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# ADVANCES IN ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM

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**Abstract:**

*Oral controlled release drug delivery systems (CRDDS) represent a major advancement in pharmaceutical technology, designed to improve therapeutic effectiveness, increase patient adherence, and reduce adverse effects. In contrast to traditional dosage forms, CRDDS deliver drugs at a consistent rate, ensuring stable drug levels in the bloodstream over a prolonged duration. Recent innovations in this area encompass new polymeric matrices, osmotic pump mechanisms, floating drug delivery systems, mucoadhesive formulations, and nanoparticle-based delivery vehicles. The integration of biodegradable polymers, hydrogels, and nanotechnology has allowed for greater control over drug release dynamics and targeted delivery. Additionally, 3D printing and microfabrication technologies are being utilized to develop customizable oral dosage forms with tailored release profiles. These advancements not only enhance treatment outcomes but also expand the potential for delivering drugs with low solubility and instability. Overall, the evolution of oral controlled release systems is transforming drug delivery science, supporting the development of personalized and effective oral therapies.*

***Keywords:*** *Oral drug delivery, controlled release, polymeric systems, nanotechnology, mucoadhesive, osmotic pump, 3D*

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## INTRODUCTION:

Oral drug delivery remains the preferred route for administering therapeutic agents due to its convenience, compliance, and cost-effectiveness. However, conventional dosage forms often suffer from fluctuating plasma concentrations, short biological half-lives, and the need for frequent dosing, which may reduce therapeutic efficacy and increase the risk of adverse effects. To address these challenges, the development of oral controlled release drug delivery systems (CRDDS) has been widely pursued. Controlled release systems aim to deliver drugs at a predictable rate, maintaining steady plasma levels and extending the duration of therapeutic action. Over the past several decades, significant advancements have been made in the design of advanced CRDDS through the use of novel materials and technologies, including polymeric matrices, osmotic pumps, floating and mucoadhesive systems, and nanoparticle-based carriers. The integration of nanotechnology, 3D printing, and smart polymers has expanded the potential for precise drug release and site-specific targeting. These innovations not only enhance drug bioavailability and reduce dosing frequency but also improve patient adherence and clinical outcomes. As research progresses, oral controlled release delivery systems are evolving toward personalized and responsive systems that adapt to physiological conditions, thereby transforming modern drug delivery and treatment strategies. Drug delivery refers to the method of administeringDrug delivery refers to the method of administering medication to a patient in a targeted way, ensuring the drug reaches the required area of the body effectively. The primary objective of a drug delivery system is to ensure the medication stays in the body for the right duration, acts only where needed, and remains safe without harming healthy tissues. Every dosage form, such as tablets, capsules, or injections, consists of two main components: the active pharmaceutical ingredient (API), which is the effective drug, and excipients or additives that play a crucial role in enhancing the preparation, stability, and effectiveness of the medicine.

In simple terms:
Dosage form = Active drug (API) + Additives/Excipients. Medication to a patient in a targeted way, ensuring the drug reaches the required area of the body effectively. The primary objective of a drug delivery system is to ensure the medication stays in the body for the right duration, acts only where needed, and remains safe without harming healthy tissues.

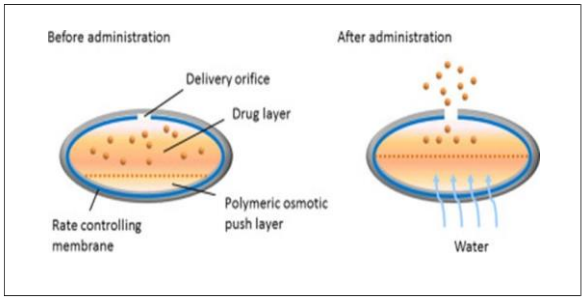


**Figure 1: Oral controlled release**

Every dosage form, such as tablets, capsules, or injections, consists of two main components: the active pharmaceutical ingredient (API), which is the effective drug, and excipients or additives that play a crucial role in enhancing the preparation, stability, and effectiveness of the medicine.

In simple terms:
Dosage form = Active drug (API) + Additives/Excipients.
When a medicine or active part of a medicine is mixed with a polymer so that the speed at which it comes out of the material is set in advance, it's called a controlled drug delivery system. The terms sustained release and controlled release are often used in similar ways, but they actually mean different kinds of drug delivery.

A sustained release system is any kind of medicine form that releases the drug slowly over a long time. These systems usually don't give a perfect, steady (zero-order) release, but they aim to get close to that by releasing at first.

On the other hand, a controlled release system lets you have more control over when and how the drug is released—either over time (temporal control) or at a particular place in the body (spatial control). The main goal of controlled drug delivery is to change how a drug works in the body. This can be done by altering the drug's structure, using the body's natural processes, or developing new ways to deliver the drug. This helps change how the body handles the drug (pharmacokinetics) and how the drug affects the body (pharmacodynamics)

- Modification type associated with CDD

### 1. Extended-Release Dosage Forms

Extended-release (ER) dosage forms are made to keep the right amount of medicine in the blood for a longer time. This means you don't have to take the medicine as often as you would with regular forms—usually at least twice as long. Examples of this type include controlled-release and prolonged-release medicines.

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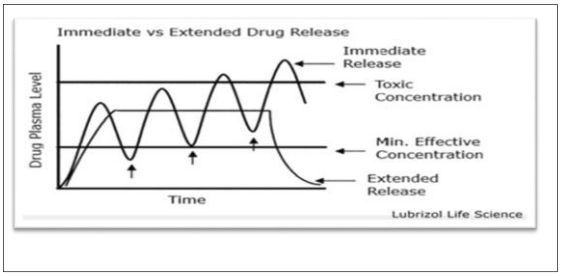



Figure 2: Drug Plasma Level for Extended-Release Tablets

**A. Sustained Release**

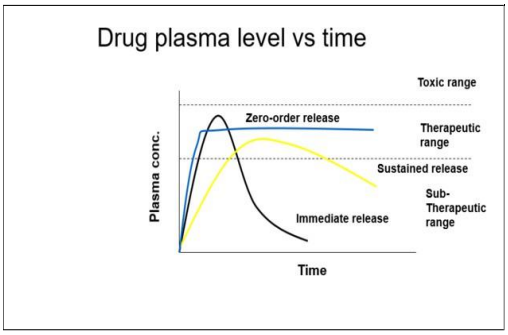
Sustained-release (SR) systems are types of medicines that slowly give out the drug over a long time. They don't always follow a fixed schedule for releasing the medicine. The goal is to keep the drug level in the blood steady for a longer period, which helps the medicine work well over time.

**B.** Controlled Release

Controlled-release (CR) forms of medicine release the drug at a steady and even pace, helping to keep the medicine working consistently for a longer time These systems are often designed to follow zero-order kinetics, meaning the drug is released at a constant rate no matter how much is left in the medicine. This is different from sustained-release systems, which mostly follow first-or

Figure 3: Arbitrary therapeutic range of different dosage from in blood

**2. Delayed Release**




Delayed-release medicines are made so that part of the dose is released right away, while the rest comes out after some time.This allows for the medicine to be given in parts over time from a single dose, which means you don't have to take the medicine as many times.

**3.** Targeted Release

Targeted-release forms of medicine are designed to deliver the active part of the drug exactly where it needs to be in the body. These systems can also release the medicine slowly, which helps the medicine work well and reduces unwanted side effects.

**4.** Repeat-Action Drug Delivery Systems

Repeat-action systems are modified-release medicines that have more than one dose of the drug inside them. These doses are released one after another at set times. This helps keep the medicine working consistently without needing to take it often.

**5.** Prolonged-Release Systems

Prolonged-release systems release the drug slowly and continuously for a long time. By avoiding quick absorption and high levels of medicine in the blood, these systems help keep the drug level steady and lower the chance of harmful side effects.

**6.** Site-Specific and Receptor-Specific Release

These advanced delivery systems are designed to direct the drug to a specific biological site. In site-specific release, the formulation targets a particular organ or tissue, while in receptor-specific release the drug interacts selectively with receptors within that target area to maximize efficacy and minimize off-target effect.

**7.** Immediate or Quick-Acting Dosage Forms

Immediate-release dosage forms release the drug rapidly after administration, resulting in quick absorption and onset of action. The plasma concentration rises swiftly, reaches a peak, and then declines below the minimum effective concentration (MEC) as the drug is metabolized or excreted. To maintain steady therapeutic levels, repeated dosing is required, leading to fluctuations between peak and trough concentrations—often described as a "teeter-totter" pattern. These variations depend on factors such as absorption rate, distribution, metabolism, elimination, and dosing interval.

- Advantage
  - Sustained Drug Release: Controlled release devices help keep a steady and proper amount of the drug in the body for a longer time, so the medicine is released consistently over time.
  - Minimized Side Effects: By slowly releasing the drug, the highest levels in the blood can be reduced, which may help reduce unwanted effects and make the medicine safer.
  - It can help patients take their medication more regularly.
  - It can improve the medicine's ability to work in the right parts of the body.
  - It helps with drugs that are hard to give, such as those that dissolve slowly in water or are quickly released from poorly soluble forms.
  - It can reduce the amount of medicine needed and how often it has to be taken.
  - It can also make the medicine less irritating to the stomach.
- Disadvantage

- One of the main issues with CRDDS is "dose dumping," which refers to the fast release of a large amount of medication from a controlled release formulation. This can be dangerous when strong drugs are involved.
- There is not enough connection between what happens in the lab and what happens in the body.
- They also can't be used for drugs that need to be absorbed at certain times in the gastrointestinal tract, and they require more costly manufacturing methods and equipment.
- There is a faster development of tolerance and the need for more counseling.
- Not all medications work well with controlled release treatment.
- There is less of the drug available in the body compared to traditional quick-release formulation.
- Some reasons for this include:

○ More metabolism happens during the first pass through the liver.
○ The drug becomes less stable.
○ The drug is absorbed differently in certain parts of the body.
○ The drug's solubility depends on the pH level.

- The effectiveness depends more on how long the medication stays in the stomach.
- It's harder to maintain a consistent dose.
- It's difficult to get the right dosage and the correct timing for the dose.
- It might increase the clearance of the drug during the first pass.

- Factors influencing the formulation of oral controlled release drug delivery system

**A. Physicochemical Factors**

**1.** solubility

Low solubility in water means that some drugs don't get absorbed well when taken by mouth. Drugs that dissolve well in the stomach are not good choices for controlled or sustained release pills. Water solubility also affects how much of the drug can be packed into delivery systems like liposomes or micro-particles. Drugs that dissolve very quickly in water tend to leave the carrier system too fast. Solubility can change depending on the pH level in the body, especially in the stomach and intestines, which can cause problems for controlled release medicines because pH levels vary along the digestive tract. The Biopharmaceutical Classification System helps understand how solubility, dissolution, and how well the drug passes through the intestine affect how well it is absorbed by the body. Drugs in Class III (high solubility but poor absorption) and Class IV (low solubility and poor absorption) are not good candidates for controlled release dosage forms.

**2.** Drug Stability

Drugs in a solid form tend to stay stable longer than those in liquid or suspended form H]. Drugs that break down in the acidic environment of the stomach can be made into slow release forms so they release later, when they reach the intestine. Drugs that break down or are broken down in the small intestine are not suitable for controlled release systems.

**3.** Molecular Size and Diffusivity

Diffusivity is the ability of a drug to move through a membrane. It is related to the size of the drug molecule, with smaller molecules diffusing more easily. The shape and size of the spaces in the membrane also affect how well the drug can pass through. Most drugs, over 95%, are absorbed through passive diffusion. The maximum molecular size for a drug to pass through a membrane by passive diffusion is 600 Daltons. Some drugs, like proteins and peptides, are hard to control the release rate of from the dosage form.

**4.** Partition coefficients

Partition coefficient is the ratio of the amount of drug found in an oil-like phase to that found in a water-like phase. This ratio affects how well the drug can move through a biological membrane. Drugs with a high partition coefficient move through membranes more easily. The movement of drugs across a membrane or through a delivery system depends on the partition coefficient. Drugs with a low partition coefficient are not good for oral controlled release systems. Drugs with a high partition coefficient also are not suitable
for oral controlled release because they won't move out of the lipid membrane once they enter it.

**5.** Drug pKa and ionization at physiological pH

Drugs pKa that are mostly ionized are not good candidates for oral controlled release systems. The absorption rate of ionized drugs is 3 to 4 times slower than that of unionized drugs. The pKa range for acidic drugs that are sensitive to pH is between 3.0 and 7.5. For basic drugs that are sensitive to pH, the ideal pKa range is between 7.0 and 11.0, which helps with maximum absorption.

**B.** Biological factors

**1.** Absorption

The goal of making a controlled release product is to manage how the drug is delivered. A good oral controlled delivery system should release all the drug and allow the body to absorb it fully. However, the amount of drug that gets absorbed may be less than expected because of things like the drug breaking down, binding to proteins, absorption depending on the site or dose, poor water solubility, and a small partition coefficient.

### 2. Distribution

Drugs that have a large volume of distribution, which affects how quickly the drug is removed from the body, are not good choices for oral delivery. The volume of distribution is an important measure that shows how much the drug spreads in the body and how much binds to proteins. The way a drug spreads can be seen through the volume of distribution at steady state and the T/P ratio.

T/P = K12 / (K21 - b)

T is the amount of drug in the peripheral area, P is the amount in the central area, K12 is the rate at which the drug moves from the central to the peripheral area, K21 is the rate from the peripheral to the central area, and b is a slow elimination constant.

### 3. Metabolism

Drug metabolism can either stop the drug from being active or change an inactive drug into an active one. Two main factors related to how a drug is broken down can make it hard to design a sustained or controlled delivery system. For long-term use, drugs that either increase or decrease enzyme production are not good for controlled delivery because it's hard to keep the blood levels steady. Also, drugs whose absorption changes due to the first- pass effect or metabolism in the intestine are not suitable for sustained or controlled release systems.

### 4. Half-life

The time a drug stays active in the body depends on its biological half-life. Drugs that have a short half-life, meaning they work for more than 2 hours, are best suited for controlled drug delivery systems. Factors that affect how long a drug stays in the body include how it is eliminated, how it is broken down in the body, and how it spreads throughout the body.

### 5. Therapeutic index

The safety of a drug can be measured using the therapeutic index, which compares the dose that causes harm to the dose that works. The therapeutic index is calculated by dividing the median toxic dose by the median effective dose. Drugs with a low therapeutic index are not good choices for controlled release formulations. By keeping the drug concentration within a safe range, side effects can be reduced.

### 6. Size of dose

If a drug normally comes in a large dose, it might not be a good candidate for a controlled release formulation. This is because the size of a single dose in a controlled release system could become too big to take easily.

### 7. Absorption window

Some drugs are only absorbed by the body from a specific part of the digestive system.

This part is called the 'absorption window'. These types of drugs are not suitable for controlled release delivery systems.

### 8. Plasma concentration response relationship [1, 5, 11, 12]

The level of a drug in the blood is more important for its effect on the body than the amount given. However, drugs that work without depending on their blood level are not good choices for oral controlled release drug delivery system.

### 9. Concentration dependency on transfer of drug

Drug transfer dependency if the movement of a drug from one area to another happens in a zero-order kinetic way, then that drug isn't a good choice for an oral controlled release system. It needs to follow first-order kinetics. The figure below shows different methods used in making oral controlled release drug delivery systems.

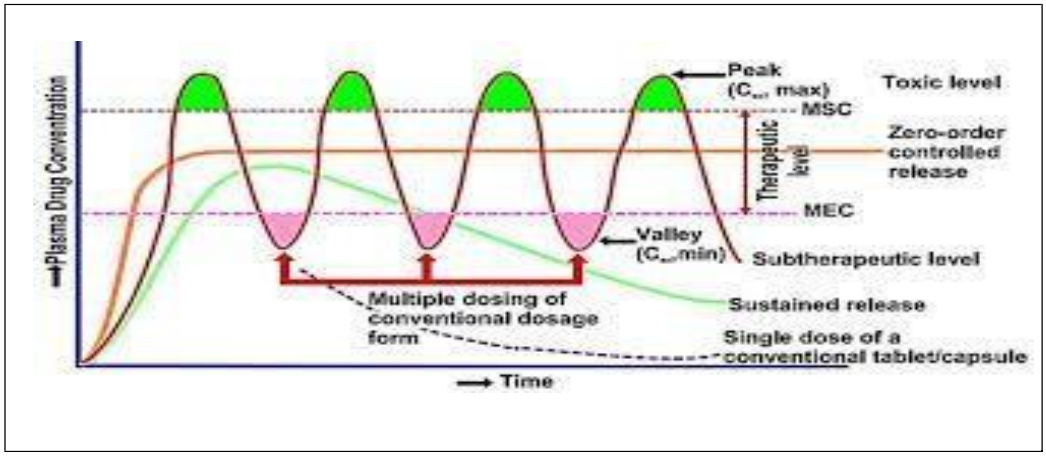



**Figure 4: Comparative graphs for Convention, Sustained and Controlled release with time.**

### 1. Dissolution controlled release

Dissolution is when a solid substance dissolves into a liquid. It is the main step that affects how fast a solid dissolves into a liquid. There are several theories that explain how dissolution works: the diffusion layer theory, the surface renewal theory, and the limited solvation theory. The Noyes Whitney Equation shows how fast dissolution happens. It is written as dc/dt = kD.A (Cs – C), where dc/dt is the dissolution rate, k is the dissolution rate constant (first order), D is the diffusion coefficient, A is the surface area, Cs is the maximum solubility of the drug, and C is the concentration of the drug in the solution. The difference between Cs and C is the concentration gradient. Another version is dc/dt = D/h A (Cs – C), where h is the thickness of the diffusion layer. Two common ways to control drug release are the encapsulated dissolution system and the matrix dissolution system.

### A. Encapsulated dissolution system

This is also called a coating dissolution controlled system. The rate at which the coating dissolves depends on how stable and thick it is. This system can hide the color, smell, and taste of the drug and reduce stomach irritation. To make a controlled release product for drugs that dissolve quickly in water, you can make them into different salts or derivatives, coat them with a material that dissolves slowly, or put them into a material that dissolves slowly. Examples of this system include Ornade spansules and Chlortrimet Repetabs.

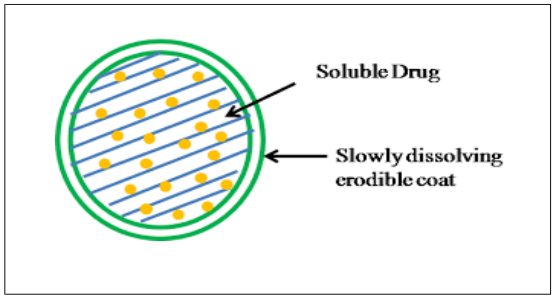
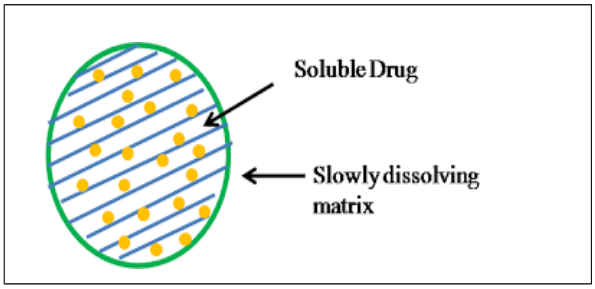



Figure : 5 Reservoir dissolution controlled drug release system

### B. Matrix dissolution system

This is also known as a monolithic dissolution controlled system. In this system, dissolution is controlled by changing the porosity of the tablet, reducing how easily it absorbs water, and making it dissolve more slowly. This type of drug release follows a first order release pattern. The rate at which the drug is released depends on how fast the polymer dissolves. Examples of this **system** include Demeaned extencaps and Dimetapp extentabs

Figure 6: Matric dissolution controlled drug release system




### 2. Diffusion controlled system

Is a major method for drug absorption that doesn't need any energy. In this process, drug molecules move from an area with a higher concentration to one with a lower concentration until both sides are balanced. The speed of this movement depends on the difference in concentration across the membrane. The release rate is controlled by how well the drug diffuses through a water-insoluble polymer. There are two types of diffusion devices: - Reservoir diffusion system - Matrix diffusion system

### 3. Reservoir diffusion system

This is also known as a laminated matrix device. It is a hollow structure that has an inner core surrounded by a water-insoluble membrane. The polymer can be added by coating or micro encapsulation. The main way the drug is released is by moving into the membrane and then diffusing into the surrounding fluid. Commonly used polymers are HPC, ethyl cellulose, and polyvinyl acetate. Examples include Nico-400 and Nitro-Bid.

**Diffusion reservoir**

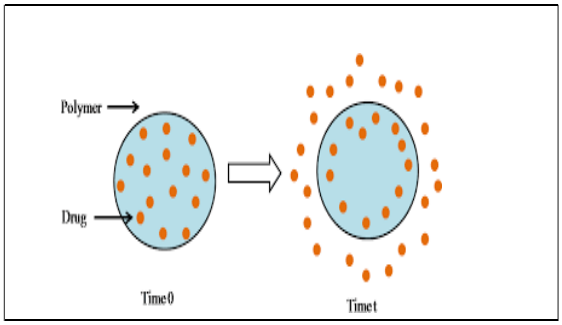



Figure 7: **Diffusion reservoir** controlled drug release system

**Rate controlled steps**: the amount of polymer in the coating, the thickness of the coating, and the hardness of the microcapsules**.**

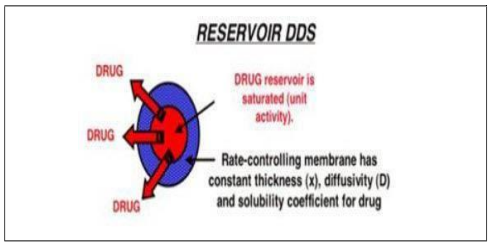



Figure: 8 Reservoir DDS

**4. Matrix dissolution system**

**(a)** Rigid Matrix Diffusion: This involves using insoluble materials such as PVP and fatty acids.

(b) Swell able Matrix Diffusion: Also known as glassy hydrogels, this type is popular for slowly releasing highly water-soluble drugs. Materials used include hydrophilic gums .Examples of natural gums are guar gum and tragacanth. Semi-synthetic options include HPMC, CMC, and xanthan gum. Synthetic options include polyacrylamides. Examples include Glucotrol XL and Procardia XL.

The Higuchi Equation describes drug release from this system:

$Q = [D\varepsilon/T (2A - \varepsilon Cs.t)] 1/2$

Where Q is the amount of drug released per unit surface area at time t, D is the diffusion coefficient of the drug in the release medium, Ɛ is the porosity of the matrix, Cs is the solubility of the drug in the release medium, T is the tortuosity of the matrix, and A is the concentration of the drug in the matrix per unit volume.

Rate controlling steps: Diffusion of dissolved drug in matrix.

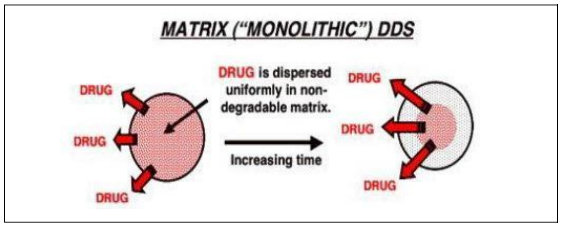



**Figure 9: matrix system**

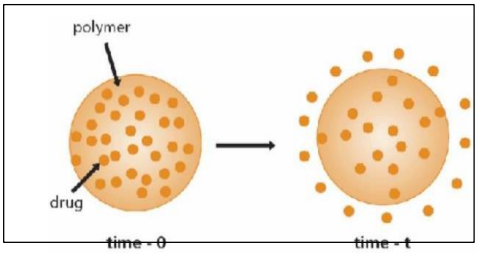



**Figure: 10 matric diffusion system**

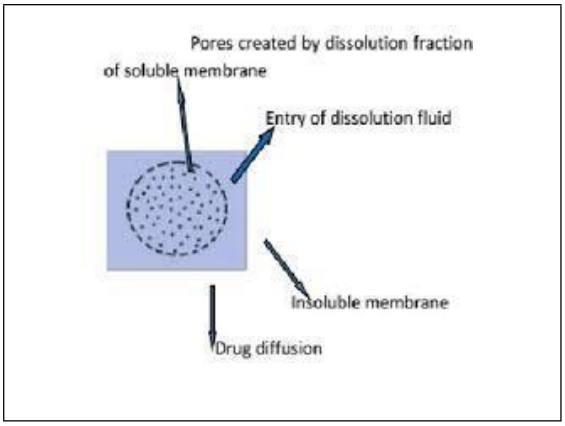
**1. Dissolution and Diffusion Controlled Release System**

In this system, the drug is enclosed in a partially soluble membrane, and pores form as parts of the membrane dissolve. This allows the aqueous medium to enter the core, and the drug dissolves or diffuses out of the system. For example, a mixture of ethyl cellulose and PVP dissolves in water, creating pores in the insoluble ethyl cellulose.

Figure: 11 Dissolution and Diffusion system

**2. Ion Exchange Resins Controlled Release System**

Ion exchange resins are cross-linked, water-




insoluble polymers that have ionizable groups. They are used for taste masking and controlled release. The drug molecules are embedded in the ion-exchange resin matrix, and this core is coated with a semi-permeable material like ethyl cellulose. This helps protect the drug from breaking down in the gastrointestinal tract. The most commonly used and safe ion-exchange resin is divinylbenzene sulphonate. In tablet form, ion-exchange resins are also used as disintegrants.

**3.** Osmotically Controlled Release System

Osmosis is the movement of a solvent, like water, from an area of lower concentration to higher concentration through a semi-permeable membrane. Osmotic pressure is the pressure that develops in a solution on one side of a semi-permeable membrane due to differences in solute concentration. This method allows for a steady, zero-order release, which is useful for hydrophilic drugs. The drug may be osmotically active, or it may be combined with an osmotically active salt, such as sodium chloride. The semi-permeable membrane is often made from cellulose acetate. Examples include Glucotrol XL and Procardia XL. The volume of water flowing into the core reservoir is given by the formula: $dv/dt = K A / h (\Delta\pi - \Delta p)$, where K is membrane permeability, A is the effective surface area, h is the membrane thickness, $\Delta\pi$ is the osmotic pressure difference, and

Δp is the hydrostatic pressure difference.

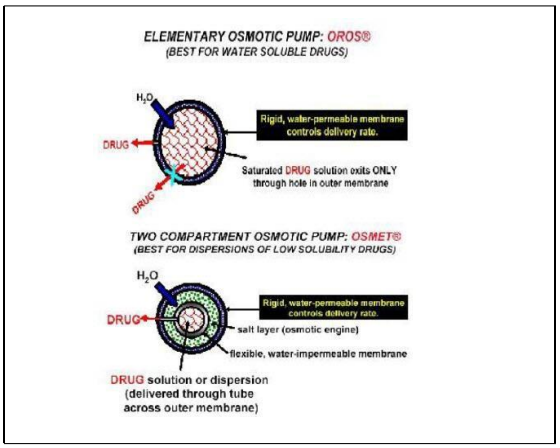



Figure: 12 Elementary osmatic pump

## 5. pH independent formulation

Most drugs are either weak acids or weak bases. The release of these drugs from controlled release formulations is affected by the pH level. To make the drug release independent of pH, buffers like salts of amino acids, citric acid, phthalic acid, phosphoric acid, or tartaric acid can be added to the formulation. This helps keep the pH constant, allowing the drug to release at a steady rate. A buffered formulation is made by mixing a basic or acidic drug with the right pharmaceutical excipient and then coating it with a film-forming polymer that allows gastric fluids to pass through. When the gastric fluid moves through the membrane, the buffering agents adjust the pH of the fluid to a stable level, which allows the drug to be released consistently

## 6. Altered density formulation

Many strategies have been developed to keep the drug delivery system in the GI tract for longer. One method uses bioadhesive polymers that stick to the mucin or epithelial surfaces of the GI tract. Another method is to change the density of the formulation.

**(I) High density approach:** this method uses pellets that are denser than normal stomach contents, so they should be at least 1.4g/cm³. To make these pellets, drugs can be coated around a heavy core or mixed with heavy inert materials like barium sulphate, titanium dioxide, iron powder, or zinc oxide. These weighted pellets are then covered with a controlled release membrane.

**(II) Low density approach:** this uses pellets that are less dense than gastric fluid, making them float on the stomach contents. Materials like polystyrol, popped rice, or popcorn can be used as carriers. The surface of these empty shells is first coated with sugar or a polymer such as meth acrylic polymer or cellulose acetate phthalate. Then the shell is coated with a mixture of drug and polymers like ethyl cellulose or hydroxypropyl cellulose. This final product floats in the stomach for a long time while slowly releasing the drug.

- Marketed drug classification

**TABLE 1: Marketed drug products with their mechanism based classification**

| S.No. | Technology | | Brand name | Drug | Manufacturer |
|---|---|---|---|---|---|
| 1. | Diffusion controlled system | | Wellbutrin XL | Buproption | GlaxoSmithKline |
| 2. | Matrix system tablet | | Ambien XL | Zolpidem tartarate | Sanofi-Aventis |
| 3. | Method using ion exchange resin | | Tussinonex Pennkinetics ER suspension | Hydrocodon Polistrex and Chlorpheneramine Polistirex | UCB inc. |
| 4. | Methods Using Osmotic Pressure | Elementary Osmotic pump | Efidac 24@ | Chlorpheneramine Maleate | Novartis |
| | | Push-pull Osmotic system | Glucotrol XL | Glipizide | Pfizer Inc. |
| 5. | pH independent formulation | | Inderal@ LA | Propranolol HCL | Wyeth Inc. |
| 6. | Altered density formulation | | Modapar | Levodopa and Benserazide | Roche Product USA |

## CONCLUSION:

Advanced oral controlled-release drug-delivery systems represent a significant evolution in pharmaceutical technology, offering improved therapeutic outcomes, enhanced patient compliance, and optimized drug utilization. By enabling precise modulation of drug release—whether sustained, delayed, pulsatile, or targeted—these systems overcome many limitations of conventional oral dosage forms, such as fluctuating plasma levels, frequent dosing, and gastrointestinal irritation. Innovations including polymer-based matrices, osmotic pumps, nanoparticle-embedded systems, and intelligent, stimuli-responsive formulations have expanded the possibilities for delivering drugs with complex pharmacokinetics or narrow therapeutic windows.

As research continues to integrate nanotechnology, biopolymers, and digital health interfaces, future oral controlled-release systems are expected to become even more personalized, efficient, and responsive to physiological cues. Overall, advanced oral controlled-release technologies hold immense promise for improving therapeutic efficacy, safety, and patient quality of life.

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