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Review on Chromatographic Techniques for the Analysis of Pharmaceutical Polymers
Short Running Title: Pharmaceutical polymer analysis by chromatographic technique

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ABSTRACT: -
In this study, typical pharmaceutical polymers such as hydroxypropyl methylcellulose, polyethylene glycol (PEG), Polyvinylpyrrolidone (PVP), Alginateas well as a difficult Polysulfonate polymer are analyzed using advanced chromatography. These tests include chromatographic methods to examine pharmaceutical polymers and help assure product quality and compatibility for medication formulation and delivery systems. The molecular weight distribution and structural changes of hydroxypropyl methylcellulose are revealed by the high-resolution analysis provided by UHPLC. Reverse phase Gradient Elution Chromatography is used to analyze PEG in order to precisely determine its molecular weight and purity. For information on molecular weight distribution and structural homogeneity, Polyvinylpyrrolidone undergoes size exclusion chromatography. To determine the monomeric content and level of polymerization of alginate, HPLC analysis is used. Last but not least, Ion exchange chromatography is applied to the difficult Polysulfonate Polymer to show off its capacity to characterize and separate complicated, negatively charged polymers. These methods ensure pharmaceutical polymer suitability for various applications, aiding safe and effective drug formulation.

Keywords: -Alginate, Polyethylene Glycols (PEG), Polyvinylpyrrolidone, Hydroxypropyl methylcellulose (HPMC), Polysulfonate polymer, HPLC, Reversed phase gradient elution chromatography

I. INTRODUCTION: -

Recent developments in pharmaceutical polymer analysis by chromatographic technique have led to the use ofvarious detectors and a range of chromatographic methods for the manufacture and analysis of pharmaceuticals.Chromatography is the most advanced and versatile methodology that supports the use of both non-enantioselective and enantioselective techniques for the study of pharmaceuticals and their metabolites.It enables quick processing times, high levels of data accuracy, and specificity.Chromatographic techniques have been developed for clinical analysis for pharmacokinetic studies or therapeutic monitoring as well as for manufacturing processes to evaluate the stability of pharmaceuticals and check for contaminants and degradation products[1]. Analyzing the multivariate distributions of a polymer sample requires separating the polymer sample first according to the molecular weight, size, or chemical composition[2,3]. Polymers may be engineered to respond to external events, such as heat or pH, and are often referred to as stimulation-responsive polymers[4].An appreciation of the basics of polymer chemistry, polymer components, and the various types of polymers is essential to comprehending the applications of polymers in the pharmaceutical industry[5]. Polymer carriers may be utilized to determine the timing and the location of medication release in both traditional and novel drug delivery procedures[6]. Additionally, polymers can be classified into either water-soluble or water-insoluble based on their solubility in water.

Overall, pharmaceutical polymers play a crucial role in drug delivery systems and are used to control drug release, improve drug efficacy, and target specific sites in the body.

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1.1 Someexamplesof Pharmaceutical Polymer and their uses: -

Polyethylene glycol (PEG): it is a water-soluble polymer commonly used as an excipient in pharmaceutical formulations. Itapplied to increase the bioavailability, solubility, and stability of medications. PEG is also utilized in controlled-release systems, topical gels, and as a carrier for targeted drug delivery[7].

Hydroxypropyl methylcellulose (HPMC): HPMC is a cellulose derivative that is widely used as a pharmaceutical excipient and coating material. It frequently appears in oral solid dosage forms as pills and capsules, where it provides controlled drug release, enhances stability, and improves drug dissolution[8].

A synthetic polymer with great solubility in water and other solvents is polyvinylpyrrolidone (PVP). It is commonly used as a binder, disintegrant, and tablet coating agent in the production of oral solid dosage forms. PVP also finds application in topical formulations, ophthalmic solutions, and as a stabilizer for amorphous drug formulations[9].

PVA, a synthetic polymer that dissolves in water, is commonly used as a covering for tablets and capsules. It can also be used as a viscosity modifier in topical gels and ophthalmic formulations. PVA has good film-forming properties and biocompatibility[10].

PEO, a water-soluble polymer, is frequently employed in formulations for controlled-release drugs. It forms a gel-like matrix when hydrated, which can control the release of drugs. PEO is also used as a thickening agent in oral liquid formulations.

II. CHROMATOGRAPHIC TECHNIQUES: -

An overview of the major chromatographic techniques used for the analysis of pharmaceutical polymers.

2.1 Size-Exclusion Chromatography with IR Spectroscopy: -

Infrared spectroscopy (IR) and size-exclusion chromatography (SEC) are two techniques that can be used to correlate molecular weight with chemical composition.The newly implemented online SECeIR technique enables the precise assessment of every polymer composition[11].This process can be implemented to study copolymers, blends, or unknown samples.SEC and IR spectroscopy are coupled online to produce a chemically sensitive, universal method for detecting polymer molecular weights and chemical compositions. Comprehensive two-dimensional liquid chromatography with FT-IR detection, online preferential solvation studies using coupled chromatographic-Fourier transform infrared spectroscopic flow cells, and online hyphenation of SEC and pyrolysis-gas chromatography are additional techniques that contribute to a thorough characterization of polymers[12]. Size-exclusion chromatography is a critical method that supplies data about the size distribution and average properties of macromolecules. It is a form of fractionating that can be used to analyze polymer quality and calculate macromolecular characteristics.

2.2ultrahigh-performance liquid chromatography: -

A wide variety of substances, including medicines, biomolecules, and polymers, can be studied using UHPLC[13]. It indicates an improvement in the resolving power of oligomer separations in pharmaceutical polymer analysis[14]. Ultrahigh-performance liquid chromatography is also used to analyze polymers that are utilized as coatings, binders, disintegrants, drug delivery agents, suspending agents, or viscosity-increasing compounds[15]. In order to maximize the analysis of chemicals, UHPLC is a quick and reliable technique that utilizes multifactorial liquid chromatographic optimization software[16]. To examine antibacterials in oral fluid, UHPLC-MS/MS is used instead of biological matrices[17,18].Overall, UHPLC is a vital technique for analyzing pharmaceutical polymers because it yields quick, precise results with great resolving power.

2.3 High-performance liquid chromatography: -

Techniques for liquid chromatography can be used to examine the stability and purity of specific polymers commonly found in pharmaceuticals[19]. HPLC can be used to determine the release of drugs from a pharmaceutical polymer matrix[20]. The HPLC method is used in analytical chemistry to isolate and quantify each component of a mixture. Pumps are used to transport the sample mixture through a pressurized liquid solvent that contains a column containing a solid adsorbent material.Using HPLC analysis, drugs can be identified, quantified, and monitored for progress during treatment[21].

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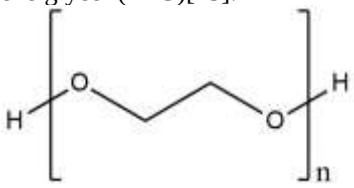
2.4 Ion-Exchange chromatography: -

This technique can be used for the analysis and purification of pharmaceutical polymers[22]. It is a flexible method that can be applied to the separation of ions and compounds that can be ionizable. Proteins can be purified, characterized, and analyzed using IEC. IEC works by separating ionic species based on their affinity for an ion exchange resin. The stationary phase of the chromatography column is typically a resin that contains charged functional groups, such as carboxylic acid or amino groups[23]. As the sample is loaded onto the column, its ionic species interact with the resin's charged functional groups. The ionic species with the strongest affinity for the resin will be retained the longest, while those with weaker affinity will be eluted first[24].

III. POLYMER ANALYSIS: -

3.1 Polyethylene Glycols (PEG): -

Polyethylene glycols are non-ionic, water-soluble polymers that find use in a variety of industries due to their wide range of applications. PEG samples produced commercially are a combination of oligomers with various molecular weights. Reversed-phase gradient elution chromatography is employed for the analysis of polyethylene glycol (PEG)[25].



Scheme 1: Chemical Structure of Polyethylene Glycols

3.1.1 Analytical Procedure[26,27]**:**

- The samples were prepared using commercially available polyethylene glycols (PEG 400, PEG 600, and PEG 960) dissolved in methanol/water (1:1) to a concentration of 1 mg/mL.
- Replicate injections (10 mL) of each sample were separated using a linear gradient on a 4.6 X 150 mm Waters XTerra RP8 column, 3.5 m in diameter. The separation was performed at a temperature of 60℃.
- Waters Alliance 2695 Separations Module and Waters 2420 ELS Detector were used for the separation.The drift tube temperature of the ELS Detector was set to 50℃, with the nebulizer heater at 50% and the nebulizer nitrogen gas pressure at 50 psi.
- **Data Analysis:** All instruments were controlled and data collected and analyzed using Empower ™ software.

3.1.2 Advantages of Evaporative Light Scattering Detection (ELS) for Analysis of Polyethylene Glycol (PEG):

Individual Component Oligomer Resolution: Separation and identification of individual PEG component oligomers are possible using reversed phase gradient elution chromatography with ELS detection. Compared to conventional gel permeation chromatography (GPC) analysis, which only provides average molecular weight information, this offers superior resolution.[28].

Compatibility with Reversed Phase Gradient Chromatography: ELS detection is compatible with reversed phase gradient chromatography, allowing for the analysis of PEG under these conditions. This technique is particularly useful for PEG analysis as UV detection is limited due to the lack of chromophores in PEG[29].

Wide Range of Applications: PEG is widely used in various industries and applications. The use of ELS detection enables the analysis of PEG samples with different average molecular weights using the same conditions, allowing for easy comparison and monitoring of PEG quality.

Good Sensitivity and Reproducibility: The Waters 2420 Evaporative Light Scattering Detector used in this study demonstrated good sensitivity and reproducibility in detecting challenging PEG samples. This ensures reliable and accurate analysis of PEG samples.

3.2Alginate: -

Alginate analysis by chromatographic technique is a method used to determine the presence and quantity of alginate in various formulations. Chromatographic analysis of alginate degradation by recombinant alginate lyases has been done to produce alginate oligosaccharides and for structural characterization or modification of alginates[30].It is a natural polymer. A validated high-performance liquid chromatographyto measure the presence of sodium alginate in pharmaceutical formulations, an assay method was created and applied[31].

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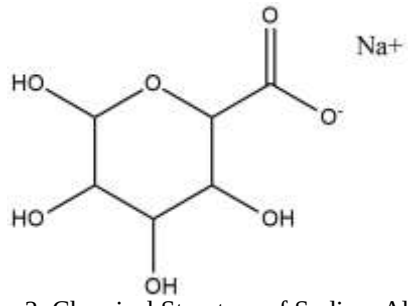


Scheme 2: Chemical Structure of Sodium Alginate

3.2.1 Analytical procedure[32–34]**: -**

- **Sample preparation:**alginate is extracted from the desired source and the extracted sample is then filtered, diluted, and centrifuged to obtain a clear solution.
- **Calibration:**A calibration curve is prepared using standard solutions of known alginate concentrations.
- **HPLC system setup:**The HPLC system is set up with a suitable stationary phase, such as a phenyl stationary phase or a C18 stationary phase and the mobile phase used is a buffer solution at pH 7.0.
- **Chromatographicseparation:**The extracted sample is then subjected to chromatographic separation using the HPLC system.The separated components are detected using a suitable detector such as a refractive index detector (RID) or a diode arraydetector(DAD).

3.2.2Application:

Determination of drug loading: HPLC can be used to determine drug loading for example cyclodextrin polymers using a dexamethasone model drug[35].

Quantification of pharmaceutical products: HPLC can be used for the quantification of pharmaceutical products.

Determination of drug release: HPLC can be used to determine the release of drugs from a pharmaceutical polymer matrix[36].

Evaluation of physicochemical properties of polymers: The physicochemical characteristics of polymers and their suitability for drug release can be evaluated using HPLC[36]

3.3.3Advantages:

Accuracy: HPLC provides accurate results, making it a reliable technique for the analysis of pharmaceutical polymers.

Quantification: HPLC can be used for the quantification of pharmaceutical products quantification, making it a useful tool in drug development and quality assurance.

Determination of drug release: HPLC can be used to determine the release of drugs from a pharmaceutical polymer matrix, which is important for drug development and quality control [37]

3.2.4 Disadvantages[38]**:**

Limited solvent choice: The choice of solvents that can dissolve a polymer is typically very limited, compared to small molecules, which limits the type of HPLC method that can be used.

Multiple peaks or broad peaks: Polymers contain a distribution of chain lengths, which often results in multiple peaks or a very broad peak during the HPLC separation.

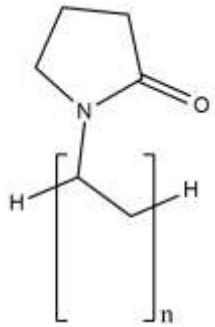
Time-consuming: Especially when complex matrices are involved.

Specialized equipment: Some sample preparation techniques, such as solid-phase extraction, require specialized equipment.

Large volumes of solvents: Some sample preparation techniques, such as liquid-liquid extraction, require the use of large volumes of solvents.

3.3 Polyvinylpyrrolidone: -

Polyvinylpyrrolidone (PVP) is a water-soluble polymer compound made from the monomer N-vinylpyrrolidone[39].PVP has various uses in different industries such as medical, food, and wine production. In the medical industry, PVP is used as a binder in many pharmaceutical tablets, as well as a film former for ophthalmic solutions, to aid in flavoring liquids and chewable tablets, and as an adhesive for transdermal systems[40,41]. Size exclusion chromatography (SEC) is a technique that can be used to analyze polyvinylpyrrolidone (PVP)[42,43].SEC can be used to determine the molecular weight and molecular distribution of PVP[44].



Scheme 3: Chemical Structure of Polyvinylpyrrolidone

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3.3.1 Analytical procedure: -

- **Sample preparation:** Prepare the sample by dissolving PVP in a suitable solvent, such as water or an aqueous buffer, and the sample should be filtered through a 0.2-micron filter to remove any particulate matter.
- **Column selection:** Choose a suitable SEC column based on the molecular weight range of the PVP being analyzed[45]. For example, a TSKgel G3000SWXL column can be used for the determination of total PVP in ophthalmic solutions. Agilent PL aquagel-OH 50 and 60 8 µm columns can also be used[46].
- **Mobile phase selection:**Themobile phase is compatible with the SEC column and the PVP being analyzed. A typical mobile phase for PVP analysis is an aqueous buffer, such as phosphate-buffered saline (PBS), with a pH between 6.5 and 7.5.
- **Calibration:** Calibrate the SEC column using standard PVP samples of known molecular weight. This will allow for the determination of the molecular weight of the PVP being analyzed.
- **Injection:** Inject the sample onto the SEC column and run the instrument according to the manufacturer's instructions.
- **Detection:** Use an appropriate detector, such as an ultraviolet-visible detector, to detect the PVP as it elutes from the column.

3.3.2 Applications:

The method provides a sensitive and chemically applicable method for determining polymer molecular weight.

With this method, it is possible to produce polyolefin graft and block copolymers containing both types of polyolefin block (PE, PP, s-PS, EP, etc)[47].

3.3.3 Advantages:

A deeper understanding of the structures and properties of polymers is possible according to the technique's non-destructive nature and information provided at the molecular level[48].

A wide range of polymers can be analyzed using this method, including copolymers, blends, and unidentified materials[49].

3.3.4 Disadvantages:

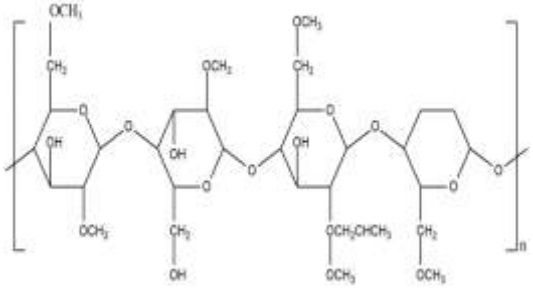
The method requires specialized tools and knowledge, which can be costly and time-consuming.

The resolution of the SEC column, which may affect the precision of the molecular weight determination, may be a limitation of the technique. [50]

The sample preparation could limit the approach and reduce the reliability of the results.

3.4Hydroxypropyl methylcellulose (HPMC): -

Water-soluble polymer used in a variety of pharmaceutical formulations as a binder, disintegrant, and viscosity-increasing agent[51,52].The analysis of hydroxypropyl methylcellulose (HPMC) is commonly carried out using ultra-high-performance liquid chromatography (UHPLC) and high-performance liquid chromatography (HPLC)[53].



Scheme 4: Chemical Structure of Hydroxypropyl Methylcellulose

3.4.1 Analytical procedure[54,55]**: -**

- **Sample preparation:** Prepare the sample by dissolving the HPMC in a suitable solvent, such as water or a mixture of water and acetonitrile.
- **Instrument setup:** Set up the UHPLC instrument with a suitable column, mobile phase, and detector. The column should be a reversed-phase column with a suitable particle size and pore size. The mobile phase should be a gradient of water and acetonitrile or methanol with a suitable buffer and pH. The detector should be a UV detector or a charged aerosol detector (CAD).
- **Calibration:** Prepare a calibration curve using standard solutions of HPMC with known concentrations. Inject the standard solutions into the UHPLC instrument and record the peak areas or heights.
- **Sample analysis:** Inject the sample solution into the UHPLC instrument and record the peak area or height. Calculate the concentration of HPMC in the sample using the calibration curve.
- **Data analysis:** Analyze the UHPLC data using suitable software, such as Empower or Chromeleon. Calculate the retention time, peak

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area or height, and concentration of HPMC in the sample.

3.4.2 Some other examples of pharmaceutical polymers analyzed using UHPLC:

Polymer polyethylene glycol (PEG): It is water-soluble andused in a variety of pharmaceutical formulations, both as a solubilizing agent and as a component of drug delivery systems. Using UHPLC, it is possible to measure the size and molecular weight of PEG. [56]

A combination of water and acetonitrile or methanol is used as the mobile phase. The water-to-organic-solvent ratio can be changed depending on the hydrophobicity of the PEG sample and the chromatographic conditions.[57]

PEG analysis is commonly performed using a reversed-phase column with great efficiency and resolution. Internal diameters range from 2.1 to 4.6 mm, while lengths range from 50 to 150 mm. The packing material's particle size is frequently less than 2 µm, allowing for high-resolution separations in a short length of time.[58]

Various detectors can be used in UHPLC, but for PEG analysis, UV-Vis (Ultraviolet-Visible) detectors are commonly employed.

Polysorbate 80: Solvent used in a variety of pharmaceutical formulations as a non-ionic surfactant.The purity and degradation products of polysorbate 80 can be examined using UHPLC.

Polyvinylpyrrolidone (PVP): It is a water-soluble polymer that functions as a binder, disintegrant, and solubilizing agent in a variety of medicinal formulations. PVP's size and molecular weight can be calculated using UHPLC. [56]

The biodegradable polymer **poly (lactic-co-glycolic acid)** is used in a number of pharmaceutical delivery techniques. UHPLC can be used to measure the PLGA weight and molecular size.[59]

The mentioned example of the pharmaceutical polymer the following mobile phase, column, and detector are used for the analysis by uhplc: -

Mobile phase: -a mixture of water and methanol or acetonitrile

Column: - UHPLC columns with small particle sizes (e.g., sub-2 µm) and dimensions of 2.1 to 4.6 mm internal diameter and 50 to 150 mm length are suitable for this analysis.

Detector: A UV-Vis detector is commonly used.

3.4.3Application:

During drug development, UHPLC can be used to evaluate the potency, purity, and identification of drug ingredients and drug products[60].

UHPLC can be used to check the consistency and quality of pharmaceutical goods by looking at the presence of active ingredients, contaminants, and degradation products[61].

The molecular weight, size, and structure of polymers used in pharmaceutical formulations, as well as the number of excipients and other ingredients, can all be determined using UHPLC.

UHPLC analysis can be used to determine the pharmacokinetic characteristics of pharmaceuticals and their metabolites in biological samples like blood and urine[62].

In regard to pharmaceutical analysis, UHPLC offers a wide range of uses, including drug development, quality assurance, pharmacokinetic research, formulation development, and environmental monitoring.

3.4.4Advantages:

High-resolution separations are possible with UHPLC and are very helpful for the investigation of pharmaceutical polymers because they can produce high-resolution separations of complicated mixtures[62].

Fast analysis: When compared to conventional High-Performance Liquid Chromatography (HPLC), UHPLC delivers quicker analytical times without sacrificing effectiveness.

Reduced solvent and sample usage: When compared to regular HPLC, UHPLC utilizes fewer samples and less solvent, which can save expenses and have a less negative effect on the environment.

Enhanced sensitivity and precision: When compared to regular HPLC, UHPLC can offer enhanced sensitivity and precision, which can increase the accuracy and dependability of pharmaceutical polymer tests.

3.4.5Disadvantages:

Small particles and narrow-bore tubing can cause polymer breakdown and deformation when used in UHPLC systems. These forces can significantly shear and extend polymer chains.

Flexible macromolecules may extend under **high-stress conditions**, and eventually, the chemical connections between the molecules may break, causing the deterioration and deformation of polymers.

column duration restriction: In UHPLC systems, the use of tiny particles and high pressures can result in more column wear and tear, which can shorten the column lifetime[63].

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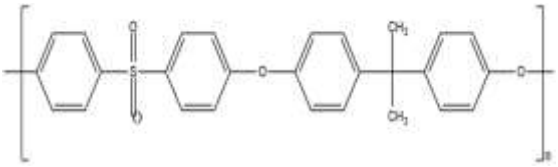
Higher cost: Some laboratories may be constrained by the cost of UHPLC systems, which are often more expensive than conventional HPLC systems.
The types of analyses possible with UHPLC may be limited by the incompatibility of certain detectors.

3.5 Polysulfonate polymer: -

Polysulfone polymer has various applications in the pharmaceutical industry due to its desirable properties, including hydrolytic, thermal, and oxidative resistance.Polysulfone is commonly used for pharmaceutical filter housings due to its durability, non-toxicity, high break resistance, and transparency[64]. Polysulfone-based coatings have been developed for biomedical devices to improve their biocompatibility and reduce the risk of infection[65]. The chromatographic technique used for the analysis of Polysulfonate polymer is ion exchange chromatography.



Scheme 5: Chemical Structure of Polysulfonate Polymer

3.5.1 Analytical procedure[66]**: -**

- Sample Preparation: To make a clear sample solution, dissolve the Polysulfonate polymer in the appropriate solvent, it is dissolved in a water/toluene mixture.
- Choose a column containing anion-exchange resin.In anion-exchange columns, positively charged functional groups interact with negatively charged sulfonate groups.
- Equilibrate the column with the mobile phase, which is commonly a buffered salt solution, before injecting the sample. Inject the prepared Polysulfonate polymer solution into the column to serve as the sample. The polymer will bond to the column due to an interaction between the negatively charged sulfonate groups on its surface and the positively charged resin.

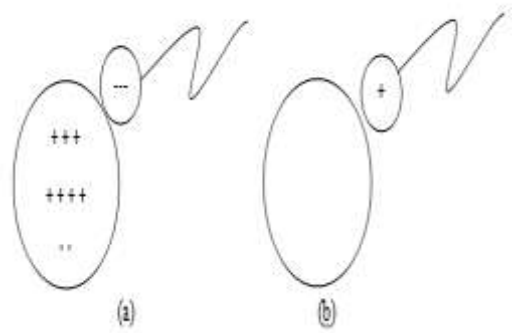


Figure 1: (a) -ve charged analyte (anion) and (b) +ve charged analyte (cation)[67]

3.5.2 Some other examples of pharmaceutical drugs that are analyzed using IEC: -

Antibody-drug conjugates (ADCs): The sites of antibody-drug conjugates (ADCs) have been examined using IEC with UV and mass spectrometry detectors.
The ADC sample is prepared by diluting the purified ADC formulation in a suitable buffer.

For Cation Exchange Chromatography (CEX):

Sodium Phosphate Buffer: A mixture of monosodium phosphate and disodium phosphate can be used to create buffer systems with different pH values (e.g., pH 6 to 8). Sodium phosphate buffers are commonly used for the separation of ADCs by cation exchange chromatography.
Sodium Acetate Buffer: Sodium acetate buffer at appropriate pH (e.g., pH 4.5 to 5.5) can also be used for CEX analysis of ADCs.[68,69]

For Anion Exchange Chromatography (AEX):

Tris Buffer: Tris buffer can be used for AEX analysis of ADCs at pH values around 7 to 9. Tris buffer is a versatile buffer system that can be adjusted to different pH values.
Phosphate Buffer: Sodium phosphate buffers can also be used for AEX analysis, depending on the specific requirements of the separation.[70]

The mobile phase buffer and salts are used to create the elution gradient for separation with charged particles. Buffers generally used for equilibration, binding, and elution in a CEX step in an ADC process are acetate, citrate, or phosphate.

UV-Vis absorbance detector is used and for advanced analysisMass spectrometry (optional) is used.It is important to consider the parameters affecting the separation, including the choice of media, pH, salt concentration, and flow rate.

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Small molecules:IEC is a popular technique for separating tiny and medium-sized proteins, with a molecular weight range of up to 70,000, as well as small molecules**.**[71]

3.5.3 Application: -

- Purification of proteins
- Analysis of pharmaceutical drugs
- Detection of residual limits

3.5.4Advantages: -

Efficient separation: It can be used to analyze and purify a wide range of biomolecules, including proteins, peptides, and nucleic acids**.**[72]

Versatility: The separation of ions and ionizable compounds can be done using that.

Specificity: IEC works by separating ionic species based on their affinity for an ion exchange resin. This means that it can provide highly specific separations.[73]

High resolution: For the investigation of complicated mixtures, IEC can offer high-resolution separations.[74]

3.5.5. Disadvantages: -

Limited resolution:IEC can provide high-resolution separations, but it may not be sufficient for the analysis of complex mixtures.Other techniques, such as SEC or hydrophobic interaction chromatography (HIC), may be needed to achieve higher resolution[75].

Limited pH range: IEC is sensitive to changes in pH, and the pH range for optimal separation is limited**.**

Limited applicability: While IEC is a versatile technique, it may not be suitable for the analysis of all types of pharmaceutical polymers. Other techniques, such as gel permeation chromatography (GPC) or Fourier transform infrared spectroscopy, may be more suitable for certain types of polymers.

Cost:IEC can be a relatively expensive technique, particularly when compared to other chromatographic techniques.

IV. CONCLUSION: -

UsingReversed phase gradient elution chromatography, UHPLC, HPLC, and IECtechniques, improvedthe understanding of pharmaceutical polymers. By combining analytical approaches, precise characterization has been improved as well as quality control measures have been enhanced and formulation strategies have been optimized. Therefore, these advances can accelerate drug development processes, refine formulation techniques, and ensure regulatory compliance within the pharmaceutical industry.

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