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RECENT APPROACH FOR DRUG RELEASE FROM MATRIX TABLET: A REVIEW

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ABSTRACT

Oral controlled release drug delivery system become a very promising approach for those drugs that are given orally but having the high dosing frequency and shorter half-life. Oral controlled release dosage form serve as an important tool for the matrix tablets. The basic rationale of controlled release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. The release of the drug through such system includes both dissolution controlled as well as diffusion controlled mechanism, 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. Tablets offer the lowest cost approach to controlled and sustained release dosage forms. Matrix tablets controlled release has given a new breakthrough for oral drug delivery system in the field of pharmaceutical technology.

KEYWORDS

Matrix system, Controlled release, Advantages, Disadvantages and Approaches of controlled release.

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INTRODUCTON

The oral drug delivery system is the popular and utilized route for the administering the therapeutic agent among the all route because it has advantages like unit dosage form, low cost, cheapest for packaging etc, and this route suffers from certain draw backs like patient noncompliance, multiple dosing, therapeutic failures that limits its use. In order to overcome these drawbacks of conventional drug delivery there is a need of development of new drug delivery system¹. Oral controlled delivery systems have gained increased importance and interest since it is necessary to improve patient compliance and show good systemic absorption.

Matrix systems are widely used for the purpose of controlled release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed, the variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, and broad regulatory acceptance².

The controlled release (CR) oral formulations are the delivery of the therapeutic agent from the formulation to the site of action or to the site of absorption. The therapeutic agent from the delivery system in a pre-designed fashion thus maintains a constant plasma level and improves the therapeutic efficacy. A successful therapy requires the elimination of those periods when plasma concentration falls below the therapeutic value. This fact is especially important in the treatment of chronic diseases, where the symptoms may occur during night or early morning. These events could not be managed by conventional formulations.

Controlled release is used as an umbrella term that involves a range of delivery systems with different release profiles³.

- Delayed release
- Repeat action
- Prolonged release
- Extended release
- Sustained release

Delayed release (DR)

Delayed release indicates that the drug is not being released immediately but at a later time.

Repeat action (RA)

Repeat action indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

Prolonged release (PR)

Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. The onset of action is also delayed due to an overall slower release of the drug from the dosage form.

Extended release (ER)

Extended release refers to the slower release of the drug so that plasma concentrations are maintained at a therapeutic level for an extended period of time (usually between 8 and 12 hrs).

Sustained release (SR)

The release of the drug is retarded for a delayed and/or prolonged period of time (slow first order release) in the systemic circulation. The onset of action and the therapeutic efficacy of the drug are often sustained in such delivery systems⁴.

ADVANTAGES AND LIMITATIONS OF CONTROL RELEASE DOSAGE FORMS⁵

Clinical Advantages

1. Reduce the frequency administration of drug
2. Increased patient compliance
3. Reduction in drug level fluctuation in blood
4. Total usage of drug is reduced when compared with conventional therapy
5. Drug toxicity is reduced (local/systemic)
6. Stabilization of medical condition (because of more uniform drug levels)
7. The bioavailability of some drugs increased because of spatial control

Commercial / Industrial Advantages

1. Product differentiation can possible
2. Market expansion
3. Patent extension

Potential Limitations

1. Delay in onset of drug action
2. Greater dependence on GI residence time of dosage form
3. Probability of less accurate dose adjustment.
4. Higher cost for the unit dose when compared with conventional doses
5. Not all drugs are suitable for formulating into CR dosage form.

Disadvantages⁶

1. Unpredictable or poor *in-vitro* and *in- vivo* correlation
2. Dose dumping
3. Reduce potential for dosage adjustment
4. Poor systemic availability in general
5. Patient variation
6. Increased potential for first pass clearance
7. Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make to product very difficult or sometimes impossible to prepare.
8. Increased cost.

9. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity in varying strengths.

METHODS USED TO ACHIEVE CONTROLLED RELEASE OF ORALLY ADMINISTERED DRUGS

Diffusion Controlled System

Basically this process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

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

Where,

J = The flux of the drug (in amount / area -time),

D = diffusion coefficient in area/ time

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

Diffusion systems are

There are basically two types of diffusion devices

Reservoir type

In this process shows the 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.

It can be calculated using the following equation,

$$\frac{dm}{dk} = \frac{ADK \Delta C}{\ell}$$

Where,

(dm/dt)=The rate of drug released

A = Area

D = Diffusion coefficient

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

ℓ = Diffusion path length

ΔC = Concentration difference across the membrane.

Matrix Type

This system characterized by the solid drug is homogeneously 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.

Dissolution Controlled Systems

This system characterized by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and

coating drug particles with polymeric materials of varying thickness. The solubility of the drug provides the source of energy for drug release.

The rate of dissolution (dm/dt) can be calculated by

$$\frac{dm}{dt} = \frac{ADS}{h}$$

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.

Reservoir Dissolution Controlled Systems

The drug particles are coated with slowly dissolving materials like cellulose, poly ethylene glycols, polymethacrylates, waxes etc. the dissolution rate is depends upon the solubility of the thickness of the coating. The maintenance of drug levels at late times will be achieved from those with thicker coating.

Matrix Dissolution Controlled Systems

This system obtained by the homogeneously dispersed drug throughout a rate controlling waxes like 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. This system is prepared by dispersing the drug in molten wax and solidifying and granulating the same.

Dissolution and Diffusion Controlled Release Systems

It is characterized by the drug core is surrounded by the partially soluble membrane. Pores are created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core. This showed drug dissolution and diffusion of dissolved drug out of the system. The example of partially soluble coat is using a mixture of ethyl cellulose with poly vinyl pyrrolidene or methylcellulose⁷.

Methods using ion exchange resin

This system is designed by the drug resin complex formation when an ionic solution is kept in contact with ionic resins. From these complexes the drug gets exchanged in gastrointestinal tract and released with excess of Na⁺ and Cl⁻ present in gastrointestinal tract. The drug is then diffuse out of the resin.

pH- Independent formulations

This system is based on the buffered controlled release formulation, it is prepared by mixing a basic or acidic drug with one or more buffering agents like citric acid, amino acid, tartaric acid and granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. This released the drug by GI fluid permeates through the membrane and the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

Altered density formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

- High-density approach
- Low-density approach⁸

Methods using osmotic pump pressure

This systems are fabricated by the semi permeable membrane like cellulose acetate is placed around the tablet, the drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery orifice in tablet core. Release of drug is independent on the environment of the system⁹.

CHARACTERISTIC THAT MAKES DRUGS SUITABLE FOR CONTROLLED- RELEASE FORMULATION

Biological characteristic

- Absorption
- Distribution
- Metabolism
- Protein binding
- Biological half-life.

Absorption

The absorption behaviour of a drug can affect its suitability as a controlled release product. The aim of formulating is a controlled release product is to place a control on the delivery system. The transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Therefore the compounds with lower absorption rate constants are poor candidates for controlled release systems. Some possible reasons for a low extent of absorption are poor water

solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

Distribution

The distribution of drugs in tissues can be important factor in the over all drug elimination kinetics. Hence it is not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue. One aspect of this distribution is binding of drug to tissue and proteins in blood. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral CR drug delivery system. For design of controlled release products, one must have information on disposition of the drug.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Drug which extensively metabolized is not suitable for CR drug delivery system and a drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for CR delivery, since it could be difficult to maintain constant blood level e.g. Levodopa, Nitroglycerine. Enzymes are most found in intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzyme system. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution¹⁰.

Protein Binding

Protein binding plays a significant role in its therapeutic effect regardless the type of dosage form. The Pharmacological action of drug depends on unbound drug concentration drug rather than total concentration. All drug bound to some extent to plasma and tissue proteins, Since blood proteins are the most part recirculated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if high degree of drug binding occurs.

Biological Half-Life

The usual goal of an oral controlled-release product is to maintain therapeutic blood levels over an extended period. Half-life can be described by the elimination rate. Each drug has its own

characteristic elimination rate, which is the sum of all elimination process, the elimination process like metabolism, urinary excretion, and all other processes that permanently remove drug from the blood stream. In general, drugs with half-lives shorter than 2 hours are poor candidates for controlled-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in controlling forms¹¹.

Physicochemical characteristics

Dose Size

In orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 gm is considered maximal for a conventional dosage form. This also holds for controlled-release dosage forms. The compounds that require large dosing size can given by multiple amounts or formulated into liquid system.

Partition Coefficient

Partition coefficient is defined as fraction of drug in oil phase to that of an adjacent aqueous phase. 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. Compounds which are lipophilic in nature having high partition coefficient because biological membrane are made from lipidic. The poorly aqueous soluble drug 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. Therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration¹².

Aqueous solubility

Most of the drugs are weak acids or weak bases drugs with low water solubility will be difficult to incorporate into controlled release mechanism. The drug having high water solubility can dissolve in water or gastrointestinal fluid readily shows the burst release and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate highly water soluble drug in the dosage form and retard the drug release especially when the dose is high.

Drug stability

Orally administered drugs undergo both acid\base hydrolysis and enzymatic degradation when administered oral rout. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach the prolong delivery to the entire GI tract are beneficial. If drug is administered in controlled release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. The greater quantity of drug is delivered in small intestine and is being subjected to more degradation. Propentherine and probanthine are representative example of such drug¹³.

CHARACTERISTICS THAT MAY MAKE A DRUG UNSUITABLE FOR CONTROLLED RELEASE DOSAGE FORM¹⁴

- Short elimination half-life < 2 hr
- Long elimination half-life >8 hr
- Narrow therapeutic index

Matrix tablet

Matrix system is one of the least complicated approaches to the manufacture of controlled release dosage forms. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic or hydrophobic polymers.

Advantages of Matrix Tablet¹⁵

1. Easy to manufacture
2. Versatile, effective and low cost
3. Can be made to release high molecular weight compounds
4. The controlled release formulations may maintain therapeutic concentrations over prolonged periods.
5. The use of control release formulations avoids the high blood concentration.
6. Control release formulations have the potential to improve the patient compliance
7. Reduce the toxicity by slowing drug absorption.
8. Minimize the local and systemic side effects.
9. Improvement in treatment efficacy.

Disadvantages of Matrix Tablet

1. The remaining matrix must be removed after the drug has been released. .

2. The release rates of drugs are variously affected by factors like food and the rate transit through the gut.
3. Achievement of zero order release is difficult.
4. The remaining matrix must be removed after the drug has been released.
5. The drug release rates vary with the square root of time.
6. Not all drugs can be blended with a given polymeric matrix.

CLASSIFICATION OF MATRIX TABLETS

On the Basis of polymer used

Hydrophobic Matrices (Plastic matrices)

In this method of obtaining controlled release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. The rate controlling step in these formulations is liquid penetration into the matrix. The dissolving drug has diffused through a network of channels that exist between compacted polymers particles in this way the controlled release can be achieved. Examples of hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acryl ate polymers and their copolymers.

Lipid Matrices

These matrices prepared by the lipid waxes and related materials. The mechanism of drug release from these matrices occurs through both pore diffusion and erosion. Release characteristics are more sensitive to gastro intestinal fluid composition than to totally insoluble polymer matrix. For many controlled release formulation Carnuba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base¹⁶.

Hydrophilic Matrices

These hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile. Hydrophilic matrix tablets may be defined as "Homogeneous dispersion of drug molecules within Hydrophilic polymers. The hydrophilic polymers with high gelling capacities with base excipients are of particular interest in the field of controlled release. The hydrophilic matrix requires water to activate the release mechanism.

Biodegradable Matrices

This system consists of the polymers which consist of monomers linked to one another through functional groups and have unstable linkage in the backbone. These systems are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted.

Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds.

Example: Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix

Designing of porous matrix is useful for stable uniform porous structure and well- defined surface properties. This system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

Macro porous Systems

In this systems the pores of matrix helpful for the diffusion of drug, the pore size range from 0.1 to 1 μm . This pore size is larger than diffusant molecule size.

Micro porous System

The diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 - 200 A° , which is slightly larger than diffusant molecules size.

Non-porous System

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present¹⁷.

Miscellaneous

Multilayered matrix system

A new multi-layer matrix tablet design has recently been proposed for constant drug release. Multilayered tablets, for controlled release usually consist of a drug core layer which sandwiched by external layers. These may contain dissimilar amounts of drug to form a concentration gradient matrix or just act as a barrier layer. Multi layered matrix devices are based firstly on the matrix

hydration rate and subsequent swelling and secondly modulation of the surface of matrix through which the drug can be delivered. Main advantage of this system is to avoid dose dumping.

Floating matrix system

The principle of these systems offers a simple and practical approach to achieve increased gastric residence time and sustained drug release for the dosage form. These systems develop by melt granulation technique that generates CO₂. Prolonged drug release obtained by reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at the desired rate. These systems are designed to retain drug in the stomach for longer period of time, and hence significantly prolong the gastric residence time of drugs.

pH sensitive matrix system

These are intestine and colon targeted delivery system with sustained release. In this system enteric coating provide the protection of the tablet matrix from acidic environment of the stomach by employing pH sensitive polymer. Which swell or solubilise in response to an increase in pH to release the drug.

Bio mucoadhesive matrix system

Mucoadhesive sustained matrix system offer several advantages over other simple matrix tablet systems. Because they provide controlled drug release over time and target and localize the dosage form to a specific site. Mucoadhesive drug delivery devices can be applied to any mucosal tissue in the body, including the ocular, respiratory, gastrointestinal, buccal, nasal, rectal. Bio mucoadhesive excipients are generally highly swellable hydrophilic polymers. Which interact with the glycoprotein's in the mucous layer¹⁸.

POLYMERS USED IN THE MATRIX¹⁹

There are number of polymers may be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required. Polymers used for matrix tablets may be classified as:

Hydrogels

1. Poly-hydroxyethyl methylacrylate (PHEMA)

2. Cross-linked polyvinyl alcohol (PVA)
3. Cross-linked polyvinyl pyrrolidone (PVP)
4. Polyethylene oxide (PEO)
5. Polyacrylamide (PA)
6. Hydroxypropyl methyl cellulose (HPMC)

Soluble polymers

1. Polyethylene glycol (PEG)
2. Polyvinyl pyrrolidone (PVP)
3. Polyvinyl alcohol (PVA)

Biodegradable polymers

1. Polylactic acid (PLA)
2. Polyglycolic acid (PGA)
3. Polycaprolactone (PCL)
4. Polyanhydrides
5. Polyorthoesters

Non-biodegradable polymers

1. Polyethylene vinyl acetate (PVA)
2. Polydimethylsiloxane (PDS)
3. Polyether urethane (PEU)
4. Polyvinyl chloride (PVC)
5. Cellulose acetate (CA)
6. Ethyl cellulose (EC)

Mucoadhesive polymers

1. Polycarbophil,
2. Sodium Carboxymethyl cellulose
3. Polyacrylic acid
4. Tragacanth
5. Methyl cellulose
6. Pectin

Natural gums

1. Xanthan gum
2. Guar gum
3. Karaya gum
4. Gum Arabic.

EVALUATION OF MATRIX TABLETS

Thickness

Thickness of the tablets was determined using a vernier caliper.

Weight variation test

The weight of tablet is measured to ensure that a tablet contain the proper amount of drug. Weigh 20 tablets individually and calculate the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits.

It is calculated by formula

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where,

PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = Initial weight of tablet.

Drug content (Assay)

Drug content was determined by taking an accurately weight amount of powdered with water and solution was filtered through 45µ membrane. The absorbance was measured in UV visible spectrophotometer.

Hardness

Hardness of the tablets was determined using a hardness testing apparatus of Monseto and Pfizer hardness tester. A tablet hardness of about 5-6 kg/cm² is considered adequate for mechanical stability.

Friability

Roche friabilator was used to measure the friability of the tablets. Initial weight of tablet (W₀) had taken in the drum for a fixed time (100 revolutions) for 4 min, and weighed (W) again. The weight loss should not be more than 1% w/w. It is calculated from the formula²⁰.

$$\% \text{ Friability} = (W_0 - W) / W_0 \times 100.$$

In-vitro drug release

Drug release study was determined in USP II dissolution test apparatus. In general, a single matrix tablet is placed in dissolution beaker containing 900 ml dissolution medium.

The beaker was maintained at 37° ± 0.5° C by a constant temperature bath. The rpm speed was adjusted to turn at the specified speed (50 rpm), and sample of the fluid are withdrawn at intervals to determine the amount of drug in the solution. Matrix tablet slowly release the drug for a prolong period of time as compare to conventional tablet²¹.

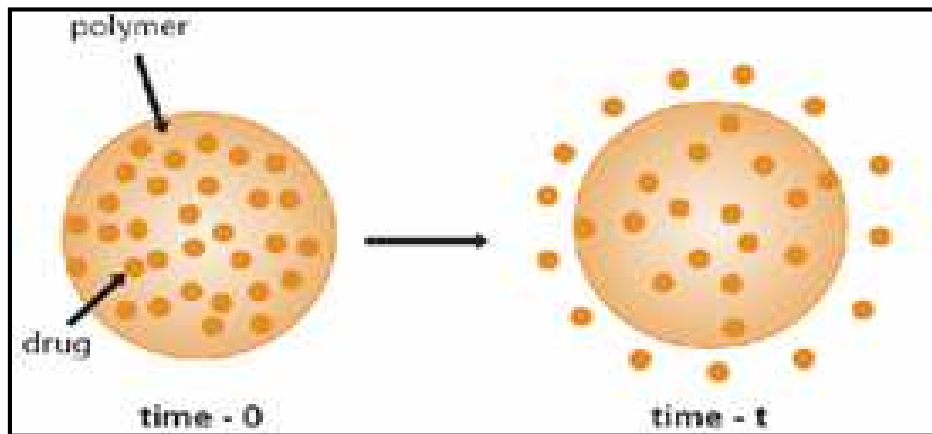


Figure No.1: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

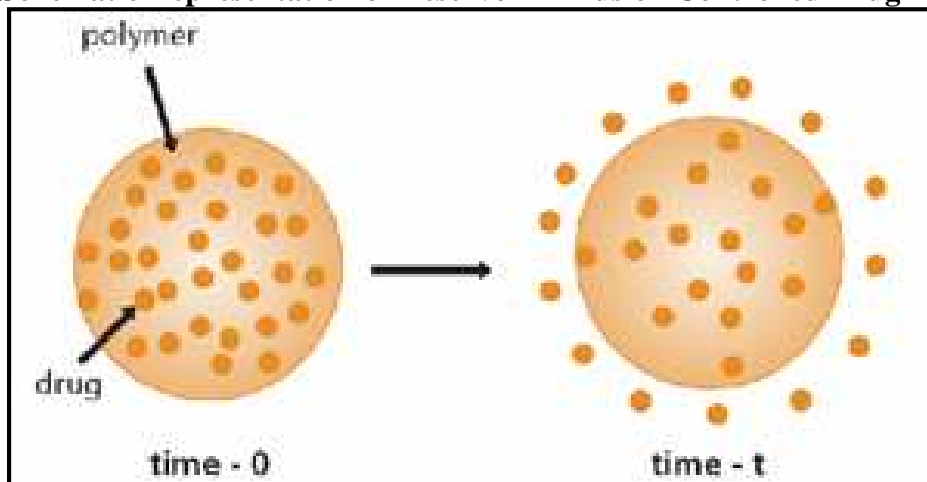


Figure No.2: Schematic Representation of matrix Diffusion Controlled Drug Delivery Device

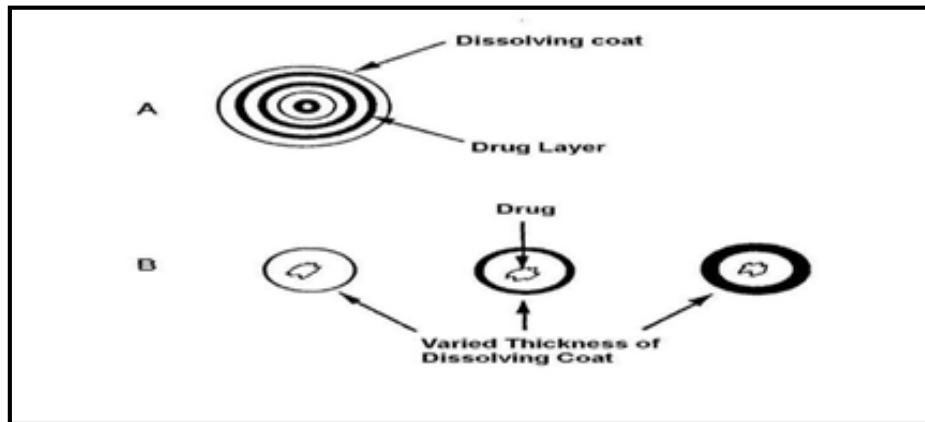


Figure No.3: Schematic representation Reservoir dissolution controlled system

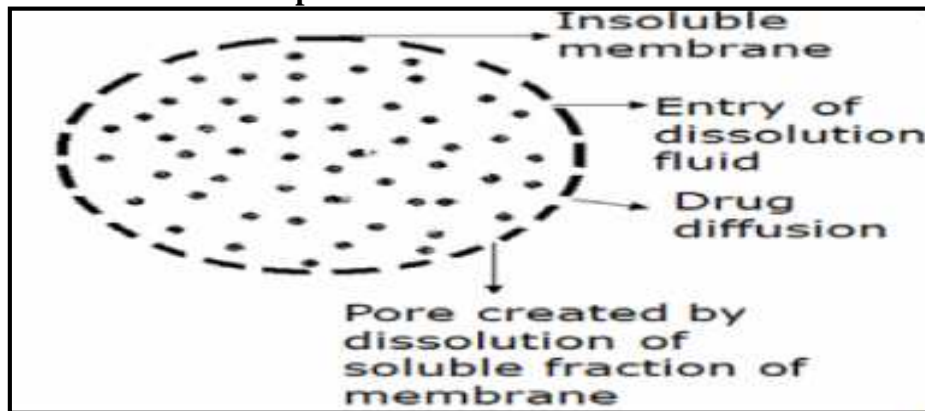


Figure No.4: Schematic representation of Dissolution and Diffusion Controlled Release System

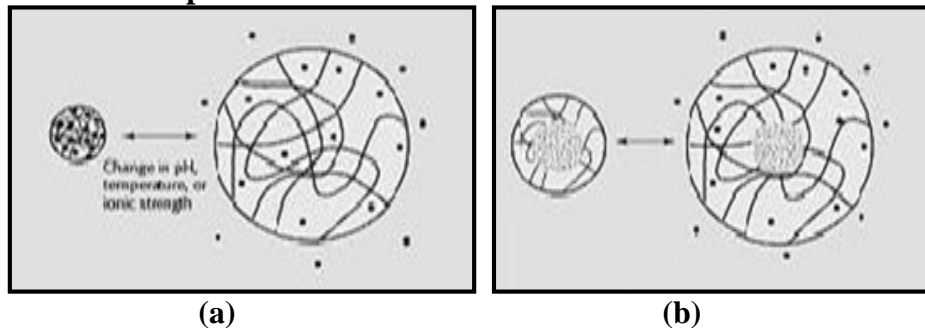


Figure No.5: Schematic representation of Drug delivery from environmentally pH sensitive release systems

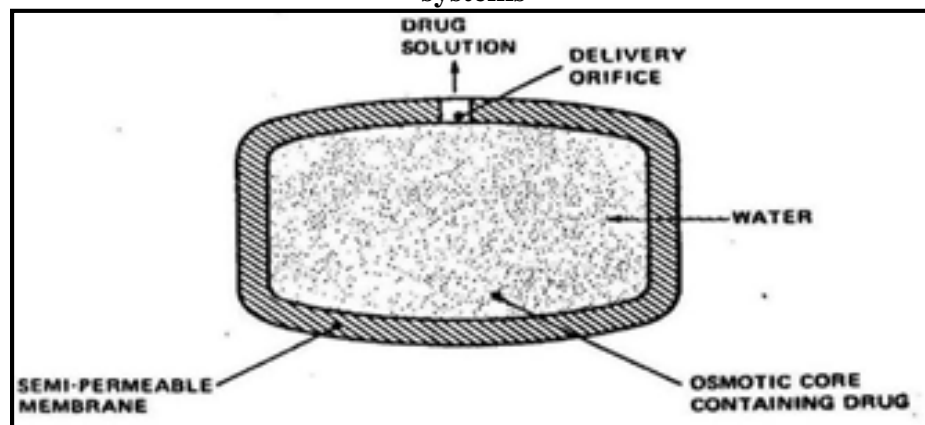


Figure No.6: Schematic representation of Drug delivery from osmotic pump pressure systems

CONCLUSION

The focus of this review article has been on the formulation of controlled-release matrix tablets, advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, controlled-release matrix tablets trends towards the optimization of the dosage form design.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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