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Ion exchange chromatography: A comprehensive review

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Abstract

Chromatography is a crucial technique in various industries, particularly in pharmaceuticals, where it is used to separate, purify, and analyze compounds. Ion exchange chromatography (IEC) is a type of chromatography that separates ions based on their electrostatic interactions with a stationary phase. The technique is widely used in biotechnology, pharmaceutical processing, and water treatment. IEC is essential for the purification of charged proteins, nucleic acids, and other biomolecules. The separation process involves the interaction between ions and a charged stationary phase, allowing for the selective retention and elution of ions. The technique has various applications, including the purification of proteins, peptides, enzymes, nucleotides, and DNA. IEC is also used in the food industry to adjust the pH of liquid media and extract important components. The instrumentation of IEC includes columns, sample injection systems, mobile phase reservoirs, pumps, detectors, and data systems. Overall, IEC is a powerful tool for the separation, purification, and analysis of ions and biomolecules, and its applications continue to grow in various industries.

Keyword: Ion exchange; Resin; Anion exchange; Cation exchange

1. Introduction

The foundation of chromatography is the idea that molecules in a mixture put on a solid surface or into a fluid stationary phase (stable phase) separate from one another as they move with the help of a mobile phase. Molecular characteristics pertaining to adsorption (liquid-solid), partition (liquid-solid), affinity, or variations in their molecular weights are among the elements that have an impact on this separation process. These variations lead certain mixture components to remain longer in the stationary phase and move more slowly throughout the chromatographic system, while other mixture components flow more quickly into the mobile phase and exit the system more quickly [1]. Because pharmaceutical goods must be both safe and effective, the pharmaceutical business is one of the most regulated in the world. Active pharmaceutical ingredients (APIs) impurity and degradation product levels must be closely regulated and adhere to the standards set by global authorities. Chromatography is widely utilized in the pharmaceutical business, from quality control (QC) labs to research and development, and has long been the method of choice for determining the chemical purity of pharmacological ingredients and products [2]. These porous substrates allow for highly customised purification methods that provide product streams that satisfy strict safety, effectiveness, and quality criteria. They are available with a broad variety of ligands, including ion exchange, hydrophobic interaction, affinity, and multimodal [3]. A fluid known as the mobile phase dissolves the mixture and transports it through a structure that contains a different substance known as the stationary phase. The mixture's diverse components separate because they move at different rates. Differential partitioning between the mobile and stationary phases serves as the basis for the separation. The separation is impacted by minute variations in a compound's partition coefficient because they cause variable retention on the stationary phase [4].

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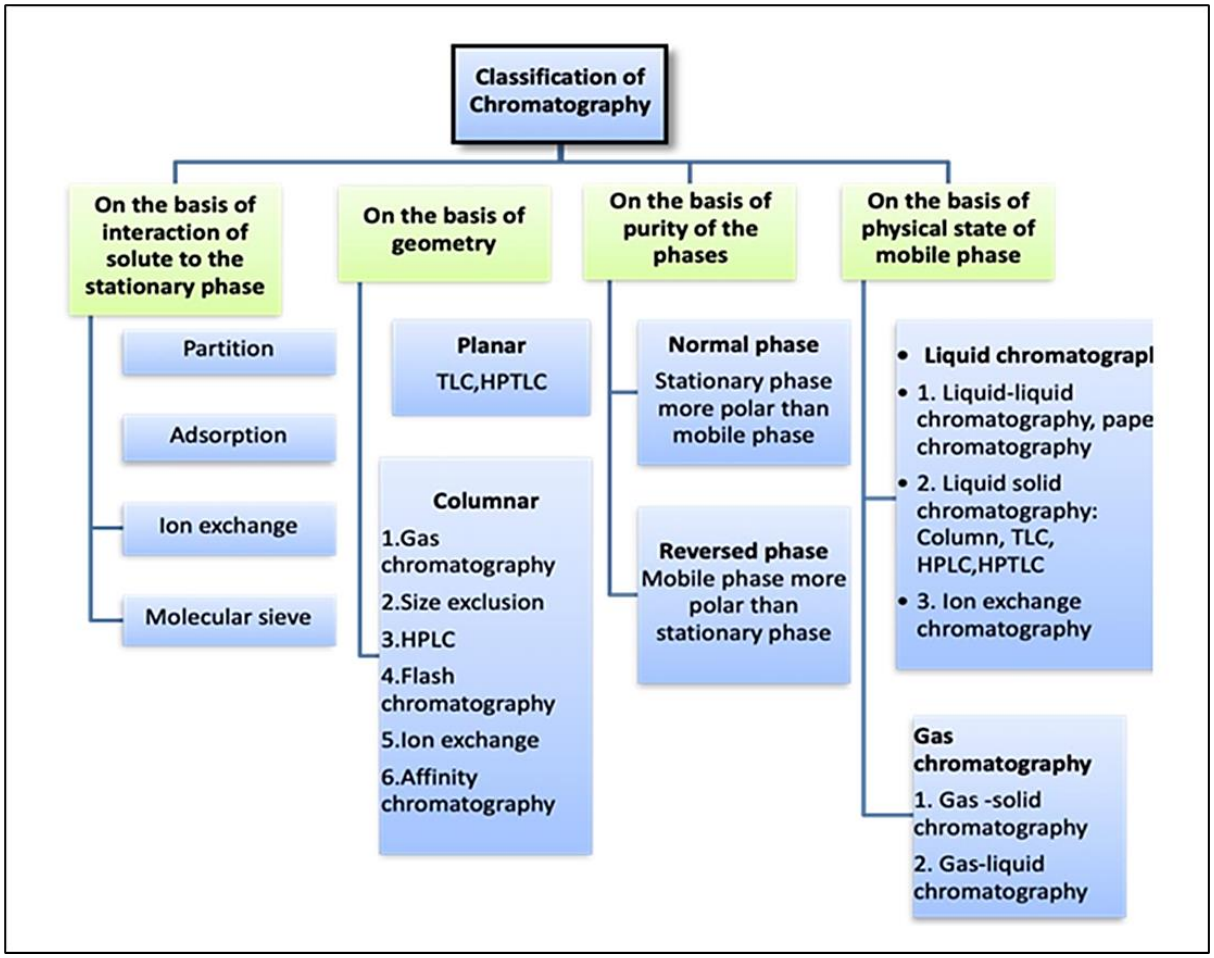

Figure 1 Classification of Chromatography Techniques [5]

2. Ion exchange chromatography

For the last 20 years or more, ion chromatography (IC), a well-established analytical technique, has been the method of choice for determining inorganic and tiny organic anions. IC is also used widely for the determination of inorganic cations, but because of the availability of several sensitive, multi-element spectroscopic methods of analysis (especially inductively coupled plasma mass spectrometry ICP/MS), IC assumes less of a dominant role in the field of cation analysis [6]. Ion exchange extraction (IX) is a particular extraction technique that effectively extracts charged polar solutes (base or acid) from polar media, such as water and less polar solvents. The high-energy electrostatic interaction between the charged functional groups of the analytes and the sorbent is the basis for the separation process in this instance. As a result, the analyte charge determines the choice of sorbent. Primary, secondary, tertiary, and quaternary amines are among the fundamental analytes that are extracted by the cation exchange (CX) column [7]. By using the interactions between solute ions and charged sites on the stationary phase, ion exchange chromatography selectively retains or elutes ions according to their electrostatic interactions. This method is essential for many applications, such as high-pH anion-exchange chromatography of carbohydrates and oligosaccharides, protein ion-exchange chromatography, ligand-exchange chromatography, and water purification. Ion exchange chromatography is a vital tool for research, development, and quality control given that it uses the charged qualities of various substances to enable precise separation, purification, and analysis across a wide range of industries and disciplines, from environmental science and pharmaceuticals to biochemistry and biotechnology [8]. In the biotechnology sector, ion exchange chromatography (IEX) is often employed to purify other proteins and monoclonal antibodies (Gagnon, 1996; Janson and Ryden, 1998). The foundation of IEX is the differential adsorption of charged materials at surface of porous chromatographic media that are oppositely charged [9].

2.1. Process of separation in chromatography

The differential movements cause the gradual separation of components over time or space. This process generates a series of distinct zones or peaks as each component exits the system at varying times (in gas or liquid chromatography)

or at different locations (as in techniques such as TLC). Factors such as the selection of mobile and stationary phases, temperature, flow velocity, and the physical properties of the components being separated influence the extent of separation [10]. AB homeostasis depends on a number of physiological ion exchange activities that are constantly maintained in the kidneys. Bicarbonate ions (HCO−3) comprise the body's most comprehensive buffer system. Water and carbon dioxide combine to create carbonic acid, which separates into H+ and bicarbonate to refill this system [11]. One of the potential options that has been studied is titanium dioxide, or TiO2. According to Marc-hand et al.'s first study, this material may be made from layered potassium titanate K2 Ti4 O9 precursor by K+/H+ ion exchange, followed by dehydration [12]. The separation concept is based on differential distribution coefficients between the mobile phase solute and the solid adsorbent stationary phase, resulting in varying retention capacities for both. The adsorption mechanism of the adsorbent material is principally based on chelation and ion exchange interactions with metal ions [13]. Proteins, polynucleotides, and other biomacromolecules can interact with ion exchangers because they reveal charged moieties at their surface. A general-purpose and adaptable method for separating proteins and plasmids is ion-exchange chromatography. It's commonly employed for analytical and Preparative purposes [14]. The analytical chemistry community most famously knows Hamish Small as the principal creator of ion chromatography (IC) [15].

One of the most popular and in-demand membrane types is the ion-exchange membrane. Their primary responsibility is to transmit certain ions selectively while preventing the transmission of other ions or molecules. For example, the most interesting aspect of electrodialysis is the separation of ions with varying charges [16]. Ion exchange systems are more environmentally sustainable and economically viable when they can be recycled and regenerated. To bring enhanced qualities, cost-effectiveness, and novel applications, scientists are continually researching ion exchange methods. The primary class of ion exchange processes is represented by the cross-linked, insoluble polymer known as ion exchange resin, which serves as a carrier for the stoichiometric exchange of ion [17]. The primary mechanism, or charge interactions, in the context of ion-exchange chromatography is well known as well as the basic notions that more strongly charged proteins (where a protein should be kept on a sorbent of opposite charge sign) [18]. Ion exchange extraction is a particular extraction technique that effectively extracts charged polar solutes (base or acid) from polar media, such as water and less polar solvents [19]. Numerous modalities have been employed alone as well as in combination. Along with other LC techniques, reversed-phase, ion-exchange, affinity, and size-exclusion chromatography all have a number of crucial traits in common. Sample preparation and handling are low as compared to gel-based separation techniques [20]. Madden ET. AL. provides an example of a simulated system that has produced software to forecast ion retention durations in ion chromatography [21]. Another method for ovomucoid purification that could be the most practical for additional biological activity research is ion-exchange chromatography [22].

The most common technique in the biopharmaceutical sector for separating proteins according to their biochemical properties such as total protein charges, sizes and shapes, particular protein interactions, and hydrophobic groups on the surface is chromatography. Over 99% purity needed for medicinal applications, high purity and product quality are crucial requirements that producers must meet. Therefore, bioprocess designs often incorporate at least one chromatography phase and sometimes two to meet regulatory purity criteria. These requirements call for chromatographic procedures that are more scalable, reliable, and efficient [23].

3. Ion exchange resins

To provide a medium for ion exchange, synthetic materials known as ion-exchange polymers (IEPs) include active, electrically charged groups along their backbone. Often referred to as ion-exchange resins, the IEPs are transformed into three-dimensional structures with enhanced structural integrity and resilience when cross-linked by copolymerisation with an appropriate organic linker [24]. An electrically polarised ion exchange resin bed was suggested by Hamish as an ion chromatography suppressor. Because of the "small" size of the ion exchange resin bed, electrochemical regeneration would take place in between each study (or many analyses). The suppressor for anion analysis with sodium hydroxide as the eluent was made comprised of two porous platinum electrodes sandwiched by a little layer of completely sulfonated cation exchange resin. Following investigation of the suppressor, the sodium form of the cation exchange resin is the predominant form. The compressor is polarised and water is pushed in the opposite direction for regeneration [15].

4. Ion-exchange membrane

Ion-exchange membranes are frequently used in separation procedures and contemporary electrochemical technologies. An examination of electro mass transfer is necessary for the creation of new materials. The primary focus of this study is on macroscopic transport mechanisms. To understand the membrane selectivity process, however, ion and molecule translation microscopic mobilities must be examined [25]. Target ions are selectively exchanged via ion-

exchange membranes (IEMs), which are made up of oppositely charged ions and immobilised ionisable functional groups. IEMs are usually made up of exchangeable counter-ions, immobilised charge groups, and inert substrates. IEM are often divided into two categories based on the kind of immobilised charge groups they contain: i) Cation Exchange Membranes (CEMs) & ii) Anion-Exchange Membranes (AEMs) [26].

Due to its high-water recovery, extended lifespan when compared to other common technologies, and reasonable energy consumption, electrodialysis (ED), which was initially developed for water treatment applications, primarily for water desalination, is still widely used and advised in this sector. New ion-exchange membranes and the creation of ED processes are examples of technological advancements that are essentially controlled to be an effective desalination technique that might be controlled by adjusting the process's current (or possible decrease). These days, new ion exchange membranes (IEMs) and advancements in ED process development technology are made possible [27]. In electrodialysis, ion exchange membranes materials with at least one ion exchange polymer with polar groups are often utilised [28]. Fuel cells, electrolysers, and electrodialysis are just a few of the numerous commercial applications for ion exchange membranes (IEM). The potential difference commonly known as the Donnan potential occurs at the polarized contact between the electrolyte solution and the ion-exchange membrane [29].

5. Anion exchange membrane

Depending on the kind of analytes, the mobile phase's composition, and the properties of the analytical support, partitioning, adsorption, and ion exchange may be responsible for the retention mechanism in aqueous organic mobile phases on bare silica columns [30].

Althrough examination of AEM that covers everything from molecular engineering to in-situ performance evaluation, mostly based on the research paths indicated by the structure of already accessible patents, to outline the future development of AEM while considering the current challenges (Figure 2).

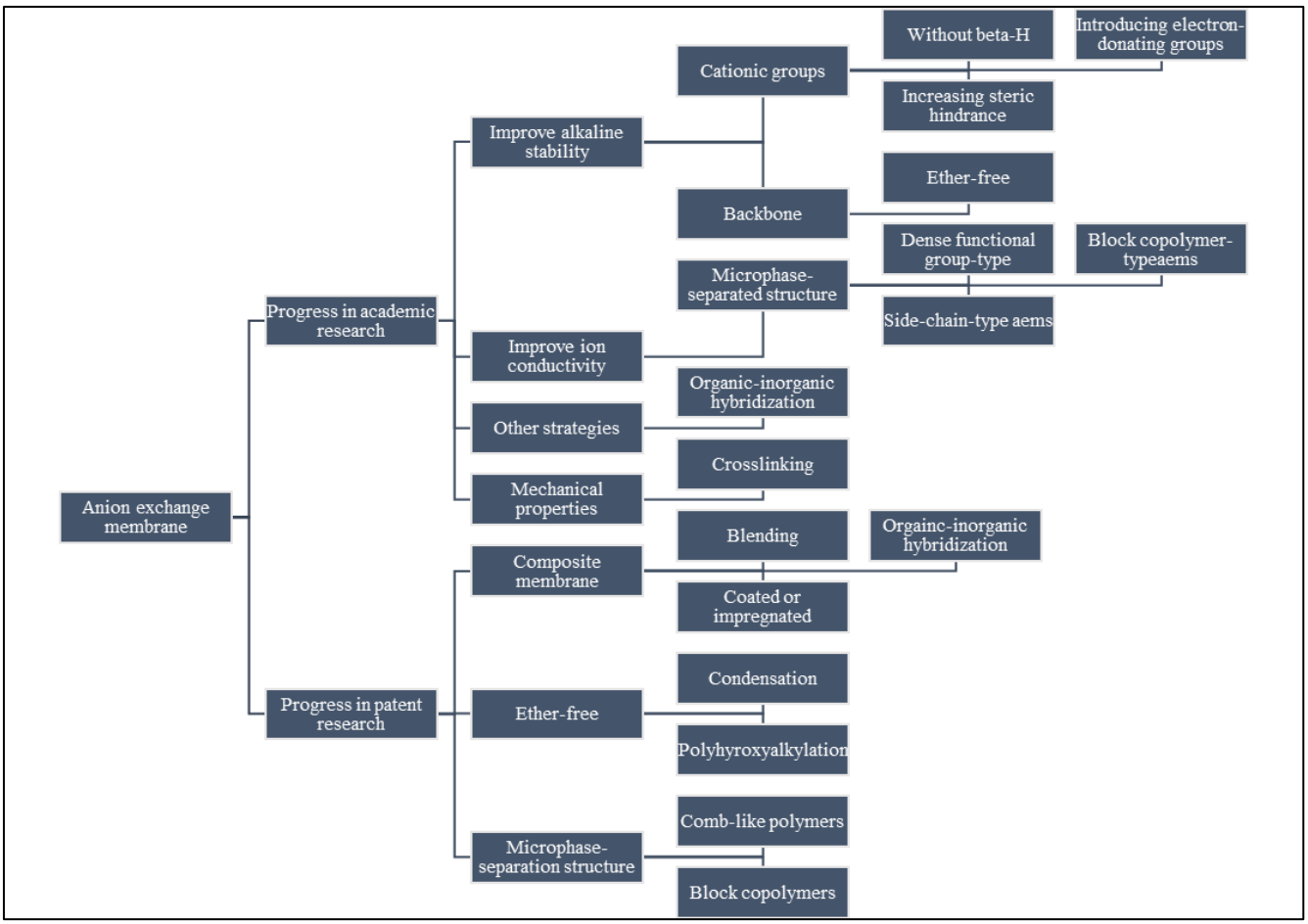

Figure 2 Various strategies and modifications to improve AEM performance, categorized under academic research and patent research. [31]

6. Cation ion exchange

A new pH-based protein separation method using cation exchange chromatography (pH-IEC) that resistant against changes in sample matrix pH and salt content, multi-product, and high-resolution [32].

7. Matrix effects in ionisation

The reversible adsorption of charged molecules to immobilised ion groups on a matrix with an opposing charge is known as ion exchange chromatography. Adsorption and sample release from the matrix allow for selective separation. Ion strength and pH are used to equilibrate the exchanger before ion exchange begins. The exchangeable groups are linked to counter-ions during equilibrium. After the sample is introduced and equilibrium is achieved, the molecules experience adsorption and addition with the counter ions are displaced and reversibly bound to the matrix by a suitable charge [33].

8. Principle of separation

The fundamental premise of chromatography is that fluid stationary phases (stable phases) and molecular mixtures applied to surfaces or solids separate from one another as they move with the aid of a mobile phase. This separation process is influenced by the molecular characteristics related to affinity, partitioning, adsorption, and changes in their molecular weights. Due to these variances, certain mixture components reach the mobile phase and leave the chromatographic system faster than others. Additionally, some combination components pass through the system more slowly and remain in the stationary phase for longer [4]. Thus, three elements form the basis of the chromatography process. A "solid" phase or "a layer of a liquid adsorbed on the surface of a solid support" always makes up the stationary phase.

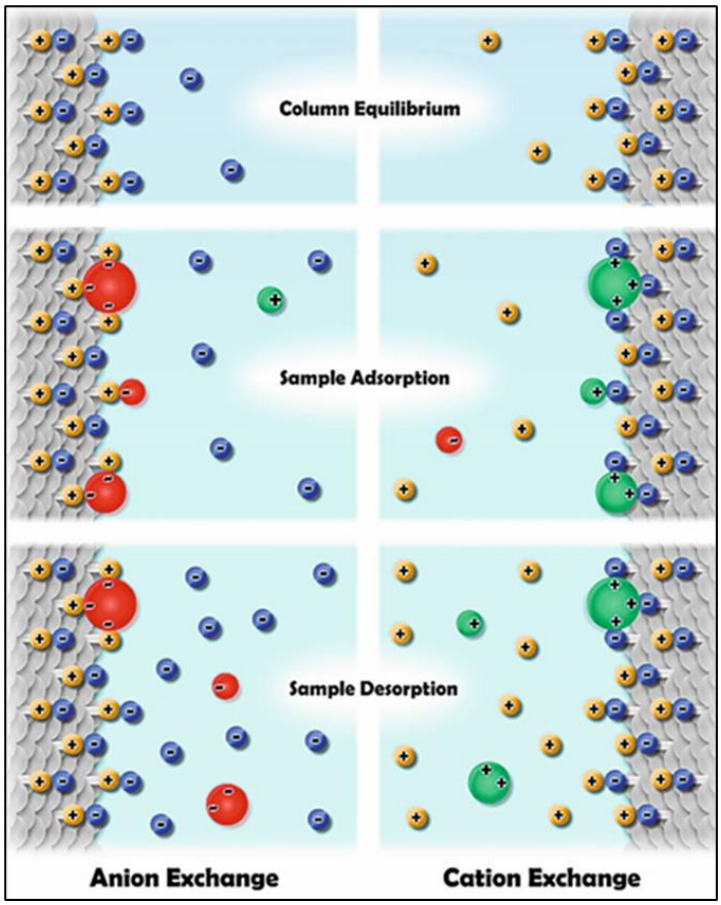

Figure 3 Ion-exchange chromatography [35]

It is the nature of the counterions displaced from the matrix functional groups which determines the IEC format. Thus, with anion-exchange chromatography (LHS), the stationary phase matrix displays a positively charged functional group with a negative counterion that can be displaced by an anionic sample, thereby enabling matrix adsorption. Cation-exchange chromatography (RHS), with the stationary phase matrix displays a negatively charged functional group with a positive counterion that can be displaced by a cationic sample, again enabling matrix adsorption with either format, sample desorption from the matrix can be achieved by increasing the counterion concentration within the mobile phase [34].

Since both methods rely on the same idea of electrostatic interaction between ions and a charged stationary phase, ion chromatography and ion exchange chromatography (IEC) are presently used interchangeably [35]. Disparities in physical and chemical characteristics, such as charge, size, and solubility, serve as the foundation for the rules that govern the selective separation of one whey protein from another. These might be the inherent characteristics of dairy systems or changed characteristics brought about by adjusting environmental factors including pH, temperature, and the ionic environment, such as the presence and conductivity of other ions [36].

Ion Exchange Chromatography is based on the ionic interactions between charged particles. The basic elements are:

- **Stationary phase**: A "solid" phase or "a layer of a liquid adsorbed on the surface of a solid support" always makes up the stationary phase. A polymeric resin matrix on the surface of ionic functional groups, such as carboxylic acids and quaternary amines, that have undergone chemical bonding makes up the stationary phase in ion exchange chromatography [37].
- **Mobile phase: "**Liquid" or "gaseous component" are always present in this phase. Ionic solutes are held in place while the mobile phases move over these surfaces by the formation of electrostatic chemical interactions with functional groups. In these kinds, the mobile phase is always liquid [37]. The sample is carried across the column by a buffer solution. The ion exchange mechanism and component separation are influenced by the buffer's composition and pH [38].
- **Ion-Exchange Mechanism**: Ions use their charge to interact with the stationary phase. Ions with a higher affinity for the stationary phase will bind more tightly and elute through the column more slowly, whereas those with a lower affinity will elute more quickly [39].
- **Elution:** Elutes the bound ions out of the column through a change in the composition or concentration of the mobile phase, often as a gradient or stepwise increase in ionic strength [37].
- **Procedure**: When the sample is placed into the column, its ions interact with the oppositely charged groups on the stationary phase. Components are categorised into many groups based on their charge and level of interaction with the ion exchanger. Elution can be achieved by changing the ionic strength or pH of the mobile phase [39].

9. Application of ion exchange chromatography: [40-44]

Chromatography is used in many different industries, most notably in the pharmaceutical sector. It is used to classify compounds according to molecular weight and element amount, identify and analyse samples for trace elements, and assess the purity of unknown chemicals. Chromatography is also essential in the production of pharmaceuticals; high-pH anion-exchange chromatography is used for carbohydrates and oligosaccharides, while gas chromatography is used for the separation of volatile mixtures. It may also be used to find contaminants in the pharmaceutical sector [5]. The purification of charged proteins and nucleic acids (biomolecules) is a typical use for IEC. Additionally, it is employed in the filtration of water and the process of inorganic ion separation [39].

Many charged or ionisable substances, such as proteins, peptides, enzymes, nucleotides, DNA, antibiotics, vitamins, and more, may be separated and purified using ion exchange chromatography from both natural and artificial sources.

Here is an example of how ion exchange chromatography is used:

- **Actinide separation**: The ion exchange chromatographic technique was initially used to identify the trans plutonium elements of the actinide class. Actinide contraction causes the actinide series to display elution in the opposite order of the atomic number since some of these elements could only be produced in atom amounts. This turned out to be the only way to find these components. It may be argued that their solitude would not have been possible with any other type of separation.

- **Organic compound purification**: It has been discovered that ions that were initially present in the water have polluted many natural goods that were recovered from it. Such ions can be eliminated via ion-exchange processes.
- **Pure Reagent Preparation**: When using sodium hydroxide solutions for volumetric calculations, carbonate is always present. Errors in acid-base titrations result from this. Running the solutions down a column of a strongly basic anion exchange resin in the hydroxide state is the most straight forward technique for eliminating carbonate. An equivalent amount of hydroxide is produced as the carbonate is absorbed.

10. Ion exchange chromatography instrumentation [38]

10.1. Column

- Purpose: Holds the stationary phase in which ion exchange takes place.
- Types:
  Cation exchange columns are filled with resin that contains groups that are negatively charged.
  Anion exchange columns are filled with resin that contains groups that are positively charged.
- Dimensions: Depending on the use, they can range from preparative columns (e.g., 25 mm ID or bigger) to analytical columns (e.g., 4.6 mm ID).

10.2. Sample Injection System

- Function: Takes the sample to the mobile phase
- Types
  Rotary Injectors: Using a syringe, introduces a known volume of sample
  Autosamplers: Carries out sample introduction automatically, hence raising throughput and reproducibility.

10.3. Mobile Phase Reservoirs

- Function: Provides buffer solutions needed for the sample to be eluted from the column.
- Components: Degassing systems are frequently included to eliminate dissolved gases that might affect chromatography.

10.4. Pump

- Function: Degassing devices are frequently included in order to eliminate dissolved gases that might affect the chromatography.
- Features: Precision pumps are necessary to obtain a repeatable flow rate and separation conditions.

10.5. Detector

- Function: Generates a signal based on the concentration of eluted components.
- Types:
  UV-Visible Absorption Detector: This type of detector measures how much UV or visible light is absorbed by proteins and nucleic acids. Conductivity detectors are effective for identifying ions and salts because they measure the eluent's ionic strength.

10.6. Data system:

- Function: Gathers, handles, and evaluates the detector's data.
- Elements: Chromatograph Program: creates and analyses chromatograms, which are graphs of detector response against time.
- Computer: Stores data and operates the gadget.

10.7. Regulators and Flow Controllers

- Function: Preserve the mobile phase's intended flow rate and pressure.

10.8. Mobility spectrometry of ions

Over the last several decades, ion mobility spectrometry (IMS) has been developed as a technique for the separation and subsequent detection of volatile and semi-volatile chemical molecules. IMS makes it possible to distinguish between

ions based on their mass, size, shape, charge, and other characteristics. This can offer crucial extra information to the mass spectrometric and chromatographic separation of ions and molecules. A thorough explanation of the ion mobility concepts has already been covered [45].

IEC separates highly polar and ionic compounds providing a unique separation space compared to other chromatography types [46].

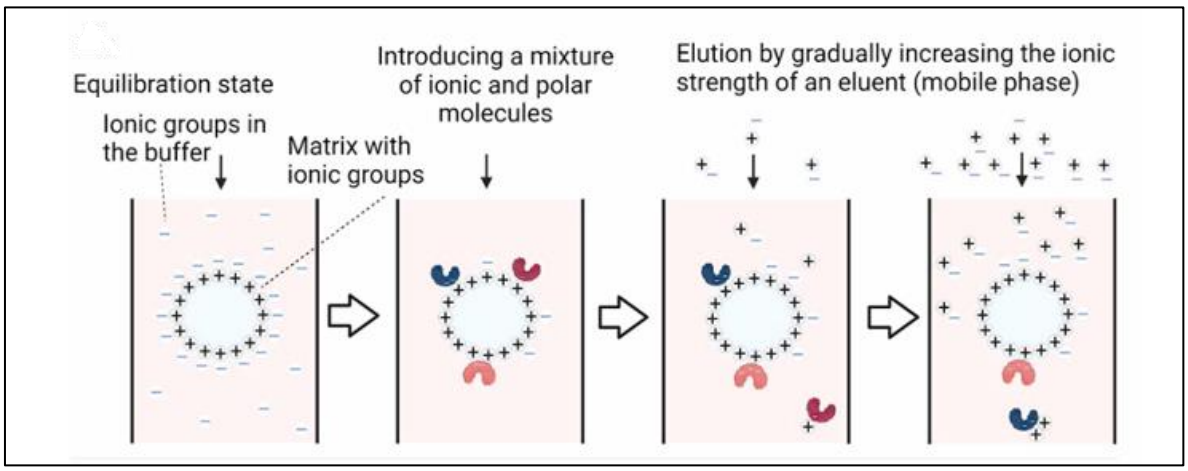

Figure 4 A schematic representation of the mechanism of anion-exchange chromatography

The column's stationary phase is positively charged and equilibrated with a mobile phase containing negative ions (e.g., OH − or another anion) at a minimal concentration. When a sample is introduced with negatively charged or polarizable analytes, the charged analytes displace the negative ions (e.g., OH − ions) from the stationary phase and bind instead, therefore being retained. Analyte ions have differential affinity for the stationary phase depending upon their charge; the affinity is directly determined by Coulombic force. The ionic strength of the mobile phase is usually increased for a gradient elution where the concentration of ions in the mobile phase (e.g., OH −) is gradually increased until the analyte ions are displaced by the increasing ion concentration in the mobile phase (isocratic elution is also sometimes used).

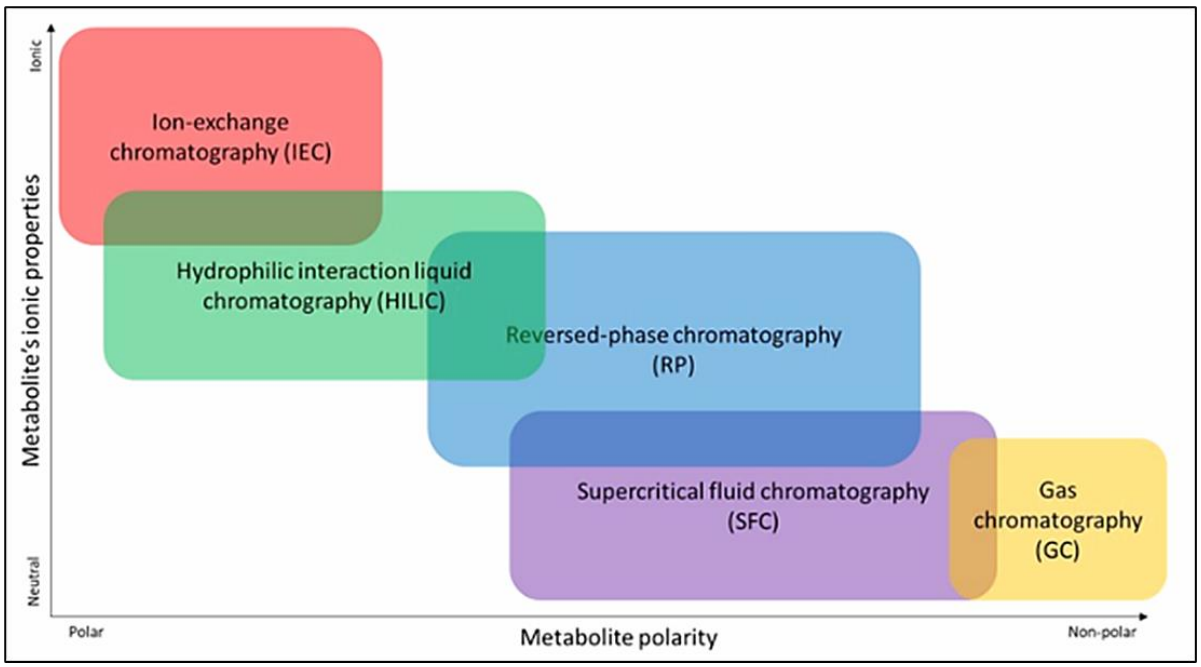

Figure 5 Indicative illustration of chromatographic separation space showing how ion-exchange chromatography extends the separation space beyond reversed-phase chromatography (RP-LC) and hydrophilic interaction liquid chromatography (HILIC) for highly polar and ionic molecules

11. Chromatography's use in medicine [4]

Pharmaceutical companies utilise chromatography to produce the vast amounts of pure components required to create further drugs.

The various inks or colours are separated from the mixture using paper chromatography. Gas chromatography can be used to detect the presence of alcohol or specific other compounds in urine or blood.

One of the most important analytical tools in pharmacy for assessing the precision of manufactured medications is chromatography.

Forensic science can help solve a number of cases by detecting flammable materials and burn residue left in body parts following fires or explosions.

12. Uses of ion exchange chromatography:

Extensively utilised in a variety of industries, including biotechnology, flow battery/fuel cell technologies, catalytic conversion processing, water treatment, pharmaceutical processing, and the manufacturing of ultrapure water for the semiconductor sector [25].

Ion Exchange Resins Used for Analysis: Automated Ion Exchange Chromatography makes it easy to separate amino acids in a protein hydrolysate for qualitative and quantitative studies. Biochemists most commonly employ two broad groups of stationary ion exchangers [32].

Used extensively in the food sector to adjust the pH of liquid media (whey, wine, fruit juices, etc.) without the need for reagents and to extract, fractionate, and concentrate important components [47].

The milk's processes (whey protein hydrolysate or isolate, acid or sweet whey, etc.) Electrostatic interactions of membranes with highly hydrated colloidal structures that form proteins, carboxylic acids, amino acids, and mineral salts (sodium, potassium, calcium, phosphorus, and magnesium) are the primary cause of the drop in IEC in animal serum electrodialysis [47].

It is used in research, analysis, and process-scale purification of proteins [4].

On exchange chromatography (IEX) is used extensively in the biotechnology industry to purify monoclonal antibodies as well as other proteins [48].

Ion exchange polymers are widely utilised in solar-powered desalination, electrodialysis for water treatment, and energy conversion and storage system [9].

Ion exchange membranes, or IEMs, are widely utilised in contemporary technologies such as sensors, electrochemical synthesis, concentration, and water purification [50].

Purification of several fucoidans using ion-exchange chromatography revealed a considerable degree of structural variation among them. The polysaccharides alginate and laminarin, as well as other impurities like proteins and phlorotannin’s, are effectively eliminated by ion-exchange chromatography from a wide variety of fucoidans from the main orders of brown algae, such as Ectocarpenes, Laminariales, and Fucale’s [51].

13. Conclusion

Chromatography, particularly ion exchange chromatography, plays a vital role in various industries, including pharmaceuticals, biotechnology, and food processing. Its ability to separate and purify complex mixtures has made it an essential tool for research, analysis, and process-scale purification of proteins, nucleic acids, and other biomolecules. The technique's versatility and effectiveness have led to its widespread adoption in quality control labs, research and development, and manufacturing processes. Ion exchange chromatography's applications extend beyond the pharmaceutical industry, with uses in water treatment, food processing, and energy conversion and storage systems. The development of new ion exchange membranes and resins has further expanded the technique's capabilities, enabling the separation and purification of a wide range of compounds. As research continues to advance, it is likely

that chromatography will remain a crucial tool in various fields, driving innovation and discovery. With its high precision, sensitivity, and versatility, chromatography will continue to play a vital role in shaping the future of various industries and improving our understanding of complex biological systems.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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