter

Thickness and diameter of tablets are determined using Vernier Caliper.

Hardness of the Tablet

Hardness of tablets has been characterized as, "the force required breaking a tablet in a diametric compression test". For every formulation, the hardness of three tablets is examined utilizing Monsanto hardness analyzer; end point is recognized by breaking the tablet.

Friability test

Twenty tablets are weighed and placed in friabilator. The chamber is rotated for 4 minutes at a speed of 25 rpm. The tablets are removed from the chamber and weighed again. Loss in weight indicates friability. The tablets to be considered of good quality if loss in weight is less than 0.8%.

Weight variation test

This is an important process which comes under quality control test as per standard in one batch all tablet ought to be in uniform weight. Twenty tablets are weighed to determine the average weight and compared with single tablet weight. The percentage weight variation is computed according to Indian Pharmacopoeia particular.

Determination of drug content

The drug content of is determined by dissolving in a suitable solvent like pH 7.4 phosphate buffer solution and sample are analyzed with the visible spectrophotometer and standard calibration curve of the pure drug.

In-vitro Dissolution Testing

In vitro dissolution testing is a vital instrument for assessment of the best formulation. The test is carried out to measure the amount of time required for certain percentage of drug to go into the solution under the specific test conditions. Rotating paddle type and rotating basket type apparatus can be used as per pharmacopoeia standards or as mentioned in monograph of particular drug Dissolution testing is likewise used to characterize the biopharmaceutical attributes and to distinguish conceivable hazard, for example, potential nourishment impacts on bioavailability or interaction with different drugs.

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