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REVOLUTIONIZING NOVEL DRUG DELIVERY SYSTEMS (NDDS) USING ION-EXCHANGE RESINS

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ABSTRACT
Resins are very important in our lives. They are found in things like the proteins in our bodies, and also in products like ceramics, cement, and plastics such as bottles. Natural resins include cellulose in plants and RNA in our bodies. Humans also make many kinds of resins. Some are made by combining chemicals from oil, like polyethylene. Resins are categorized into natural and synthetic (industrial). Ion exchange resins used in medicine have several advantages. They are cheap and easy to get, and they aren't toxic. Ion exchange resins used in medicine have several advantages. The ion exchange process involves interactions between an Ion Exchange Resin (IER) and a drug. These interactions are primarily chemical but also involve some physical adsorption. Ion exchange resins have several uses, one of which is taste masking. Bitter-tasting drugs can make it hard for people to take their medicine. Taste masking helps by making the drug taste better. They can also stabilize drugs that tend to degrade, like Vitamin B12. By complexing Vitamin B12 with a weak acid cation exchange resin, its shelf life can be extended, reducing the need for excess vitamin in the formulation and lowering costs. Strong oxidizing agents can damage resins. Even oxygen or chlorine can cause slow degradation. The design of SR dosage forms necessitates that several variables including the physicochemical properties of API, route of administration, type of delivery system, disease, patient and the length of the proposed therapy be considered.

KEYWORDS: Monomers, Cellulose, Aromatic, Regenerated, Ammonia, Novel Drug Delivery.

INTRODUCTION

1.1 Introduction of Resins

Resins, also called polymers, are long chains of repeating units called monomers. They exist naturally and are also made by humans. Resins are very important in our lives. They are found in things like the proteins in our bodies, and also in products like ceramics, cement, and plastics such as bottles.[1]

Several processes are used to make resins and turn them into useful products. This section will discuss these processes in detail.[1]

1.2 Types of Resins

Resins were important even before industrialization. Natural resins include cellulose in plants and RNA in our bodies. Humans also make many kinds of resins. Some are made by combining chemicals from oil, like polyethylene. Others are made from inorganic materials, like cement and ceramics.[36] Figure (1.1) shows a diagram of the different types of resins.[1]

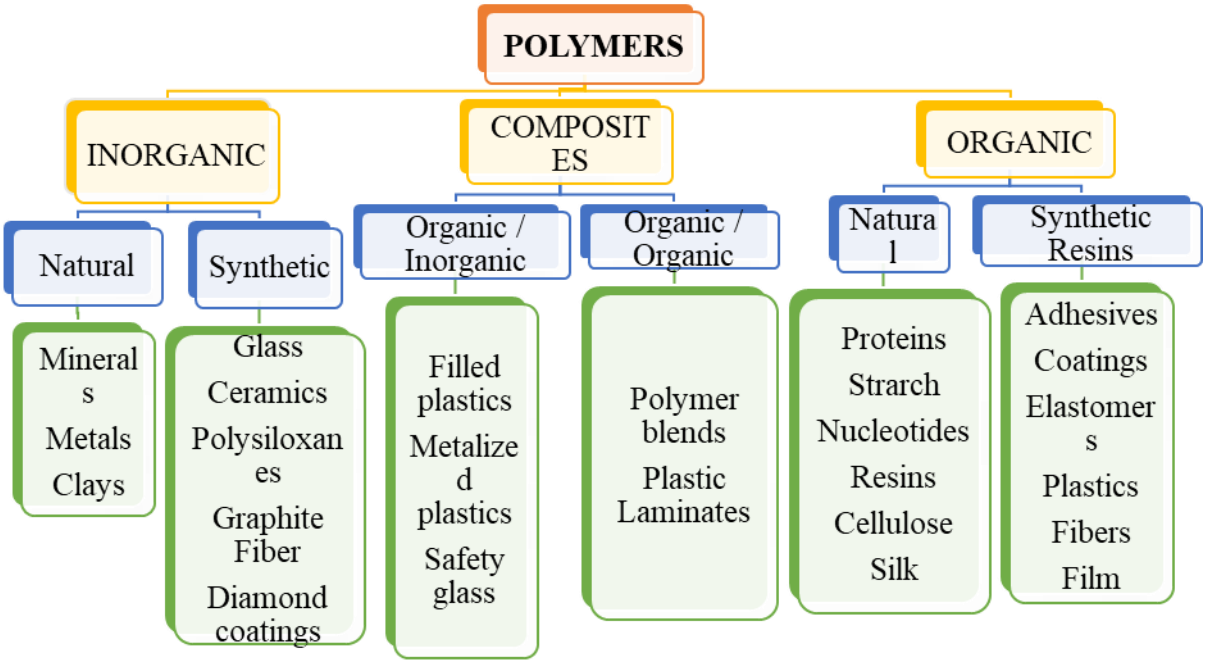

Figure (1.1): Resins types diagram.[1]

Resins are categorized into natural and synthetic (industrial) types.[1]

1.2.1 Natural Resins

These are formed naturally without human intervention. They are more complex than synthetic resins. Examples include proteins (found in the human body), DNA, RNA, cellulose, and natural rubber.[1]

1.2.2 Synthetic (Industrial) Resins

These are made by humans. They can be further divided into inorganic and organic resins.[1]

1.2.2.1 Inorganic Resins

These have been used for a long time. Ancient Egyptians used alkaline silicate glass (similar to cement) as early as 12000 BC. Modern examples include cement and concrete.[1]

1.2.2.2 Organic Resins

These are the most common type. Many are made from chemicals derived from crude oil, like ethylene and propylene. They are used in various products such as paints, plastics, and foams.[1]

Organic resins are further categorized into:

1.2.2.2.1 Thermoset Resins

These are strong due to their high aromatic content (like polycarbonates and epoxies). They are used in applications needing high strength.[1]

1.2.2.2.2 Thermoplastic Resins

These have a high aliphatic content, making them less strong. Examples include polyethylene and polypropylene. They are used for applications where less strength is needed.[1]

Application Of Ion Exchange Resins In Cardiovascular Diseases

2.1 Introduction of Ion Exchange Resins

Ion exchange resins are like tiny, insoluble sponges made of large molecules called polyelectrolytes. Imagine these sponges have little "hooks" or "grabbers" on them, which are actually mobile ions (think of them as electrically charged particles). These "hooks" can grab onto ions in a liquid that's passed over the resin. The special thing about these "hooks" is that they don't hold onto the ions permanently. Instead, they can swap the ions they've grabbed for other ions that are also present in the liquid. This swapping, or exchange, happens in a very precise and balanced way – it's called a stoichiometric exchange. For every ion that's grabbed, another ion of the same charge is released. And the best part is, all this swapping happens without the resin itself changing physically. It stays intact and can be used over and over again.[2]

These ion exchange resins are typically made into small, round beads, kind of like tiny marbles, usually white or yellowish in colour. The material they're made from is a type of organic polymer, which is a long chain of molecules. These beads aren't solid all the way through;

they're porous, meaning they have lots of tiny holes and spaces inside. This porous structure is really important because it creates a huge surface area. Think of it like this: a sponge can absorb more water than a solid block of the same size because of all the pores. The same goes for the resin beads – the large surface area allows them to interact with more ions in the liquid, making the ion exchange process much more efficient. So, to sum it up, ion exchange resins are materials that can selectively grab and swap ions in a liquid, thanks to their special structure and properties.[33]

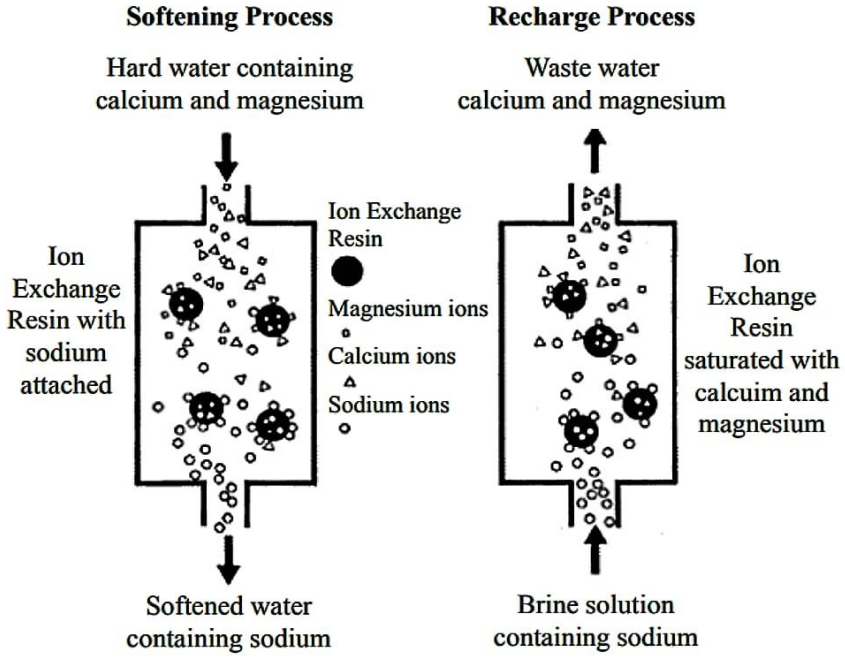

Figure (1.1.1): Ion Exchange Resin diagram.[2]

2.2 Types of Ion Exchange Resins

Ion-exchange resins come in two main types.

2.2.1 Cation Exchange Resins

2.2.2 Anion Exchange Resins

These two main types are explained in more detail below.

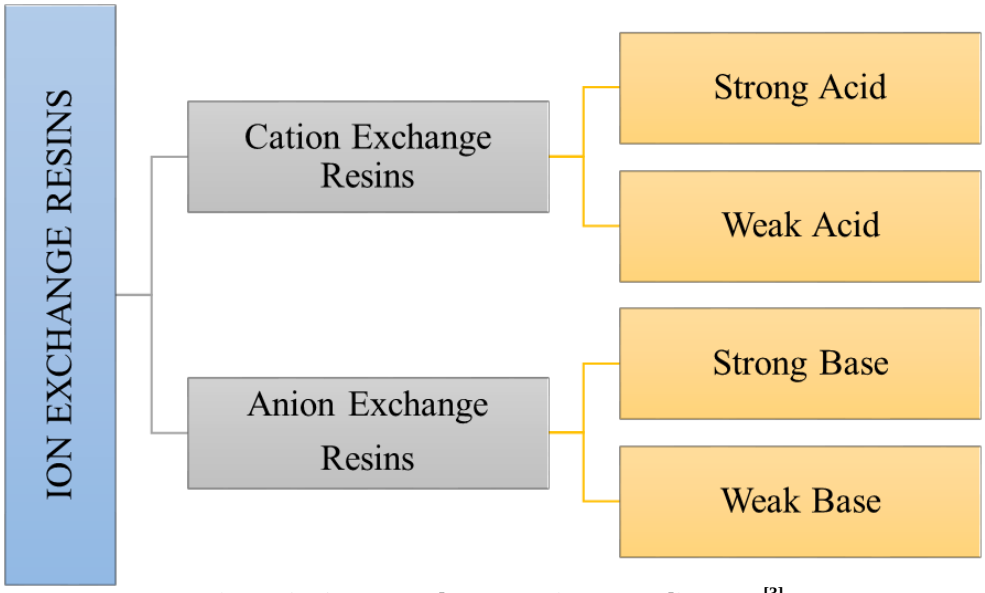

Figure (1.2): Ion Exchange Resins types diagram.[3]

Ion exchange resins are used to swap ions in a solution. There are two main types: cation and anion.

Cation exchange resins are negatively charged and swap positive ions. They're made by combining two chemicals (styrene and divinyl benzene) and adding

sulfonic acid. They work by trading a positive ion on the resin for one in the solution.[3]

There are two subtypes
strong acid and weak acid. **Strong acid resins** are always charged and work at any pH. They can even turn metal salts into acids. **Weak acid resins** are only slightly charged, and their effectiveness depends on the pH. They don't work well in acidic conditions.[3]

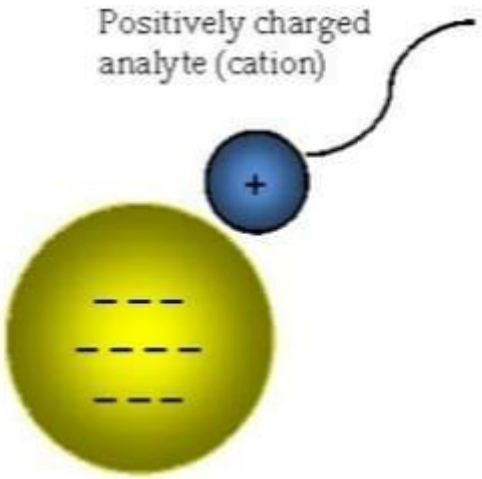

Figure (1.2.1): Cation Exchanger Stationary Phase Particle diagram.[3]

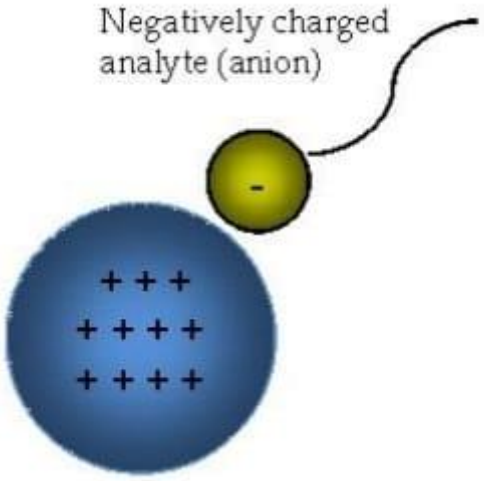

Figure (1.2.2): Anion Exchanger Stationary Phase Particle diagram.[3]

Anion exchange resins are positively charged and swap negative ions. They're made by adding specific chemical groups to a base material. They work by trading a negative ion on the resin for one in the solution.[3]

There are also two subtypes
strong base and weak base. **Strong base resins** are always charged and work at any pH. They're often used to purify water. They react with negative ions and can even neutralize acids, turning them into pure water. They do this by reacting with an acid (like HCl) to form a salt and water. They can be regenerated (restored) by washing them with a strong base like sodium hydroxide (NaOH). **Weak base resins,** unlike strong base resins, are only partially charged, and their effectiveness depends on the pH. They work best above a pH of 7. They don't have an OH form like strong base resins, so they are regenerated with less expensive chemicals like ammonia or sodium carbonate.[3]

Cation exchange resins are typically made by combining styrene and divinyl benzene. This creates a network of polystyrene chains linked together by divinyl benzene. Adding sulfuric acid then attaches sulfonic acid groups, creating the final cation exchange resin.[3]

Anion exchange resins are made by first attaching chloromethyl groups (-CH2Cl) to the same styrene-divinylbenzene network. Then, reacting these groups with a tertiary amine, like trimethylamine, creates the

positively charged sites on the resin, making it a strong base anion exchanger.[3]

2.3 Advantages and Disadvantages of Ion Exchange Resins

2.3.1 Advantages

Ion exchange resins used in medicine have several advantages. They are cheap and easy to get, and they aren't toxic. They can be made into various forms like pills, capsules, and liquids. They can also be used for different purposes, such as hiding bad tastes, making drugs last longer, or releasing them quickly. Because they work well even in small amounts, you don't need a lot of the drug-resin combination. Resins can also hold a lot of drug.[4]

Clinically, these resins offer benefits like fewer doses needed, which makes it easier for patients to follow their treatment. They also help keep drug levels in the blood more consistent, avoiding big swings. This can reduce drug buildup in the body over time and lower the risk of side effects. More stable drug levels can also help stabilize a patient's condition. For some drugs, they can even improve how well the body absorbs them. Finally, they can be more affordable for both patients and healthcare providers.[4]

2.3.2 Disadvantages

However, there are also some disadvantages. It can be harder to adjust the dose. A single dose can be more expensive than regular medications. They might increase how much of the drug is broken down by the liver before it reaches the bloodstream. Patients might need extra instructions on how to take them correctly. And, compared to regular, fast-release medications, the amount of drug that actually gets into the bloodstream might be lower, and it can be difficult to predict how the drug will behave in the body.[4]

3.1 Introduction of Cardiovascular Diseases

Heart disease is a major health problem worldwide. It affects people of working age and costs a lot of money. While it's more common in people over 65 (likely due to aging-related issues like atherosclerosis), it starts developing earlier. In men, this development often begins up to age 60. In women, it usually starts after menopause, around age 50. Heart disease is the top cause of death and disability for women, and the second leading cause for men, both globally and within countries. The World Health Organization (WHO) reports that in 2019, about 18 million people died from heart disease, which was almost a third of all deaths worldwide. Most of these deaths (85%) were from heart attacks and strokes.[8]

Portugal faces a similar problem, where heart disease is the main cause of death and disability, particularly for women, and the second leading cause for men. Across Europe, heart disease costs about 169 million euros each year.[8]

On top of the direct costs, heart disease also leads to a loss of productivity costing Europe 35 billion euros, which makes up 21% of the total cost of heart disease. In Portugal, the National Health Service spends over 476 million euros on heart disease medications and hospital stays. Another report shows that Portugal spent over 1 billion euros on heart disease in 2018. The World Health Organization (WHO) predicts that heart disease, the world's leading cause of death, will keep increasing until 2030, leading to more deaths and lower quality of life. Even though deaths from stroke and heart attacks have gone down in the last 20 years, they were still the top two causes of death in Portugal in 2018. Other major causes of death in Portugal include lung problems like pneumonia and COPD, as well as lung and colon cancer. Since the risk factors for heart disease change with age, this study looks at three different generations to understand how social and psychological factors play a role in heart disease.[8]

Since heart disease is common in people over 45, this study looks at three generations: the Silent Generation (born 1925-1942), Baby Boomers (born 1945-1964), and Generation X (born 1965-1981). These groups fall within middle and late adulthood. Middle-aged adults often feel their lives are stable and under control because they have many responsibilities at home and work. They also tend to feel they are at their most productive at work. However, their bodies start to change. In their 50s, the heart may start pumping slower and less regularly. Heart disease often starts to appear around age 40 or 50 because the walls of the arteries thicken and stiffen. The heart's condition tends to decline sharply after age 45.[8]

Besides the physical changes, middle-aged adults often experience stress related to family, finances, and work, especially when these areas change. Getting heart disease can be very stressful because it can affect a person's roles at home and on the job. People in this age group are also more likely to experience psychological distress like sadness, anxiety, or nervousness, which can make them more vulnerable to heart disease. Late adulthood, which includes the Silent Generation and some Baby Boomers, is often marked by stable personalities that are still influenced by their surroundings. Many in these generations are strongly attached to their work, so retirement can be difficult due to the emotional and financial impact. Heart disease, like other illnesses, is linked to several risk factors, including high blood pressure, poor diet, high cholesterol, air pollution, smoking, high body weight, high blood sugar, kidney problems, environmental factors, and lack of exercise.[8]

Concerning gender, some research suggests that while the death rates may be similar, women tend to develop heart disease about 10 to 15 years later than men. The COVID-19 pandemic, with its initial unknowns, uncertainties, and stay-at-home orders, increased stress and anxiety. As we learned more about the virus, it also became clear that having heart disease made COVID-19

infection more dangerous, increasing the risk of death. Even dealing with illness is difficult, but knowing that a COVID-19 infection could be fatal likely caused even more anxiety and fear. This review will examine the main findings of studies published in the last 20 years about the social and psychological factors related to heart disease, as well as psychological treatments.[8]

2.4 Applications of Ion Exchange Resins

2.4.1 Taste Masking

Ion exchange resins have several uses, one of which is taste masking. Bitter-tasting drugs can make it hard for people to take their medicine. Taste masking helps by making the drug taste better. Many drugs have charged parts, and resins with opposite charges can loosely bind to them. This drug-resin complex prevents the drug from being released in the saliva, so you don't taste it. Less cross-linked resins are usually better for taste masking. Weak cation or anion exchange resins are used, depending on the drug. The bond between the drug and resin is designed to stay intact in the mouth (where the pH is around 6.7 and cation concentration is low) but break down in the stomach's acidic environment. This means the drug is tasteless going down, but it's still absorbed by the body later. Ranitidine, paroxetine, and dextromethorphan are examples of drugs where taste masking has been successful. The same idea is used in some fast-dissolving tablets. Studies have also shown that this technique can be used to mask the taste of ciprofloxacin hydrochloride, an antibacterial drug.[5]

2.4.2 Disintegrant / Superdisintegrant

Ion exchange resins have several pharmaceutical applications beyond taste masking. They can act as superdisintegrants in tablets. Many disintegrants help tablets break apart quickly by absorbing water and swelling. Some resins, like polacrilline, swell a lot and are very effective disintegrants. They work even better than regular disintegrants because they don't clump and they also make the tablets stronger. Studies have shown that some resins can be used as superdisintegrants in fast-dissolving tablets.[5]

2.4.3 Improved Dissolution

Resins can also improve how well poorly soluble drugs dissolve. When a drug is bound to a resin, it's often in an amorphous form, which dissolves more easily. When the drug is released from the resin, it dissolves quickly.[5]

2.4.4 Drug Stabilization

They can also stabilize drugs that tend to degrade, like Vitamin B12. By complexing Vitamin B12 with a weak acid cation exchange resin, its shelf life can be extended, reducing the need for excess vitamin in the formulation and lowering costs.[5]

2.4.5 Powder Processing Acid

Resins can even improve the handling of some drug powders. Hygroscopic (water-absorbing) drugs or drugs that tend to clump can be easier to work with after they're complexed with a resin. The rigid structure of the resin helps with this.[5]

2.4.6 High purity water

Finally, ion exchange resins are used for water purification. In water softening, they remove calcium and magnesium ions (which cause hardness) and replace them with sodium ions. This prevents scaling on equipment like reverse osmosis membranes. The hard water is passed through a resin bed, and the resin captures the calcium and magnesium. Eventually, the resin needs to be regenerated by flushing it with a salt solution.[5]

2.5 Properties of Ion Exchange Resins

2.5.1 Physical properties of IER

Ion exchange resins are made of linked polymer networks with charged sites. Cation resins are negatively charged and swap positive ions. They come as spheres or granules in different sizes. Most are spheres, either a mix of sizes (0.3-1.2mm) or all the same size. When wet, they're slightly denser than water (specific gravity 1.1-1.5). Packed in a column, they have empty spaces (35-40% of the volume). The wet resin's weight in that space is typically 560-960 grams per litter.[6]

2.5.2 Chemical properties of IER

2.5.2.1 Capacity

A resin's capacity is how many ions it can exchange. Total capacity is measured after cleaning the resin and converting it to a specific ion form. The ions are then removed and measured. Capacity is based on dry weight, wet weight, or wet volume. Water uptake affects wet weight and volume, depending on the polymer and environment. A graph (Figure 2) shows how dry weight and wet volume change with cross-linking. Operating capacity is how well the resin works in a column under specific conditions. It depends on total capacity, regeneration level, the solution, flow rate, temperature, and particle size. Figure 3 shows an example for water softening.[6]

2.5.2.2 Swelling

Resins swell because the charged groups attract water. More charged groups mean more swelling. The resin's volume changes depending on which ions are attached. For example, a cation exchanger swells differently with lithium, sodium, potassium, etc. Highly charged ions cause less swelling. Concentrated solutions mean less water uptake.[6]

2.5.2.3 Selectivity

Ion exchange is reversible. With lots of a specific ion (B+), the resin will switch to that form. With a limited amount of B+, the resin reaches a balance between the original ion (A+) and B+. This depends on the amounts of A+ and B+ and the resin's preference (selectivity). This preference is measured by the selectivity coefficient.[6]

2.5.2.4 Kinetics

How fast ion exchange happens depends on diffusion through the solution around the resin and within the resin. At low concentrations, diffusion through the solution is the limiting factor. At high concentrations, diffusion inside the resin is the limiting factor. Smaller, uniform particles make the exchange faster.[6]

2.5.2.5 Stability

Strong oxidizing agents can damage resins. Even oxygen or chlorine can cause slow degradation.[57] Cation exchangers are attacked on the polymer backbone. Highly cross-linked resins last longer. Anion exchangers are attacked on the functional groups, reducing capacity. Anion resins are less thermally stable, especially at high pH. They are generally recommended for use up to 60°C. Cation resins are more stable and can handle up to 150°C.[6]

2.6 Uses of Ion Exchange Resins

Ion exchange resins have many uses in medicine.

2.6.1 Targeted Drug Delivery

Resins can be used to deliver cancer drugs directly to cancer cells in a controlled way. They can also be used in stomach-retaining systems to release drugs and bicarbonate over a longer period. For targeted release in the intestines, resins can be coated with special polymers that dissolve at a specific pH.[7]

2.6.2 Taste Masking

Many drugs taste bitter. Resins can bind to these drugs, making them tasteless. This can be done in batches or in a column. Several studies have shown this works for drugs like ciprofloxacin, dextromethorphan, and pseudoephedrine.[7]

2.6.3 Nasal Drug Delivery

Resins can be used to deliver peptides or drugs through the nose. For example, they've been used to deliver nicotine in a controlled way.[7]

2.6.4 Drug Stabilization

Some drugs, like Vitamin B12, break down easily. Resins can stabilize these drugs, extending their shelf life. Resins can also be used to hold enzymes, making them work for longer in a specific location.[7]

2.6.5 Controlled/Sustained Release

Resins can be used to control how quickly a drug is released. Coating the drug-resin complex can make the release depend on diffusion. Studies have shown this works for drugs like dextromethorphan. Resins are available that provide more moderate release than others.[7]

2.6.6 Tablet Disintegrants

Some resins swell a lot when they absorb water, which can help tablets break apart quickly. Polymethacrylic carboxylic acid resins are used for this.[7]

2.6.7 Transdermal Drug Delivery

Resins can be used in transdermal (through the skin) drug delivery, especially when using iontophoresis (using an electric current to push drugs through the skin). Studies have shown that combining different drugs with resins can improve their delivery.[7]

2.6.8 Dissolution Enhancement

Resins can help poorly soluble drugs dissolve better. When a drug is bound to a resin, it's often in a form that dissolves more easily.[7]

2.6.9 Polymorphism

Some drugs can exist in different crystal forms (polymorphism), which can affect how they work. Drugs bound to resins are typically amorphous (non-crystalline), which avoids this problem.[7]

2.6.10 Deliquescence

Some drugs absorb so much water that they become difficult to handle. Resins can prevent this deliquescence, making these drugs easier to work with.[7]

2.7 Advantages and Disadvantages in the Use of Ion Exchange Resins

The advantages and disadvantages of using ion-exchange resins.[34]

Advantages

Low Running Costs:

- Uses very little energy.
- Regenerating chemicals are inexpensive.
- Resins can last a long time if properly maintained.[34]

Disadvantages (Limitations)

Calcium Sulfate Fouling:

- Using sulfuric acid to clean the resins can cause calcium sulfate to build up, clogging them.
- This is more likely with water containing high calcium levels.
- Hydrochloric acid can be used instead, but it is more expensive.[34]

Iron Fouling:

- Water from underground sources often contains iron.
- If the iron is exposed to air, it turns into a solid that clogs the resins.
- This is a very common problem.[34]

Organic Matter Adsorption:

- Water from lakes and rivers contains organic matter that can stick to the resins, reducing their effectiveness.
- This can be prevented by pre-treating the water with chemicals and filters.[34]

Organic Contamination from the Resin:

- New resins may release leftover chemicals from manufacturing.
- Old resins may break down and release small pieces.
- Ultrafiltration can remove this.[34]

Bacterial Contamination:

- Resin beds don't remove bacteria and can actually encourage their growth.
- The organic matter trapped in the resins provides food for bacteria.
- Sterilization methods like heat or UV light are needed for bacteria free water.
- Chemical disinfection of the resin bed is possible, but certain chemicals like chlorine will damage the resin.[34]

Chlorine Contamination:

- Chlorine damages resins, so even tap water (which contains chlorine) needs to be treated before using it in an ion-exchange system.
- Activated carbon filters are used to remove chlorine.[34]

Environmental Implications:

- Waste Water:
- The wastewater from cleaning the resins contains the removed minerals and chemicals.
- The amount of wastewater is relatively small compared to other industrial processes, so disposal is usually not a major issue.[34]

2.8 Mechanism of Ion Exchange Process

The ion exchange process involves interactions between an Ion Exchange Resin (IER) and a drug. These interactions are primarily chemical but also involve some physical adsorption. The process is often referred to as 'adsorption on IER' rather than complexation. Ion exchange is considered a double-decomposition process where the IER provides ions to replace those adsorbed from the solution.[2]

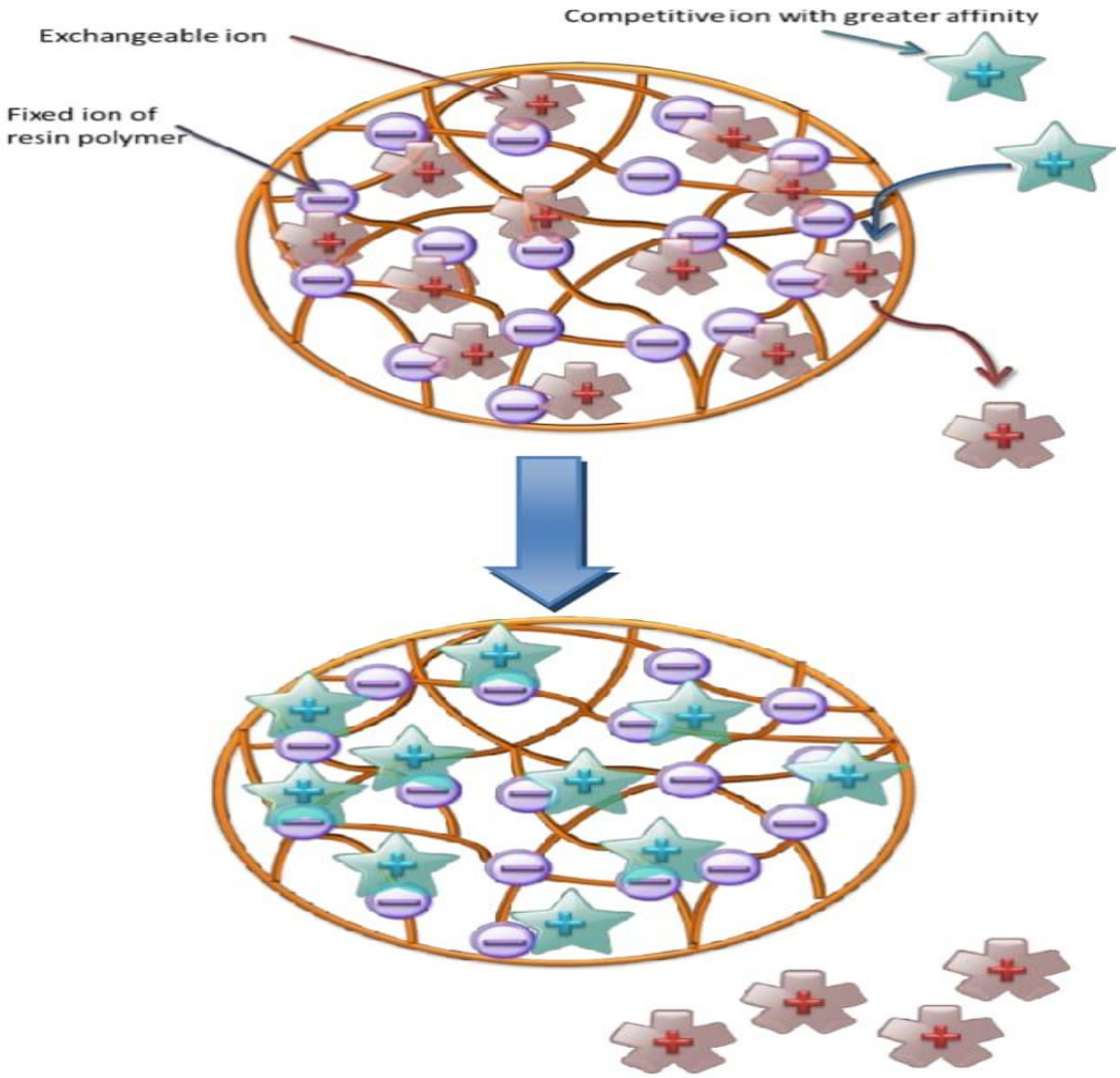

Figure (1.2.3): Schematic Diagram of Ion Exchange Process.[2]

3.1.1 Introduction Angina pectoris

Angina is chest pain that happens when your heart muscle doesn't get enough oxygen. This usually happens because the blood flow through the arteries supplying your heart is reduced. Think of it like this: your heart is a muscle, and just like any muscle, it needs oxygen to work. If it doesn't get enough, it hurts.[9]

This reduced blood flow can be caused by a few things:

- Spasm: The arteries can tighten up, reducing blood flow.
- Narrowing: The arteries can become narrowed due to a buildup of plaque (fatty material). This is called atherosclerosis.
- Blood clots: A blood clot can form and block an artery, either partially or completely.[9]

Your heart needs more oxygen when it's working harder, like during exercise. Things that make your heart work harder include a faster heart rate, stronger contractions, higher blood pressure, and more blood filling the heart. If your arteries are already narrowed, they might not be able to deliver enough oxygen when the heart's demand increases, leading to angina.[9]

Angina is often a sign of coronary artery disease, which is a common heart problem. Coronary artery disease is when plaque builds up in the arteries that supply blood to your heart. This plaque makes the arteries narrower and stiffer, reducing blood flow and potentially causing angina or even a heart attack.[9]

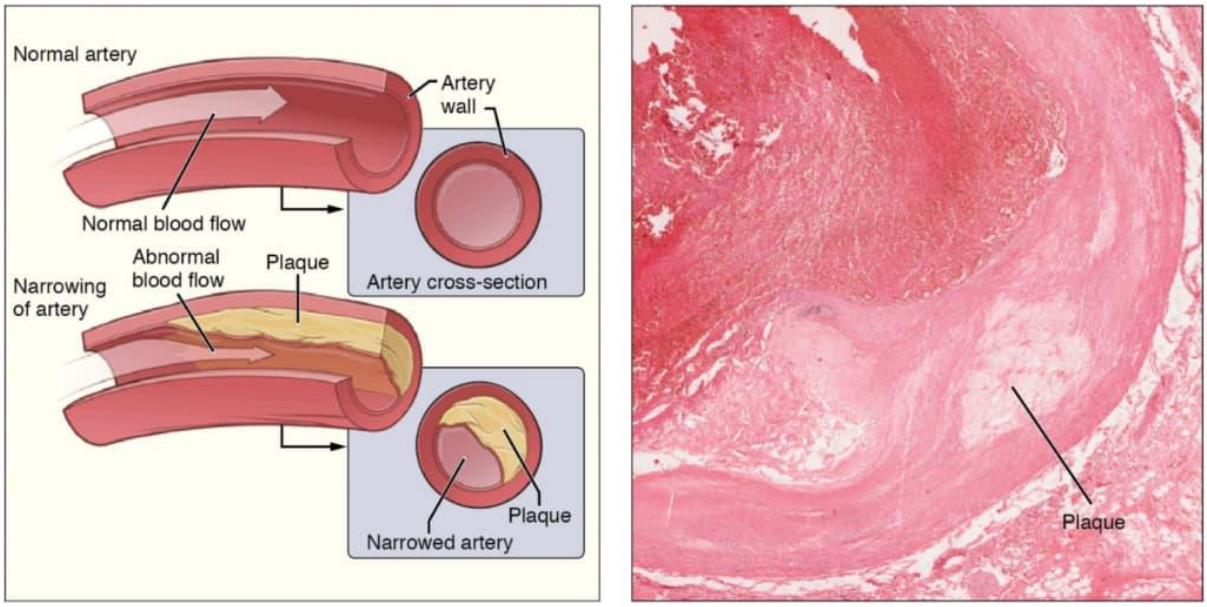

Figure (1.3): A normal artery with normal blood flow and an artery containing plaque buildup.[10]

3.1.2 Types of Angina

There are three main types of angina: stable, unstable, and variant (also called Prinzmetal's). It's important to know the differences because each type has its own symptoms and needs different treatment.[10]

3.1.2.1. Stable Angina

This is the most common type. It happens when your heart works harder than usual, like when you're exercising or stressed. It follows a predictable pattern – the pain usually comes on with activity and goes away when you rest or take your medicine. While stable angina itself isn't a heart attack, it does mean you're at a higher risk of having one in the future.[10]

3.1.2.2. Unstable Angina

This is more serious. It doesn't have a regular pattern like stable angina. It can happen even when you're resting, and the pain might be more severe or last longer. Resting or taking your usual angina medicine might not help. Unstable angina is a warning sign that a heart attack could be coming soon, so you need to get emergency medical help right away.[10]

3.1.2.3. Variant (Prinzmetal's) Angina

This is a less common type. It usually happens when you're resting, often between midnight and early morning. The pain can be very strong. It's caused by spasms in your heart's arteries, which temporarily reduce blood flow. Medicine usually helps relieve the pain. While it can be a sign of heart disease, sometimes tests don't show any problems with the arteries even though you're having this type of angina. It affects men and women equally.[10]

3.1.3 Signs and symptoms of Angina

The main sign of angina is pain or discomfort, usually in your chest. People describe it in different ways, like a pressure, squeezing, burning, or tightness. It often starts in the center of your chest, behind your breastbone.[11]

The pain can also spread to your arms, shoulders, neck, jaw, throat, or back. Sometimes it can even feel like indigestion.[11]

Besides chest pain, you might also experience other symptoms like feeling sick to your stomach (nausea), tiredness (fatigue), shortness of breath, sweating, feeling

light-headed, or weakness. It's worth noting that women are more likely to feel the discomfort in their back, shoulders, or belly area.[11]

3.1.4 Underlying causes of Angina

Angina is usually caused by problems with the arteries that supply blood to your heart. Several things can increase your risk of developing these problems, including:

- Unhealthy cholesterol levels:

Too much "bad" cholesterol can clog your arteries.

- High blood pressure:

This puts extra strain on your heart and blood vessels.

- Smoking:

Smoking damages your blood vessels and makes it harder for your blood to carry oxygen.

- Diabetes or insulin resistance:

These conditions can damage your blood vessels.

- Being overweight or obese:

Excess weight puts extra stress on your heart.

- Metabolic syndrome:

This is a group of risk factors, including high blood pressure, high blood sugar, unhealthy cholesterol levels, and excess belly fat.

- Lack of exercise:

Regular physical activity is good for your heart.

- Age:

The risk of heart disease increases as you get older (men over 45, women over 55).

- Family history:

If your close relatives had heart disease at a young age, you're also at higher risk.[11]

3.1.5 Treatment of Angina

Angina treatment aims to do two main things:

- Relieve pain:

Reduce how often you have angina pain and how severe it is.

- Prevent heart attack:

Lower your risk of a heart attack and death by addressing the underlying heart problem.[11]

Treatment options include

- Lifestyle changes:

These might be enough if your angina is mild and not worsening.

- Medications:

These can help control angina symptoms.

- Medical procedures:

If lifestyle changes and medicine aren't enough, you might need a procedure.

- Cardiac rehabilitation:

This program helps you recover and improve your heart health.

It's important to remember that unstable angina is a medical emergency. If you have unstable angina, you'll need immediate treatment in a hospital.[11]

3.1.6 Medicines for treatment of Angina

Several medications are used to treat angina, but nitrates are the most common. They work by relaxing and widening your blood vessels, which lets more blood reach your heart and reduces how hard it has to work.[11]
The most common nitrate is nitroglycerin. It comes in a few forms:

- Under the tongue or cheek:

This type is used to quickly relieve angina pain when it's happening.

- Pills or skin patches:

These are used regularly to help prevent angina attacks, but they don't work fast enough to stop pain once it starts.[11]

Other medications that might be used for Angina include

- Beta blockers:

These slow your heart rate and reduce blood pressure.

- Calcium channel blockers:

These also relax blood vessels and lower blood pressure.

- ACE inhibitors:

These help relax blood vessels.

- Antiplatelet medications:

These help prevent blood clots from forming.

- Anticoagulants:

These also help prevent blood clots.[11]

4.1 Sustained release drug delivery

A drug substance or active pharmaceutical ingredient (API) is rarely, if ever administered alone[12] and is usually administered as a component of a drug delivery system. The delivery system is usually comprised of the API, and pharmaceutical adjuvant or excipients, which are included in the formulation to facilitate manufacturing, or perform specialized functions in the delivery system, and were different delivery systems, are unique with respect to their physical and pharmaceutical characteristics.[13] The goal of drug delivery systems is to deliver a specific amount of an API such that an appropriate therapeutic response is attained at the proper site in the body whilst achieving and maintaining an adequate concentration at that site of activity.[14, 15] Some API's have intrinsically long half lives and are thus inherently long lasting and may only require once daily oral dosing to achieve a suitable therapeutic effect. However the vast majorities of API's have relatively short half-lives and are thus shorter acting and require multiple daily dosing from conventional immediate release (ImR) dosage forms to achieve a constant and sustained therapeutic effect.[16]

The use of multiple dosing with immediate release(ImR) dosage forms has several limitations, including the requirement that the patient follows a strict dosing regimen in order for optimum therapeutic benefits to be achieved.[12, 14-16] However the need to adhere rigidly to a dosing regimen often leads to non-compliance or lack of adherence by patients with the result that doses are missed thus impacting negatively on desired therapeutic

outcomes.[15] If doses are administered too frequently minimum toxic concentrations may be reached with the result that unwanted side effects become prevalent, whereas infrequent dosing may lead to sub-therapeutic blood levels being achieved.[17] A hypothetical blood-level-time curve obtained following the administration of a conventional ImR product is depicted in Figure 1.2 whereas the blood levels that may be expected following administration of a controlled release dosage form are shown in Figure 1.3.[14] Low patient adherence combined with the fluctuations in steady state drug concentrations following conventional ImR medication administration have led to the development of sustained release dosage forms to counteract therapeutic variations.[16]

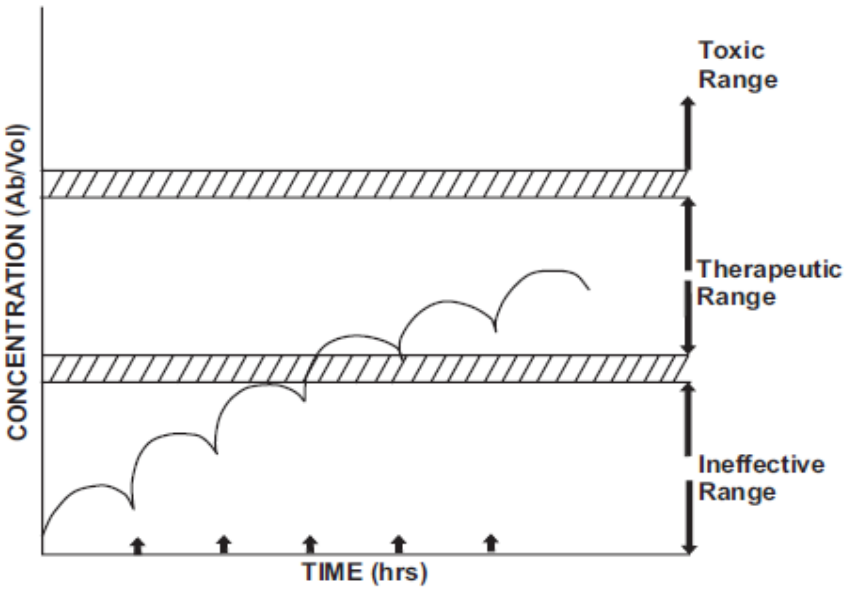

Figure (1.4): Hypothetical blood concentrations following multiple dosing of conventional IR dosage forms. Dosage intervals are represented by arrows.

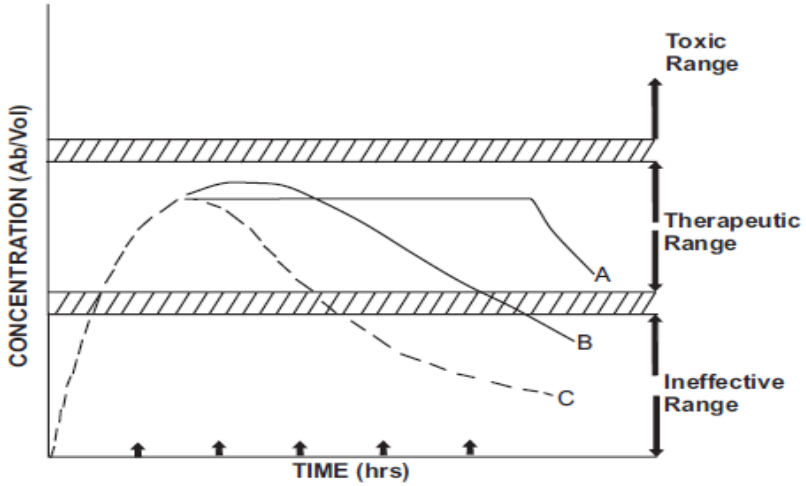

Figure (1.5): Hypothetical blood concentrations following administration of sustained or controlled release dosage forms. IR dosing intervals are represented by arrows for comparison. Curves A, B and C represent controlled, prolonged release and immediate release products, respectively.

The term sustained release (SR) is a broad expression that describes drug delivery in systems where the API is released in a controlled manner, at a predetermined rate, duration or location to achieve and maintain optimum therapeutic blood levels of an API. SR dosage forms include extended release (ER), delayed release (DR), repeat action (RA), controlled release (CR) and prolonged release (PR) systems.[17]

The design of SR dosage forms necessitates that several variables including the physicochemical properties of API, route of administration, type of delivery system,

disease, patient and the length of the proposed therapy be considered. Drugs that are best suited for incorporation into modified release dosage forms are those that exhibit neither slow nor fast absorption or elimination rates Potential candidates for inclusion in SR delivery systems must be uniformly absorbed along the gastro-intestinal tract and be administered in relatively small doses for chronic rather than acute conditions, and have a reasonably good margin of safety.[18]

➢ **Advantages of sustained release drug delivery**

- Reduced frequency of drug administration.
- Improved patient compliance.
- Reduced blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- Reduced amount of drug administration.
- Maximizing the availability with a minimum dose.
- Control of drug absorption; high blood level peaks that may be observed after administration of high availability drugs can be reduced.
- Safety margin of high potency drugs can be increased.
- Incidence of both local and systemic effects can be reduced.
- Increased reliability of therapy.

➢ **Disadvantages of sustained release drug delivery**

- Administration of sustained release medication does not lead to prompt termination of therapy.
- The physician has less flexibility in adjusting dosage regimen.
- Sustained release forms are designed for normal population.
- Economic factors must also be assessed.[14]

4.1.1 Categories of oral sustained release delivery systems

Oral sustained release delivery systems can be separated into one of four categories viz., monolithic matrix systems, reservoir or membrane-controlled systems, osmotic pump systems and ion exchange systems.[18]

4.1.1.1 Monolithic matrix systems

Monolithic matrix type systems can be further subdivided into two subgroups. One type of system is that in which the API is dispersed in a soluble matrix and from which the drug becomes available as the matrix swells and/or erodes following administration.[19] The second type of system is that in which the API is dispersed in an insoluble matrix and from which the drug becomes available as solvent enters the matrix and dissolves the drug prior to its release from the device.[20] The release rates of API from these systems may be described using the Higuchi model.[21] The pattern of API release from these monolithic matrix systems that are not controlled by zero order release kinetics may be clinically equivalent to a constant rate of release, for many drugs.[22] A schematic representation of drug release from these types of delivery system is depicted in Figures (1.6) and (1.7).[16]

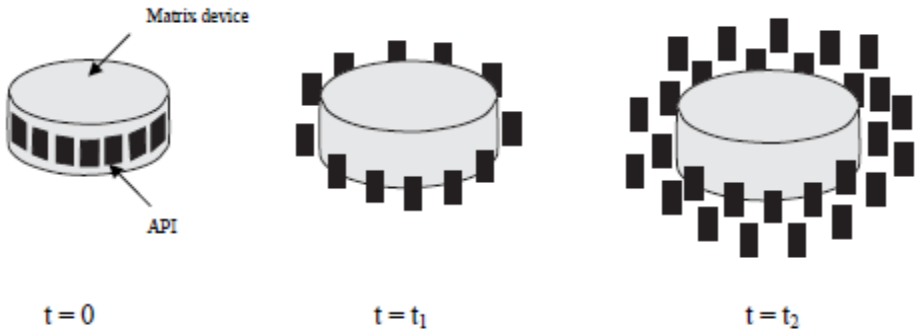

Figure (1.6): Drug release form conventional non-eroding SR matrix systems.

Figure (1.6) depicts drug release from a non eroding matrix dosage form. The API is initially dispersed in the matrix system, which at time t = 0 has 100% drug in the dosage form. Subsequently, following administration at some time t = t_1 some of the drug has been released from the matrix system and as t approaches t_2 more drug has been released from the system. Drug release would continue from these systems provided there is drug present in the system.

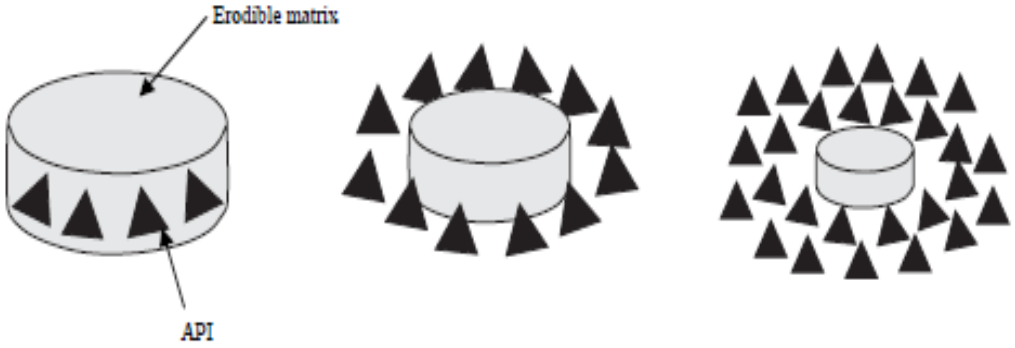

Figure (1.7): Drug release from an eroding matrix SR matrix system.

In contrast to drug release from non-eroding systems, the release from erodible delivery systems relies on the dissolution or degradation of the polymeric material in which the drug is dispersed to achieve constant release rates as depicted in Figure (1.7).

4.1.1.2. Membrane controlled or reservoir Systems

Membrane-controlled or reservoir systems are manufactured with a drug reservoir in which the API is either dispersed as solid particles, or as a solution that has been encapsulated by an outer rate controlling polymeric membrane that is usually semi permeable. These systems differ slightly from matrix systems in that the membrane does not swell on hydration and does not erode with time. The rate of release of drug from these systems is primarily controlled by interfacial partitioning of the drug from the reservoir into the membrane or by matrix diffusion controlled process.[23] A schematic representation of the drug release process from a membrane controlled delivery system is depicted in Figure (1.8).[16]

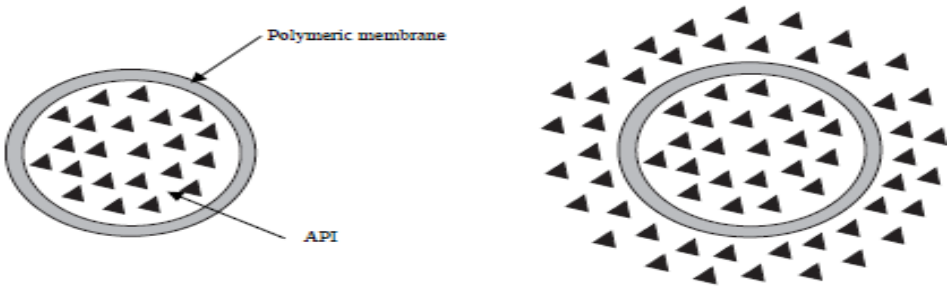

Figure (1.8): Schematic representation of drug release from a membrane controlled sustained release delivery system.

The reservoir containing API is encapsulated with a membrane through which the drug must diffuse in order for drug release to occur. Constant rates or zero-order release from devices such as those depicted in Figure (1.8) will be achieved, provided that a constant concentration gradient is maintained across the rate controlling membrane.

4.1.1.3 Osmotic pump systems

Osmotic pump systems may be considered as an alternate type of membrane controlled systems; however the energy source that drives drug delivery from such systems is a direct result of the properties of the API or other osmotic pressure generating substance that may be included in these systems.[24] In osmotic pump systems the API is usually included in a water-soluble tablet core, which is subsequently coated with a semi-permeable membrane. The properties of the membrane are such that only water can penetrate to the tablet core, dissolve the API or energy source and creates hydrostatic or osmotic pressure within the delivery device. The pressure build up within the device, provides the impetus for release of API from the dosage form. The release of drug from these systems occurs as a result of the diffusion of water into the device on the basis of an osmotic potential difference between the interior and exterior of the device and constant drug release will be achieved until the concentration of API or energy source inside the dosage form falls below saturation levels.[25] A schematic representation of drug release from a simple osmotic delivery system is depicted in Figure (1.9) and shows API release through an aperture in the coating following permeation of solvent into the device.[16]

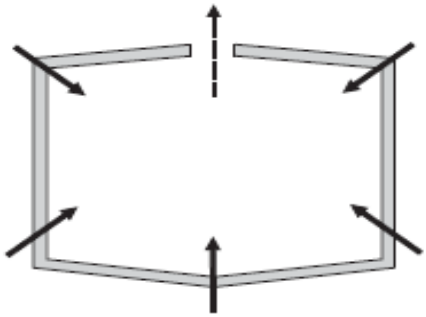

Figure (1.9): Schematic representation of a simple osmotic pump SR system

4.1.1.4 Ion exchange sustained release systems

Ion exchange systems are those in which an API is bound to an ion exchange resin to form a drug-resin complex (DRC).[26] The resins that are used to form the backbone of the delivery system are water insoluble cross-linked polymers containing either cationic or anionic salt forming functional groups repeated across the polymeric chain.[27] The release of an API from these dosage forms occurs by ion exchange in the gastro-intestinal tract, allowing for dissolution of drug molecules from the drug-resin complex (DRC). The rate and extent of drug release from these systems is controlled by the cross sectional diffusion area, the path length for drug transport and degree of water infiltration within the resin, and the extent of cross-linking of the polymeric subunits that make up the resin.[28] A schematic of resin being applied to drug particles to form a DRC is depicted in Figure (2.0)

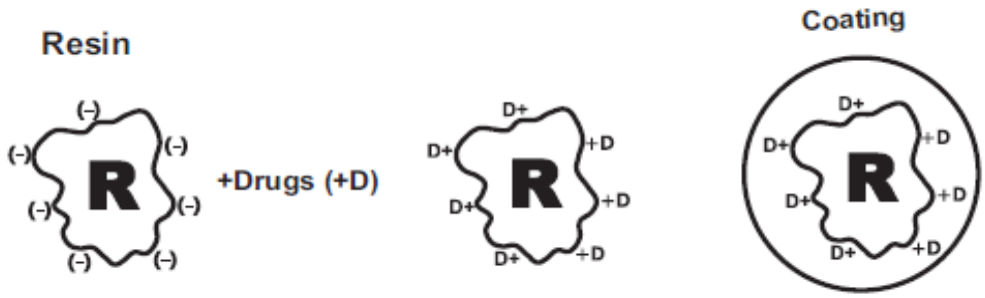

Figure (2.0): Schematic representation of a resin applied to drug particles to form a drug resin complex (DRC)

5. Ion-exchange resins as drug delivery carriers

There has been significant interest in the development of drug delivery systems to optimize the drug therapeutics and to improve patient compliance. An ideal drug delivery system should deliver a drug to the target site for absorption or action at a controlled rate over a period of time. The rate of drug delivery, the intensity and the duration of drug action have been the subject of many multidisciplinary researches. Formulation methods used to manipulate the drug release profiles are based mainly on two principles— physical (diffusion, erosion, and osmotic pump) and chemical principles (drug–polymer complex, drug–polymer conjugate, prodrug and ion exchange resin). Generally, the drug release from chemically controlled systems is by a chemical reaction such as hydrolysis, enzymatic degradation, and ion dissociation. The advantages of these systems include high drug loading, simple drug release mechanism, and protection of unstable drugs.[29]

CONCLUSION

Ion Exchange Resins (IERs)

- **Versatile Drug Delivery:** IERs are promising drug delivery carriers due to their ability to control drug release.

This is achieved through

- **Sustained Release:** Forming drug-resin complexes (DRCs) allows for controlled drug release over extended periods.
- **Targeted Delivery:** IERs can be designed to release drugs at specific sites in the body (e.g., intestines) or under specific conditions (e.g., pH).
- **Improved Drug Properties:** IERs can enhance drug stability, mask taste, and improve dissolution.
- **Mechanism:** Drug release from IERs involves an ion exchange process, where ions from the resin are swapped with ions from the surrounding solution.

Angina and Cardiovascular Diseases

- **Angina:** A common symptom of coronary artery disease, characterized by chest pain due to reduced blood flow to the heart.
- **Treatment:** Nitrates are the most common medication for angina, but other drugs and procedures are also used.

Potential of IERs in Cardiovascular Diseases

- **Improved Angina Management:** IERs could be used to develop sustained-release formulations of antianginal drugs, improving patient compliance and therapeutic outcomes.
- **Targeted Therapies:** IERs could potentially deliver drugs directly to the heart or coronary arteries, minimizing side effects and maximizing efficacy.
- Overall, IERs offer a promising approach for developing novel drug delivery systems for cardiovascular diseases, including angina. However, further research is needed to fully explore their potential and optimize their use in clinical settings.

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