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Sustained and Controlled Drug Delivery System: A Review

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Keywords: Controlled release drug delivery system (CRDDS), Sustained release drug delivery system (SRDDS), Classification, Advantages, Disadvantages, Drug design, Polymers used, and Market formulations.

ABSTRACT

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of a controlled drug delivery system that could revolutionize the method of medication and provide a number of therapeutic benefits like multiple dosing and single doses of sustained and controlled delivery formulations. Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout GI transit and also the system that target the delivery of a drug to a specific region within the Gastro-Intestinal (GI) tract for either a local or systemic action. Over the past decades, an entirely new technique for the delivery of a drug and other biologically active agents has been developed this technique for drug administration is termed Sustained-release or controlled release. These tablets owe a twofold or greater reduction in the frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended Period. Maintainingconstantbloodlevelsofthedruginthebloodstreamincreasesthetherapeuticeffectivenessofthedrug. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained, or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology.

INTRODUCTION

Drugs can be administered through various routes; however, of all the routes of administration, the oral route of administration is the most convenient for administering and for dosage adjustments. An important reason for their popularity is their convenience of application and the ease of preparation on an industrial scale [1].

Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed. Controlled and Sustained Release, have been used inconsistent and confusing manner. Both represent a separate delivery process. Sustained-release 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. A sustained-release system generally does not attain zero-order type release and usually tries to mimic zero-order release by providing the drug in a slow first order. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using a novel drug delivery system or by modifying the molecular structure and /or physiological parameters [2].

CONTROLLED RELEASE SYSTEM

Controlled drug delivery is that type of system which releases the medicaments from the dosage form at a predetermined specified rate locally or systemically for a specified period of time.

SUSTAINED RELEASE SYSTEM

Sustained drug delivery is that type of system which achieves a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

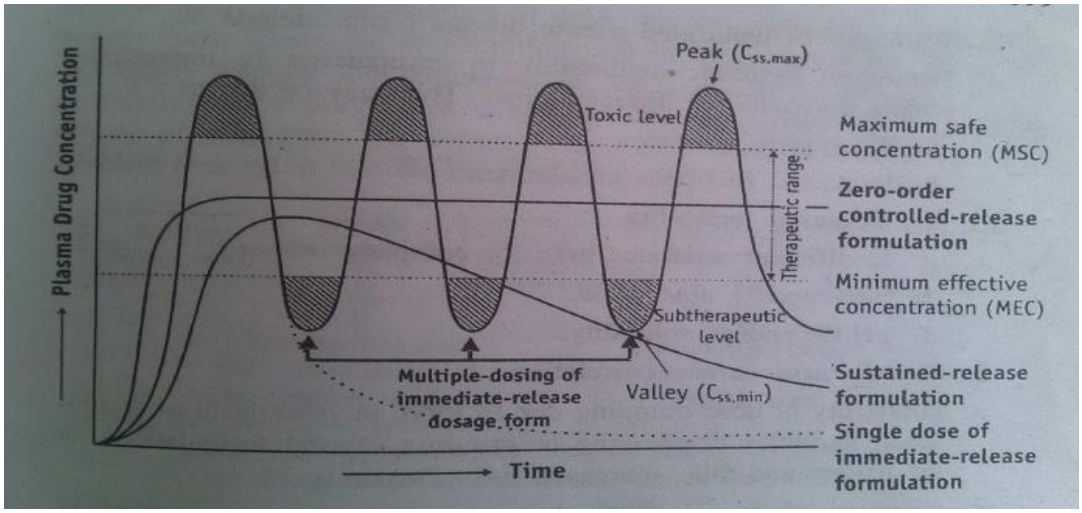

Fig. 1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release, and a zero-order controlled release formulation.

➢ ADVANTAGES

- Enhance patient compliance and convenience.
- Reduction in dosing frequency.
- Reduced fluctuations in circulating drug levels.
- More uniform effect.
- Employ less total drug that will:
- Minimize or eliminates local side effects.
- Minimize or eliminate systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtains less potentiating or reduction in drug activity on chronic use.

- Safety margin of potent drug is increased by technically excellent designing of the formulation.[3]

Industrial Advantages

- Illustration of innovative/technological
- Leadership
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension[4]

➢ **DISADVANTAGES**

- If there requires immediate change during the therapy or if any significant adverse effect is noted and prompt termination of therapy is needed, the Sustained release does not permit immediate termination of therapy.

- More costly processes and equipment are needed in the manufacturing of these dosage forms.

- The physician has less flexibility in adjusting the dosage regimen as this is fixed by the design of the dosage form. Risk of dose dumping, usually SRDDS contain drug amount that is 3-4 times more than conventional formulations. Sometimes this large quantity of drug may get rapidly released leading to toxicity.

- Reduced drug absorption may delay the onset of action. The effect of food on drug absorption.

- Kinetics may differ markedly from one SR formulation to another.

- Drugs absorbed at a specific time in GIT cannot be formulated in this type of system.

- Increased potential for the first pass clearance.

- For oral effective drug release is influenced and limited by GI residence time.

- These are designed for a normal population that is on the basis of the biological half-lives. Since disease state that alters drug dispositions, as well as interpatient variability in pharmacokinetic parameters, are not accommodated.

- Drugs that are acted upon by enzymes in the intestine undergo significant enzymatic breakdown as the drug remains in the body for a longer time.

- In case of accidental failure of the product effective antidote may be difficult to employ.[3]

➢ **DRUG SELECTION (FORMULATION APPROACHES)**

➢ **FACTORS AFFECTING THE FORMULATION**

There are two major factors that affect the release rate from the DDS. They are:

1. Physicochemical factors
2. Biological factors

1. PHYSICOCHEMICAL FACTORS

a) Aqueous solubility

b) Partition coefficient (P[O/W])

c) Drug pKa and ionization at physiological pH

d) Drug stability

e) Molecular weight and diffusivity

f) Protein binding

g) Dose size

a) AQUEOUS SOLUBILITY

Most of the drugs are weak acids or weak bases. Drugs with low water solubility will be difficult to incorporate into the SR mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high-water solubility can dissolve in water or GI fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to a less soluble drug. It is often difficult to incorporate a highly water-soluble drug in the dosage form and retard the drug release, especially when the dose is high. The pH-dependent solubility, particularly in the physiological pH range, would be another problem for SR formulation because of the variation in the pH throughout the GI tract and variation in the dissolution rate[5,6].

The biopharmaceutical classification system allows estimation of the likely contribution of three major factors which affect oral absorption.

- Solubility
- Dissolution and
- Intestinal permeability.

Class III(high solubility-low permeability)and Class IV (low solubility-low permeability) drugs are poor candidates for SR dosage form compound with solubility

< 0.1 mg/ml face significant solubilization obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilization dosing formulation. In general, highly soluble drugs are undesirable for formulation into an SR product[7].

Table no. 1: Physicochemical parameters for drug selection

Parameter	**Preferred value**
Molecular weight/size	<1000 Daltons
Solubility	>0.1 mg/mlfor pH1-7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

b) PARTITION COEFFICIENT

The partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Partition coefficient influences not only the permeation of the drug across the biological membranes but also diffusion across the rate-controlling membrane or matrix between the time when a drug is administered, and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in the evaluation of the ability of a drug to penetrate these lipid membranes(i.e., its membrane permeability) in its apparent oil or water partition coefficient is defined as,

$$K = Co/Cw$$

Where, Co = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,

Cw = Equilibrium concentration of all forms in an aqueous phase.

In general, drugs with an extremely large value of K are very oil soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug is generally defined by the Hansch correlation, which describes a parabolic relationship between the logarithm of its partition coefficient as shown in Fig. 2 [6,8].

c) DRUGPKAANDIONIZATIONAT PHYSIOLOGICAL PH

Drugs existing largely in an ionized form are poor candidates. Absorption of the unionized drugs is well whereas permeation of ionized drugs is negligible because the absorption rate of the ionized drug is 3-4 times less than that of the unionized drug. The pKa range for an acidic drug whose ionization is pH sensitive is around 3.0-7.5 and the pKa range for a basic drug whose ionization is pH sensitive is around 7.0-11.0 is ideal for optimum positive absorption. A drug shall be unionized at the site to an extent of 0.1-5.0%[7,9].

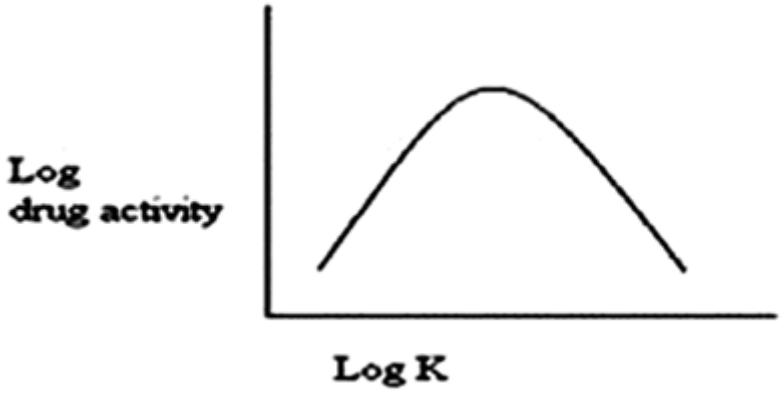

Fig.2: A relationship between drug action and partition coefficient

d) DRUG STABILITY

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. Drugs that are unstable in gastric pH can be developed as slow-release dosage forms and drug release can be delayed until the dosage form reaches the intestine. Drugs that undergo gut wall metabolism and show instability in the small intestine are not suitable for SR system. In such a case, the drug can be modified chemically to form prodrugs, which may possess different physicochemical properties or a different route of administration should be chosen [10,11].

e) into the liquid system. Another consideration is the margin of safety involved in the administration of large MOLECULAR WEIGHT AND DIFFUSIVITY

Diffusivity is defined as the ability of a drug to diffuse through the membrane. Diffusivity depends on the size and shape of the cavities of the membrane. The diffusion coefficient of intermediate drug molecular weight is 100- 400 Daltons; through the flexible polymer, the range is 10−6- 10−9 cm2 /seconds. Molecular size or weight is indirectly proportional to the diffusibility. Drugs with larger molecular size are a poor candidate for oral SR system [7].

f) PROTEIN BINDING

It is well-known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are four the most part re-circulated and not eliminated, drug-protein binding can serve as the depot for drug-producing a prolonged release profile, especially if a high degree of drug binding occurs. The drug interaction and the period of binding with mucin-like protein also influence the rate and extent of oral

absorption[10,12,13].

g) 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 0.5-1.0 g is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing sizes can sometimes be given in multiple amounts or formulated amounts of a drug with a narrow therapeutic range[14].

2. BIOLOGICAL FACTORS

a) Absorption

b) Distribution

c) Metabolism

d) Biological half-life/duration of action

e) The margin of safety/therapeutic index

f) Side effect

g) Disease state

a) ABSORPTION

The constant blood or tissue concentration of drug can be obtained from the oral SR systems through uniform and consistent release as well as absorption of the drug. The desirable quality of the sustaining system is that it should release completely absorbed. Apparently, the release of the drug from the system is the rate-limiting step, where rapid absorption relative to the drug release is always expected,

i.e., **Kr << Ka**[10].

If we assume the transit time of dosage forms in the absorptive areas of the GI tract is about 8-12 hrs, the maximum half-life for absorption should be approximately 3-4 hrs. Otherwise, the dosage form will pass out of absorptive regions before drug release is complete.

Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for the low extent of absorption are poor water solubility, small partition co-efficient, protein binding, acid hydrolysis, and metabolism or site-specific or dose-dependent absorption. Drugs with a high apparent volume of distribution, which influence the rate of elimination of the drugs, are a poor candidate for oral SR DDS. A drug that extensively metabolizes is not suitable for SR DDS. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption, or first-pass effect is the poor candidate for this delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in the lumen or the tissues of the intestine, can show decreased bioavailability from the sustained releasing systems [7].

b) DISTRIBUTION

The distribution of drug molecules into the tissue and cells can be the primary factor in particularly drug elimination kinetics. Since it not only lowers the concentration of circulating drug, but it also can be rate-limiting in its equilibrium with blood and extravascular tissue. The distribution includes the binding of the drug to the tissues and blood proteins. Protein-bound drugs molecules are considered inactive and unable to permeate biological membranes, and a high degree of protein binding provides prolonged therapeutic action. The apparent volume of distribution is one of the important parameters of the drugs that describes the magnitude of distribution as well as protein binding within the body. The apparent volume of distribution is the proportionality constant of the plasma concentration of the drug to the total drug amount in the body. Thus, for the design of sustain release products, one must have information on the disposition of the drug[10,13].

c) METABOLISM

Metabolism of the drug is either inactivation of an active drug or conversion of an inactive drug to an active metabolite. Metabolism of the drug occurs in a variety of tissues, which are containing more enzymes. 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. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, the less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolites. The formulation of these enzymatically susceptible compounds as prodrugs is

another viable solution. Drugs that are capable of either inducing or inhibiting enzyme synthesis, are the poor candidate for the SR delivery system due to difficulty in maintaining uniform blood levels. Drugs possessing variation in bioavailability due to the first-pass effect or intestinal metabolism are not suitable for SR DDS [10,12].

d) BIOLOGICALHALF-LIFE/DURATION OF ACTION

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The duration of action significantly influences the design of oral SR delivery system and it is dependent of the biological half-life. Factors influencing the biological half-life of a drug include its elimination, metabolism, and distribution patterns. Drugs with short half-lives required frequent dosing to minimize fluctuations in the blood levels. SR dosage forms would appear very desirable for such drugs. For a given steady-state drug concentration, the zero-order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus, a drug with very short half-lives requires a faster rate of release, for a modest duration of time while dosage form requires a large dosage. In general, drugs with half-lives shorter than 2 hrs are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already sustained [10,11,12].

e) MARGIN OF SAFETY/THERAPEUTIC INDEX

The margin of safety of a drug can be described by considering the therapeutic index, which is the ratio of median toxic dose and median effective dose.

Therapeutic index = TD50/ED50

A drug is considered to be relatively safe with a therapeutic index of more than 10 i.e., the larger the ratio the more safely is the drug. The margin of the safety of the drugs determined on the basis of therapeutic index is the range of plasma concentration in which the drug is considered to the safe and therapeutically effective. For the drugs, with narrow therapeutic indices, the release pattern should be more precise to maintain the plasma concentration within the narrow therapeutic and safety range. The unfavorable therapeutic index of a drug can be overcome by suitable employment of the SR mechanisms[10,11].

f) SIDE EFFECT

The side effects of some drugs are mainly developed due to fluctuation in the plasma concentrations. The incidences of side effects can be minimized by controlling the concentration within the therapeutic range at any given time. The SR drug delivery is the most widely used to incidences of the GI (local) side effects rather than a systemic side effect of the drug. The drug properties which induce local or systemic side effects can be circumvented or modified by their incorporation in a suitable oral SR delivery system that employs a specific controlled release mechanism[10].

g) DISEASE STATE

Disease state and circadian rhythm are not drug properties, but they are equally important as drug properties in considering a drug for SR.

For example: -

- Aspirin is a drug of choice for rheumatoid arthritis though it is not suitable for SR dosage form. Still, aspirin SR dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.

- Asthma attacks are commonly occurring before bedtime, due to a low cortisol level. The highest cortisol level occurred between 12 midnight and 4 a.m. These variations entail the design of an oral SR delivery in accordance with circadian rhythm[10,11].

➢ **POLYMERS USED**

Since the structural and physicochemical characteristics of the polymer are decisive in the drug release mechanism, some will be more suitable than others, depending on the aim pursued and the drug desired [15,16].

1. Hydrophilic polymers

✓ **Cellulosic**

- Methylcellulose
- Hydroxypropylmethylcellulose (Hypromellose, HPMC)

- Hydroxypropylcellulose (HPC)
- Hydroxyethylcellulose (HEC)
- Ethylhydroxyethylcellulose (E-HEC)
- Sodium carboxymethylcellulose (Na-CMC)

✓ **Non-cellulosic**

- Sodium alginate
- Xanthan gum
- Carrageenan
- Chitosan
- Guar gum
- Pectin
- Cross-linked high amylose starch
- Polyethylene oxide
- Homopolymers and copolymers of acrylic acid

1. Hydrophobic polymers

- Ethylcellulose
- Hypromellose acetate succinate
- Cellulose acetate
- Cellulose acetatepropionate
- Methacrylic acid copolymers
- Polyvinyl acetate

Apart from these two types, **waxes** and **insoluble polymers** are also used.

- **Waxes**

Carnauba wax, beeswax, candelilla wax, microcrystalline wax, ozokerite wax, paraffin waxes, and low molecular weight polyethylene.

- **Insoluble polymers**

Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethylcellulose, cellulose acetate butyrate, cellulose acetate propionate, and latex dispersion of methacrylic ester copolymers.

➢ CLASSIFICATION

Based upon the mechanism used for obtaining sustained and controlled release of the drug, these systems are classified as follows,

1. Diffusion Controlled System

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

$$J = - D \, dc/dx$$

Where, D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance 'x'

Diffusion systems are characterized by the release rate of a drug that is dependent on its diffusion through an inert water-insoluble membrane barrier. [17,18]

There are basically two types of diffusion devices.

a) Reservoir Type

In the system, a water-insoluble polymeric material encloses a core of the drug, which controls the release rate. Drugs will partition into the membrane and exchange with the fluid surrounding the particle or tablet. The additional drug will enter the polymer, diffuse to the

periphery, and exchange with the surrounding media. The polymers commonly used in such devices are Ethylcellulose and Poly-vinyl acetate.

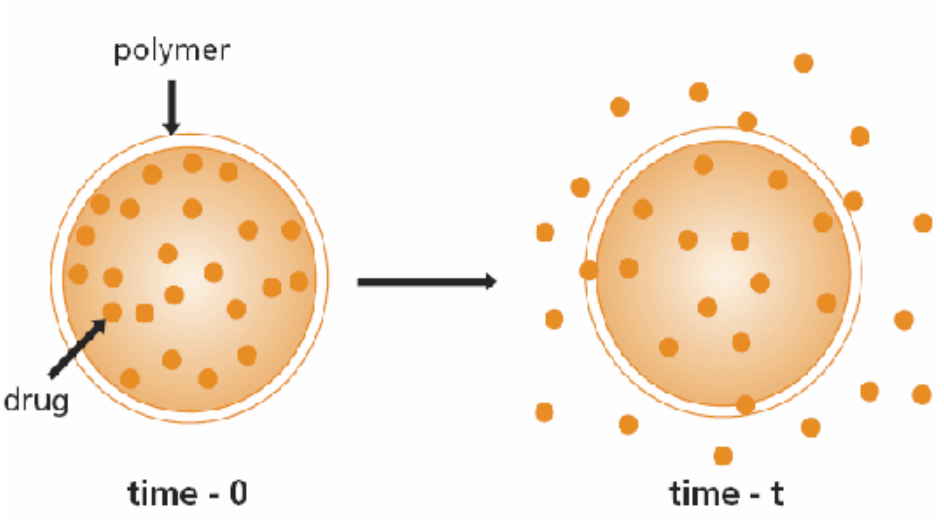

Fig 3: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

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

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

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: The system must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if the system fails. [19,20]

b) Matrix Type

A 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.

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

Disadvantages: Cannot provide zero-order release, removal of the remaining matrix is necessary for the implanted system. [21,22]

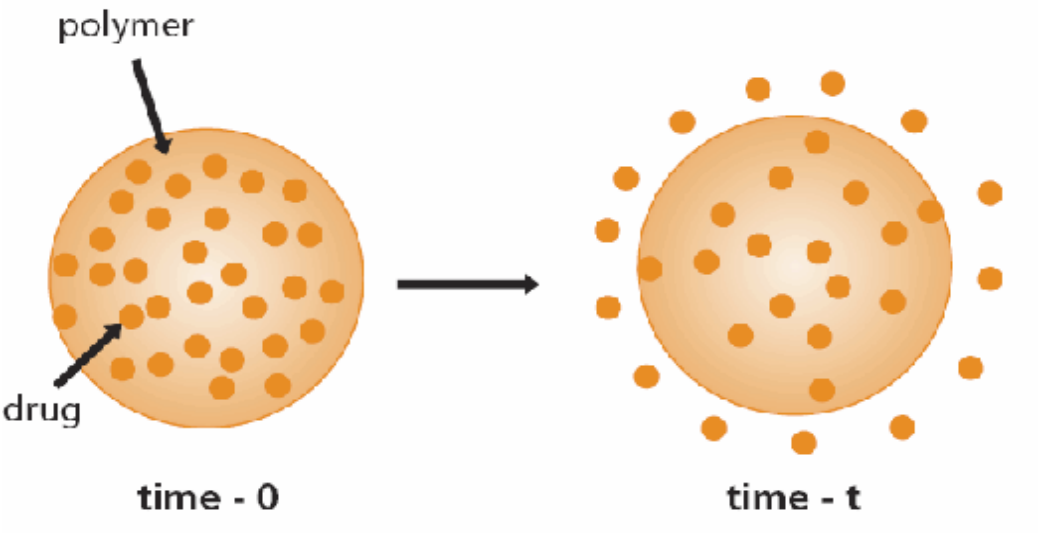

Fig 4: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery Device

2. Dissolution Controlled Systems

Drugs having high aqueous solubility and dissolution rate, show challenges in controlling their dissolution rate. The 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 the 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,

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

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. [23,24]

a) Encapsulation Dissolution Controlled Systems

The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, sspolyethylene glycols, polymethacrylates, waxes, etc. the dissolution rate of the 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.[25]

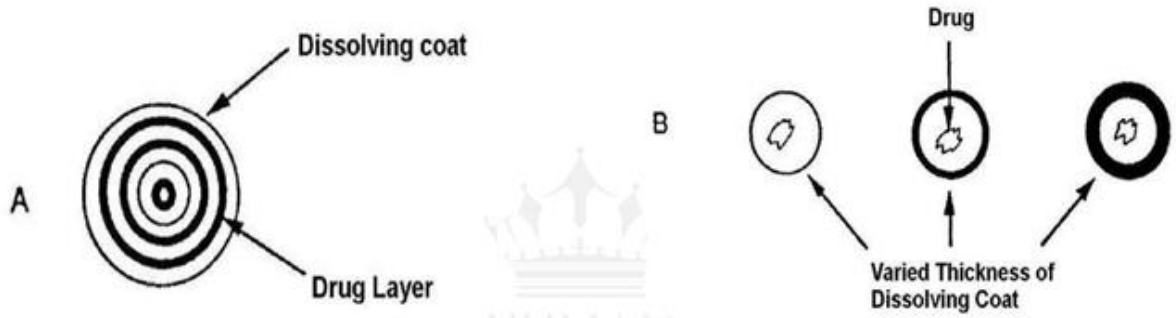

Fig 5: Encapsulation Dissolution Controlled Systems

b) 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 ordered from such matrices. The wax-embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.[26]

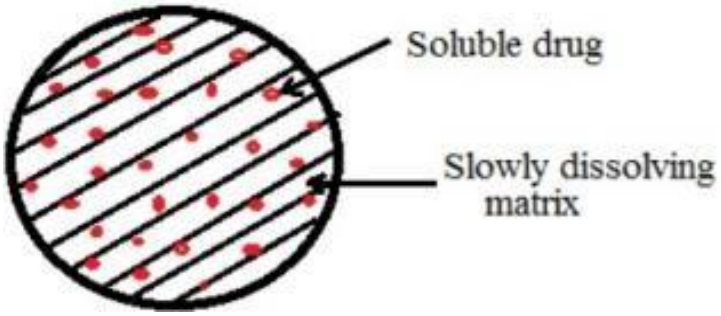

Fig 6: Schematic Representation of Matrix Dissolution Controlled Drug Delivery Device

3. Dissolution and Diffusion Controlled Release Systems

The drug core is enclosed in a partially soluble membrane. Pores are thus created due to the dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and diffusion of the dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethylcellulose with polyvinyl pyrrolidine or methylcellulose.[27-29]

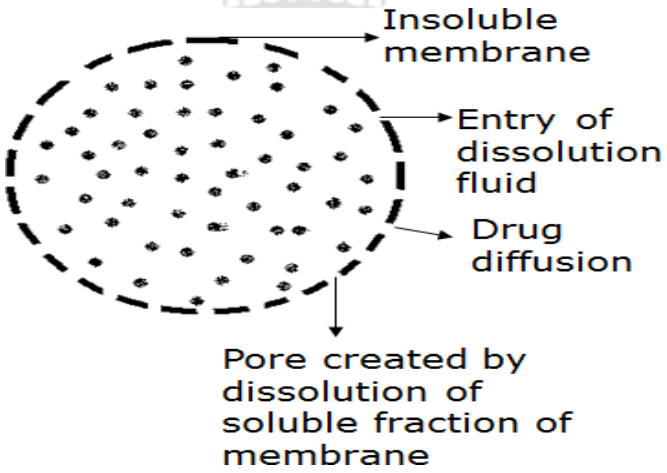

Fig 7: Dissolution and Diffusion Controlled Release System

4. Water Penetration Controlled Systems

In water penetration-controlled delivery systems, rate control is obtained by the penetration of water into the system. [30]

a) Swelling Controlled Systems

Swelling controlled release systems are initially dry and when placed in the body absorb water or other body fluids and swell. Swelling increases the aqueous solvent content within the formulation as well as the polymer meshes size, enabling the drug to diffuse through the swollen network into the external environment.[31]

b) 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 a biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is created, under which the drug solutes are continuously pumped out of the tablet through a small delivery orifice in tablet coating over a prolonged period through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero-order rate. The release of the drug is independent of the environment of the system.[32,33]

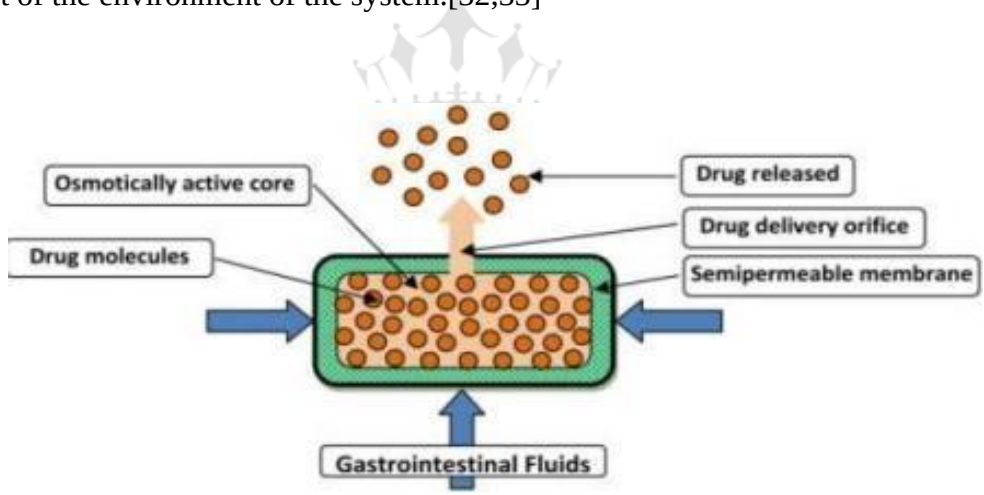

Fig 8: Schematic Representation of Osmotic ally Controlled Drug Delivery Device

Methods using ion-exchange

This system is designed to provide the controlled release of the anionic 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 copolymer 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 diffused out of the resin.

Resin+ - drug-+X- ➡resin+ - X- + drug- Where, X- are ions in the GItract.

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 the 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 the administration site. So variable diet, water intake & intestinal contents affect the release rate of the 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 SO - group. In the GI tract Hydronium ion (H+) in the gastrointestinal fluid penetrates the system and activity the release of cationic drugs 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 (CH) +] group. In the GI tract, the Chloride ion (Cl-) in the gastrointestinal fluid penetrates the system and activates the release of anionic drugs from the drug resin complex.[34-36]

Cl- + Resin – [N (CH) +]-Drug- ➡ Resin– [N (CH) +] - Cl- + Drug-

5. 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 systems.

- **Erodible Systems**:

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

a) 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 compounds 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. polylactide, polyglycolic acid.

b) Surface Erosion process

Polymers like polyorthoesters and polyanhydrides etc. occur 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 compounds 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.

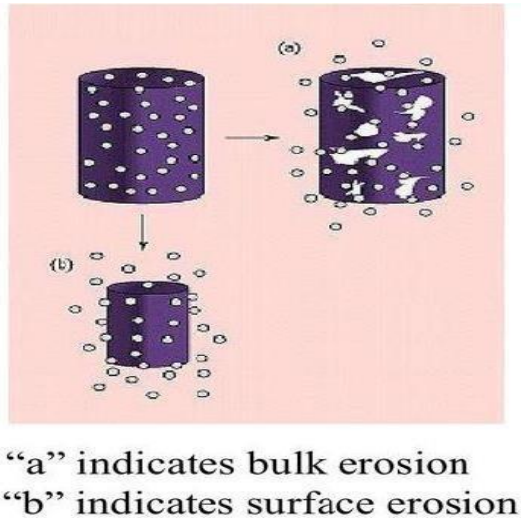

Fig 9: Bulk Erosion and Surface Erosion

- **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 liken-(2-hydroxypropyl) methacrylamide etc.[37]

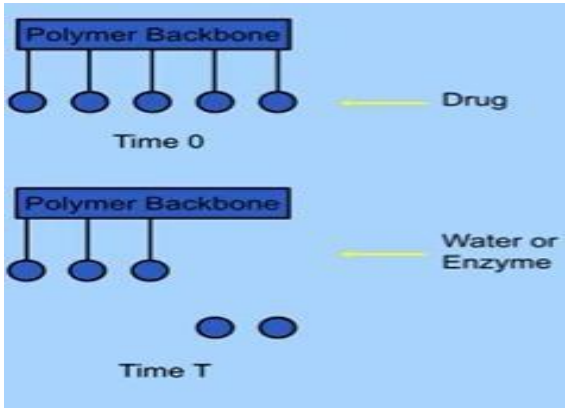

Fig 10: Pendant chain system

6. pH– Independent Formulations

The gastrointestinal tract presents 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 the gastrointestinal tract is a constraint on dosage form design. Since most 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-independent drug release. A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients, and coating with a 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 the drug.[38,39]

7. Hydrogels

Hydrogels are water-swollen three-dimensional structures composed of primarily hydrophilic polymers. They are insoluble because of chemical or physical cross-links. The physical cross-links include crystallites, entanglements, or weak associations like hydrogen bonds or van der Waals forces. These cross-links provide physical integrity and network structure. Hydrogels provide desirable protection of labile drugs, peptides, and proteins. [40,41]

8. Altered Density Formulations

Several approaches have been developed to prolong the residence time of the drug delivery system in the gastrointestinal tract like the High-density approach and the Low-density approach. [42,43]

- **Low-density approach**
- **High-density approach**

➢ **MARKETED FORMULATIONS**

Tablets		
Composition	**Product name**	**Manufacturer**
Carbamazepine	Zen retard	Intas
Diclofenac sodium	Dic-SR	Deep pharma limited
Diclofenac sodium	Nac-SR	Systopic
Diclofenac sodium	Voveran-SR	Ciba- Geigy
Nifedipine	Depine retard	Cadila health care
Theophylline	Theo PA	Welcome
Capsules		
Diazepam	Elcoin	Ranbaxy
Diclofenac sodium	Diclotal CR	Blue cross
Indomethacin	Indoflam TR	Recon
Nitroglycerine	Angispan	Lyka
Transdermal		
Nitroglycerine	Nitroderm TTS	Ciba-Geigy
Nicotine	Nicotine patch	Ciba-Geigy

➢ CONCLUSION

Now a day's modern technologies including the target concept have emerged for successful oral controlled delivery. Oral controlled release products provide advantages over conventional dosage form by optimizing bio-pharmaceutics, pharmacokinetics, and pharmacodynamics properties of the drug in such a way that it reduces dosing frequency to an extent that once-daily dose is sufficient for therapeutic management through uniform plasma concentration provide the maximum utility of drug. From the above discussion, it is concluded that the oral controlled release drug delivery system has been commonly adopted and is the most convenient route for drug delivery.

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