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Controlled release matrix drug delivery system – a review

A.Madhusudhan Reddy*, R.Karthikeyan, Ramya Sri.Vejandla, G.Divya, P.Srinivasa Babu

Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi – 522213.Andhra Pradesh
***Corresponding Author**: **A.Madhusudhan Reddy**
Email id: **msreddympharm@gmail.com**

ABSTRACT

Oral controlled release drug delivery system becomes a very promising approach for those drugs that are given orally but having the high dosing frequency and shorter half life. Matrix tablets serves as an important tool for oral controlled release dosage forms. Problems like patient compliance drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels, associated with their counter parts, the conventional dosage forms were rectified. Tablets offer the lowest cost approach to controlled and sustained release dosage forms. Matrix tablets controlled release has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. This review focus on the various types of matrix system based on polymer used and porosity of matrix system i.e hydrophilic, hydrophobic, fat wax, porous, nonporous, pH sensitive. An effort has been made to consolidate different types of patents granted across the globe for last thirty years in the field of matrix system viz. tablets, pellets etc

Keywords: Hydrophilic polymer, Matrix system, Novel drug delivery system, Controlled release.

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Conflict of interest

The authors are not showing any conflict upon publishing this review article.
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INTRODUCTION

These are the type of 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. One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. [1-4] Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems

include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and cross-linked homopolymers and co-polymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface. Introduction of matrix tablet as controlled release (CR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. [5-7] It excludes complex production procedures such as coating and palletization 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 a controlled release dosage form.

MECHANISM OF CONTROLLED DRUG RELEASE SYSTEMS

Diffusion Controlled 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.

$$J = - D \frac{dc}{dx}$$

Where, D = diffusion coefficient in area/ time

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

Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. There are basically two types of diffusion devices.

Reservoir Type

In the system, a water insoluble polymeric material encloses a core of drug, which controls release rate. 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. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate. [8]

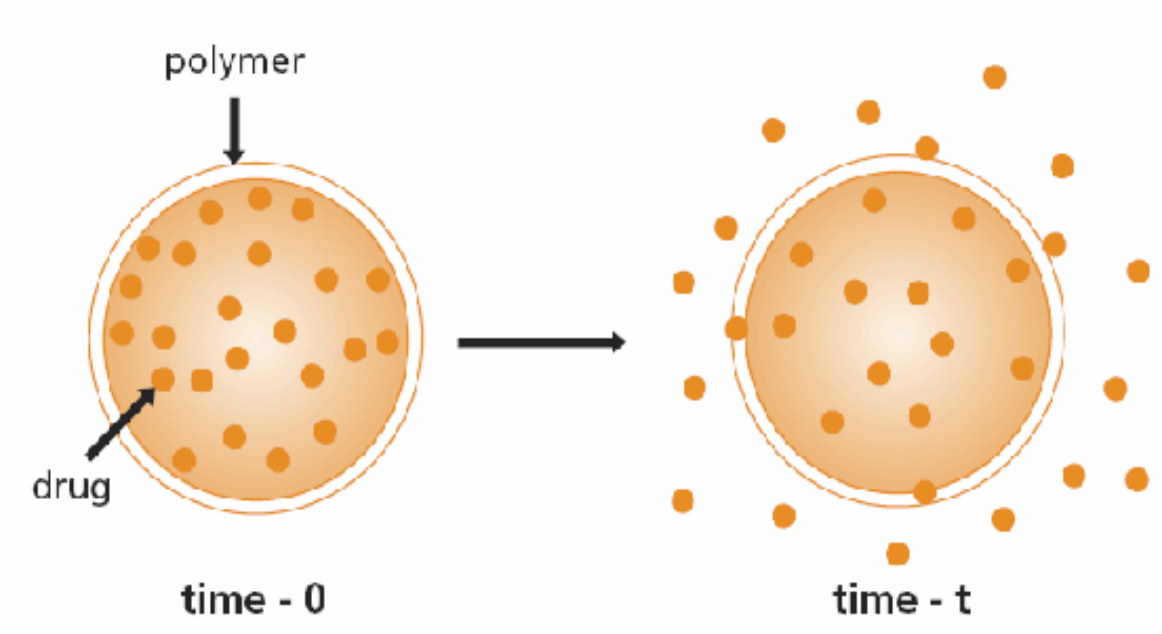


Fig 1: Schematic Representation of Reservoir

Diffusion Controlled Drug Delivery Device

The rate of drug released (dm/dt) can be calculated using the following equation

dm/dt = ADK ΔC/L

Where, A = Area,
D = Diffusion coefficient,
K = Partition coefficient of the drug between the drug core and the membrane,
L = Diffusion pathlength and
ΔC= Concentration difference across the membrane.

Advantage

By this system 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.

Matrix Type

A solid drug is homogenously 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.

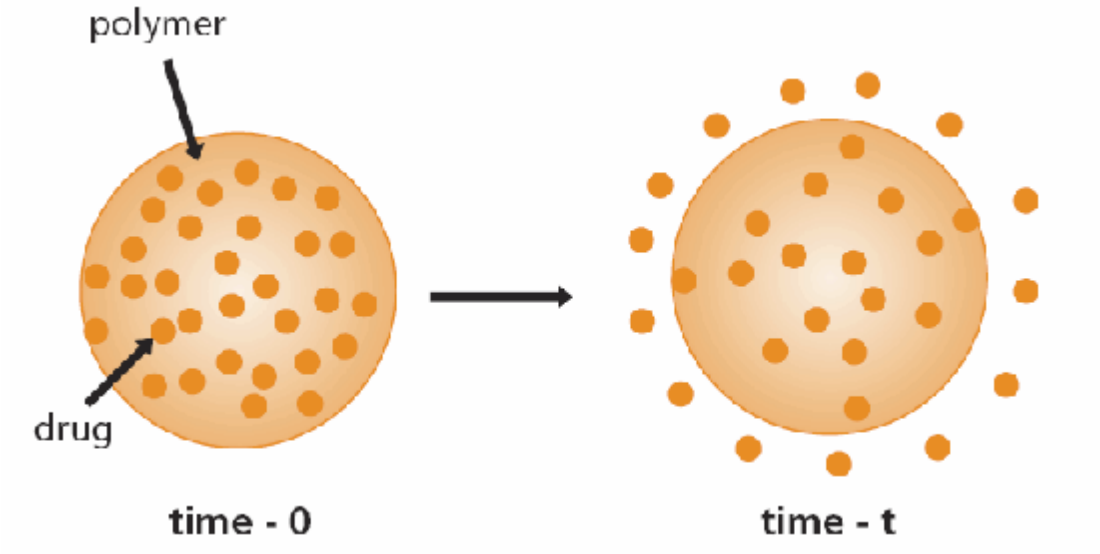


Fig 2: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery Device

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.

Dissolution Controlled Systems

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, in corporating 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

dm/dt = ADS/h

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.

Encapsulation Dissolution Controlled Systems

The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, poly ethylene glycols, polymethacrylates, waxes etc. the dissolution rate of coat depends upon the solubility and thickness of the coating. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. [9]

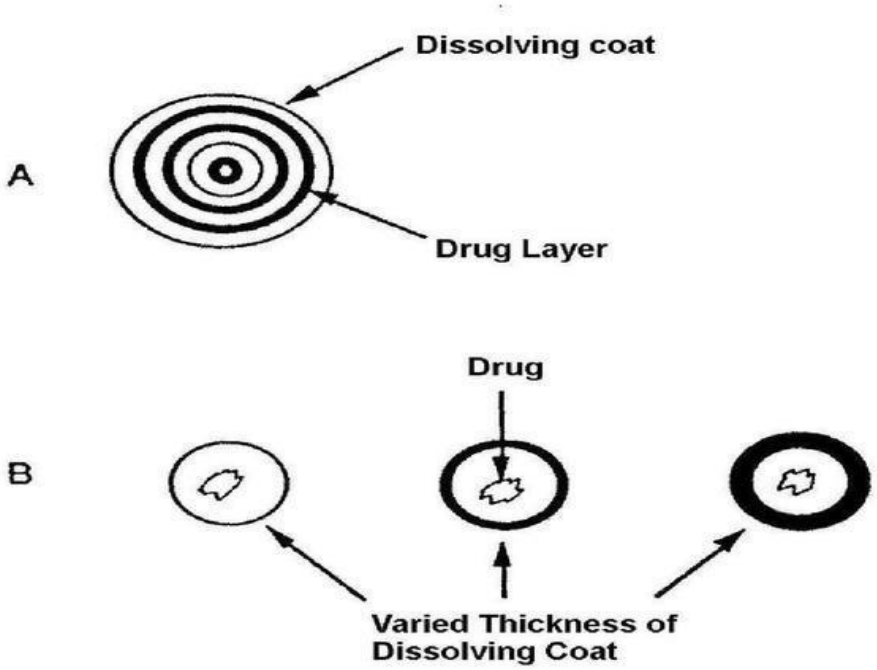


Fig 3: Encapsulation Dissolution Controlled Systems

Matrix Dissolution Controlled Systems

In matrix systems the drug is homogeneously dispersed throughout a rate controlling medium. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil etc which control drug dissolution 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. The wax embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.

Dissolution and Diffusion Controlled Release Systems

The drug core is enclosed 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 diffusion of dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethyl cellulose with poly vinylpyrrolidiene or methylcellulose.

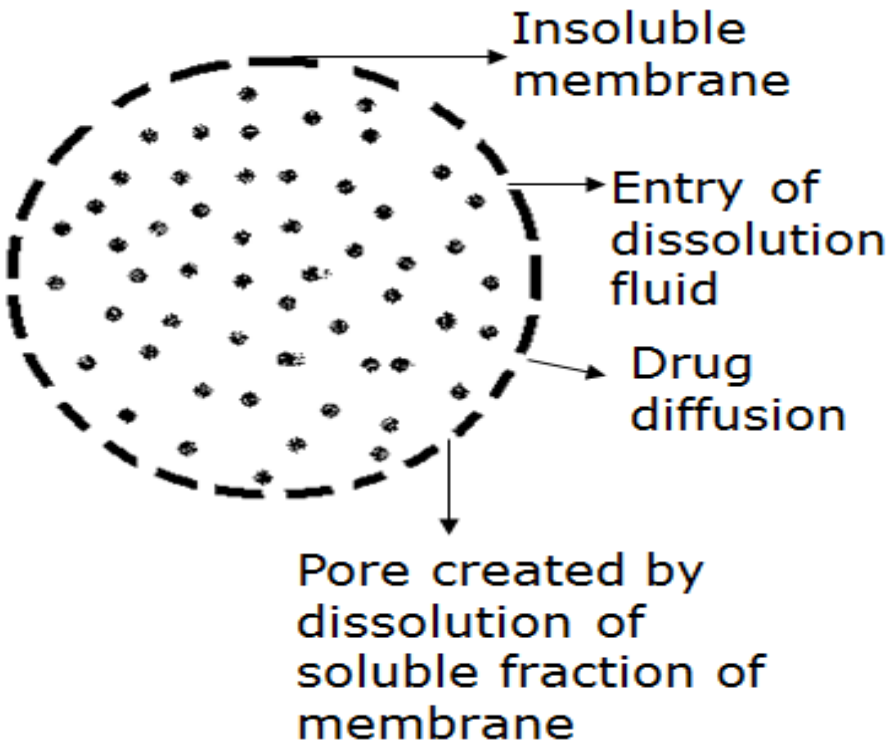


Fig 4: Dissolution and Diffusion Controlled Release System

Water Penetration Controlled Systems

In water penetration controlled delivery systems, rate control is obtained by the penetration of water into the system. They are

Swelling Controlled Systems

Swelling controlled release systems are initially dry and when placed in the body absorbs water or other body fluids and swells. Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

Osmotically Controlled Release Systems

These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt eg NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is they created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero order rate. Release of drug is independent on the environment of the system. [10-12]

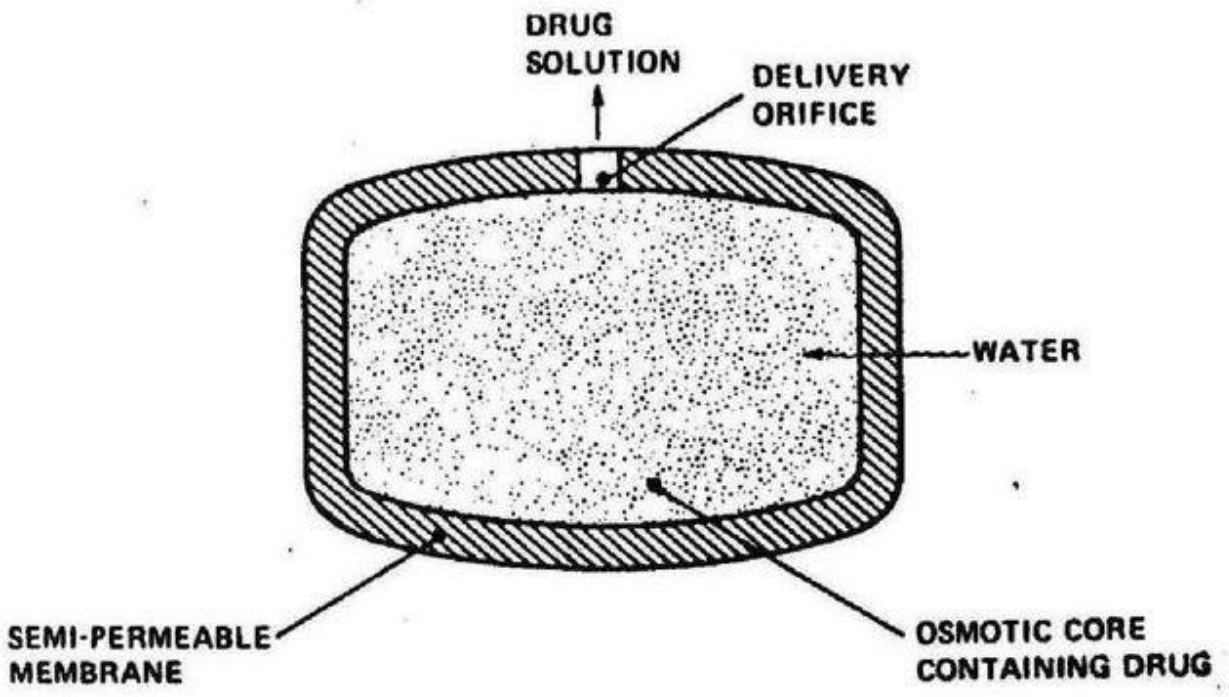


Fig 5: Osmotically Controlled Release System

Methods using Ion Exchange

This system is designed to provide the controlled release of an ionic or ionizable drug. It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules such as codeine base with Amberlite, and then after filtration from the alcoholic medium, coating the drug resin complex granules with a water permeable polymer, e.g. a modified co-polymer of polyacrylic and methacrylic ester, and then spray drying the coated granules to produce the polymer coated drug resin preparation. The drug is released by exchanging with appropriately charged ions in the GIT. The drug is then diffuse out of the resin.

Resin+ - drug- + X^- → resin+ - X- + drug-

Where X- are ions in the GI tract

- The rate of diffusion control by: the area of diffusion, diffusion path length and rigidity of resin.
- Thus, drug release depends on the ionic environment (pH, electrolyte conc.) and the properties of resin.
- **Advantage -** for those drugs which are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism by temporarily altering the substrate.
- **Limitation -** The release rate is proportional to the conc. of the ions present in the vicinity of administration site. So variable diet, water intake & intestinal contents affects the release rate of
- drug.

They are mainly of **2 types -** cation exchange and anion exchange resin.

- **Cationic Drugs**
- A cationic drug forms a complex with an anionic ion exchange resin e.g. a resin with a SO3 - group. In the GI tract Hydronium ion (H+) in the gastrointestinal fluid penetrates the system and activity the release of cationic drug from the drug resin complex.

H+ + Resin – SO3 - Drug + → Resin – SO3 -H+ + Drug+

Anionic Drugs

An anionic drug forms a complex with a cationic ion exchange resin, e.g. a resin with a $[N(CH3)3^+]$ group. In the GI tract, the Chloride ion (Cl-) in the gastrointestinal fluid penetrates the

system and activates the release of anionic drug from the drug resin complex.

Cl- + Resin – [N (CH3)3+] - Drug- → Resin– [N (CH3)3+] - Cl- + Drug-

Chemically Controlled Release Systems

Chemically controlled release systems are the systems that change their chemical structure, when exposed to biological fluid. Mostly, biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically safe and progressively smaller moieties. It is of two types and they are **Erodible systems** and **Pendent chain system.**

Erodible Systems

In erodible systems, the mechanism of drug release occurs by erosion. Erosion may be two types and they are

- **Bulk Erosion** process polymer degradation may occur through bulk hydrolysis
- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse out of the matrix through the voids caused by swelling
- Loss of the small compounds accelerates the formation of voids thus the exit of drug
- Molecules.
  e.g. poly lactide, polyglycolic acid
- **Surface Erosion** process Polymers like polyorthoesters and polyanhydrides etc occurs degradation only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the delivery system.
- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse from the interface of the polymer
- Loss of the small compounds leads to drug loss
- Note these polymers do not swell.
  e.g. polyanhydrides

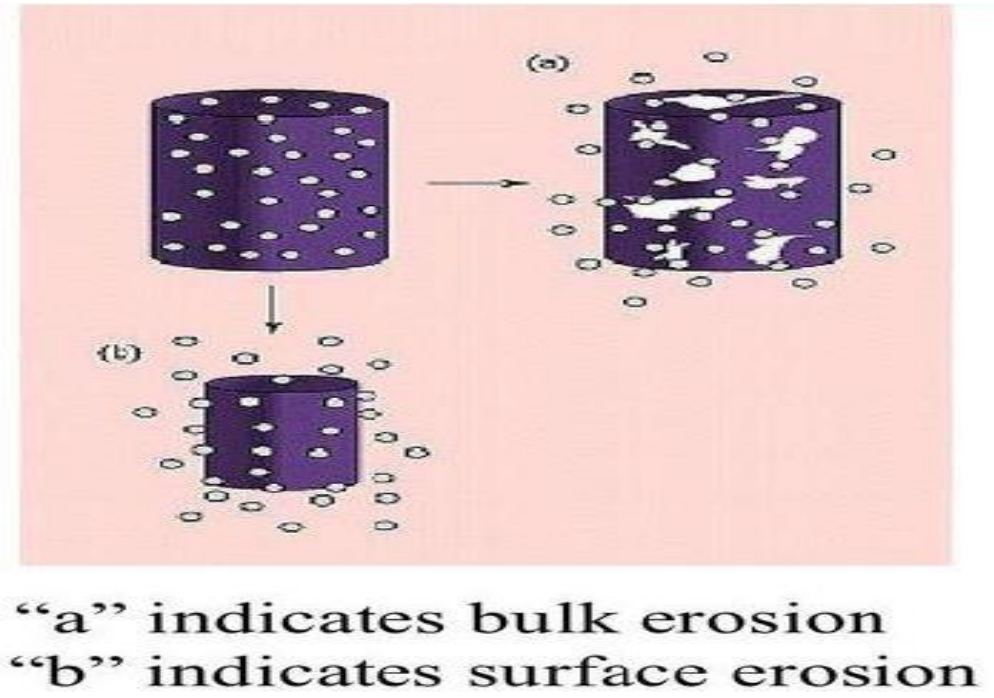


Fig 6: Bulk Erosion and Surface Erosion

Pendent Chain System

Pendent chain systems consist of linear homo or copolymers with the drug attached to the backbone chains. The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages. Zero order can be obtained and the cleavage of the drug is the rate controlling mechanism. Example for polymers used in pendent

chain systems like n-(2-hydroxy propyl) methacrylamide etc.

pH–Independent Formulations

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of

prolongation, further the chemical environment throughout the length of gastrointestinal tract is

constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from controlled 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 independent drug release. A buffered controlled 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. [13-15]

Hydrogels

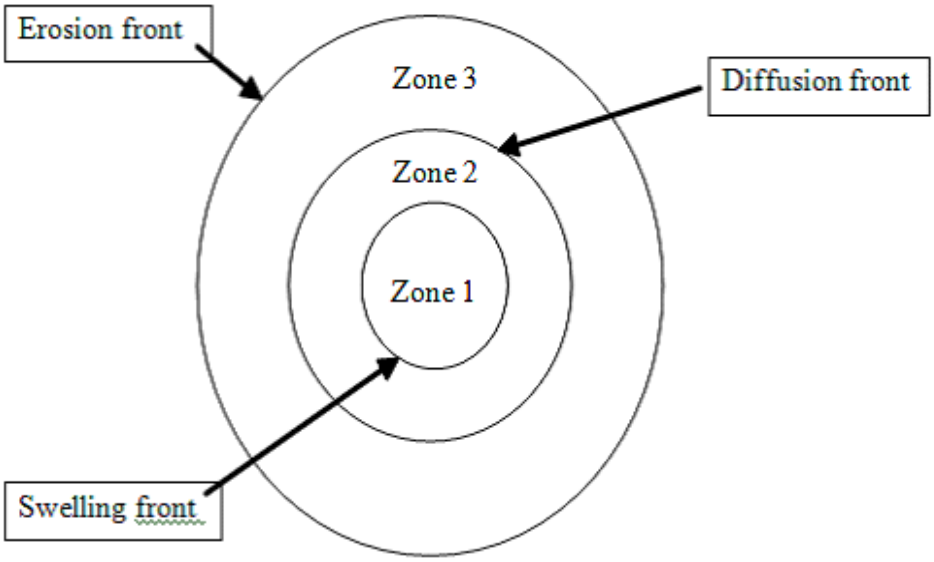
Hydrogels are water swollen three dimensional structures composed of primarily hydrophilicpolymers. They are insoluble because of chemical or physical cross-links. The physical cross-links include crystallites, entanglements or weak associations like hydrogen bonds or vander waals forces. These crosslinks provide the physical integrity and network structure. Hydrogels provide desirable protection of labile drugs, peptides and proteins.

Altered Density Formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract like High density approach and Low density approach.

MATRIX SYSTEM

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, 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 towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion rate of dissolved drug leaving the matrix.



Advantages of Matrix system

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) Better drug utilization.
7) Minimize drug accumulation with chronic dosing.
8) Can be made to release high molecular weight compounds.
9) Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
10) Reduction in health care cost.
11) Usage of less total drug.
12) Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
13) Improved patient compliance.

Disadvantages of Matrix system [16-17]

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.

CLASSIFICATIONS OF MATRIX SYSTEM BASED ON POLYMER TYPE

Hydrophilic matrix system

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tabulated by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behavior from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true formulation of water soluble drug. 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,

Cellulose derivatives

- Hydroxyethyl cellulose,
- Hydroxypropylmethyl cellulose (HPMC) 25, 100,
- 4000 and 15000 cps,
- Sodium carboxyl methyl cellulose

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

- Polymer which is used in acrylic acid category is Carbopol 934.

Hydrophobic Matrices

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. Controlled 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. In this type of matrix system, a hydrophobic polymer material is granulated with a drug by using latex or pseudo latex as granulating fluid. Examples of materials used in this system are: polyvinyl chloride, ethyl cellulose, cellulose acetate and polystyrene. Controlled release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between thecompacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminute or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.[18-20]

Fat-wax matrix system

In this type of matrix system, lipid waxes or other related materials are used in the preparation of the matrices. The drug released in this system occurs through both pore diffusion and erosion. The matrices are more sensitive to digestive fluid in the gut as compared to an insoluble polymer matrix. Examples of retardant materials used in the matrix bases of this system are: carnauba wax in combination with stearyl alcohol or stearic acid.

Biodegradable matrix system

In this type of matrix system, the polymeric materials used consist of monomers which are linked to each other through functional groups with instable functionality. The degradation of polymeric materials into oligomers and monomers occurs through either biological enzymes produced by surrounding tissues or non-enzymatic processes. Examples of natural polymers used in thismatrix base are proteins, polysaccharides, aliphatic polyesters, and polyanhydrides are synthesized polymers.

Mineral matrix system

In this type of matrix system, the polymeric material used is hydrophilic carbohydrate and it can be obtained from different species of brown seaweeds by the use of dilute alkali.

CLASSIFICATIONS OF MATRIX SYSTEM BASED ON POROSITY SIZE

Macro-porous matrix system

In this type of matrix system, drug diffusion occurs through pores with a size range of 0.1 to 1 µm. This system is suitable for drug molecules with molecular sizes less than 1 µm.

Micro-porous matrix system

In this type of matrix system, drug diffusion occurs through pores with a size range of 50 up to 200 A °. This system is suitable for small drug molecules with molecular sizes less than 200 A°.

Non-porous matrix system

In this type of matrix system, drug diffusion occurs through the network meshes rather than by diffusion through small pores. [21]

CLASSIFICATIONS BASED ON OTHER MISCELLANEOUS WAY OF MATRIX PREPARATIONS

Multilayered matrix system

In this type of matrix system, the matrix core is made of hydrophilic substances in which the drug molecules are coated with a semi-permeable polymeric material. This semi-permeable polymeric material is utilized as a barrier-layer on both surfaces of the core during preparation. An

alteration of the swelling rate of the core can occur due to the presence of barrier-layers, resulting in minimizing the surface area for drug molecules during the release process. Different drug release profiles can be obtained by varying the geometry of the barrier-layer in the matrix. The drug release is controlled by swelling, gelling and finally dissolving the barrier-layers of the matrix.

Floating matrix system

In this type of matrix system, the bulk density of the matrix is lower than the gastric fluid in the stomach. After creating buoyancy in the stomach, the release of drug molecules from the matrix can occur slowly. Drug release can occur over a long period of time, which prolongs gastric residence time and thereby increases the bioavailability of fast release drug molecules.Diltiazem HCl is one of the examples of a fast release drug which was successfully prepared in a controlled release using the floating matrix system and detected on the sensitive HPLC method. The steady release of drug from this hydrophilic matrix system is supported bycontrol of the buoyancy effect and continuous release. HPMC is a widely used polymer in this type of hydrophilic matrix system. It has a pH independent gelling agent property. As a result of this effect, swelling and erosion mechanisms can be obtained together to control and slow down the fast release drug in a steady manner.

pH sensitive matrix system

In this type of matrix system, an enteric coating of the solid dosage form can provide protection for the drug from the harsh acidic media of the stomach. Thus, low pH sensitive drug molecules can reach the small intestine and colon safely. This type of matrix system is applicable to protect antigen or protein molecules from the harsh acidic media of the stomach after oral administration. PH sensitive polymers such as HPMC phthalate or cellulose acetate phthalate can be used in this type of matrix system. These types of polymers are pH-sensitive materials. This matrix system works by releasing the enteric coated drug at a specifically high pH value in the GIT, where drug absorption can occur in the right location.

Mucoadhesive matrix system

In this type of matrix system, the drug is released over a controlled period of time. The targeted tissues can be ocular, respiratory, gastrointestinal, buccal, nasal, rectal, urethral and vaginal tissues. In addition, this type of matrix system can be applied to any mucosal tissue in the body in the GIT. The used materials in this system are swellable hydrophilic polymers which can interact with the glycoproteins being available in the mucous layer of the gut.

FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS

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.

Polymerhydration

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, 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.

Drugsolubility

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.

Solution solubility

In view of in vivo (biological) sink condition maintained actively by 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.

Polymerdiffusivity

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and 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.

Polymer particle size

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.

Polymerviscosity

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.

Polymerconcentration

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.

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. [22]

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 ofdrug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

Drugloadingdose

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.

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 found that release from small tablet is faster than large cylindrical tablets.

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.

Additives

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble 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. [23]

POLYMERS USED IN MATRIX TABLETS

Hydrogels

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

Soluble polymers

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

Biodegradable polymers

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

Non-biodegradable polymers

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

Mucoadhesive polymers

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

Natural polymers in controlled release drug delivery

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

METHODS OF PREPARATION OF MATRIX TABLETS

Direct Compression

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

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.

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.

EVALUATION PARAMETER

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study etc.

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Uniformity of weight

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg. Weight control is based on a sample of 20 tablets.

Dimensions

The dimensions (diameter and thickness) were then determined to within ± 0.01 mm by using digital vernier calipers. Thickness of the tablets was determined using a vernier caliper.

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability**.** Hardness of the tablets was determined using a hardness testing apparatus (Monsanto Type). A tablet hardness of about 5-6 kg/cm2 is considered adequate for mechanical stability.

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) or a sample of tablets is dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w.10% Friability = $(W_0\text{-}W)/ W_0 \times 100$

In-vitro dissolution study

The release rate of tablet was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml solvent and set RPM. A sample of the solution was withdrawn from the dissolution apparatus at different time interval. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a membrane filter. Absorbance of these solutions was measured using a UV is double beam spectrophotometer.[24-25]

CONCLUSION

By the above discussion, it can be easily concluded that controlled-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. Preparatory procedures easily allow adaptation of release kinetics to delivery needs. This suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose administration etc. So matrix tablets can overcome the above problems of conventional oral drug delivery.

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