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Advances in oral controlled release drug delivery systems

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Abstract

Controlled Drug Delivery Systems (CDDS) represent a significant advancement in pharmaceutical technology, designed to deliver therapeutic agents in a controlled and sustained manner over an extended period. These systems aim to optimize the drug's efficacy by maintaining therapeutic drug levels in the body, reducing side effects, and enhancing patient compliance. CDDS can be classified into various categories, including polymeric, liposomal, and nanoparticle-based systems, each offering unique benefits. Polymeric systems, for example, allow for the precise release of drugs through diffusion, degradation, or swelling mechanisms**.** Drugs can be targeted to certain tissues with the use of liposomes and nanoparticles, increasing the therapeutic index while lowering systemic exposure. To further improve the accuracy of drug administration, CDDS can also be made to react to environmental stimuli like pH, temperature, or electromagnetic fields. The creation of CDDS has been the subject of extensive research in recent decades in order to solve issues such patient adherence, drug stability, and bioavailability. With the development of new materials and technology, CDDS remains a promising treatment option for cancer, chronic diseases, and other complex medical problems, offering more individualized and efficient therapeutic alternatives.

Keywords: Controlled Release Drug Delivery Systems; Prolonged; Bioavailability; Compliance; Medicine

1. Introduction

The field of controlled release drug delivery systems (CRDDS) is receiving more attention [1]. The maintenance of medication levels within a desired range, the requirement for fewer administrations, the best possible usage of the medicine in question, and Improved adherence from patients [2,3]. These are several ways to give drug of all administration routes, including oral administration and conventional delivery is the most practical for dose modification and administration [4,5]. Currently, the oral prescription medicine significant drug delivery methods, primarily for medications with high water solubility and a brief half-life in biology [6]. The utilization of controlled medication delivery systems is essential for optimizing treatment efficacy and reducing adverse effects. By precisely controlling medication release, these devices guarantee the best possible drug concentrations at the intended locations. Numerous technologies, including Hydrogels, liposomes, nanoparticles, and micro particles have all been used to accomplish Regulated administration of medication [7]. The process of administering medication to a patient in a way that enhances the concentration of the drug in some body regions relative to other parts is known as drug delivery. The ultimate objective of any delivery system is to extend, confine, and target the Medication having a protected interaction in the infected tissue. Each dosage form consists of a blend of medication, active pharmaceutical ingredients (APIs), and the non-pharmacological element known as Additives and excipients (Figure 1). The actual chemical elements that are employed to treat Illnesses

Dosage form=Active Pharmaceutical Ingredients (API)+Excipients/Additive.

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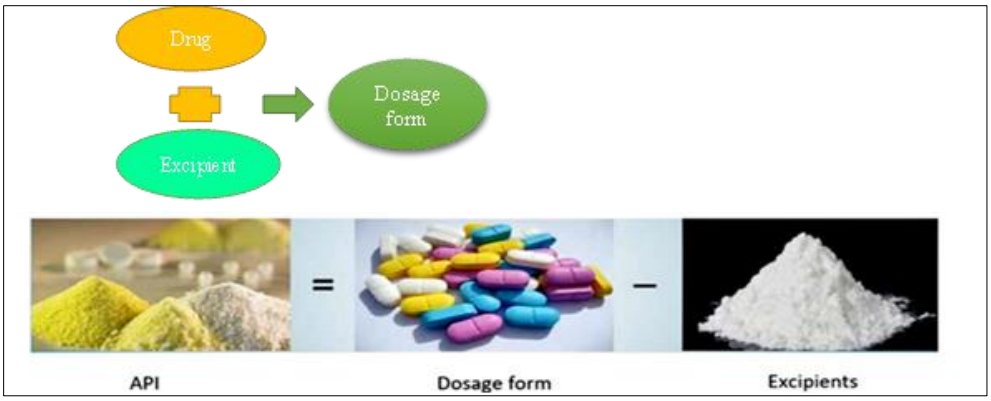

Figure 1 Dosage form composition [8]

When an active ingredient or medication is mixed with a polymer so that the release from the bulk material is predetermined, this is known as controlled drug delivery. Both sustained release and controlled release have been applied inconsistently and erratically. Each one stands for a different delivery method. Any dosage type that delivers medication over a lengthy period of time is considered sustained release. Indicates that some real therapeutic control can be provided by the system, whether this is of an either of two natures: temporal or spatial. In general, sustained release systems don't reach zero order type release and typically make an effort to resemble zero order release by administering the medication slowly at beginning. The main goal of controlled drug delivery is to modify the molecular structure, physiological factors, or innovative drug delivery mechanism in order to change the pharmacokinetics and pharmacodynamics of pharmacologically active moieties [7, 9, 10].

2. Modification types associated with CDDS

2.1. Extended-release dosage forms

A medication supplied in an extended-release dose form that permits a minimum of a twofold decrease in dosing frequency. For example, controlled release, prolonged release.

2.1.1. Sustained release

It encompasses all drug delivery methods that produce a prolonged, gradual release of drugs preferably not particularly at pre-determined rate [11, 12].

2.1.2. Controlled Release

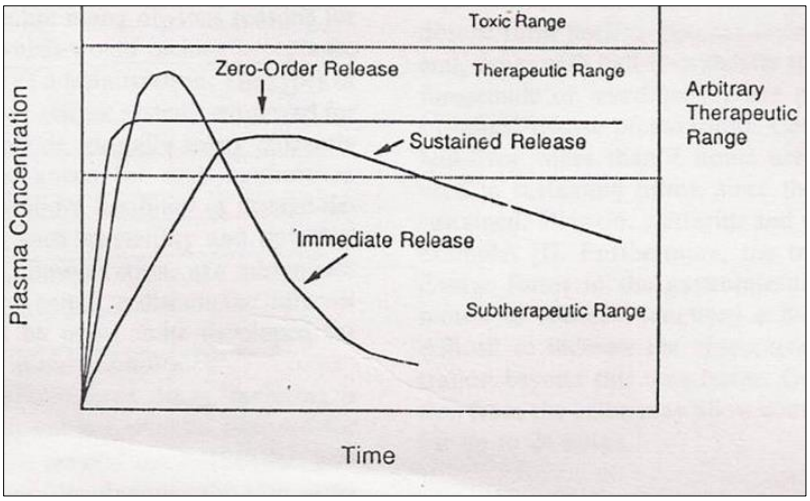

Figure 2 Arbitrary therapeutic range of different dosage form in blood [14]

They are the class of medications or other biologically active material that release a drug from the delivery mechanism in a predictable, planned and longer-lasting manner than usual [13]. Zero-order release is used in this system, which is independent of SRDDS adheres to first order release, whereas initial drug concentration is followed.

2.2. Delayed release

Drugs from in which one portion may release immediately and remaining release discrete a fraction of time combined into a single dosage form are dosed repeatedly and intermittently in delayed release systems [13].

2.3. Targeted Release

A dose form where the medication is released at or close to the desired physiological site of action Extended-release properties are possible with targeted release dose formulations [12,15].

2.4. Repeat action DDS

These are the alternate SR systems, where each dose of the medication is released at regular intervals and numerous doses are contained within the dosage form [13].

2.5. Prolonged release system

It's made to release the medication gradually and to keep the substance flowing continuously for a long time [13, 15]. They stop the medication from being absorbed too quickly, which could lead to very high drug peak plasma concentration [13].

2.6. Site-specific and receptor release

They are made to route the medication toward a certain biological site. Whereas a medicine targets a certain organ or tissue directly in site-specific release, a drug targets a specific receptor within an organ or tissue in receptor release [13].

2.7. Quick-acting dosage form

These are conventional drug forms that release the medication as it is administered, allowing for rapid and complete systemic absorption. The drug's plasma concentration after absorption follows its pharmacokinetic profile, progressively falling below the minimum therapeutic concentration (MEC) and ending the therapeutic effect. The time it takes to sustain a therapeutic level is indicated by the duration of action, and the point at which maximal concentration is reached is indicated by the start of action. It takes several dosages to maintain a steady-state concentration, which causes a "Teeter-totter" crest and trough pattern. Drug concentration fluctuations vary in size according to parameters such as distribution, excretion, absorption rate, and dose intervals [16].

2.8. Advantages

- Sustained Drug Release: By ensuring a steady and therapeutic concentration of the drug in the body over an extended period of time, controlled release devices deliver a consistent and sustained medication release.
- Minimized Side Effects: Peak plasma concentrations can be lowered by carefully releasing the medication, which may lessen negative effects and improve the drug's safety profile [17].
- It is possible to increase patient compliance [18].
- An increased level of pharmacological activity selectivity [19].
- The administration of "difficult" drugs: slowly releasing water-soluble medications or rapidly releasing poorly soluble medications [5, 20].
- Decrease in dosage and frequency of medication [21, 22].
- Less irritability in the digestive tract [23].
- Increases some medicines bioavailability [24, 25, 26].

2.9. Disadvantages

- One of the main drawbacks of CRDDS is "dose dumping," which is the term used to describe the quick release of a sizable amount of medication from a formulation with controlled release. When strong medications are used, this phenomenon gets dangerous [21, 22].
- Insufficient in vivo-in vitro connection [1, 6, 20, 25, 27-36].

- Additionally, they cannot be employed for medications absorbed in the GIT at particular times and necessitate more expensive manufacturing procedures and equipment [28, 37].
- More rapid growth of tolerance and counselling [38].
- Not every medication is a good fit for controlled release therapy [39].
- Reduced systemic availability as compared to traditional dose formulations with quick release. One possible cause of this is:
    - An incomplete release.
    - Higher metabolism in the first pass.
    - A rise in instability.
    - Absorption peculiar to a site
    - Solubility dependent on pH [28].
- Increased reliance on the dose form's stomach residence duration [20].
- Challenges in keeping a steady dosage [41].
- Optimizing the precise dosage and dosing period is challenging [30].
- Could raise the clearance for the initial pass [10].

3. Factors influencing the drug delivery system for controlled release

3.1. Physicochemical

3.1.1. The Aqueous Solubility of the Drug

Preferred options for oral controlled release dose forms are medications with excellent water solubility that is not affected by pH changes. The solubility profile of a drug is a key consideration when choosing the right mechanism for creating a Controlled Release Drug Delivery System (CRDDS). Diffusional systems usually aren't good for drugs that don't dissolve well because the rate at which they dissolve limits how much they can be absorbed. When this happens, controlled release devices aren't the best choice because they can't effectively control the absorption process. However, different formulation techniques can be used to make drugs that don't dissolve easily more soluble and faster to dissolve, which could make it possible to use them in controlled release systems. Solubilizing agents, amorphous solid dispersions, lipid-based formulations, or salt formation are some of these methods that can be used [42].

3.1.2. Partition Co-efficient

Since the drug must pass across a lipophilic biological barrier, the partition coefficient of the drug has a significant impact on its bioavailability. Because they will have very little lipid solubility and be localized at the first water phase they come into touch with, drugs with lower partition coefficient values than the optimal activity are undesirable for oral ER drug delivery systems. Because more lipid-soluble drugs won't partition out of the lipid membrane once they're within, drugs with partition coefficient values higher than the optimal activity are unsuitable for oral ER drug delivery systems [43].

3.1.3. Drug pKa and ionization at physiological pH

A medication's pKa value reveals how strongly acidic or basic it is. The pKa value of a pharmacological molecule can be used to calculate its charge at a certain physiological pH. Only in their unionized form do drug molecules have therapeutic benefits because they are more easily absorbed through lipophilic cellular membranes. The medication's dissociation constant and the pH of the fluid near the absorption site determine how much of the drug is still in its unionized form. Therefore, medications that are mostly found in ionized form at the sites of absorption are not good choices for dosage forms with sustained release or controlled release (SR/CR). Drugs should be non-ionized at the absorption site to a degree of 0.1-5% for the best passive absorption. Medications like hexamethonium, which mostly in ionized forms, making them unsuitable for distribution methods that are under control. The physiological pH levels throughout the gastrointestinal tract must be considered, as the drug's ionization state might change and impact its solubility, permeability, and total bioavailability [42].

3.1.4. Protein Binding

All medications have some degree of binding to plasma and/or tissue proteins, and the pharmacological response of a drug is dependent on the unbound drug concentration rather than the total concentration. Regardless of the dosage form, a drug's ability to bind to proteins plays a crucial part in its therapeutic effect. When a drug has a large binding to plasma, it increases its biological half-life and releases the drug for a longer amount of time, negating the need for extended-release drug delivery [43].

3.1.5. Drug stability

For controlled release systems, medications that are unstable in the gastrointestinal (GI) environment are not good options. It is possible to formulate drugs that will degrade in the stomach's acidic pH and release most of their release in the intestine and very little or none. On the other hand, medications that are unstable in the alkaline pH of the intestine can be made to release mostly in the stomach and very little in the intestine. The stability profile of the medicine must be carefully considered to produce the intended controlled release behaviour. Several formulation techniques, such as pH modifiers, antioxidants, or specialty coatings that shield the medication from deterioration, can be used to solve stability concerns. Additionally, alternative routes of administration (e.g., parenteral, transdermal) may be explored for drugs that exhibit poor stability in the GI tract [42].

3.2. Biological Properties

3.2.1. Biological half-life

Maintaining therapeutic blood levels for a longer amount of time is the goal of designing an oral sustain release product. The medicine must enter the blood circulation at a rate that is about equal to its rate of elimination to have the same effect. The half-life ($t_{1/2}$) provides a quantitative description of the elimination rate. Every medicine has a unique elimination rate characteristic. The total of all elimination processes, such as metabolism, urine excretion, and other processes that permanently remove the drug from the bloodstream, is the elimination rate. Short half-lives of therapeutic substances make them ideal for formulations involving sustained release. It can lower the frequency of dosage, which is the same cause. In general, medications like levodopa or furosemide that have half-lives less than two hours are not good choices for preparation for sustained release. Digoxin and phenytoin are two examples of compounds having lengthy half-lives more than eight hours that are typically not utilized in sustaining form as their effects are already sustained.

3.2.2. Absorption

The rate of release must be substantially slower than the rate of absorption to establish control over the drug delivery system, which is the goal of creating a sustain release product. If it has the maximal half-life for absorption should be roughly 3–4 hours, as it has been believed that most medications transit through the GI tract's absorptive sections in 8–12 hours. If not, the formulation will exit the potential absorptive regions before the drug release is finished. Corresponds to an 80–95% overtime period with a minimum apparent absorption rate constant of 0.17–0.23 h-1T. Therefore, it has been expected that the medicine will be absorbed over the entire length of the small intestine at a consistent rate. It is untrue for many compounds that the medication will be absorbed along the full length of the small intestine at a comparatively constant rate. A medication's absorption may be hampered by sustained release preparation if it is absorbed by active transport or if transport is restricted to a particular area of the intestine. Maintaining the chemicals in the stomach is one way to give sustaining mechanisms of delivery. Therefore, the drug can be released slowly and then move to the site where it will be absorbed. Because it has been seen that co-administration leads to sustaining effects, these ways have been created. One way to try this is to make a low-density pellet or pill. An alternative method is the use of bio-adhesive materials [44].

3.2.3. Distribution

Drug distribution within the body can affect a controlled release product's release kinetics. The way the medication is delivered to its intended location is influenced by variables such as blood-brain barrier permeability, tissue binding, and protein binding. These elements must be taken into consideration by controlled release systems to insure that the medication reaches the intended tissue or organ and sustains therapeutic concentrations over time.

3.2.4. Metabolism

Drug breakdown and excretion may be impacted by metabolic processes in the body, which are mostly carried out by liver and other organ enzymes. Some medications can undergo significant metabolism, which could result in a shorter half-life or decreased bioavailability. Drug metabolism rates must be considered when designing controlled release products to provide a continuous release for the intended amount of time [45].

3.2.5. Dose size

The CRDDS developed to avoid the repeated dosing must have a higher dosage than Conventional dosages form. However, the dose in the traditional dosage form indicates the dose that should be used in the CRDDS. The sustained dosage volume ought to be as high as is permitted by the acceptance criteria.

3.2.6. Therapeutic window

Steady release is frequently utilized for medications with a limited therapeutic range. To maximize effectiveness and reduce side effects, these medications need to be taken precisely, and their therapeutic levels need to be maintained for a long time within a certain range [46].

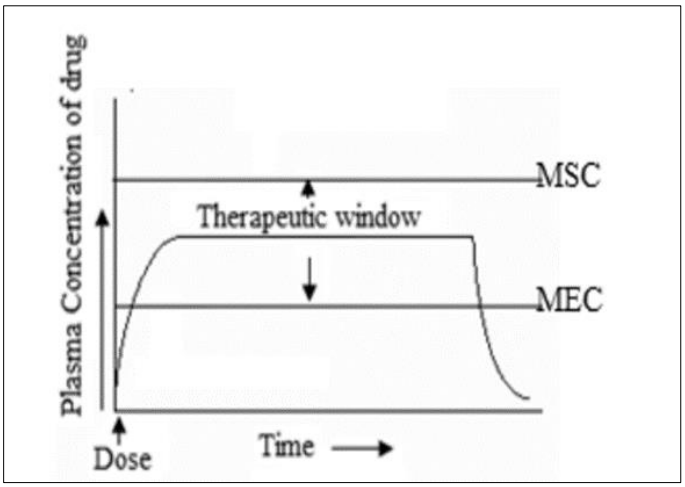

Figure 3 Therapeutic window [6]

3.2.7. 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.

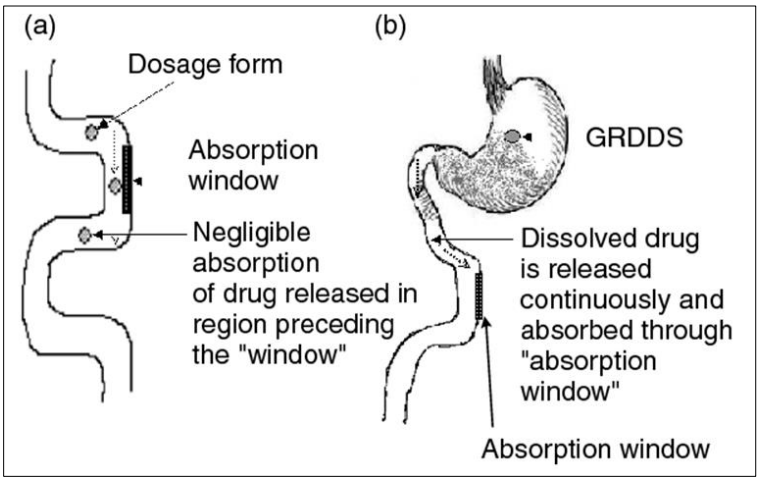

Figure 4 Absorption window [30, 46]

3.2.8. Patient physiology

The patient's physiological state, including GI disorders, residential duration, and gastric emptying rate, affects the drug's release from the dosage form either directly or indirectly [30, 46].

4. Classification of oral controlled drug delivery systems

4.1. Dissolution controlled system

It can be manufactured in numerous ways i.e.., by modifying the layers of medicine with rate controlling coatings & pulse delivery can be obtained. The outer layer is a rapidly dispersing drug bolus; initial drug levels can be generated fast and then released in pulsing intervals. It is divided into two categories:

4.1.1. Matrix type

Controlled dissolution by:

- Altering porosity of tablet
- Decreasing its wettability
- Dissolving at slower rate
- The drug release is determined by dissolution of the polymer.

e.g., Dimetapp extentabs & Dimetane extencaps.

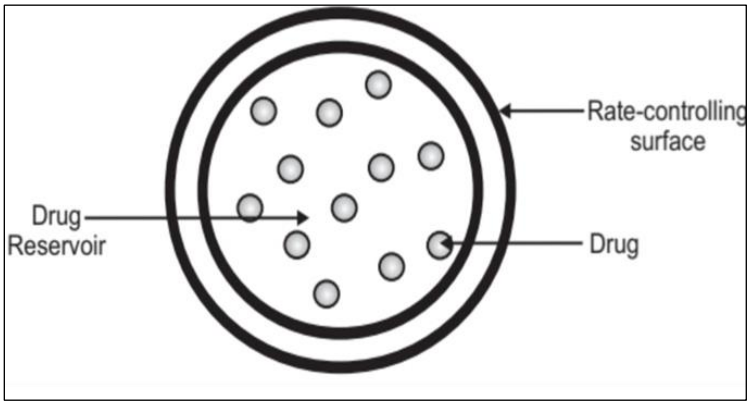

Figure 5 Matrix Type Dissolution [47]

4.1.2. . Encapsulation type:

The process of microencapsulation is used to coat the medication particles. The entire medicine within the microcapsule is readily available for absorption and disintegration as soon as the covering material dissolves. Dissolution rate and thickness of polymer membrane determine the drug release; its range is 1 to 200 μ. It is entirely dependent upon coating thickness and stability. The hard gelatine capsules, often known as spansules, are filled with the pellets. (Figure 6) For example, ornade spansules [47].

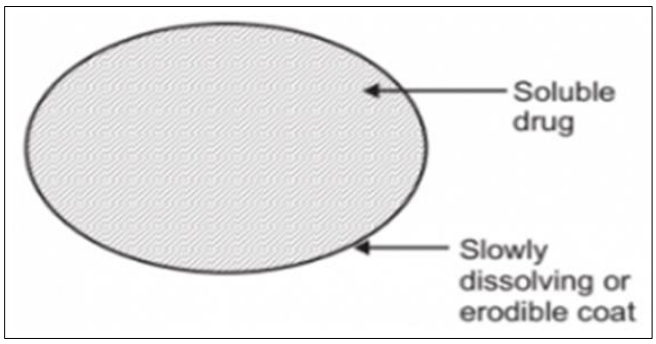

Figure 6 Encapsulation Type [47]

4.2. Diffusional system

Drug release rates in diffusion systems are determined by the drug's ability to diffuse through an inert membrane barrier. There are two types of insoluble polymers that make up this barrier [31].

4.2.1. Reservoir type

A drug's core is covered with a water-insoluble polymeric substance in a diffusion reservoir system. The medication will enter the membrane and swap places with the fluid that surrounds the pill or particle. More drug will enter into the polymer, spread to the edges, and interact with the surrounding substances. The diffusion process is responsible for the drug's release.

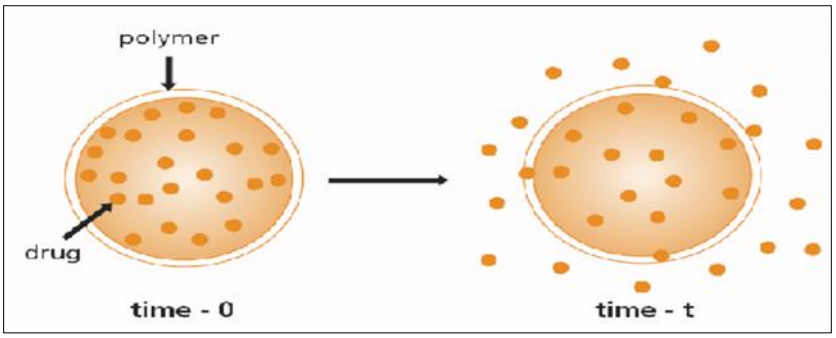

Figure 7 Schematic Representation of Diffusion Type Reservoir System [48]

4.2.2. Matrix type

A solid drug is distributed in an insoluble matrix; so, the rate of drug diffusion determines the rate of drug release rather than the rate of solid dissolution. It is made up of medication evenly distributed within a matrix [48].

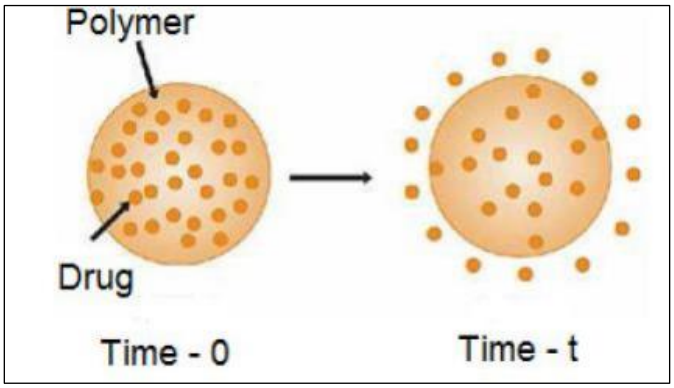

Figure 8 Schematic Representation of Diffusion Type Matrix System [48]

4.3. Biodegradable and combination of diffusion and dissolution

However, a class of systems known as bioerodable devices has quite sophisticated mathematical explanations of their release characteristics. Diffusion and dissolution of the drug and matrix material can be combined in these systems. The system becomes complex due to the possibility of a change in the drug's diffusion path length as the polymer dissolves. Usually this produces a shifting boundary diffusion system. Only when surface erosion takes place and surface area does not change with time will zero order release be possible. Drug in an erodible matrix has a homogenous distribution [49].

4.4. Osmotically controlled systems

Usually, they manifest in two distinct ways. The medication is present in the initial forms as an electrolyte and solid core that is dissolved by the incoming water. The strong osmotic pressure is supplied by the electrolyte. The second system contains the drug in the solution in an impermeable membrane. The bag is surrounded by electrolyte. To allow drug release, holes are punched through the membrane in any or both systems.

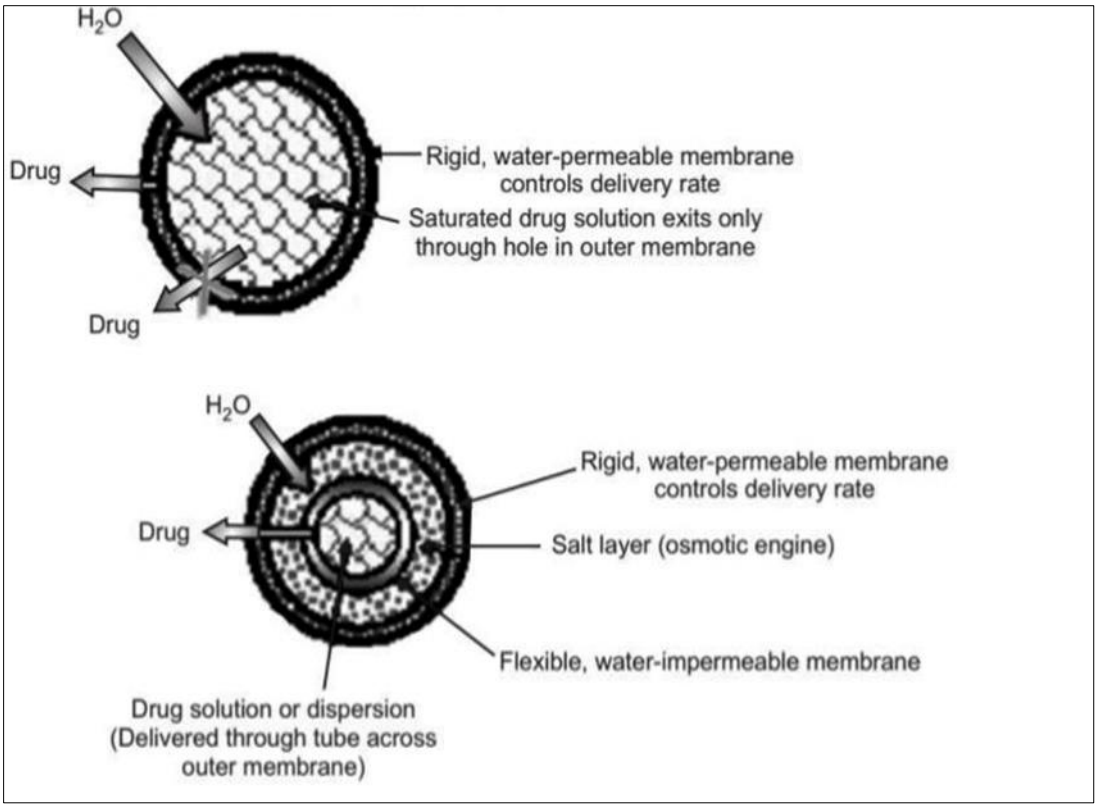

Figure 9 Osmotically controlled release system [47]

4.5. Ion-exchange controlled drug delivery system

These systems involved the cross-linked resin containing water-insoluble polymers. Functional groups that produce salts are repeatedly present in the polymer chains. The release of the resin-bounded medication causes the dosage form exposed to the ion exchange resin in the dissolving media or gut to exchange appropriately charged ions, such as Na+, H+, Cl-, or OH. The drug then effluxes out of the resin. The formation of the drug-resin complex can be achieved through extended interaction between the drug and resin in solution or by repeatedly exposing them to the drug in a chromatogram. The site, the distance to be travelled, and the stiffness of the system, which depends upon the concentration of the substance involved in the formulation of resin, all affect the rate of drug efflux from such dosage forms. This type of system is useful because it integrates medications that are very susceptible to enzymatic degradation [50].

5. Conclusion

A very efficient way to increase the safety, effectiveness, and administration of medications is using controlled drug delivery systems, or CDDS. Many of the drawbacks of traditional medication formulations, including low bioavailability, inconsistent dosing schedules, and unfavourable side effects, are addressed by these systems sustained, targeted, and controlled release. For these systems to reach their full potential, however, issues with patient variability, production costs, and design complexity must be resolved. As technology, materials, and personalised medicine continue to progress, CDDS will remain a crucial component of pharmacological therapy in the future, providing fresh possibilities for more efficient and patient-friendly therapies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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