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Course	Novel Drug Delivery System
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Unit	1(Part 1)
Topic	Introductiin of NDDS and Controled drug delivery system
Sub- topic	Advantages and disadvantages
Diffusion and dissolution	
Ion exchange principle	
Physiochemical and biological properties	

Novel Drug Delivery Systems

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.

POLYMER USED IN CONTROL DRUG DELIVERY SYSTEM

Polymers are becoming increasingly important in the field of drug delivery. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. The review focuses on the significance of pharmaceutical polymer for controlled drug delivery applications. Sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of the medicines they need to fight a variety of human ailments, including cancer. Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing.

CONTROL RELEASE DOSAGE FORM

The United States Pharmacopoeia (USP) defines¹ the modified-release (MR) dosage form as “the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or

convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms”. One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms “controlled release (CR)”, “prolonged release”, “sustained or slow release (SR)” and “long-acting (LA)” have been used synonymously with “extended release”.

Nearly all of the currently marketed monolithic oral ER dosage forms fall into one of the following two technologies:

1. Hydrophilic, hydrophobic or inert matrix systems: These consist of a rate controlling polymer matrix through which the drug is dissolved or dispersed.
2. Reservoir (coated) systems where drug- containing core is enclosed within a polymer coating. Depending on the polymer used, two types of reservoir systems are considered.
 - (a) Simple diffusion/erosion systems where a drug-containing core is enclosed within hydrophilic and/or water- insoluble polymer coatings. Drug release is achieved by diffusion of the drug through the coating or after the erosion of the polymer coating.
 - (b) Osmotic systems where the drug core is contained within a semi-permeable polymer membrane with a mechanical/laser drilled hole for drug delivery. Drug release is achieved by osmotic pressure generated within the tablet core.

Advantages and Limitations of Control Release Dosage Forms

Clinical Advantages^{2, 6}

- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)
- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient

Commercial / Industrial Advantages

- Illustration of innovative/technological leadership
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension

Potential Limitations

- Delay in onset of drug action
- Possibility of dose dumping in the case of a poor formulation strategy
- Increased potential for first pass metabolism
- Greater dependence on GI residence time of dosage form
- Possibility of less accurate dose adjustment in some cases
- Cost per unit dose is higher when compared with conventional doses
- Not all drugs are suitable for formulating into ER dosage form

Selection of drug for formulation into extended release dosage form is the key step. Following candidates are generally not suitable for ER dosage forms

Characteristics That May Make A Drug Unsuitable For Control release Dosage Form

- Short elimination half-life^{3, 4, 5.}
- Long elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect

Control release dosage form Release Formulation Designs

1. Dissolution controlled release
 - Encapsulation Dissolution control
 - Seed or granule coated
 - Micro encapsulation
 - Matrix Dissolution control
2. Diffusion controlled release⁷
 - Reservoir type devices
 - Matrix type devices
3. Diffusion and Dissolution controlled systems
4. Ion exchange resins
5. Osmotically controlled release

BIOPHARMACEUTIC AND PHARMACOKINETIC ASPECTS IN THE DESIGN OF CONTROLLED RELEASE PER ORAL DRUG DELIVERY SYSTEMS

Controlled release drug delivery systems are dosage forms from which the drug is released by a predetermined rate which is based on a desired therapeutic concentration and the drug's pharmacokinetic characteristics

Biological half-life ($t_{1/2}$)

The shorter the $t_{1/2}$ of a drug the larger will be the fluctuations between the maximum steady state concentration and maximum steady state concentration upon repetitive dosing. Thus drug product needs to be administered more frequently.

Minimum effective concentration (MEC)

If a minimum effective concentration, MEC is required either frequent dosing of a conventional drug product is necessary or a controlled release preparation may be chosen.

Dose size and Extent of duration

The longer the extent of duration the larger the total dose per unit delivery system needs to be. Hence there is a limitation to the amount of drug that can be practically incorporated into such a system.

Relatively long $t_{1/2}$ or fluctuation desired at steady state

It is the belief of some that neither a SR nor a CRDDS is needed or useful for drugs having a $t_{1/2}$ of 12 hours or more. This is not so because there are two cases for which a 12 or 24 CRDDS seems to be indicated:

1. A drug having a $t_{1/2}$ between 12 and 72 hours may be designed for a CRDDS permitting application for every two to three days. The decline of the blood level time curve after release of the drug from the system will depend on the drug's $t_{1/2}$. Naturally, fluctuation between $C_{ss\ max}$ and $C_{ss\ min}$ may accordingly be relatively large in other words on adds slow release to the slow elimination process.

For some drugs having a $t_{1/2}$ between 20 and 100 hrs, and which are intended for long term use, one may desire small fluctuations between peaks and troughs at steady

2. states either to achieve a certain therapeutic effect or because the therapeutic range is narrow.

DESIRED BIOPHARMACEUTIC CHARACTERISTICS OF DRUG TO QUALIFY FOR CDDS

Molecular weight or size

Small molecules may pass through pores of a membrane by convective transport. This applies to both, the drug release from the dosage form and the transport across a biologic membrane. For biologic membranes the limit may be a molecular weight of 150 and 400 respectively for spherical molecules and chain like compounds respectively.

Solubility

For all mechanisms of absorption the drug must be present at the site of absorption in the form of solution. During the Preformulation study it is necessary to determine the solubility of the drug at various pH values. If the solubility is less than

0.1 $\mu\text{g/ml}$ (in acidic medium) one may expect variable and reduced bioavailability. If the solubility is less than $\mu\text{g/ml}$ absorption and availability most likely become dissolution limited dissolution limited. Hence driving force for diffusion may be inadequate.

It seems that drugs are well absorbed by passive diffusion from the small intestine upon per oral administration if at least 0.1 to 1% is non ionised form.

Apparent partition coefficient (APC)

Drugs being absorbed by passive diffusion must have a certain minimal APC. The higher the APC in an n-octanol/buffer system the higher is the flux across a membrane for many drugs. The APC should be determined for the entire pH range in the GI tract. The APC must also be applied for partition of the dru

between CRDDS and the biological fluid.

General absorption mechanism

For a drug to be a variable candidate for per oral CRDDS, its absorption mechanism must be by diffusion throughout the entire GI tract. The term diffusion here refers to the dual pathway of absorption either by partitioning into the lipid membrane (across the cells) or by passing through water filled channels (between the cells). It is also important that absorption occurs from all segments of the GI tract which may depend on the drug's pKa, the pH in the segment, binding of drug to mucus, blood flow rate, etc. The absorption process seems to be highly dependent on the hydrodynamics in the GI lumen.

Even though that first order and square root of time release can result in highly effective drug delivery systems it is widely believed that the ultimate goal is zero order release profile.

Zero order release *invitro* release will produce zero order *in vivo* release and zero order *in vivo* absorption only if; (1) the entire GI tract behaves as a one compartment model, i.e. the various segments throughout the GI tract are homogeneous with respect to absorption, and (2) drug release rate is the rate limiting step in the absorption process.

With first order release on the other hand, smaller and smaller amounts are released per unit of time with increasing time. Assuming that rate of absorption gets slower past the small intestine due to increased viscosity, decreased mixing, and decreased intestinal surface area, less drug is absorbed.

In any case, the drug release from the CRDDS should not be influenced by pH changes within the GI tract, by enzymes present in the lumen, peristalsis, etc

For all practicality, the one compartment open model is quite suitable to design CRDDS for most drugs.

Pharmacokinetic parameters Elimination half life ($t_{1/2}$)

Drugs having a $t_{1/2}$ of 8 hours are ideally suited for CRDDS. If the $t_{1/2}$ is less than 1 hour the dose size required to be incorporated for a 12 hour or 24 hour duration dosage form may be too large. If the $t_{1/2}$ is very long there is usually no need for a CRDDS, unless it is simply intended for a reduction in fluctuation of steady state blood levels.

Total clearance (CL)

CL is a measure of the volume of distribution cleared of drug per unit of time. It is the key parameter in estimating the required dose rate for CRDDS, and predicting the steady state concentration.

Terminal disposition rate constant (K_e or λ_z) The terminal disposition rate constant or elimination rate constant can be obtained from the $t_{1/2}$ and is required to predict a blood level time profile.

Apparent volume of distribution (V_z)

The V_z is the hypothetical volume of a drug would occupy if it were dissolved at the same concentration as that found in blood. It is the proportionality constant relating the amount of drug in the body to the measured concentration in the blood.

Among the trio CL, V_z , and $t_{1/2}$, the former two parameters are the independent variables and the last one is the dependent variable.

The V_z or CL is required to predict the concentration time profile.

Absolute bioavailability (F)

The absolute bioavailability is the percentage of drug taken up into systemic circulation upon extravascular administration. For drugs to be suitable for CRDDS one wants an F value to be close to 100%.

Intrinsic absorption rate constant (K_a)

The intrinsic absorption rate constant of the drug administered peroral in the form of a solution should be high, generally by an order of magnitude higher than the desired release rate constant of the drug from the dosage form, in order to insure that release process is the rate controlling step.

Therapeutic concentration (C_{ss})

The therapeutic concentrations are the desired or target steady state peak concentrations ($C_{ss \text{ max}}$), the desired or target steady state minimum concentrations ($C_{ss \text{ min}}$), and the mean steady state concentration (C_{ss}^{avg}). The difference between $C_{ss \text{ max}}$ and $C_{ss \text{ min}}$ is the fluctuation. The smaller the desired fluctuation the greater must be the precision of the dosage form performance.

The lower C_{ss} , the smaller V_z , the longer $t_{1/2}$, the higher F and The less amount of drug is required to be incorporated into a CRDDS.

INTRODUCTION

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s. First of all, the controlled release of marine antifoulants (the 1950s) and controlled release of fertilizer (1970s) were formulated which had only a single application in the soil science. The development of the pharmacology and pharmacokinetics demonstrated the importance of drug release rate in determining therapeutic effectiveness of therapy. This becomes the reason behind the development of controlled release. The modified release dosage forms are entirely new. The first time Rhazes formulates mucilage coated pills about A.D 900^[4]. This technique widely adopted in the 10th century by European countries, in the form of gold, silver and pearl coated tablets; this coating modifies the drug release rates. Advancement in the coating technology including sugar & enteric coating on the pills & tablets in the late 1800s^[5]. The further coating developed to the enteric coating of tablets followed by incorporation of the second drug to sugar coating layer, this happened near about 1938. However, the first patent for oral sustained release preparation went in the favour of Lipowski; his preparation contained small coated beads that were releasing the drug slowly & constantly^[6]. This idea later developed by Blythe and launched the first marketed sustained release product in 1952. Over the past 30 years as the complication involves in the marketing of new drug increased and various advantages recognized of Controlled release drug delivery system (CRDDS), the greater attention is being paid in this field. Today the oral controlled drug

delivery system becomes major drug delivery systems mainly drugs having high water solubility and short biological half-life^[7]. Other than oral, the various routes like transdermal, ocular, vaginal & parenteral route use for controlled release of various drugs.

(1) CONTROLLED RELEASE

An ideal dosage regimen of drug therapy is one which rapidly attained the required plasma concentration and maintained for the entire period of treatment. The frequencies of drug administration primarily depend on the biological half-life of the drug and mean residential time (MRT). Conventional drug delivery system often produces over or under medication result in various adverse drug reactions (ADRs) due to unpredictable drug release pattern. The CRDDS alters the drug distribution along with are duction in drug toxicity^[9]. The term controlled release (CR) implies the predictability and reproducibility in the drug release kinetics which means the drug release from the delivery system proceed at the rate profile not only expected kinetically but also reproducible from one division to another. CRDDS intended to exercise control drug release in the body; this may be temporal or spatial nature or both.

The term sustained release also mentioned during the description of controlled release. Sustained release (SR) used to describe a pharmaceutical dosage form formulated to retard the release of API such a way that its appearance in the systemic circulation is delayed or prolonged and plasma concentration sustained in duration. The onset of drug action delayed and duration of therapeutic effect is maintained.

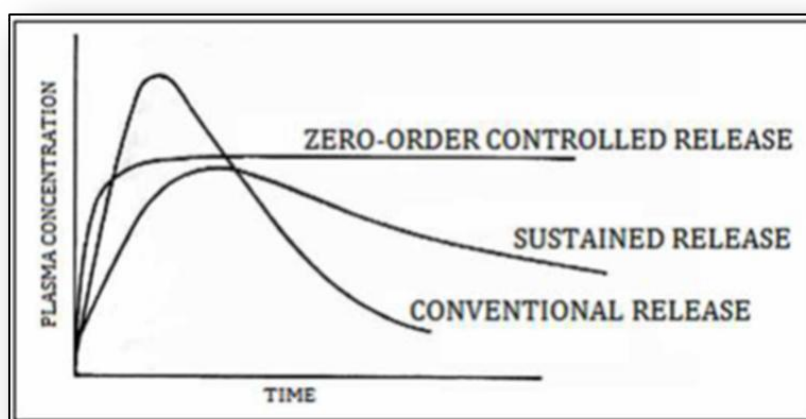


Fig. 1- Plasma drug concentration-time profile

ADVANTAGES OF CONTROLLED DRUG THERAPY

- This delivery system improved the patient compliance especially with long-term treatments for chronic diseases.
- Conventional dosages form produce fluctuation in plasma drug concentration. These

fluctuations depend on the drug kinetics within the body like absorption, distribution, metabolism and excretion. Controlled release eliminates this type of fluctuation in plasma drug concentration.

- Reduction in dose and dosing frequencies
- Maintenance of required drug concentration in plasma thus eliminates the failure of drug therapy and improved the efficiency of treatments.
- A suitable delivery system for drugs which having a short biological half-life (3-4 hrs) and drug rapidly eliminate from the body.

DISADVANTAGES

- Dumping is a major disadvantage of CRDDS, which refers to the rapid release of a relatively large quantity of drug from a controlled release formulation. This phenomenon becomes hazardous with potent drugs.
- Poor in-vivo & in-vitro correlations
- Difficult to optimize the accurate dose and dosing interval
- Patient variability affects the release rate like GI emptying rate, residential time, fasting or non-fasting condition, etc.

(2) FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

(1) Physiological properties

(1) Aqueous Solubility's: Most of the active pharmaceutical moiety (API) are weakly acidic or basic in nature that affect the water solubility of API. Weak water soluble drugs are difficult to design the controlled release formulations. High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration. These types of drugs are a good candidate for CRDDS. The pH dependent solubility also creates a problem in formulating CRDDS. BCS class-III & IV drugs are not a suitable candidate for this type of formulations.

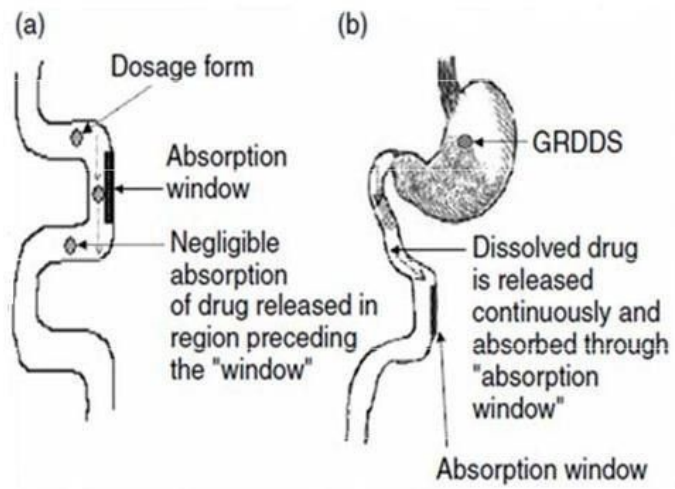
(2) Partition coefficient (P-value): P-value denotes the fraction of the drug into oil & aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane. The drugs are having high or low P value not suitable for CR, it should be appropriate to dissolve in both phases.

(3) Drug pKa: pKa is the factor that determined the ionization of drug at physiological pH in GIT. Generally, the high ionized drugs are poor candidates for CRDDS. The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes. The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11.

- (4) **Drug stability:** Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS. If drug degraded in the stomach and small intestine, it not suitable for controlled release formulations because it will decrease in bioavailability of concern drug.
- (5) **Molecular size & molecular weight:** The molecular size & molecular weight are two important factors which affect the molecular diffusibility across a biological membrane. The molecular size less than 400D is easily diffuse but greater than 400D create a problem in drug diffusion.
- (6) **Protein binding:** The drug-protein complex act as a reservoir in plasma for the drug. Drug showing high plasma protein binding are not a good candidate for CRDDS because Protein binding increases the biological half-life. So there is no need to sustain the drug release.

(2) Biological factors

- (1) **Absorption:** Uniformity in rate and extent of absorption is an important factor in formulating the CRDDS. However, the rate limiting step is druged release from the dosage form. The absorption rate should rapid then release rate to prevent the dose dumping. The various factors like aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs.
- (2) **Biological half-life ($t_{1/2}$):** In general the drug is having short half-life required frequent dosing and suitable candidate for controlled release system. A drug with long half-life required dosing after a long time interval. Ideally, the drugs having $t_{1/2}$ 2-3 hrs are a suitable candidate for CRDDS. Drugs have $t_{1/2}$ more than 7-8 hrs not used for controlled release system.
- (3) **Dose size:** The CRDDS formulated to eliminate the repetitive dosing, so it must contain the large dose than conventional dosage form. But the dose used in conventional dosage form give an indication of the dose to be used in CRDDS. The volume of sustained dose should be as large as it comes under acceptance criteria.
- (4) **Therapeutic window:** The drugs with narrow therapeutic index are not suitable for CRDDS. If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity.
- (5) **Absorption window:** The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS. Drugs which absorbed throughout the GIT are good candidates for controlled release.



(6) Patient physiology: The Physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

Pharmacokinetic parameters consider during the drug selection listed as follow.

Table. 1-Pharmacokinetic parameters for drug selection

Parameter	Comment
Biological or elimination half-life	Should be between 2 to 6 hrs
Elimination rate constant(K_E)	Required for design
Total clearance(CL_T)	dose independent
Intrinsic absorption rate	should be greater than the release rate
Apparent volume of distribution (V_d)	V_d effect the required amount of the drug
Absolute bioavailability	Should be 75% or more
Steady state concentration (C_{ss})	lower C_{ss} and smaller V_d
Toxic concentration	The therapeutic window should be broader

(3) CLASSIFICATION OF CONTROLLED RELEASE SYSTEM

The controlled release system divided into following major classes based on release pattern

(1) Rate pre-programmed drug delivery system

(2) Activated modulated drug delivery system

(3) Feedback regulated drug delivery system

(4) Site targeting drug delivery system

(1) Rate pre-programmed drug delivery system:

In this, the release of drug molecule from the delivery system is pre-planed with particular flow rate profile of medicine. The system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system.

(1) Polymer membrane permeation controlled system

In this system, the drug is completely or partially encapsulated in a drug reservoir cubicle whose drug-releasing surface is covered by flow rate controlling polymeric membrane. In drug reservoir, the drug can be solid or dispersion of solid drug particle or concentrated drug solution in a liquid or in a solid type dispersion medium. The polymeric membrane may be made-up of the fabricated form of homogeneous or heterogeneous non-porous or partial microporous or semipermeable membrane.

(2) Polymer matrix diffusion-controlled system

In this drug, the reservoir is prepared by the homogeneously dispersing drug particles in the rate controlling hydrophilic or lipophilic polymer matrix. The resultant medicated polymer matrix provides the medicated disk with defined surface area and controlled thickness.

(3) Micro reservoir partition controlled system

The drug reservoirs are a suspension of solid particle in the aqueous solution of the water- miscible polymer. Micro-dispersion partition controlled system is prepared by the applying high dispersion techniques. In short reservoir and matrix dispersion forms micro-reservoir

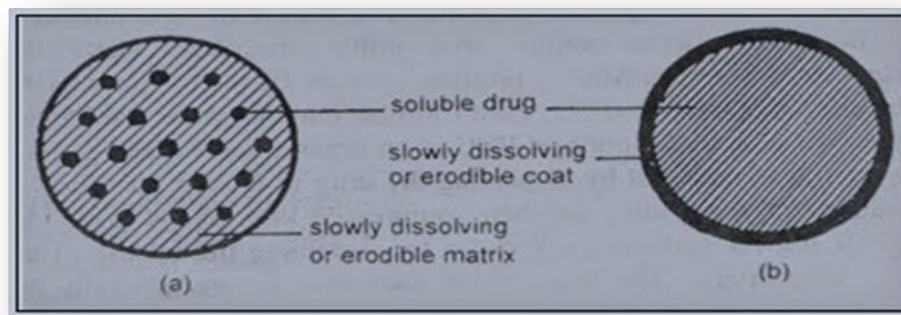
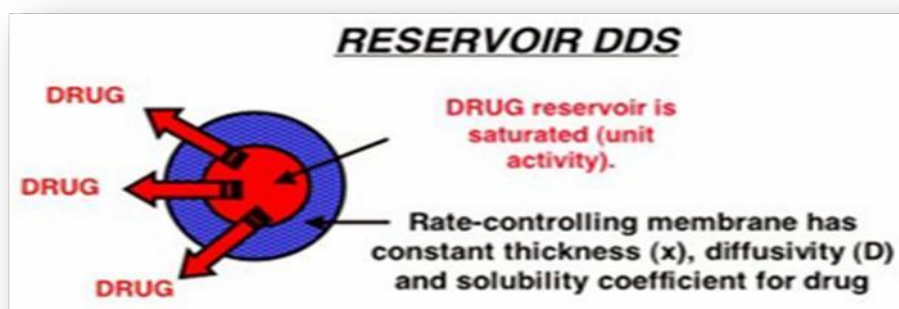


Fig. 3-Matrix and membrane type delivery systems



Reservoir type drug delivery system

(2) Activated modulated drug delivery system

In this, the release of drugs from the delivery system is controlled or activated by the some physical, chemical and biological process or by any supplied external energy source. Drug release controlled by the energy input or any applied process. This activation process can be classified into the following categories.

(1) Activation by physical process

(1) Osmotic pressure activated system

In this osmotic pressure is used as the driving force for the release of drug in a controlled manner.

(2) Hydrodynamic pressure activated system

In this drug is placed into the collapsible impermeable container which contains liquid drugs and forms drugs reservoir compartment. It is present inside the rigid shape cover

(3) Vapour pressured activated system

In this, a liquid exists in equilibrium with its vapor phase and pressure of the independent volume of fluid. One device is used for pressure control delivery, device consist of two chambers, one contains the drug solution and second with a vaporizable fluid such as fluorocarbon. After shooting of drug, volatile liquid vaporizes at the body temperature and creates a vapour pressure that compresses the below chamber, which releases the drug in a controlled way.

(4) Mechanically activated system

In this, a storage place or drug reservoir equipped with a mechanically activated pumping system. A controlled amount drug is delivered into the body cavity, such as nose or mouth, through a spray system which works on mechanically drug delivery pumping system. The spray volume of delivered drug is fixed in each pumped spray. Ex metered-dose nebulizer for the luteinizing hormone-releasing hormone (LHRH)

(5) Magnetically activated system

In this, Drug reservoir is made-up of peptide or protein powder in a polymer matrix. These reservoirs contain the macromolecule drug which is magnetically controlled and delivered the drug. In some cases, electromagnetically vibration mechanism is also used.

(6) Sonophoresis activated system

In this, the ultrasonic device is used for the activation of drug delivery. A very low frequency (55 kHz) for very short time (15seconds) is used for the drug delivery through the skin. This ultrasonic device is a battery operated a handheld system which contains a control unit, ultrasonically generated horn, disposable coupling medium sealed unit, and a return electrode. These devices are fabricated by Bio-degradable and non-degradable polymer.

(7) Iontophoresis activated system

Iontophoresis activated the system in which the penetration of ionized drug

molecules through the biological membrane under the presence of external electric current. In this a small amount of electric current is used to penetrate the drug (charge) into the skin by using

an electrode of the same polarity as the charge on the drug. The drug enters the skin due to only electrostatic repulsion force. The penetration of the drug into the skin is directly proportional to the current density which can be adjusted.

Hydration activated system

In this drug, the reservoir is homogeneously dispersed in a swellable polymer matrix fabricated from a hydrophilic polymer. The induced hydration systems stimulate the release the drug. The release of the drug is controlled by the rate of swelling of polymer matrix

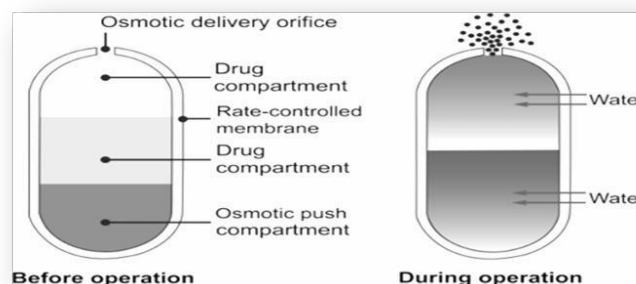


Fig. 5-Osmotic drug delivery

1. Activation by chemical process

(8) pH-activated system

In this drugs are developed to target the drug delivery only in the intestinal tract, not in the stomach. Drugs are coated with the gastric fluid-sensitive drug with a combination of intestinal fluid-insoluble polymers like ethyl cellulose and hydroxyl methyl cellulose phthalate. The coated drugs have resistant against the gastric fluid ($\text{pH} < 3$) thus drugs are protected from the acidic degradation. In the small intestine, the intestinal fluid dissolves the coated membrane of drugs due to high pH of intestinal fluid ($\text{pH} > 7.5$). Thus, pH controls the delivery of drugs inside the human body.

(9) Ion activated system

In this, only ionic and ionizable drugs are prepared because the gastrointestinal fluid has regularly maintained the level of ions and the delivery of drugs modulated by this method.

(10) Hydrolysis activated system

In this, the drug reservoir is encapsulated in a microcapsule. It is also made up of the implantable device. All these systems are prepared from biodegradable polymers. The release

of drug activated by the hydrolysis degradation of the polymer chain and the rate of drug delivery is controlled by the polymer degradation rate.

(2) Activation by biochemical means

In this drug release is activated by the biochemical reaction.

(3) Enzymatic activated system

In this system is depends upon the enzymatic activity for the release of drugs.

(4) Feedback regulated drug delivery system

In this, a physiological response activates the release of drugs from the carrier. A triggering agent activates the process of release of the drug, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is synchronized by the concentration of a triggering agent that is detected by a sensor used in the feedback-regulated drug delivery system.

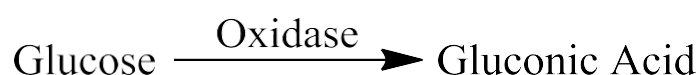
Feedback regulated drug delivery system are divided into three part

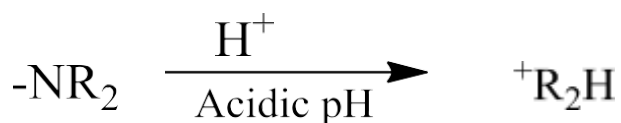
Bio-erosion regulated system

In this, drug fabricated with polyvinyl methyl ether and coated with a layer of immobilized urease. In a solution with close to neutral pH, the polymer polyvinyl methyl ether erodes very slowly but in the presence of urea, urease forms ammonia at the surface of drug and metabolize the urea. The cause of the change of pH increases the rapid degradation of polymer matrix and release of drug molecules.

(1) Bio-responsive regulated system

In this, the drug reservoir is enclosed in the bioresponsive polymeric membrane and permeability of drug molecule is controlled contraction of biochemical agents in the tissue. Ex. Glucose- triggered insulin delivery system. In this delivery system, insulin reservoir is covered by the hydrogel membrane which contain NR₂ (amide group) group. In alkaline solution, NR₂ group is fixed, and the membrane is unswollen and impermeable to insulin. As glucose entered into the membrane, oxidized inside the membrane and forms gluconic acid. This process triggered the protonation of NR₂ into N⁺R₂H and hydrogel layer become swollen and thus permeable to insulin molecule by the process of self-regulated processes.





(2) Self-Regulating Drug Delivery Systems

This mechanism is regulated by the reversible and competitive binding mechanism for the activation and release of drugs. In this, drug reservoir encapsulated within a polymeric semipermeable membrane. The release of the drug is activated by the biochemical agent of the tissue. Ex. A biological derivative complex (insulin-sugar-lactin) is encapsulated within a semipermeable membrane to produce controlled drug delivery system. As blood glucose diffuses into this system (CrDDS), it binds with lectin molecules and activates the release of insulin sugar from the binding site, and its concentration depends on the concentration of glucose. Thus, the whole process completed by self-regulating drug delivery system.

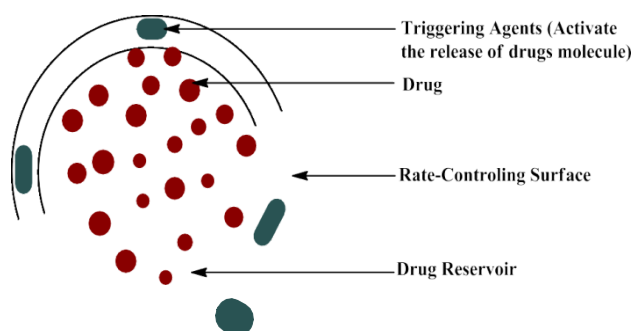


Fig.6- Feedback drug delivery system. Triggering agents activate the release of drugs

(5) Site targeting drug delivery system

Delivery of drugs to the targeted site (tissue) is complex, and it consists of multiple steps of diffusion and partitioning. It is an uncontrolled release of drugs from the drug delivery system, but the path of drug release should be in control. To get rid of uncontrolled drug release, drug delivery system should be site targeting specific. It is divided into three parts. **(1) First order targeting:** - In this, drugs carrier release the drugs at the targeted site such as organ, tissue, cavity, etc.

(2) Second order targeting: - In this, drugs carrier release the drugs in the specific cell such as tumors cells not to the normal cells. This is also called as the selective drug delivery system.

(3) Third order targeting: - In this, drugs carrier release the drugs to the intracellular site of targeted cells.

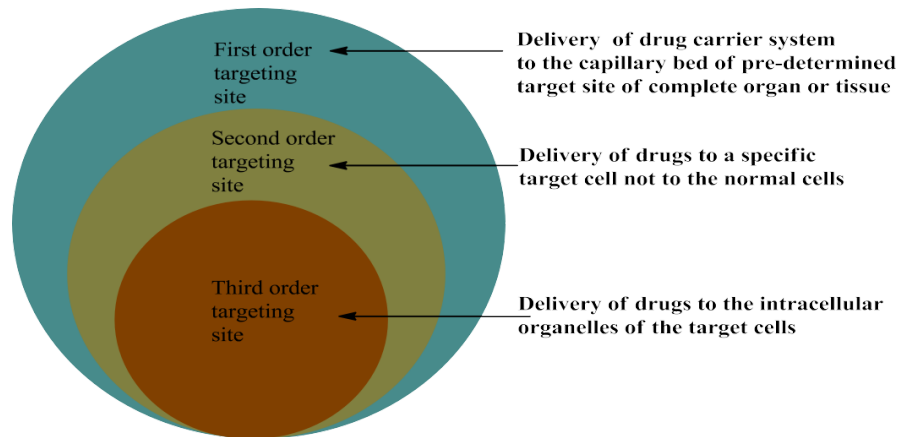


Fig: 7- Site targeted drug delivery system

Site targeting drug delivery system also classified as

- (1) **Passive targeting:** -In this, drugs carrier releases the drug at the particular site due to the cause of physicochemical or pharmacological signal.
- (2) **Active targeting:** Active targeting is also called as the ligand-mediated targeting. In this ligand (drugs) are present on nanoparticle surface and interact with the cells or diseased cell. Ligand molecules are selected with the interaction of infected cell, and it should not disturb the healthy cells. Therefore, it is aimed that to design the specific ligand for specific diseased cells. Some physicochemical properties may affect the interaction of ligands cell binding, as the ligand density, the size of nanoparticles and choice of targeting ligand for cells. Example of active targeting is the use of the monoclonal antibody for the treatment of cancer.

(4) ORAL CONTROLLED RELEASE SYSTEM

Oral controlled release system (OCRS) is the widely used system for delivering the drugs to body in a controlled release pattern because:

- Easy and convenience administration
- Easy to formulate or design the dosage form
- Easy production and low-cost system
- Greater flexibility in dosage form due to versatility in GI anatomy and physiology

OCRS mainly given as solid form and the drug release depend on:

- Drug dissolution rates from polymeric matrix
- Drug diffusion from polymeric membrane
- Combination of both

Depending on drug release pattern OCRS classified into three major classes.

- ❖ Continuous release system
- ❖ Delay transit & continuous release system
- ❖ Delay release system

❖ **Continuous release system:** These systems release the drug throughout the GIT especially terminal end of the small intestine.

This included:

- Dissolution controlled release system
 - ✓ Matrix dissolution controlled
 - ✓ Encapsulation dissolution controlled
 - Diffusion controlled release system
 - ✓ Matrix diffusion controlled
 - ✓ Reservoir/ laminated matrix device
 - Dissolution & diffusion-controlled release system
 - Osmotic pressure controlled release system
 - Hydrodynamic controlled release system
 - Ion-exchange resin drug complexes
 - pH-dependent system
- ❖ **Delayed transit & continuous release system:** This system formulated in such a way their residence time in GIT increased and released the drug throughout GIT^[45]
- ✓ altered density system
 - ✓ mucoadhesive system
 - ✓ size-based system.
- ❖ **Delay release system:** These systems formulated to deliver the drugs in the controlled release manners.
- ✓ Intestinal release system
 - ✓ Colon targeted system

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