Review Article
Available online at www.ijpras.com

ISSN 2277-3657

Volume 2, Issue 3 (2013),1-17

International Journal of Pharmaceutical Research & Allied Sciences

Review on Matrix Tablet as Sustained Release

N. G. Raghavendra Rao*, K. Richard Prasanna Raj, B. Sanjeev Nayak
PG Department of Pharmaceutics, Jyothishmathi Institute of Pharmaceutical Science, Thimmapur, Karimnagar - 505481, AP. India
Email: ngraghu@rediffmail.com

Subject: Pharmaceutics

Abstract

Recently, sustained release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Sustained release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The release of the drug through such system includes both dissolution controlled as well as diffusion controlled mechanisms, Most of 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. This article contains the basic information regarding sustained-release formulation and also the different types of the same**.**

Key words: *Matrix tablets, Sustain release polymers, Patient convenience and compliance.*

Introduction

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes[1]. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose'[2].

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[3]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems [4]. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers [5]. The goal of an extended release dosage form is to maintain therapeutic drug level in plasma for extended period of time.

The major Drawbacks Associated with Conventional Dosage Forms are[6]

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a

drug with small Therapeutic Index (TI) whenever over medication occur.

- Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/ or targeting the delivery of drug to a tissue.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. 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.[7-11] Because of increased complication complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems.[12]Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms. Time release technology, also known as sustained release (SR) sustained action (SA), extended release (ER, XR or XL), time-release or timed-release, controlled-release (CR), modified release (MR) or continous-release (CR) is a mechanism used in pill tablet or capsules to dissolve slowly and release a drug over a prolong period of time. Matrix system is widely used for the purpose of sustained release. It is the system which prolongs and controls the release of drug that is dissolved or dispersed.

Matrix Tablets

A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral extended release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick's first law of diffusion.

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a hydrophobic polymer (such as wax, polyethylene, polypropylene, and ethyl cellulose) or hydrophilic polymer (such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methylcellulose, sodium carboxy methylcellulose, alginates and scleroglucan). In this sense, the term "matrix" indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation. Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly.

Thereafter, drug particles at successively increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer.

The drug is dispersed in the polymer matrix either by (1) blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain, (2) mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum. The rate of drug release from this polymer matrix diffusion – controlled drug delivery system is time dependent and is and is defined at steady state by

$$Q/t1/2 = (2ACRDp)1/2$$

Where,

A is the initial loading drug dose in the polymer matrix;

CR is the drug reservoir concentration in the system;

Dp is the diffusivity of the drug molecules in the polymer matrix.

Drug release is controlled by controlling the loading dose, polymer solubility of drug and its diffusivity in the polymer matrix and the porosity of the release unit. [13]

Sustained Release Drug Delivery System

The term sustained release has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its loading dose, polymer solubility of drug and its diffusivity in the polymer matrix and the porosity of the release unit plasma profile is sustained in duration. [14-16]

Limitations of Matrix System

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix based technologies such as layered tablets are required.

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core.
Matrix systems can be divided into three types:

1. Monolithic matrix tablets
2. Gel forming hydrophilic matrix tablet
3. Erodible (hydrophobic) matrix tablets

1. Inert monolithic matrix tablets:

Probably the simplest method of obtaining sustained release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. Here inert means non-interacting with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter and intra patient variability (pH, viscosity).

During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in faeces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophillic compounds. The first polymers to be used for the preparation of matrix tablets were (semi) synthetic polymers such as polyethylene, polyvinyl chloride, poly methyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax, hydrogenated castor oil, and tristearin.

Major drawback of most of the inert polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problematic cleaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

Mechanism of release of inert monolithic matrix tablets:
Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 volume %, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

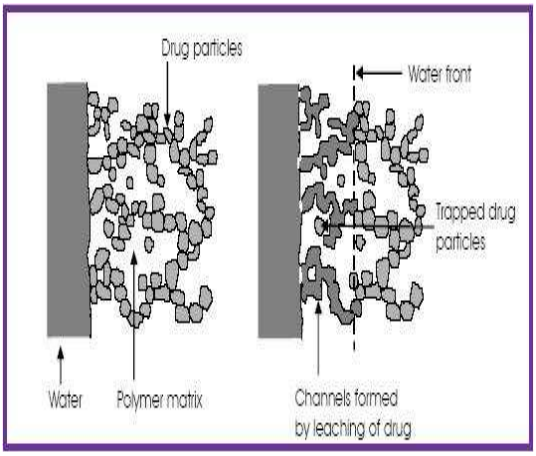

Fig. 1: Schematically presentation of a leaching-based release mechanism

Solvent activated matrix tablets:

The use of solvent activated matrix tablets as a method to obtain zero order Hoffenberg first proposed release i.e. constant release rates over an extended period. Solvent activated drug delivery system is a collective term comprising those systems in which the interaction between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticization, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets.

Gel-forming hydrophilic matrix tablets:
Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offer the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics.

Upon swallowing gel forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro intestinal fluids into tablet,

a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release controlling gel.

The mechanism of drug release from swellable devices is determined by the relative position of the rubber glass interface, the rate at which it penetrates the tablet, the diffusion coefficient of the drug and the erosion rate of the gel. When the penetration rate is high as compared to the drug diffusion rate through the swollen gel layer, release is controlled by the diffusion rate of the drug through the gel layer and a diffusion controlled (Fickian) release mechanism is observed. If diffusion of drug through the gel layer is fast as compared to the water penetration rate, release of the incorporated drug is governed by the penetration rate of the interface and zero order drug release with constant release rate may be achieved. Several dimensionless parameters have been developed to characterize drug release from swelling controlled dosage forms. The Deborah number (De) represents the ratio of the characteristic relaxation time of the swelling polymer (τ) relative to the characteristic diffusion time of the water into the polymer (θ) [17,18]. The swelling interface number (Sw) represents the ratio of the solvent penetration front velocity (ν) to the rate of drug diffusion through the swollen polymer:

$$De = \theta / \tau \qquad Sw = \nu.\delta(t) / ID$$

Where ID is the diffusion coefficient of the drug in the swollen layer and $\delta(t)$ is the thickness of the latter. In order to characterize release behavior, it is necessary to determine both De and Sw since neither of these values is sufficient by it. Peppas and co-workers [8] have extensively investigated diffusion and solvent controlled drug release from swellable polymeric devices with various geometries. Release from swellable tablets can easily be analyzed by the following simple equation:

$$M_t / M_\infty = kt^n$$

Where M_t / M_∞ is the fractional drug release, k is a constant representing structural and geometrical characteristic of the device, and n gives the type of release mechanism.

When the rate at which the penetration front moves inward into the glassy core is high as compared to the diffusion rate of dissolved drug molecules through the swollen gel layer, release is controlled by the diffusion rate of the drug through the gel layer and a Fickian diffusion controlled release mechanism with $n \approx 0.5$ is observed. If diffusion of the drug through the gel layer is fast as compared to the solvent penetration rate, release of the incorporated drug is governed by the penetration rate of the interface. For dosage forms with slab geometry, this leads to zero-order release (n=1), which is also called non-Fickian, case II or solvent penetration controlled release. Release profiles with intermediate n-values ($0.5 < n < 1$) are classified as anomalous.

Other swellable polymers, which have been applied in swelling controlled oral drug delivery systems, which show solvent controlled release, are guar gums, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene vinyl alcohol copolymers (EVA) and dextrans.

Erodible matrix tablets:

Erodible polymers such as polyanhydrides offer another interesting material platform for zero order drug release. Like several HPMC grades, upon water penetration, polyanhydrides form a gel layer, which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel layer may remain constant with time resulting in a constant release rate until depletion of the drug[19].

Sustained Release Oral Dosage Forms:

Not all drugs are suited for formulation into sustained release products and not all medical conditions require treatment with such a product. The drug and the therapeutic indication must be considered jointly in determining whether or not to develop a sustained release dosage form.

Drug candidates suitable for sustained release products:

For a successful sustained-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.

In general, the drugs best suited for incorporation into a sustained release product have the following characteristics.

1. They exhibit neither very slow nor very fast rates of absorption and excretion. Drugs with slow rates of absorption and excretion are usually inherently long acting and their preparation into sustained release dosage forms is not necessary. Drugs with very short half-lives, i.e., <2 hrs, are poor candidates for sustained release dosage forms because of the large quantities of drug required for such a formulation.
2. They uniformly absorbed from the gastrointestinal tract. Drugs prepared in sustained release dosage forms, must have good aqueous solubility and maintain adequate residence time in the gastrointestinal tract. Drugs absorbed poorly or at varying and unpredictable rates are

not good candidates for sustained release products.

3. They are administered in relatively small doses. Drugs with large single doses frequently are not suitable for the preparation of an sustained release product because the oral dosage unit (tablet or capsule) needed to maintain a sustained therapeutic blood level of the drug would have to be too large for the patient to easily swallow.

4. They possess a good margin of safety. The most widely used measure of the margin of a drug's safety is its therapeutic index, i.e., the median toxic dose divided by the effective dose. For very potent drugs the therapeutic index may be narrow or very small. The larger the therapeutic index, the safer the drug. Drugs, which are administered in very small doses or possess very narrow therapeutic indices, are poor candidates for formulation into sustained release formulations because of technological limitations of precise control over release rates and the risk of dose dumping due to a product defect. They are used in the treatment of chronic rather than acute conditions. Drugs for acute conditions require greater physician adjustment of the dosage than that provided by sustained release products [20].

Table 1: Characteristics of drugs unsuitable for per oral sustained release dosage forms:

Characteristics	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, ferrous salts
Absorbed and excreted rapidly; Short biologic half lives (<1hr)	Penicillin G, furosemide
Long biologic half lives (>12hr)	Diazepam, phenytoin
Large doses required (>1g)	Sulfonamides
Cumulative action and undesirable side effects; drugs with low therapeutic indices	Phenobarbital, digitoxin
Precise dosage titrated to individual is required	Anticoagulants, cardiac glycosides
No clear advantage for sustained release formulation	Griseofulvin

In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing controlled release dosage forms because it makes such manufacturing easy. A wide range of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems.

The second class represents hydrophobic and water insoluble materials, which are potentially erodible; while the third group includes polymers those form hydrophilic matrices. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for controlling the release of the drug. Liquid penetration into the matrix is the rate limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier, which controls the drug release from, and the liquid penetration into the center of the matrix system[21].

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxy propyl methylcellulose has been extensively used since the early 1960s as a rate controlling polymer in oral extended release dosage forms [22].

Hydrophilic matrix systems are popular and versatile controlled release system. Amongst polysaccharide derivatives used to produce such systems, these are a range of cellulose ethers, e.g., hydroxy propyl methylcellulose (HPMC) and a diverse range of other materials, including sodium alginate, carrageenan, chitosan, and xanthan gum[23].

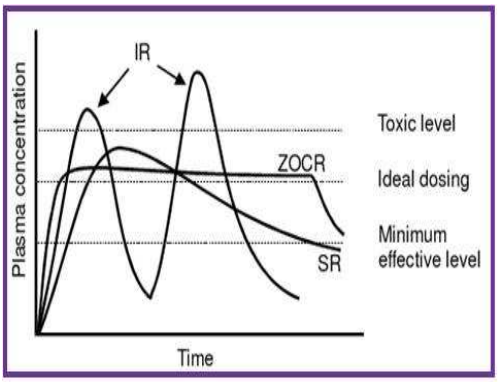

Fig 2: Characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

Recently, controlled release drug delivery[24] has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate sustain release system for in order to achieve even plasma concentration profile up to 24 hrs.

Reason for the selection of -API as a model drug,

- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to sustain the drug release.
- Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
- Less risk of dose dumping.
- Less inter and intra subject variability.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
- Transport of drug is independent of gastric emptying.

Advantages of Matrix Tablet [25-26]

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.
- **Ex**: Morning relief of arthritis through bed time dosing.
- Very easy to fabricate in a wide range of shape and size.
- Suitable for both non degradable and degradable system.
- No danger of dose dumping in case of rupture.
- Versatile, effective and low cost.
- Can be made to release high molecular weight compounds.

Disadvantages of Matrix Tablet [25-26].

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- 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 any applications are indistinguishable from zero-order.
- Achievement of zero order release is difficult.
- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time.
- Not all drugs can be blended with a given polymeric matrix.

Terminology:

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 [27,28].

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 latter time.

Prolonged Action Dosage Forms: It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period of time.

Classification of Matrix Tablets:

***On the Basis of Retardant Material Used*:**
Matrix tablets can be divided in to 5 types [29-31]

1. Hydrophobic Matrices (Plastic matrices) [29]: The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an 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 [30]: 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[31]: Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy ethyl cellulose; Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.

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

Polymers of acrylic acid: Polymers which are used in acrylic acid category is Carbopol 934.
Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums

Fat- wax matrix tablet:
The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

4. Biodegradable Matrices [32]:
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; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices [33]: 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.

Table 2: Two Classes of Retardant Material used to Formulate Matrix Tablet

Sr. No.	Matrix Characteristics	Material
1	Insoluble, inert	Polyethylene, Polyvinyl chloride, Ethyl cellulose
2	Insoluble, erodible	Carnauba wax, Stearic acid, Polyethylene glycol

Polymers Used In Matrix Tablet [34].

Hydrogels: Poly hydroxyl ethyl methylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Poly acryl amide (PA)

Soluble polymers: Poly ethylene glycol (PEG), polyvinyl alcohol (PVA), Poly vinyl pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC)

Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Poly caprolactone (PCL), Poly anhydrides, Poly orthoesters

Non-biodegradable polymers: Polyethylene vinyl acetate (PVA), Poly dimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

Mucoadhesive polymers: Poly carbophil, Sodium carboxy methyl cellulose, Poly acrylic acid, Tragacanth, Methyl cellulose, Pectin

Natural gums: Xanthan gum, Guar gum, Karaya gum, Locust bean gum

Method of Preparation of Matrix Tablet
1) Wet Granulation Technique
- Milling and gravitational mixing of drug, polymer and excipients.
- Preparation of binder solution
- Wet massing by addition of binder solution or granulating solvent
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules
- Blending with lubricant and disintegrants to produce “running powder”
- Compression of tablet.

2) Dry Granulation Technique
- Milling and gravitational mixing of drug , polymer and excipients
- Compression into slugs or roll compaction
- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrants
- Compression of tablet.

3) SinteringTechnique
- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix

tablets for the stabilization and retardation of the drug release.

Mechanism of Drug Release From Matrix Tablet: [35-37]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$$dM/dh = Co.\ dh - Cs/2 \quad \text{…… (1)}$$

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

$$dM = (Dm.\ Cs / h)\ dt \quad \text{..... (2)}$$

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 1 and equation 2 and integrating:

$$M = [Cs.\ Dm\ (2Co - Cs)\ t]^{1/2} \quad \text{…… (3)}$$

When the amount of drug is in excess of the saturation concentration then:

$$M = [2Cs.Dm.Co.t]^{1/2} \quad \text{…… (4)}$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.\ Ca.\ p/T.\ (2Co - p.Ca)\ t]^{1/2} \quad \text{…. (5)}$$

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional path length

For pseudo steady state, the equation can be written as:

$$M = [2D.Ca\ .Co\ (p/T)\ t]^{1/2} \quad \text{…….. (6)}$$

The total porosity of the matrix can be calculated with the following equation:

$$p = pa + Ca/\rho + Cex / \rho ex \quad \text{…… (7)}$$

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k.\ t^{1/2} \quad \text{…….. (8)}$$

Where,

k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

Designing Sustained-Release Drug Delivery System

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For

this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such System[38].

1. Oral Controlled Release Systems

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1) Continuous release systems

These 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,

A. Dissolution controlled release systems
B. Diffusion controlled release systems
C. Dissolution and diffusion controlled release systems
D. Ion exchange resin- drug complexes
E. pH dependent formulation
F. Osmotic pressure controlled systems

A. dissolution controlled release systems

These types of systems are easiest to design. The drug present in such system may
be the one:

- With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- That produces slow dissolving forms, when it comes in contact with GI fluids.
- Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. 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 Equation 1.

$$\frac{dm}{dt} = \frac{ADS}{h} \qquad \ldots\ldots\ldots 1$$

Where,
S = Aqueous solubility of the drug.
A = Surface area of the dissolving particle or tablet.
D = Diffusivity of the drug and
h = Thickness of the boundary layer.

a) Matrix (or monolith) dissolution controlled systems

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employ waxes such as beeswax, carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices.

b) Reservoir dissolution controlled systems

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

B. diffusion controlled release systems

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 diffusion 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 2

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell} \qquad \ldots\ldots\ldots 2$$

Where,
A = Area,
D = Diffusion coefficient,
K = Partition coefficient of the drug between the drug core and the membrane,

ℓ = Diffusion pathlength and
C= Concentration difference across the membrane.

In order to achieve a constant release rate, all of the terms on the right side of equation 2 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. Equation 3 describes the amount of drug released from the systems as derived by Higuchi,

$$Q = \left[\frac{}{} \quad (2C^{D} \varepsilon S)\, S \right] \quad \ldots\ldots\ldots\ldots 3$$

Where,
Q = Amount of drug released per unit surface area,
D = Diffusion coefficient of the drug in the release media,
ε = Porosity,
τ = Tortuosity of the matrix,
S = Solubility of the drug in the release media and
C = Concentration of the drug in the tablet.
The two types of diffusion controlled systems are,

Reservoir type

In this type the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of coating.

In the system, a water insoluble polymeric encases a core of drug. Drug with partition into the membrane and exchange with the fluid surrounding the particle or tablet

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= Dε/T [2 A-εCs].Cs.t%

A third possible diffusional mechanism is the 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 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.

C. 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 system.

D. Ion Exchange Resins Controlled Release

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway, and the amount of cross-linked polymer in the resin moiety governs the rate of drug release. Sriwongjanya and Bodmeier investigated the effect of ion exchange resins as release modifiers in matrix formulations containing oppositely charged drugs and they concluded that addition of ion exchange resins to HPMC-matrices significantly modified the release of oppositely charged drug molecules, because a complex formed between the drug and resin retarded drug release [39].

E. pH dependent formulation

The gastrointestinal tract represent different chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. since most of drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent.

However, buffers such as salts of amino acids, Citric acid, Phthalic acid, Phosphoric acid or Tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH Polyethylene glycol 4000 to retard the rate of swelling in water and then further coated with a water-permeable polymer such as Ethyl cellulose to acts as rate-limiting barrier to control drug release.

2. Delayed Transit and Continuous Release Systems

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size based systems.

3. Delayed Release Systems

The design of such systems involves release of drug only at specific site in the GIT.

The drugs contained in such a system are those that are:

- ❖ Destroyed in the stomach or by intestinal enzymes
- ❖ Known to cause gastric distress
- ❖ Absorbed from a specific intestinal site
- ❖ Meant to extent local effect at a specific GI site

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release systems.[40,41].

Effect of Release Limiting Factor on Drug Release [42,43]:

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A. 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 JPSBR: Volume 1, Issue 3: Nov Dec 2011 (143-151) Patel H. *et* al 147 places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

Drug solubility: Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

B. Solution solubility: In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

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 of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors viz, i. Polymer particle size ii. Polymer viscosity iii. Polymer concentration.

i. Polymer particle size: Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution

iii. Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

D. Thickness of polymer diffusional path: The controlled release of a drug from both capsule and

matrix type polymeric drug delivery system is essentially governed by

Fick's law of diffusion: **JD = D dc/dx**

Where, JD is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

E. Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

F. Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. 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. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

G. Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretical and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

H. Diluent's effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

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

Biological Factors Influencing Release From Matrix Tablet [42,44].

- ❖ Biological half-life.
- ❖ Absorption.
- ❖ Metabolism
- ❖ Distribution
- ❖ Protein binding
- ❖ Margin of safety

Biological half-life: The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

Absorption: Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be

Table 3: List of drugs formulated using different polymer and method

DRUGS USED	CATEGORY	METHOD USED	POLYMER USED
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934
Venlafexine	Anti-depressant	Wet Granulation	Beeswax, Caranuaba wax
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit
Minocycline	Antibiotic	Wet Granulation	HPMC-K4M, K15M, EC
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP
Metformine HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
Acarbose	Anti-diabetic	Direct Compression	HPMC, Eudragit
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Ambroxol HCL	Expectorant, Mucolytic	Direct Compression	HPMC-K100M,
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100, S100
Diclofenac Na	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diethylcarbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV
Diltiazem	Ca+2 channel blocker	Direct Compression	HPMC-K100M, K4M, Karaya gum, Locust bean gum, Sod.CMC
Enalpril meleate	ACE inhibitor	Direct Compression	HPMC-K100M, K4M,
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Indomethacin	Anti-inflammatory	Direct Compression	EC, HPMC
Chlorphenarimine meleate	H1 antagonist	Melt-extrusion	Xanthan gum,Chitoson
Losartan potassium	Anti-Hypertensive	Direct Compression	HPMC-K100M, K4M, EC
Metoclopromide	Anti-emetic	Direct Compression	HPMC-K100M, K4M, Eudragit
Naproxen	Morphine antagonist	Direct Compression / Wet Granulation	HPMC, CMC, EC, SSG
Ondansertan	Anti-hypertensive	Direct Compression / Wet Granulation	HPMC-K100M, K4M, K15M
Phenytoin Na	Anti-epileptic	Direct Compression	Tragacanth, Acacia, Guar gum,
Ranitidine HCL	H2 antagonist	Wet Granulation	Chitoson, Carbopol-940
Theophylline	Respiratory depressant	Wet Granulation	Carbopol-934P, HPMC-K100M, K4M,
Tramadol	B2 blocker	Wet Granulation	HPMC-K4M, Karaya gum, Carrageenam gum
Verapemil	Ca+2 channel blocker	Direct Compression	HPMC-K100M, K4M, K15M
Amlodipine	Anti-arrythmatic	Direct Compression	HPMC, EC

approximately 3-4 hours; otherwise, the device will pass out of the potential 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. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.

Metabolism:
Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

- Drug should have law half-life (<5 hrs.)
- Drug should be freely soluble in water.
- Drug should have larger therapeutic window.
- Drug should be absorbed throughout the GIT

Above table show the drug to be formulated as a matrix tablet with polymer and method used for its preparation:

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

Distribution: Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.

Protein Binding: The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless 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.

Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

Physicochemical Factors Influencing Release from Matrix Tablet [42, 44];

Dose size: For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems.
Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

Ionization, *pka* and aqueous solubility: Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise 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. Compounds with very low solubility (<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.

Partition Coefficient: When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes 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 for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

Stability: Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form 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 that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug [45,46].

Conclusion

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

"Cite this article"

N.G.R. Rao, K.R.P. Raj, B.S. Nayak . "Review on Matrix Tablet as Sustained Release" Int. J. of Pharm. Res. & All. Sci.2013; Volume 2, Issue 3, 1-17

Reference:

1. Gupta PK and Robinson JR. Oral controlled release delivery. Treatise on controlled drug delivery. 1992;93(2):545-555.
2. Jantzen GM and Robinson JR. Sustained and Controlled- Release Drug Delivery systems. Modern Pharmaceutics. 1995; 121(4): 501-502.
3. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, and Robert MS. Modified Release Drug Delivery Technology, Marcel Dekker Inc., New York, 2003; 126: 996.
4. Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds. Modern Pharmaceutics, Marcel Dekker Inc. New York, 1996; 72(3): 575.
5. Salsa T, Veiga F and Pina ME. Oral controlled release dosage form. I. cellulose ether polymers in hydrophilic matrices. Drug Develop. Ind. Pharm. 1997; 23: 929-938.
6. Wani MS et al. Controlled Release system-A Review. Pharmaceutical Reviews. 2008; 6(1): 41-46.
7. Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003. JPSBR: Volume 1, Issue 3: Nov Dec 2011 (143-151) Patel H. 151
8. Vidyadhara S, Rao PR, Prasad JA. Formulation And Evaluation Of Propranolol Hydrochloride Oral Controlled Release Matrix Tablets. Indian J.Pharm Sci, 2004; 66: 188-192.
9. Reddy KR, Mutalik S, Reddy S. Once-daily sustained release matrix tablets of Nicorandil: Formulation and in vitro evaluation,AAPS Pharm. Sci. Tech.,2003; 4: 1-9.
10. Mohammed AD, James LF, Michael HR, John EH, Rajabi-Siahboomi AR. Release of Propranolol hydrochloride from matrix tablets containing sodium carboxy methylcellulose and Hydroxy propyl methyl cellulose. Phar. Dev. Tech.,1999; 4: 313-324.
11. Lee BJ, Ryu SG, Cui JH. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. Drug Dev. Ind.Pharm.,1999; 25: 493-501.
12. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd Edn, Vol. 72, Marcel Dekker Inc. New York, 1996: 575.
13. Borguist P, Korner A, Larsson A: A model for the drug release from a polymeric matrix tablets-effect of swelling and dissolution. J Controlled Release 2006; 113: 216-225.
14. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Dev Rev 2001; 48:139-157.
15. http://dissertations.ub.rug.nl/Files/faculties/science/2005/r.steendam/c2.pdf(5Aug, 2006).
16. Reza MS, Quadir MA, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled release drug delivery. J Pharm Pharmaceut Sci 2003; 6 (2): 282-291.
17. Brazel CS, Peppas NA. Dimensionless analysis of swelling of hydrophilic glassy polymers with subsequent drug release from relaxing structures. Biomaterials 1999 Apr; 20 (8): 721-732.

18. Brazel CS, Peppas NA. Modeling of drug release from swellable polymers. Eur J Pharm Biopharm 2000 Jan; 49 (1): 47-58.
19. http://dissertations.ub.rug.nl/Files/faculties/science/2005/r.steendam/c2.pdf(5Aug, 2006).
20. Hariharan M, Wheatley TA, Price JC. Controlled release tablet matrices from carrageenans: compression and dissolution studies. *Pharm Dev Technol* 1997; 2(4): 383–393.
21. Takka S, Rajbhandari S, Sakr A. Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. Eur J Pharm Biopharm 2001; 52:75-82.
22. Alderman DA. Review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage form. Int. J. Pharm. Technol. Prod. Mfr. 1984; 5: 1-9.
23. Melia CD. Hydrophilic matrix sustained release systems 395- based on polysaccharide carriers. Crit. Rev. Ther. Drug Carrier Sys. 1991; 8(4): 421.
24. Aulton Michael .E, The Design and Manufacture of Medicines, Church Hill Living Stone Vol. 3, 2007: 483-494.
25. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and the Pharmaceutical Sciences, vol 72, Marcell Dekker, Inc. New York, 1995: 575-609.
26. Alford N Martin, Patrick J. Sinko. Martin's Physical pharmacy and pharmaceutical sciences, 2006.
27. L. Lachman, HA Lieberman, Joseph L Kanig. The theory and practice of Industrial pharmacy, Verghesh publishing house, 3rd edition, 1990; 346.
28. mamidala RK, Ramana V, sandeep G, "Factors influencing the design and performance of oral, sustained /controlled Release dosage forms" UPSN,2009,S83-S86.
29. Leon S, Susanna W, Andrew BC , "Applied Biopharmaceutics and Pharmacokinetics", 5th edition McGraw-Hill's Access Pharmacy, 2004, 17.1-17.9.
30. Sayed I. Abdel-Rahman, Gamal MM, El-Badry M, Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets, Saudi Pharmaceutical Journal ,2009 ; 17: 283-288.
31. Chandran S, Laila FA and Mantha N, Design and evaluation of Ethyl Cellulose Based Matrix Tablets of Ibuprofen with pH Modulated Release Kinetics, Indian Journal of Pharmaceutical Sciences, September-October 2008.
32. Gothi GD, Parinh BN, Patel TD, Prajapati ST, Patel DM, Patel CN, Journal of Global Pharma Technology, 2010; 2(2): 69-74.
33. Aulton Michael .E, The Design and Manufacture of Medicines, Church Hill Living Stone Vol. 3, 2007: 483-494.
34. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th edition, 1999: 169-171.
35. Muzib Y.Indira, Padma Sree.Kurri: Formulation and evaluation of gum olibanumbased sustained release matrix tablets of Ambroxol hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(2): 195-199.
36. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Ist ed. vallabh prakashan, 2002:156-189.
37. Brahmankar HA, Jaiswal SB. Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000, 348-357 and 337.
38. Venkatraman S, Davar A, Chester A, Kleiner L, Wise DL. An overview of controlled release systems, Handbook of Pharmaceutical Controlled Release Technology, New York, Marcel Dekker, Inc.,2000, 431-465.
39. Sriwongjanya M and Bodmeier R. Entrapment of drug loaded ion exchange particles within polymeric microparticles. Int. J. Pharm. 1988; 48: 217-222.
40. Brahmankar HA, Jaiswal SB, Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000, 348-357 and 337.
41. Venkatraman S, Davar A, Chester A, Kleiner L, Wise DL, An overview of controlled release systems, Handbook of Pharmaceutical Controlled Release Technology, New York, Marcel Dekker, Inc.,2000, 431-465.
42. Brahmankar HA, Jaiswal SB, Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000, 348-357 and 337.
43. Wani MS, Controlled Release System- A Review, 2008, 6 (1), www.pharmainfo.net/review
44. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill. 1999; 169-171
45. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and the Pharmaceutical Sciences, Vol 72, Marcell Dekker, Inc. New York, 1995: 575-609.
46. ICH Guideline on Stability study; 2005