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Pharmaceutical Sciences **Review Article……!!!**

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AN OVERVIEW ON SUSTAIN RELEASE MATRIX DRUG DELIVERY SYSTEM

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ABSTRACT

The pharmaceutical market requires more efficient drug development and production. Product Lifecycle Management (PLM) has the opportunity to make pharmaceutical production more effective and lower risk. The product lifecycle management creates and manages a company's product-related intellectual capital starting from an idea to its final development. The Pharma industry, it benefits through enhancing the life of patient and pricing strategies. Improved patient compliance, growth, expanded clinical benefits; cost advantages, Leaders are actively implementing PLM and are reaping the benefits of fewer problems, lower costs, higher yields, and audits that make everyone more confident. The present manuscript focuses on problems and the key solutions for a successful product lifecycle management in pharmaceuticals.

INTRODUCTION [1,2,3]

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.

Controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. Most of drugs, conventional methods of drug administration are effective, but some drugs are unstable or poisonous and have narrow therapeutic ranges. Several drugs also possess solubility problems. In such cases, a technique of continuous administration of therapeutic agent is desirable to sustain fixed plasma levels as shown in Fig.

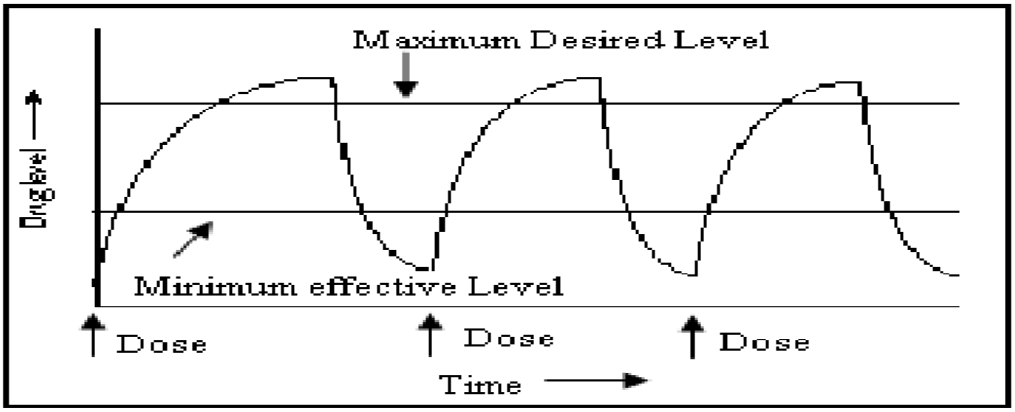

Fig: Drug levels in the blood with Conventional drug delivery Systems

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period.

Introduction of matrix tablet as sustained release (SR) has given a new break through for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface. It excludes complex production procedures such as coating and

pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.

Concentration of the drug in the body remains constant, two conditions must be fulfilled, namely 1) The zero order rate of drug release must determine the absorption rate of the drug, and 2) The rate at which the drug is released from maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration a list of important terms that describe different modified release dosage forms are defined below.

1. Modified release dosage forms

Those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic and/or convenience objectives not offered by conventional dosage forms.

2. Controlled release

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.

3. Delayed release

The drug is released at a time other than immediately after administration.

4. Extended release

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time usually between 8 and 12 hours.

5. Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

6. Repeat action

Indicates that an individual dose is released fairly soon after administration, and secondor third doses are subsequently release that intermittent intervals.

7. Sustained release

The drug is released slowly at a rate governed by the delivery system.

Oral Sustained Release dosage form:

Sustained release, sustained action, prolong action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

Advantages of Controlled Drug Delivery System [4,5]

1. Maintains therapeutic concentrations over prolonged periods.
2. Avoids the high blood concentration.
3. Reduction in toxicity by slowing drug absorption.
4. Minimize the local and systemic side effects.
5. Improvement in treatment efficacy.
6. Minimize drug accumulation with chronic dosing .

Disadvantages of Matrix Tablets [4,5]

1. The remaining matrix must be removed after the drug has been released.
2. Greater dependence on GI residence time of dosage form.
3. Increased potential for first-pass metabolism.
4. Delay in onset of drug action.
5. Release rates are affected by food and the rate transit through the gut.

Drug Selection for Oral Sustained Release Drug Delivery System: [6,7,8]

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

Table 1: Parameter for Drug Selection

Parameter	Preferred value
1 Molecular Weight / Size	< 1000
2 Solubility	>0.1um / ml for pH 1 to 7.8
3 Pka	Non ionized moiety > 0.1% at pH 1 to 7.8
4 Apparent partition coefficient	High
5 Absorption Mechanism	Diffusion
6 Absorbability	From all G.I.Segments
7 Release	Should not be influenced by pH and Enzyme

Table No 2:Pharmacokinetic Parameter for Drug Selection

Parameter	Preferred Value
1 Elimination half life	Preferbly between 0.5 and 8 hrs
2Total Clearance	Should not be dose dependent
3 Elimination rate constant	Required for design
4 Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size
5 Absolute bioavailability	Should not be 75% or more
6 Intrinsic absorption rate	Must be greater than release rate
7 Therapeutic concentration	The lower and smaller Vd, the loss among the drug required
8 Toxic concentration	Apart the values of MTC and MEC, safer the dosage form.

Polymers used in Matrix tablets [9,10,11]

a) Hydrogels

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

b) Soluble polymers

Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

c) Biodegradable polymers

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

d) Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

e) Mucoadhesive polymers

Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, cellulose, Pectin

f) Natural polymers in sustained release drug delivery

Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan

Table 3: Different Drug And Polymer Used In Sustained Release Matrix Tablet

Drug	Polymer
1 Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose(Hpmc) Carboxymethylcellulose (Cmc) Ethyl Cellulose(Ec)
2 Ibuprofen	Ethyl Cellulose, Cellulose acetate pthallate
3 Metoprolol Succinate	HPMCK100M, Xantham gum, HPMC
4 Amroxol Hydrochloride	HPMC
5 Tramadol Hydrochloride	Carrageenan gum, Karaya gum, HPMC15.
6 Aceclofenac	Carbopol 971P, Carbopol

Design And Formulation Of Oral Suatained Release Drug Delivery System [11,12]

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

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

1. Diffusion sustained system.

i) Reservoir type.

ii) Matrix type.

2. Dissolution sustained system.

i) Reservoir type.

ii) Matrix type.

3. Methods using Ion-exchange.

4. Methods using osmotic pressure.

5. pH independent formulations.

6. Altered density formulations.

1. Diffusion Sustained System

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by 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 encloses a core of drug, it must diffuse through the membrane. The drug release rate dm/ dt is given by.

dm/ dt= ADKΔ C/L

Where; A = Area.

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

L= Diffusion path length (i.e. thickness of coat)

Δc= Concentration difference across the membrane.

i) Reservoir Type

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

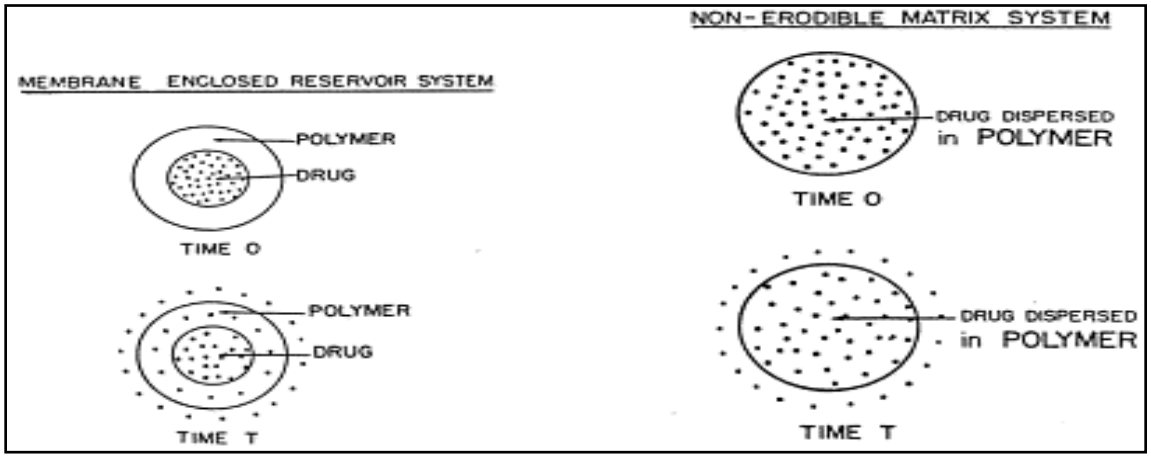

Figure: Diffusion sustained drug release: reservoir system

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages: Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

ii) Matrix Type

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

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

$Q = D\varepsilon / T [2 A - \varepsilon Cs] Cst^{1/2}$

Where; Q = Weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix.

Cs = Solubility of drug in release medium.

T= Tortuosity of the matrix.

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

Description: Homogenous dispersion of solid drug in a polymer mixture.

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system. Diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat. 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 = Diffusional path length.

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The

second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymercoat diffuses through an unstirred film of liquid into the surrounding fluid.

2. Dissolution Sustained Systems

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

i) Reservoir Type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. Maintenance of drug levels at late times will be achieved from those thicker coating.

ii) Matrix Type:

These are common type of dissolution sustained dosage form. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Two types of dissolution sustained pulsed delivery systems.

- . Single bead type device with alternating drug and rate-controlling layer.
- . Beads containing drug with differing thickness of dissolving coats.

Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages.

- Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
- Simple effective manufacturing using existing tableting unit operation equipment.
- Broad regulatory and patient acceptance.

3. Methods Using Ion Exchange

It is based on the formation of drug resin complex formed when aionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract.

Anion Exchangers: Resin+ - Drug- + Cl- goes to Resin+- Cl-+ Drug-

Cation Exchangers: Resin-- Drug+ + Na+ goes to Resin- - Na+ + Drug+

These systems generally utilize resin compounds of water insoluble cross linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.

4. Methods Using Osmotic Pressure

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

Two types of osmotically sustained systems are

Type A contains an osmotic core with drug.

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

5. pH– Independent Formulations

The gastrointestinal tract present some unusual features forthe oral route of drug administration with relatively brief transit time through the gastrointestinal tract. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

CLASSIFICATION OF MATRIX TABLETS

On the Basis of Retardant Material Used

1. Hydrophobic Matrices (Plastic matrices):[16]

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist

between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

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.

3. Hydrophilic Matrices:

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

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

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.

Methods of preparation of Matrix Tablet [13]

1.Direct Compression

In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

2.Wet Granulation

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

3.Melt Granulation

In this process use of a substance, 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 binders were tried by using melt granulation technique.

4.Hot-Melt Extrusion Process

In the hot-melt extrusion process, 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 materials are transferred inside the heated barrel by a rotating screw.

The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Evaluation of Sustained release Matrix tablets:[14,15]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

• **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.

• **Kinetic Studies**

• ***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.

• **Stability Studies:**

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

• ***In–Vivo* Methods**

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

• a. Clinical response

• b. Blood level data

• c. Urinary excretion studies

• d. Nutritional studies.

• e. Toxicity studies

• f. Radioactive tracer techniques

CONCLUSION

The aim of this review article has been on the formulation of sustained-release matrix tablet, advantages and disadvantages and various polymer used to design such dosage form. Above discussion concludes that many oral delivery problems like drug fluctuation in plasma levels, low bioavailability, patient compliance and more frequent dose administration. So matrix tablet

can overcome the above problems of conventional oral drug delivery. It can easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatability matrix forming polymer can be successfully used to prepare Matrix tablet,releasing drug in a controlled manner.

REFERENCES

1 Tapsawi Rani Dash, Pankaj Verma. Matrix Tablet An Approch toward oral Extended Release Drug Delivery, International of Pharma Research & Review. 2013; Issue 2(2) Pp- 12-24.

2 Ashish Sharma and Vikas Bhatt. Sustained Release Matrix Type Drug Delivery System A Review.World Journal of Pharmacy And Pharmaceutical Science.2015; Issue 2, Pp-1002-1022.

3 Nisargi Shah, Chintan Oza, Shital Trivedi. Review On Sustained Release Matrix Tablet: An Approch to prolong the Release of Drug, Journal of Pharmaceutical Science And Bioscientific Research. 2015; Issue (3), Pp- 315-321.

4 Higuchi T. Mechanisum of Sustained Action Medication: Theoretical Analysis of rate of Release of Solid Drug Dispersed in Solid Matrices. Journal of Pharmaceutical Sciences, 1963; 52 (1): Pp- 1145-1149.

5 Kumar Kirans . Rao Rama T, Jayaveera K.N, Matrix Tablet as Controlled Drug Delivery System. Indo American Journal of Pharmaceutical Research. 2011; Issue 1 (4),Pp- 343-350.

6 Charman S, Charman W, Rathbone M, Hadgraft J, Robert M. Modified Release Drug Delivery Technology. 2003; Pp-129.

7 Lachman L, Lieberman H, Kanig J. The Theory and Practice of Industrial Pharmacy.3rd ed. Verghese publishing house.Bombay; 1990.141,346.

8 Brahmankar H, Jaiswal S. Biopharmaceutics and Pharmacokinetics A Treatise. VallabhPrakashan; 2000:337,348–57.

9 Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. In vitro and in vivo sustained-release characteristics of theophylline matrix tablets and novel cluster tablets. Int. J. Pharm. Sci. 2006;112:51–6.

10 Chaudhari AR, Gujarathi NA, Rane BR, Pawar SP, Bakliwal SP. Novel Sustained Release Drug Delivery System : A Review. A J. Pharm. Res. 1999;8(1):80–97.

11 Lee VHL, Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design, Marcel Dekker, (2nd) INC, NewYork. 1987:16-29.

12 Rane Manish, ParmarJayesh, Siahboomi Ali Rajabi. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. Pharma Times - Vol 42 - No. 04 - April 2010.

13 Misal R, Atish W, Aqueel S. Matrix tablets: A promising Technique for controlled drug delivery. Indo Am. J. Pharm. Res. 2013;3(5):3791–805.

14 Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of Release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 1961;52(1):1145–9.

15 Zalte H, Saudagar R. Review On Sustained Release Matrix Tablet. Int. J. Pharm. Biol. Sci. 2013;3(4):17–29.

16 Parmar NS, Vyas SK, Jain NK. Advances in controlled and novel drug delivery. CBS publisher & distributers. New Delhi. 2001, 18-39.