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REVIEW ON SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT

Sustained release matrix tablet is formulated mainly by wet granulation or direct compression method or by dispersion of solid particle within solid particle within a porous matrix formed by using different polymers like Poly methyl methacrylate (PMMA), Polyglycolic acid, HPMC etc. The matrix controls the release rate of drug. Release retardants like HPMC can aid in sustained release and thus they form core excipient of the formulation. The method involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix core of the retardant, alternatively granulation can be carried out prior to compression. The matrices used may be of hydrophilic, hydrophobic, mineral, or biodegradable types. The drug release rate can be studied by in-vitro dissolution studies. Some drugs that have been formulated as sustained release matrix tablets are Ambroxol HCl, Nateglinide etc. Thus, sustained release matrix tablets can assure better patient compliance through reduction in total dose and dosage regimen, which can be of great help to treat chronic diseases.

KEY WORDS

Sustained release, Polymer, Matrix tablet.

INTRODUCTION

The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration.[1]The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time.[2]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 formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now a days the

technology of sustained release is also being applied to veterinary products also.[3]

DRAWBACK OF CONVENTIONAL DOSAGE FORM

1) Poor patient compliance: Chances of missing of the dose of a drug.
2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.
4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.[4][5][6]

ADVANTAGES

i) Patient compliance:

Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

ii) Reduced 'see-saw' fluctuation:

Drug concentration in the systemic circulation and tissue compartments show 'see saw' pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also mainta in a steady drug concentration in blood circulation and target tissue cells.

iii) Total dose reduction:

To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv) Improvement of deficiency in treatment:

Optimal therapy of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

v) Economy:

The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[5][7][8]

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

1. Dose dumping: Dose dumping may occur with faulty formulation.
2. Reduced potential for dose adjustment.
3. Cost is more than conventional dosage form.
4. Increase potential for first pass metabolism.
5. For proper medication patient education is necessary.
6. Possible reduction in systemic availability.
7. Poor in vivo and in vitro correlations.[2][4][9]

Characteristics of drug unsuitable for Peroral sustained release forms:

Characteristic	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, Ferrous salts
Absorbed and excreted rapidly short biological half-life<1hr	Penicillin G, Furosemide
Long biologic half life(>12 hr)	Diazepam, Phenytoin
Large dose required	> 1gm sulfonamide
Cumulative action and desirable side effect drug with low therapeutics indices	Phenobarbital, Digitoxin
Precise dosage titrated to individual is required	Anticoagulants, Cardiac glycosides[9]

CRITERIA TO BE MET TO INCORPORATE THE DRUG INTO SUSTAINED RELEASE DOSAGE FORM:

Some physicochemical parameters for the Selecting of the drug to be formulated in sustained release dosage form which mainly includes the knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G.I.) tract.

Physicochemical parameters for drug selection:

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

Pharmacokinetic parameters for drug selection:

Parameters	Comment
Elimination half-life	Between 2 to 8 hrs
Absolute bioavaliability	Should be 75% or more
Absorption rate constant (K_a)	Must be higher than release rate
Apparent volume of distribution(V_d)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (C_{ss})	The lower C_{ss} and smaller V_d, the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form[4][10][11]

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

Biological half-life:

Absorption:

Metabolism:

Distribution:

Protein binding:

Margin of safety:

1) 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.

2) 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.

3) 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. But during this crystallization of the drug is possible when the drug is entering into the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

4) 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 SR drug delivery system. E.g. Chloroquine.

5) 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.

6) 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.

7) 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.[7][12][13][14]

PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

a) Dose size:

In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventi-onal dosage form. Same criteria also hold for sustained release dosage form. Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety which involves administration of large amount of a drug with a narrow therapeutic range.

b) Ionization, pka and aqueous solubility:

Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important. For drug permeation presenting the drug in an unchanged form is advantageous. The aqueous solubility unfortunately will be decreased by conversion to unchanged form, which is more complex. Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Low soluble Compounds (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

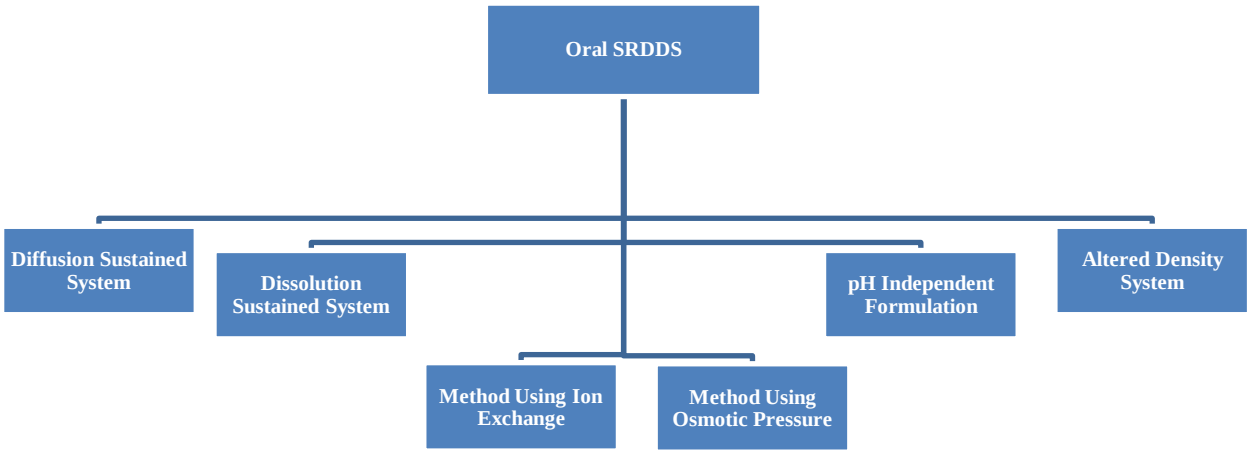
c) Partition Coefficient:

To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes is mainly depend on the partitioning characteristics of the drug.

d) Stability:

The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.[7][8][10][12]

FORMULATION



A) Diffusion sustained system:

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount/area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx

D = diffusion coefficient in area/ time

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

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

dm/dt= ADK. C/L

Where,

A = Area

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

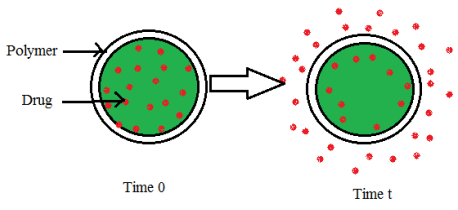
L= Diffusion path length (i.e. thickness of the coat in ideal case).

C = Concentration difference across the membrane.

i) Diffusion reservoir system:

In this system, a water insoluble polymeric material which covers a core of drug. Drug will partition into the membrane and exchange with the surrounding fluid the particle or tablet. Additional drug will enter into polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism.

Figure 1: Diagrammatic representation of Diffusion Type Reservoir System



ii] Diffusion Matrix type:

A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system.

Q = D/T [2A–Cs] Cst ½

Where,

Q = weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε= porosity of the matrix.

Cs = solubility of drug in release medium.

T = Tortuosity of the matrix.

A = concentration of drug in the tablet, gm/ ml.

The release rate can be given by following equation:-

Release rate = AD/ L = [C1-C2]

Where,

A = Area

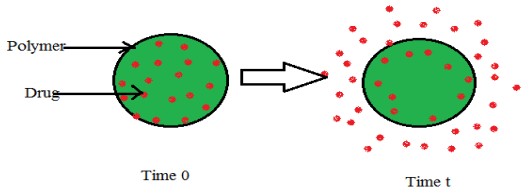
D = Diffusion coefficient

C1 = Drug concentration in the core

C2 = Drug concentration in the surrounding medium

L = Diffusion path length

Figure 2: Diagrammatic representation of diffusion sustained drug release: matrix system.



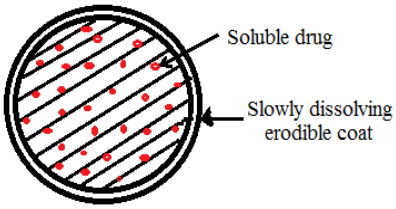
B) Dissolution sustained systems:

A drug which having a slow dissolution rate this drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation. These systems are generally employed in the manufacturing of enteric coated dosage forms. Protection of 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 dosage form until it reaches the higher pH of the intestine.

a) Soluble reservoir system:

In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats.

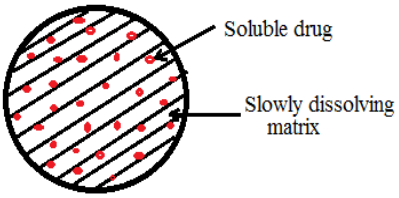
Figure 3: Diagrammatic representation of soluble reservoir system



b) Soluble matrix system:

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

Figure 4: Diagrammatic representation of soluble matrix system



C) Methods using Ion Exchange:

The use of ion exchange resin is attractive method for sustained drug delivery as drug release characteristic largely depends only on the ionic environment of resins containing drug and is less susceptible to environmental condition like enzyme contents and pH at the absorption site zero order release kinetic can satisfactorily be attained using this approach.

Ion exchange based delivery system represent better approach for a drug that is highly susceptible to degradation by enzymatic process. Ion exchange resin which are divided into types:

a) Cation exchange resin:

b) Anion exchange resin:

Cationic exchange resin: Contains acidic functional group generally they contain polysteryne polymer with either phenolic carboxylic phenolic group.

Anion exchange resin: Involved basic functional group capable for extracting anions from acidic solution.

Ion exchange resin are used to sustain the effect of drug based on concept that negatively or positively charge drug moiety combine with appropriate resin producing insoluble poly salts resonates.

Where, R-SO-H and R-NH–OH represent cationic and anionic resin respectively where as H N-A and HOOC-B Depicts basic and acidic drug respectively. Where administered orally resins come in contact with acidic fluids which contain HCl with a pH 1.2 following reaction takes place:

$R\text{-}SO_3\text{-}H^+ + H_2N\text{-}A \rightarrow R\text{-}SO_3^- + H_3N^+\text{-}A$

$R\text{-}N^+H3OH^- + HOOC\text{-}B \rightarrow R\text{-}N^+H3\text{-}00C\text{-}B + H_2O$

Subsequently when the system reaches to intestine where it is exposed to a fluid of slightly alkaline pH.

Following reaction occurs:

$R\text{-}SO^3\text{-}H3N^{+-}A + HCl \rightarrow R\text{-}SO_3\text{-}H^+ + A\text{-}N^+H_3Cl^-$

$R\text{-}N^+H_3\text{-}OOC\text{-}B + HCl \rightarrow R\text{-}N^+H_3Cl^- + B\text{-}COOH$

$R\text{-}SO_3\text{-}H_3N^+\text{-}A + NaCl \rightarrow R\text{-}SO3\text{-}Na^+ + A\text{-}N^+H_3Cl^-$

$R\text{-}N^+H3\text{-}OOC\text{-}B + Nacl \rightarrow R\text{-}N^+H_3Cl^- + B\text{-}COO^-Na^+$

These are some type of resins:

Resin type	Chemical constituent
Strong acidic cationic exchanger	Sulfonic acid group attached to astyrene and divinyl benzene copolymer.
Weak acidic cationic exchanger	Carboxylic acid group linked to an acrylic acid and divinyl benzene copolymer.
Strong basic anion exchanger.	Quarternary ammonium groups attach to astyrene and divinyl benzene copolymer.
Weak basic anion exchanger	Polyalkylamine copolymer group linked to astyrene and divinyl benzene copolymer

4) pH– Independent formulations:

There are unwanted features for oral route of administration which give prolong transit time through GI tract which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are weak acids or weak bases, the drug release from

sustained release formulations is depend on pH. For maintaining the constant pH to help thereby rendering pH independent drug release buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid added to the formulation. Preparation of buffered sustained release formulation is generally done by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastro-intestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH there by rendering a constant release rate of drug.

5) Altered density formulations:

If all contains of dosage form is not released in GI tract then it have a limited use. To this end, various approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High density approach:

In this approach the density of the pellets should be more than that of normal stomach content and should therefore, be at least 1-4gm/cm3.In preparing such formulation drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate titanium dioxide iron powder and zinc oxide.

Low density approach:

Globular shells which have density lower than that of gastric fluid used as a carrier of drug for sustained release purpose polystyrol, pop rice and popcorn are all use as carriers the surface of these empty shell is undercoated with sugar or with polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by mixture of drug with polymer such as ethyl cellulose and Hydroxy propyl cellulose. Thus the final product floats on the gastric fluid for a prolonged period, while slow releasing drug. [15][16][17][18]

MATRIX TABLET

For the manufacturing of sustained release dosage forms least complicated method involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix core of the retardant.

Alternatively drug and retardant blend may be granulated prior to compression. The materials which include both hydrophilic and hydrophobic polymers.

Matrix tablet generally classified into different types:

a) Hydrophilic Matrix Tablet:

Hydrophilic matrix generally used to control the release rate of drug. The matrix can be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. Water is required for the hydrophilic matrix to activate the release mechanism and explore several advantages, which includes simplicity of manufacture and excellent uniformity of matrix tablets. Use of matrix building material with fast polymer hydration capability is a best choice for formulation of a hydrophilic matrix tablet. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is suitable for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow:

1) Cellulose derivatives:

Hydroxyethylcellulose,
Hydroxypropymethylcellulose(HPMC)
25,100,4000and15000cps, sodium
carboxy methyl cellulose and Methylcellulose 400 and 4000 cps.

2) Non-cellulose natural or Semi-synthetic polymers:

Agar-agar, Carob Gum, Alginates, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.

3) Acrylic acid polymer:

Carbopol 934 Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

b) Fat-wax Matrix Tablet:

Various technique used for incorporation of drug into fat wax granulation which involve spray congealing in air, blend congealing in an aqueous media with or

without the aid of surfactant and spray drying Technique. Bulk congealing method, a suspension of drug and melted fat wax is allowed to solidify and then comminuted for sustained-release granulations. Mixing of active ingredients waxy materials and fillers when the mixing is over this mixture converted into granule by compacting with s compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. The drug which is embedded into a melt of fats and wax released by leaching and hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GI tract. Addition of various surfactants to the formulation can also influence both the release rate of drug and the total drug proportion that can be incorporated into a matrix.

c) Plastic Matrix Tablet (Hydrophobic matrices):

Sustained release tablets based upon an inert compressed plastic matrix have been used widely. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

1) The solid drug which is mixed with plastic powder and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2) An organic solvent which is used for dissolution of drug in the plastic and granulated upon evaporation of the solvent.
3) Using latex or pseudo latex as granulating fluid which is used to granulate the drug and plastic masses.
   Example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

d) Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to each other by functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

e) Mineral Matrices:

Mineral matrices consist of polymers which are obtained from various species of seaweeds.
Example: 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 is also classified according to their porosity.

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 diffusion 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 – 200 A°, which is slightly larger than diffusion 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.
4. Hybrid system: System in which the drug in matrix of release retarding material is further coated With increase controlling polymer membrane.

POLYMERS USED IN MATRIX TABLET:

Hydrogels:

Polyhydroxyethylemethylacrylate(PHEMA),Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP),Polyethylene-oxide(PEO), Polyacrylamide (PA)

Soluble polymers:
Polyethyleneglycol (PEG), Polyvinyl alcohol(PVA), Polyvinylpyrrolidone (PVP), Hydroxypropylmethylcellulose (HPMC)

Biodegradable polymers:
Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters

Non-biodegradable polymers:
Polyethylene vinyl acetate (PVA), Polydimethylsiloxane(PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

Mucoadhesive polymers:
Polycarbophil,Sodium carboxy methyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum, Karaya gum, Locust bean gum.[2][3][9][20]

KINETICS OF DRUG RELEASE[2, 21]

Zero order kinetics:
Drug dissolution from pharmaceutical dosage form that does not disaggregate and drug release in slow manner represented by,

$$W_o - W_t = K_o t$$

Where,
W_o =Initial amount of drug concentration in solution.
W_t = Amount of drug release dissolved in time t.
$K_0 t$= 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 pharmacological action.

First order kinetics:
Release of drug expressing in this model:

$$\text{Log } Q_t = \text{Log } Q_o + K_1^{t/2}.303$$

Q_t=Amount of drug release in time t.
Q_0=Initial amount of drug in solution.
$K_1 t$ =First order release rate constant.

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

Korsmeyer Peppas model:
In 1983 Korsmeyer-peppas developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$$A_t/A = kt^n$$

Where, k = Constant.
n =Release.
t = Time.
At and A∞= Absolute cumulative amount of drug released at time (t)
This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.
Higuchi model:
Drug release from the matrix device by diffusion has been described by Higuchi's Diffusion equation:

$$ft = Q = \sqrt{D\delta/\tau}\,(2C - \delta Cs)Cst$$

Where, Q = Amount of drug released in time t.
D = Diffusion coefficient of the drug in the matrix.
Cs = Solubility of the drug in the matrix.
δ= Porosity of matrix.
τ= Tortuosity.
t = Time (h).
The equation may be simplified then equation becomes;

$$ft = Q = KH\ Xt1/2$$

Where,
KH = Higuchi dissolution constant.

When data was plotted according to this equation, i.e.cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.[2][21]

EVALUATION TEST FOR SUSTAINED RELEASE TABLETS:

Weight Variation:
Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.
Hardness:

Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.

Friability:

The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.

Thickness: The thicknesses of tablets were determined using micrometer screw gauge.

Content Uniformity:

Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.

IN VITRO DISSOLUTION STUDY:

Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 370C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time.

Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.[22][23][24]

LIST OF VARIOUS DRUGS WHICH CAN BE FORMULATED AS A MATRIX TABLET WITH POLYMER AND METHOD USED OR ITS PREPARATION ARE SHOWN IN TABLE:

DRUGS	CATEGORY	METHOD USED	POLYMER USED
Ambroxol HCl	Secretolytic agent	Direct compression	Methocel K15MCR, PVP K30[25]
Diclofenac Sodium		Wet granulation	Pectin, Guar gum[26]
Metformin hydrochloride	Anti-inflammatry Antidiabetic	Direct compression	Chitosan, Ethyl cellulose HPMC, Xanthan gum[27]
Cefpodoxime	Antibiotic	Direct compression	HPMC(K4M),HPMC(K100M) and Xanthan gum[28]
Risperidone	Antipsychotic	Direct compression	HPMC (K100), HPMC (K4M), Xanthan gum[23]
Lamivudine	Antiviral	Direct compression	HPMC(Methocel K15M CR) Avicel 102[29]
Isoniazide	Anti-tuberculer	Direct compression	Guar gum, Tragacanth gum PEG-6000[24]
Terbutaline sulphate	bronchodilator	Wet granulation	HPMC K200M, Ethyl cellulose[30]
Indomethacin	Anti-inflammatory	Wet Granulation	Hibiscusrosa-sinensis, Microcrystalline cellulose, Magnesium stearate[31]
Nateglinide	Antidiabetic	Wet Granulation Wet granulation	Xanthan gum, Guar gum[32]
Zidovudine	Anti viral		HPMC, Xanthan gum, ethyl cellulose[33]

CONCLUSION:

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to overcome

the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

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