A New Process for Small-Batch Purification of the Medical Isotope Molybdenum-99: Non-Technical Overview

Internship Paper

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November 2022

National Nuclear Security Administration

1. Introduction

The U.S. medical community depends on a reliable supply of the radioisotope molybdenum-99 (Mo-99) for nuclear medical diagnostic procedures. Mo-99's decay product, technetium-99m (Tc-99m), is used in over 40,000 medical procedures in the United States each day to diagnose heart disease and cancer, to study organ structure and function, and to perform other important medical applications. For example, patients undergoing a common procedure—the cardiac "stress test"—likely have benefited from Tc-99m.[20]

Historically, Mo-99 was primarily produced through the fission of uranium-235, in the form of highly enriched uranium (HEU) targets irradiated in research and test reactors. HEU is a proliferation-sensitive material that, if diverted or stolen, could be used as a component of a nuclear weapon. NNSA's Office of Material Management and Minimization (M3) manages the Molybdenum-99 (Mo-99) Program as part of its mission to minimize the use of HEU in civilian applications. The Mo-99 Program assists global Mo-99 production facilities in converting to non-HEU processes and supports the establishment of domestic supplies of Mo-99 without the use of proliferation-sensitive HEU. [20]

As part of this program, M3 funds U.S. national laboratories to provide non-proprietary technical support to U.S. companies working to establish non-HEU-based Mo-99 production capabilities. The results of this research are published on OSTI.gov for the benefit of the Mo-99 community and the public. However, it can be difficult for readers without a scientific background to understand and interpret these publications.

In order to increase public understanding of the work being done in M3's Mo-99 Program, this paper aims to provide an overview of a key, recent national laboratory technical publication in terms that can be understood by readers without a technical background. To accomplish this, the paper first explains key scientific concepts—primarily related to chemistry—that provide a foundation for understanding research in this area. This includes chromatography, absorption vs. adsorption, dissolution and precipitation, and liquid-liquid extraction. Drawing on these concepts, the paper then provides an explanation for non-technical audiences of the Argonne National Laboratory publication entitled *Recovery of High Specific Activity Molybdenum-99 from Accelerator-Induced Fission on Low-Enriched Uranium for Technetium-99m Generators* (Brown, M.A. et al., 2021) and related article *Separation and Purification of Mo-99 Produced from Natural U_3O_8 Targets via Photo-Fission* (Brown, M.A. et al., 2021).

2. Key Technical Concepts to Know

The section that follows is a list of concepts relevant to gaining a reasonable understanding of the Argonne National Laboratory publication. Each subsection contains a "Key Points" portion which summarizes the entire subsection into a couple sentences in order to quickly gain a basic understanding of a concept. For a more comprehensive explanation, the bulk text should be read. Throughout the entire paper, certain terms will be bolded. This means that the concept was explained in a previous section, so readers can refer back to it if needed.

2.1 Common Units and Their Uses

The table below is a list of units commonly used in natural sciences or that are relevant to this paper. Each unit is accompanied by its abbreviation, fundamental units as well as examples of their use.

Unit	Abbreviation	Base Units	Use(s)	Example/Explanation
Mole	mol	N/A	Amount or quantity of a substance	Analogous to the term "dozen," a mole is the number of particles equal to the number of atoms in exactly 12 grams of carbon-12. This is equal to 602214150000000000000000. For simplification, it can be expressed as 6.022 x 10^{23}.
Molar	M	$\frac{\text{mol}}{\text{L}}$	Concentration in terms of moles of substance per unit volume of solution	A 1 M solution of HCl contains 6.022×10^{23} molecules of HCl per liter of solution.
Becquerel	Bq	Decay events × s^{-1}	The level of radioactivity for a certain substance or quantity of a substance.	1 Bq is the activity of a quantity of radioactive material in which one nucleus decays per second.
Curie	Ci	3.7×10^{10} s^{-1} (Bq)	The level of radioactivity of a substance or the quantity of a substance.	One curie is equivalent to 3.7×10^{10} Bq. Units of activity can be back solved to quantity of a radioactive substance since the probability of decay for a known number of atoms is constant. Typical commercial Tc-99m generators contain between 1-19 Ci of Mo-99.
6-day Curie	6-D Ci	3.7×10^{10} s^{-1} (the unit is based in curies however equivalence between Ci and 6d-Ci depends on the material)	For a given radioactive substance, the level of radioactivity or quantity that will remain after six days of radioactive decay.	The 6-day calibration in the 6-day curie was originally intended to account for the time needed to move Mo-99 through the supply chain to end users.
pH	pH	-log{H^+} or -log(mol H^+/L)	Hydrogen ion activity or concentration. Used to determine the acidity or basicity of an aqueous solution.	The lower the pH, the more acidic a solution. A 1 M HCl solution has a pH of 0. Stomach acid is pH ≈ 1-2. The ocean has a pH of ≈ 8. Sodium hydroxide and drain cleaners are often pH > 10.

2.2 Atom Basics & Isotope Notation

The three fundamental particles that make up every atom (not including antimatter materials) are protons, neutrons, electrons. These particles combined in different amounts make up every element on the periodic table. Each of these fundamental particles impact the element in different ways. The proton, which is positively charged, is found in the nucleus of the atom and its number determines the element (i.e, 1 proton for hydrogen, 2 protons for helium, etc.). Electrons are negatively charged particles which orbit around the nucleus. In a neutrally charged atom the number of electrons equal the number of protons, and the overall charge of an atom can be changed by adding or removing electrons, making the atom more positively and negatively charged, respectively. Changing the number of electrons on an atom also can impact some of its chemical properties. Finally, neutrons are neutrally charged particles found in the nucleus and contribute to the stability of an atom. Due to the proton's positive charge, protons in the nucleus repel each other (like charges repel). This electrostatic repulsion is greater than the nuclear attraction between the protons resulting in instability. Neutrons reduce electrostatic repulsion by distancing the protons from each other, thus stabilizing the nucleus. The mass defect or the nuclear binding energy represents the slight loss in mass as a result of proton-neutron bond and can be quantified using Einstein's equation $\Delta E = \Delta mc^2$ (E: energy, m: mass, c: speed of light). Consequently, massive amounts of energy can be harvested by splitting the atom's nucleus. Neutrons are also essential in nuclear fission as they are both used to initiate fission and are also released during fission.

The number of neutrons in an atom can vary drastically, especially in elements with a high number of protons (high-Z). Due to the neutron's impact on various nuclear properties a labelling/naming system has been made called isotope notation to differentiate these atoms.

There are three different numbers/variables that are accounted for in isotope notation: A, Z and e, as well as X which is a placeholder for the element's atomic symbol. The system for isotope notation is demonstrated in **(S. 1)**

$$^{A}_{Z}X^{e}$$

(S. 1)

A - Mass Number: The sum of the number of protons and neutrons in an atom
Z - Atomic Number: The number of protons in an atom
e - Electronic Charge: The overall charge of the atom (difference between number of protons and electrons)
X - Atomic Symbol: The chemical symbol for an element (e.g., H for hydrogen, He for helium, etc.)

Isotope notation allows for general information about the nuclear structure of an atom to be known. Uranium with 143 neutrons is often used in nuclear reactors as fuel due to its ability to undergo nuclear fission. This uranium can be written out in isotope notation as $^{235}_{92}\mathrm{U}$ and is called uranium-235. For ease of writing, isotope notation is often abbreviated, leaving the atomic number out since it can be determined based on the atomic symbol in the top right or center of every element in most periodic tables making the abbreviated form: $^{235}\mathrm{U}$. As mentioned prior, a single element can have different number of neutrons in its nucleus such as $^{98}\mathrm{Mo}$, $^{99}\mathrm{Mo}$, and $^{100}\mathrm{Mo}$. These are called isotopes, in this case, isotopes of molybdenum. Isotopes for each element occur in nature at different amounts called isotopic abundances. Uranium-235 has an isotopic abundance of 0.7198-0.7202%. Typical light water reactor cores require this value to be enriched to higher levels, though some technologies can use uranium at the natural isotopic abundance (i.e. CANDU reactors). The overall charge of atoms can also vary as well. $^{23}_{11}\mathrm{Na}$ is the isotope of sodium with the highest abundance. In its elemental form it is neutrally charged. However, if it were to be reacted to make NaCl (sodium chloride, also known as table salt) the charge of the sodium would change. If NaCl were to be dissolved in water (or any solution) the NaCl would break apart into what are called ions which are charged atoms normally found in solutions (though there are other ways to form ions). If we were to write out the isotope notation for the sodium-23 ion it would be written as $^{23}_{11}\mathrm{Na}^{1+}$ since the charge of a sodium ion is 1+.

2.3 Chemical Separations

The nature of fission implies more elements present than the initial starting conditions. In the case of Mo-99 production from uranium, a target initially contains two elements: U and oxygen (O) (or U and aluminum (Al)). Following the irradiation, nearly 1/3 of the periodic table is present, or roughly 40 different elements comprised of hundreds of isotopes, including Mo-99. Thus, chemical separations are an integral part of Mo-99 production technologies. A number of methods common to Mo-99 and isotope purifications are described below. In practice, more than one may be utilized to best suit the technologies surrounding the target and desired product. Furthermore, chemical separations are important for quality assurance and control (QA/QC).

2.4 Chromatography

Key Points: Chromatography is a class of laboratory techniques where the components of a liquid mixture travel through a substance at different rates based on a predetermined criterion. This allows the chemist to see which chemicals are in a mixture or to qualitatively analyze the properties of those chemicals

Chromatography is a technique used in many labs to separate the components of a solution based on a predetermined criterion. It is used in many fields for various purposes, such as, a means of analysis to identify things dissolved in a solution by separating them based on certain criteria (i.e., size, charge, polarity). Chromatography can be used to purify a substance by separating it from impurities and it can also be used to identify certain chemical properties of compounds dissolved in solution.

There are many types of chromatography including thin-layer chromatography (TLC), column chromatography (CC), high performance (or pressure) liquid chromatography (HPLC), and gas chromatography (GC). Though there are many types and methods of chromatography used based on the type of sample or end goal (i.e., purification, analysis, etc.), the result of most of these methods are in general very similar, where the components of a sample are separated based on a predetermined factor. This section will go over the basics of thin-layer chromatography and column chromatography.

2.4.1 Thin-Layer Chromatography

Key Points: A chemical mixture is dotted near the base of a plate. The components of the mixture separate as they travel up the plate at different rates. This allows the chemist to see which chemicals are in a mixture or to qualitatively analyze the properties of those chemicals.

In TLC, an inert surface, normally a thin metal plate or glass pane, is coated in what is called the stationary phase. Stationary phases for TLC are most commonly silica gel, but other materials such as aluminum oxide and magnesium silicate can also be used. This plate is then dotted with samples which are dissolved in a solvent. After being dotted, the plate is then placed vertically in a solvent called the mobile phase such that the solvent covers only the very bottom of the plate. The solvent is allowed to travel up most of the plate. While this happens, the sample dots also travel up the plate at different rates depending on their attraction—or strength of adsorption—to the stationary phase[1]. Distance from the start correlates to an element's speciation or the presence of an impurity. After, the plate is removed from the solvent, the distance the solvent travelled up the plate is marked along with the blots from each sample. The distance the mobile phase travelled up the plate as well as the distance the samples travelled is measured and a value called the retention factor, R_f, is determined using **Equation 1**.

$$R_f = \frac{\text{distance traveled by sample}}{\text{distance traveled by solvent}} \tag{1}$$

The retention factor of a sample allows its relative attraction to the stationary phase to be determined, where if R_f is low (i.e., the blot does not travel far up the plate), the sample exhibits a high attraction to the stationary and vice versa[2]. Retention factors can be used to determine the relative polarities of certain molecules. Polar compounds are molecules with an uneven charge distribution around it, whereas nonpolar compounds have a relatively even charge distribution. Polar compounds are more likely to dissolve in polar solvents and nonpolar compounds are likely to dissolve in nonpolar solvents. If the stationary phase on a TLC plate was nonpolar and the mobile phase was polar, the polar compounds would be expected to travel further up the plate and have a higher R_f, due to their attraction to the solvent. Nonpolar compounds would be expected to not travel as far up the TLC plate having a lower R_f, due to their attraction to the stationary phase[1,2]. A demonstration of a TLC setup is shown in **Figure 1**.

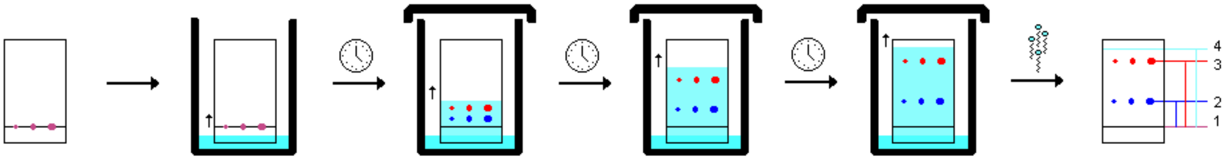

Figure 1: A schematic showing the process of thin-layer chromatography where 1 is the sample line, 2 and 3 are the distance travelled by component A and B, and 4 is the solvent front. ("Thin Layer Chromatography" by LibreTexts is licensed under CC BY-NC-SA.)

In **Figure 2** a TLC plate that was dotted with three different samples on the sample line (1) is placed in a beaker containing the solvent that makes up the eluant/mobile phase. The beaker is then covered, and the solvent is allowed to travel up the plate. As the mobile phase travels up the plate, the sample dots will split into different blots that travel up the plate based on their attraction to the stationary and mobile phases. The splitting of each sample dot into different blots indicates the sample mixture has components that adsorb to the stationary phase at different strengths. Once the mobile phase gets close to the top of the plate it is removed from the beaker. Next, the distance the solvent travelled up the plate is measured (from 1 to 4) and the distance each blot travels is also measured (from 1 to 2 and 1 to 3). The retention factor is then determined using **Equation 1**.

In radiochemistry and isotope production, radioactive signals from selected isotopes can be used to quantify retention factors. In lieu of using the blots described above, a TLC plate can be analyzed for radiation signatures along the stationary phase's height. The distance and distribution of the radioactive signal can be correlated to the isotope's chemistry or the presence of an impurity.

2.4.2 Column Chromatography

Key Points: A glass column is packed with wet powder, and then a liquid mixture is added onto the top of the column. The components of the mixture separate as they travel down the column at different rates. This allows the chemist to separate and purify the chemicals in the mixture or to analyze the properties of those chemicals.

In column chromatography, rather than using an inert plate coated in the stationary phase, the chemist uses a glass (or other inert material) column packed with the stationary phase. The stationary phase is then topped off with a small amount of sand or other inert powder to prevent the surface of the stationary phase from being disturbed. The sample to be analyzed or separated is then added and allowed to soak into the sand. The column is then topped off with solvent that makes up the mobile phase and the sample and solvent are allowed to pass through the column by gravity (or, in the case of HPLC, it is forced through the column at high pressure)[3]. As the sample passes through the column, various bands develop will start to develop (such as the ones in **Figure 2**) based on the components' attraction to the stationary phase. The bands that travel through the column more slowly have a greater attraction to the stationary phase. In the case of **Figure 2,** this would be the brown-orange compound acetylferrocene, and the bands that travel faster through the column have a lesser attraction to the stationary phase (such as the yellow ferrocene in **Figure 2**). If a sample were to be collected as the yellow band in **Figure 2** elutes out of the bottom of the column, the sample will have a significantly higher concentration of ferrocene and a decreased concentration of acetylferrocene. The amount by which each band separates is referred to as the resolution of the elution. In **Figure 2,** the two bands are highly resolved, meaning that the sample collected when ferrocene elutes from the column would contain very little acetylferrocene, if any[3,4].

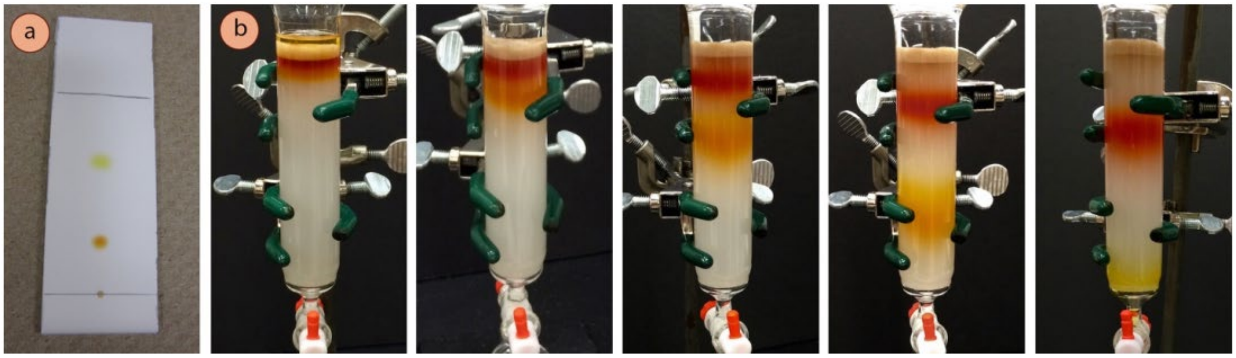

Figure 2: An example of a completed thin-layer chromatography trial using a sample containing ferrocene (yellow) and acetylferrocene (brown-orange) (a), and a column chromatography trial of the same sample as it develops over time (b). ("Macroscale Columns" by Lisa Nichols, LibreTexts is licensed under CC BY-NC-ND.)

Column chromatography uses what are called elution profiles such as the one in **Figure 3** to show how samples elute from the column. In an elution profile, the y-axis is usually the concentration of, or a quantity proportional to, the components within a sample and the x-axis is the time in which the sample eluted from the column.

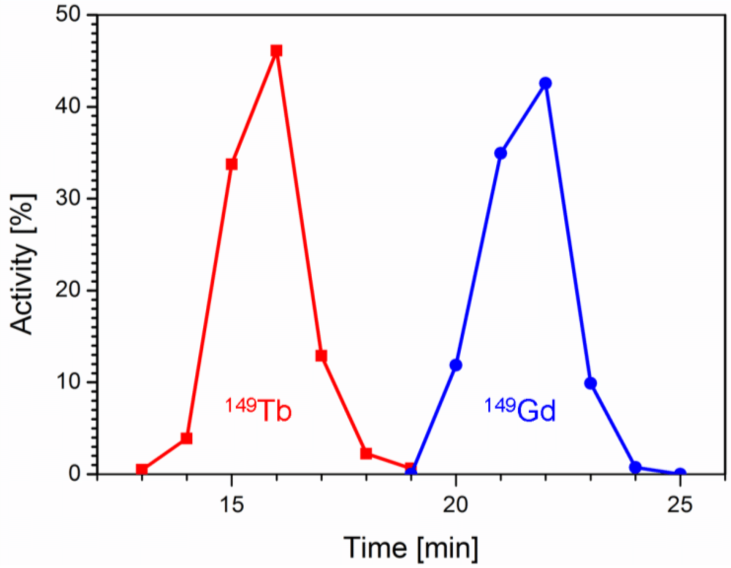

Figure 3: An elution profile of terbium-149 and gadolinium-149 that were run through a cation exchange column. Adapted from Ref. 5.

It can be seen in **Figure 3** that the y-axis is in units of percent activity which is proportional to concentration. The x-axis shows elution time in minutes. Based on this, we can see that terbium-149 eluted before gadolinium-149. This elution was performed with an ion exchange column. Ion exchange is a type of column chromatography, which is explained in the section below.

2.4.3 Ion Exchange Chromatography

Key Points: Ion exchange chromatography is a type of column chromatography that selects based on the charge of the **ions** passed through a column. Ion exchange chromatography can be used to separate charged compounds (either positively or negatively charged) that are part of a solution.

Ion exchange chromatography takes advantage of the fact that different charges attract to separate chemicals chromatographically. In anion exchange chromatography, the packing material is positively charged which allows anions (negatively charged **ions**) to have a greater affinity to the stationary phase, thus eluting later. In cation exchange chromatography, the packing material is negatively charged allowing it to have a greater affinity to cations (positively charged **ions**), causing them to elute later[6]. For samples containing analytes of the same charge, the elution order can be manipulated to reflect the different sizes of the ions.

Ion exchange chromatography is performed using a special material known as ion exchange resin, which makes up the stationary phase in the column. Ion exchange resins are primarily composed of three parts: a solid support, a charged molecule that is bound to the solid support, and a counterion that is fixed to the charged molecule. Ion exchange resins can be composed of many different types of charged groups and counterions. The type of counterion used in an ion exchange resin determines its properties and best use cases. This is known as the resin's "form".[7] For example, in order to treat "hard water" (water that contains a high quantity of calcium **ions**), a sodium form cation exchange resin is used. The sodium **ions** from the resin will replace the calcium **ions** in solution and vice versa. Selection of the correct form of resin is important, because elution rates can change depending on the form of the exchange resin and what is being passed through the column[6]. Other common uses for ion exchange chromatography include purification of water, where poisonous or hazardous **ions** such as lead, copper and cadmium are removed; and juice purification, where components in the juice that can give a bad taste can be removed.

In **Figure 4** an illustration of the general process of ion exchange is shown for the purification of water by removal of NaCl. Water containing NaCl is first passed through one column with a hydrogen form cation exchange resin. In the figure, the solid support is symbolized by a line stemming from the side of the column, the charged group is symbolized with a circle containing a minus which is attached to the solid support, and the counterion is the H^+ near the charged group of the resin. As the water containing NaCl (i.e., water containing both positively charged sodium ions and negatively charged chloride ions) passes through the ion exchange resin of the first column, the Na^+ from the water will attach to the charged group, kicking off and separating the H^+ from the charged group. In this way, the Na^+ and H^+ are exchanged. The Na^+ will travel down the column more slowly than the rest of the solution, enabling its separation for purification purposes.[6]

However, the process added H^+ to the water, and the water still contains the original Cl^-. The additional H^+ lowers the pH of the water, making it more acidic. To return the pH to neutral and to remove the chloride ions (Cl^-) the water is passed through another ion exchange column containing hydroxide form anion exchange resin. As the solution passes through the resin, the chloride ions will exchange with the hydroxide ions (OH^-). Since hydrogen ions are acidic and hydroxide ions are basic, these ions will react together to form water (H_2O) and thus return the pH to 7 (neutral). This completes the water purification process.[6]

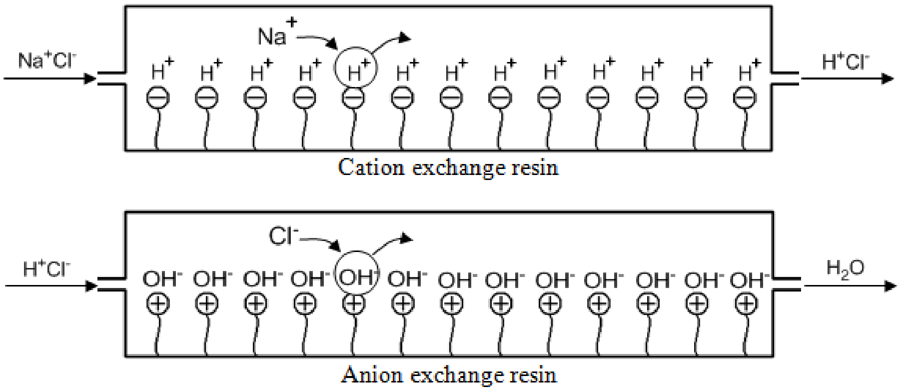

Figure 4: An example of ion exchange chromatography in water purification where NaCl is removed using one column with a hydrogen form cation exchange resin and another column with a hydroxide

form anion exchange resin. (“Ion-Exchange Chromatography” by LibreTexts is licensed under CC BY-NC-SA.)

2.5 Absorption vs. Adsorption

Key Points: Absorption is when a fluid passes through or enters a material (e.g., a sponge absorbing water). Adsorption is when a fluid adheres to the surface of a material without entering it (e.g., water fogging up a window).

The term adsorption is very often seen in the context of chromatography, however many who are not familiar with the term often confuse it with absorption due to its similar spelling and contextual usage. However, these two terms have very different meanings. Absorption, a term many are familiar with, is when a fluid (i.e., a liquid or gas) passes through or enters a bulky material. The most common example of absorption is a sponge absorbing water. The water enters insides the sponge and can be released by squeezing it.

By contrast, adsorption is when a fluid adheres to the surface of the bulky material without entering it[8]. This adhesion usually occurs via different forms of attraction (e.g., electrostatic, Van der Waals). An example of adsorption would be a glass window fogging up. When a window gets foggy, water condenses and adheres to the surface of the glass but does not enter into the bulk solid of the glass. To summarize, absorption is when a fluid enters into the bulk of a material, and adsorption is when atoms or particles adhere to the surface of another material. This process is demonstrated pictorially in **Figure 5**.

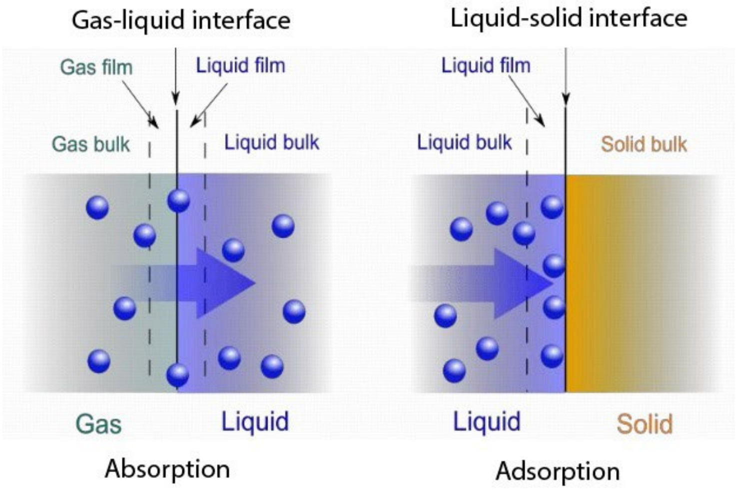

Figure 5: An image demonstrating the difference between absorption and adsorption. Where particles enter the bulk material in absorption and adhere to the surface of the bulk in adsorption. ("Absorption vs. Adsorption" by Daniele Pugliesi , is licensed under CC BY-SA 3.0.)

2.6 Dissolution and Precipitation

Key Points:

- Dissolution is when two substances form a uniform mixture called a solution, in which the components cannot be distinguished from one another with the naked eye nor separated through means such as filtration.
- Precipitation is when part of a liquid mixture transforms into a solid form, such as a crystal, and separates from the liquid mixture. This can be a good way to isolate a desired product from a mixture.
- Coprecipitation is when trace amounts of another substance are incorporated into or stick to a crystal that was formed through precipitation.

2.6.1 Dissolution & Solubility

It is well known that many substances can dissolve into others, such as salt into water or Styrofoam into nail polish remover (acetone). When a substance can completely dissolve into another, it is known as being soluble. To understand the process of dissolution, one must first understand the terms used to refer to components of a solution as well as what a solution itself is. A solution is what is referred to as a homogenous mixture, meaning that it is two or more substances that are evenly mixed in a solvent. Solutions are most commonly solids that have been dissolved in liquids or liquids dissolved in other liquids, but they can also be gases dissolved in gases or gases dissolved in liquids.[9] The components that make up a solution are referred to as the solute and the solvent. The solute is the substance that is being dissolved while the solvent is the substance doing the dissolving. For example, in a solution of salt water, the salt would be the solute and the water would be the solvent.

The degree or amount in which a substance can dissolve in another, known as molar solubility, varies between compounds as well as the conditions of those compounds. For example, at 25 °C ~0.60 moles (the SI unit for quantity) of NaCl (table salt) can dissolve in 100 mL of water, whereas only 0.000013 moles of calcium carbonate (the substance that makes up chalk) can dissolve in the same amount of water. There are many things that can impact a substance's solubility. Beginning with physical properties, temperature is a major factor in a chemical's solubility. In general, as temperature increases, a substance's solubility increases, but there are exceptions to this rule. In the case of gases as well, pressure has an impact on solubility, where a higher pressure of the chemical that makes up the solute surrounding the solution will increase that solute's solubility. An example of solubility of gases in terms of both temperature and pressure is when a can or bottle of soda is opened. Depending on the temperature of the can when it is opened, different amounts of gas can be heard escaping the can. When a cold can of soda is opened, less gas will be heard escaping than when the can is at room temperature. Additionally, when a bottle of soda is opened, bubbles are observed to form within the soda. This is because when the bottle is opened, the pressure within it decreases, causing the carbon dioxide (CO_2) in the soda to become less soluble, resulting in some of it leaving solution in the form of bubbles.

Some molecules are more soluble in certain solvents than others. This can be observed in the prior example comparing sodium chloride and calcium carbonate. Since there are a vast number of factors that go into determining the solubility of a compound, only the most general factors will be explained. The first major factor is referred to in many introductory chemistry courses as "like dissolves like." This is in reference to how polar solutes tend to dissolve better in polar solvents, and nonpolar solutes tend to dissolve better in nonpolar solvents. The polarity of a compound has to do with how electronic charge (i.e. charge from electrons) is distributed throughout a molecule, however, for the purpose of this paper these properties can be thought of as polar compounds being hydrophilic (water loving) and nonpolar compounds being hydrophobic (water hating). Compounds that dissolve in water will likely be able to dissolve in polar solvents, while substances that cannot dissolve in water will likely be able to dissolve in nonpolar solvents.[9] Another major factor for a substance's solubility is its molecular size. For a substance to dissolve in solution it must undergo a process called solvation, where particles of solute are surrounded by particles of solvent. However, as a molecule gets bigger it becomes more difficult for solvent particles to surround the molecules of the solute.[10] The final major factor that will be mentioned here has to do with the strength of what is called an "ionic bond". Ionic bonds form mostly between a metal and a nonmetal, where in order to reach a greater stability, one component transfers one or more electrons to the other component, creating an ionic bond and thus an ionic compound. When ionic compounds dissolve in solution they form **ions,** however some ionic bonds are so strong that the ionic compound cannot be dissolved.[9,10]

2.6.2 Precipitation

Precipitation can be thought of as the opposite of dissolution, where substances dissolved in solution separate from it. While this paper will focus primarily on precipitation as it relates to solids dissolved in liquids, precipitation can also occur with liquids and gases. For example, rain is a result of water precipitating from the air in the atmosphere. There are two major causes for precipitation: the conditions the solution is in, and the occurrence of a chemical reaction.

Precipitation from Changes in Conditions

As discussed, above, there is a limit to the amount of a substance which can dissolve in another; this is called the saturation point (there are ways to go past this limit in which a solution becomes supersaturated, but that is outside the scope of this paper). The saturation point can increase or decrease based on the conditions that the solution is in. For example, for solids dissolved in liquids, decreases in volume or temperature of the solution generally lower the saturation point. If a solution is already at the saturation point, and the conditions change in a way that lowers the saturation point, then precipitation can occur. In this case, the solute leaves solution, forming nearly pure crystals in the case of solids (unless coprecipitation occurs, which is addressed in a later section).

This property is taken advantage of in a technique called recrystallization. In recrystallization, a final product, in its solid form, is taken and redissolved in a solution by either heating the solution or by introducing it to enough solvent. The solution is then allowed to cool, or the solvent is allowed to evaporate, reducing the molar solubility and causing the product to precipitate out in a purer form than what was dissolved initially. It should be noted that the primary downside of this technique is that not all of the product will precipitate out of solution, causing some losses. Recrystallization is often used to purify active pharmaceutical ingredients for use in medicine.

Precipitation from a Chemical Reaction

Precipitation can also occur as a result of a chemical reaction. This normally happens due to the formation of a product that is either less soluble than its components or not soluble at all. The most basic example of this is called a double displacement reaction (sometimes called a precipitation reaction). This occurs when two ionic compounds react with each other in such a way that two ionic bonds are reacted, and two new ionic bonds are formed. A simple example of such a reaction is between silver nitrate ($AgNO_3$) and potassium chloride (KCl). Both of these compounds are soluble in water, and if you were to mix a solution of $AgNO_3$ and KCl together, a white substance would precipitate out of solution. This substance is silver chloride (AgCl), which is insoluble in water, whereas potassium nitrate (KNO_3) will not precipitate out as it is very soluble in water. Precipitation as a result of a chemical reaction can also occur in organic (carbon containing) compounds, however this process is significantly more complex than a double displacement reaction and thus will not be covered in this paper. Precipitation due to a chemical reaction can be used to obtain a product of interest.

2.6.3 Coprecipitation

Coprecipitation occurs when substances that are normally soluble are carried out of solution by another precipitate through various mechanisms. Coprecipitation is usually an undesirable effect, as it can lower the purity of product since impurities can often coprecipitate with the desired product.[12] However, this property can be taken advantage of in the context of radiochemistry, where it is often the only way of separating out trace fission side products.

There are three major mechanisms in which coprecipitation can occur: inclusion, occlusion, and adsorption. Due to the relation both inclusion and occlusion have to crystallography, in addition to explanations of the coprecipitation mechanisms, the following will include a section on the basics of crystal structures.

Basics of Crystal Structures

A crystal is a solid material made of components that are highly ordered or arranged in a uniform manner microscopically. Crystals greatly vary in size, from microscopic to large enough to be seen with the naked eye. A crystal's structure or lattice is a uniform arrangement of atoms that can be subdivided into what are called unit cells, these unit cells can be thought of as the lowest common divisor of uniformity where these unit cells cannot be subdivided into smaller uniform unit cells.[13] An example of a crystal lattice and its unit cells can be seen in **Figure 6.**

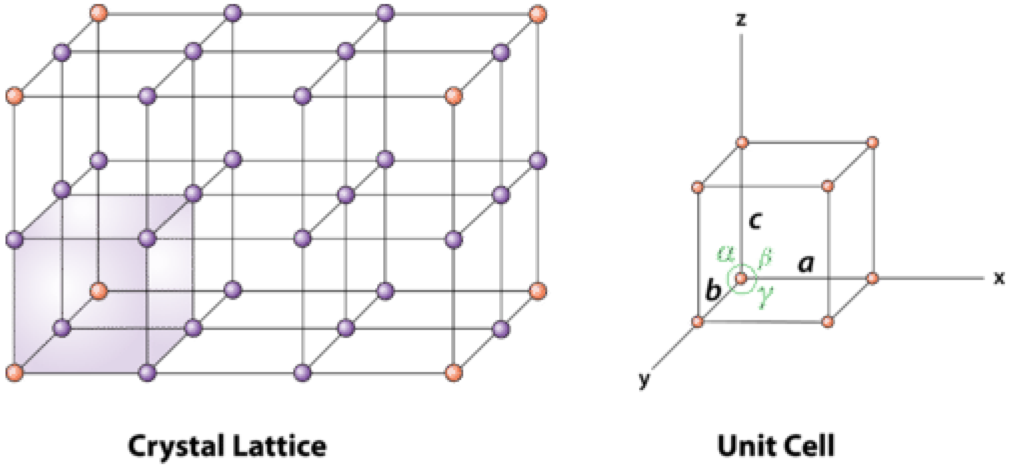

Figure 6: A diagram of a unit cell (right, and the shaded area of the crystal lattice) and a crystal lattice, the spheres seen throughout both the unit cell and crystal lattice are called lattice points; in a real crystal these would be the atoms/molecules that make up the crystal. (Credit: Christopher Auyeung; Source: CK-12 Foundation; License: CC BY-NC 3.0)

Depending on how atoms are arranged in each unit cell, the structure or shape of the overall lattice can vary. While crystals are defined as being uniform, some can have variations or imperfections within their structure. Variations in the crystal structures can cause various effects. Most notably, the color of a crystal can change as a result of various contaminants. For example, lattices of SiO_2 are what make up quartz crystals. These crystals are normally white or transparent, but if the lattice contains impurities such as iron, titanium, or manganese, the color of the crystal can become a range of colors, including pink and purple. Pink and purple quartz are known as rose quartz and amethyst, respectively. The two types of imperfections that will be summarized in the following sections are inclusion and occlusion, due to their relevance in coprecipitation.

Inclusion

The first mechanism for coprecipitation is called inclusion. Inclusion occurs during the formation of a crystal where there is a defect at a lattice point.[13] An example of an inclusion is calcium inclusions in sodium chloride (NaCl) crystals. The lattice of a NaCl crystal very much resembles the lattice demonstrated in **Figure 6** where the blue lattice points are Na^+ atoms and the red lattice points are Cl^- atoms. During the crystallization of NaCl, Ca^{2+} atoms can replace the lattice points where the Na^+ atoms are. The amount this occurs depends on various factors. This mechanism occurs in coprecipitation when impurities get included in the crystal lattice of the product that the chemist is attempting to precipitate, lowering the purity of the product.

Occlusion

The second mechanism for coprecipitation is called occlusion. Occlusion occurs when a rapidly growing crystal physically entraps a foreign ion. It should be noted this is different to inclusion as the impurity does not become a part of the lattice structure but rather becomes encased within it. A subtype of occlusion, called entrapment, happens the same way as general occlusion, however instead of a singular or set of **ions** getting trapped within a lattice, some of the solution the crystal forms in is trapped within the lattice.[13] This can occur in many crystals, including quartz, where natural quartz crystals have been found containing cavities filled with water.

Adsorption

Adsorption is relevant to both chromatography, as discussed above, and coprecipitation. Impurities can adsorb to the surface of the product of interest as it crystalizes out of solution. Adsorbed impurities can normally be removed from the surface of the product by either redissolving the product and allowing it to crystalize again and/or by washing the precipitate that has been filtered out of solution using solvent.[12,13] The stronger the attraction between the product and impurity, the more difficult it is to remove.

2.7 Liquid-Liquid Extraction

Key Points: The chemist has a liquid mixture that contains a product of interest as well as undesirable impurities. The chemist seeks to separate and purify the product of interest. The chemist adds a second liquid that does not mix with the first liquid (like oil and water). The chemist shakes the two liquids together, causing either the product of interest or the impurities to transfer from the first liquid to the second liquid. This separates the product of interest from the undesirable impurities. The chemist allows the liquids to settle, causing them to separate so they can be transferred into separate containers.

Liquid-Liquid Extraction (LLE) is a type of solvent extraction process performed as part of a process to isolate and purify products of a chemical reaction. These processes are commonly referred to as a “work-up”. The term “contacting” also refers to the LLE process. The general process for LLE involves taking two immiscible or partially miscible solvents (e.g., oil and water are immiscible) and contacting them to maximize the interfacial surface area between the two solvents. When the two phases are rigorously mixed, an emulsion forms that represents a dispersion of both phases. Over time – and dependent on the composition of the solvents – they will disengage to form two phases. This is normally done with an aqueous (water containing) solvent and an organic solvent referred to as the aqueous and organic phases, respectively. Based on the solubility of the product of interest, it will move from one phase to another. This can occur independently, or the chemist can manipulate the product of interest to become more soluble in the new phase.[14]

The process of LLE is often altered based on the desired product(s) being extracted. Most commonly, pH is altered in order to increase solubility of the desired product in the other phase. In **Figure 7,** a mixture of benzoic acid and cyclohexane are in the organic phase, and the chemist seeks to separate the benzoic acid from the cyclohexane. In **Figure 7a**, pure water is added to the separatory funnel, and some benzoic acid transfers over to the aqueous phase due to it having some solubility in water. To increase the phase transfer of the benzoic acid, a dilute solution of sodium hydroxide is used as the aqueous phase, instead of pure water. The sodium hydroxide deprotonates (neutralizes/removes the acidic hydrogen) from the benzoic acid, making it more soluble in the aqueous phase[15], this is shown in **Figure 6b**.

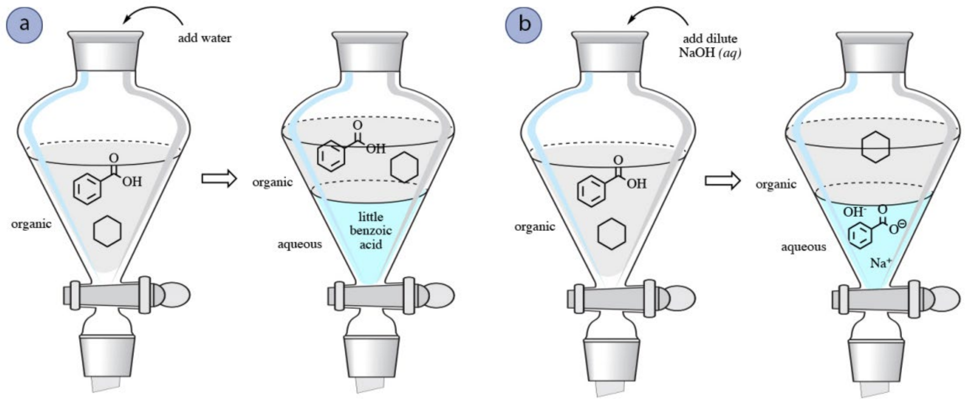

Figure 7: A liquid-liquid extraction of benzoic acid into the aqueous phase from an organic phase containing both benzoic acid and cyclohexane where, (a) uses pure water as its aqueous phase and (b) uses a dilute sodium hydroxide solution as its aqueous phase. ("Acid-Base Extraction" by Lisa Nichols, LibreTexts is licensed under CC BY-NC-ND.)

In practice, multiple contacts of the same aqueous or organic solutions are implemented to maximize separations. Chemists will often designate the ‘number of contacts’ required to achieve a desired purity or separation factor. Terms such as scrub and strip represent cleaning the organic phase or removing an analyte of interest from the organic to the aqueous phase, respectively.

3. Recovery of High Specific Activity Mo-99 Produced from LEU

As discussed above, Mo-99 is primarily produced through the fission of uranium-235. Irradiated uranium-235 contains Mo-99, bulk uranium, and fission products. A key part of the Mo-99 production process is to separate out a pure stream of Mo-99. One method of performing this separation is known as the LEU Modified Cintichem Process. However, the Cintichem process is not ideally suited to the production of smaller batches of Mo-99, because it requires the addition of a stable Mo “carrier.” While the addition of stable Mo in larger batches (>1000 Ci) may not pose an issue, in smaller batches of 100 Ci or less, it can reduce the specific activity of the Mo product. Conventional alumina-based ^{99}Mo/ ^{99m}Tc generators are strongly dependent on the specific activity of the Mo supplied, and decreasing the specific activity results in decreased generator performance and possible contamination of Tc product with Mo.

As part of the Mo-99 laboratory technical support program, Argonne National Laboratory has developed a new method of performing this separation. This method uses a uranium extraction (UREX) and molybdenum liquid-liquid extraction (MoLLE) process which, unlike the LEU Modified Cintichem Process, allows for the purification of Mo-99 without the addition of stable Mo carrier. This facilitates Mo-99 purification for processes with relatively low Mo-99 activity.

Drawing from the explanations of key scientific concepts above, this section will explain the UREX + MoLLE process, and how it compares to the previously established LEU Modified Cintichem Process. It should be noted that the procedures for both the LEU Modified Cintichem Process and the UREX + MoLLE process can change based on a variety of conditions and contexts. Additionally, the following procedures are not intended to be used as instructions to be followed, but rather as a general explanation of the process. Thus, quantities of reagents as well as certain steps (e.g., beaker rinses, and steps taken to determine quantity of reagents needed) may be omitted unless it is necessary to adequately explain a specific step in the process. The procedure for the LEU Modified Cintichem Process is adapted from Ref. 17, and the procedure for the UREX + MoLLE process is adapted from Refs. 18 and 19.

3.1 LEU Modified Cintichem Process

One of the methods for purifying Mo-99 from the irradiated uranium target containing fission products is the LEU Modified Cintichem Process (LMC). After the acidic **dissolution** of the irradiated uranium in nitric acid, the LMC process is based on the addition of various carriers to **precipitate** out fission side products. Radioiodine is present in significant quantities after irradiation, and is one of the major Mo-99 contaminants. While most of the radioiodine vaporizes during the **dissolution** of the irradiated uranium, some remains in the liquid solution in various forms, increasing the difficulty of its removal due to the variation of chemical properties between each form. The remaining radioiodine is **coprecipitated** out of solution with the addition of a sodium iodide (NaI) carrier along with silver nitrate ($AgNO_3$) in nitric acid (HNO_3) which causes the **dissolved** iodide to **precipitate** out as silver iodide (AgI). **Dissolved** iodine (I_2) that is not removed with the silver **ions** can be **coprecipitated** as AgI using silver metal. Iodate (IO_3^-) and periodate (IO_4^-) can also be removed with AgI (due to isotopic exchange), however a longer time is needed due to slower kinetics of isotopic exchange, making these compounds more difficult to remove than iodine and iodide. The silver that remains in solution is then **precipitated** out as silver chloride (AgCl) using hydrochloric acid (HCl). The **precipitates** formed are separated out of the solution using filtration, being washed with HNO_3 to remove any compounds potentially **adsorbed** to the **precipitate**. This step also serves to increase the acidity of the reaction mixture which is important for later steps. At this point, the majority of U and I have been removed; however, additional steps are necessary to remove other fission products.

Ru and Rh carriers are added to prevent ruthenium and rhodium from **coprecipitating** with Mo when alpha-benzoin oxime (ABO) is added. Additionally, stable Mo carrier is added to the solution to assist in Mo **precipitation** during the ABO steps. The addition of stable Mo here can reduce the **specific activity** of the final product, especially in smaller batches. To keep Mo in a state that allows for **precipitation** with ABO, potassium permanganate ($KMnO_4$) is added until a dark pink color is reached. The addition of too much $KMnO_4$ can result in losses of Mo. ABO in sodium hydroxide (NaOH) is then added to the reaction mixture. When ABO complexes with Mo it forms a white **precipitate** which can be filtered off from the rest of the solution.

As a final purification step, the ABO-Mo precipitate is **redissolved** in a solution of sodium hydroxide (NaOH) and hydrogen peroxide /(H_2O_2). It is then passed through a silver-coated charcoal (Ag/C) **chromatography column** which filters out any residual carbon-containing compounds remaining in solution, as well as any dissolved iodine. It is then passed through another **chromatography column** containing Ag/C, hydrated zirconium oxide (HZO), and charcoal to remove any final impurities.

3.2 UREX + MoLLE

Argonne National Lab (ANL) as part of the Mo-99 laboratory technical support program has worked on the development of a new procedure that can be used to separate Mo-99 from U_3O_8 and uranyl sulfate through uranium extraction and molybdenum **liquid-liquid extraction** (UREX + MoLLE). By not requiring the addition of stable Mo to **coprecipitate** Mo-99 from solution, UREX + MoLLE can be used to quickly recover Mo-99 from irradiated uranium targets, including in production processes with relatively low Mo-99 activity.

The UREX + MoLLE process begins similarly to LMC, where the irradiated uranium is **dissolved** in HNO_3 within an apparatus where any gases let out during this process are collected (e.g., radioiodine, radioxenon and gaseous nitrous and nitrogen oxides). To conduct the UREX process, the irradiated uranium in HNO_3 is combined with tributyl phosphate (TBP) dissolved in n-dodecane, where they are contacted through **liquid-liquid extraction.** This process removes the bulk uranium that can be recovered. For the MoLLE process, the raffinate from UREX is combined with di-2-ethylhexyl phosphoric acid (HDEHP) and contacted via **liquid-liquid extraction** for three rounds. During this process, the Mo-99 transfers over to the organic phase containing the HDEHP. The HDEHP is then contacted with acetohydroxamic acid (AHA) via **liquid-liquid extraction** three times to strip the Mo-99 from the HDEHP.

The final step in the UREX + MoLLE process is the removal of any remaining impurities through the use of a **chromatography column**, more specifically, an **anion exchange column**. The column is packed with AG® MP-1M anion exchange resin. This resin, which is initially in the chloride form, is converted to hydroxide form to allow for increased separation of the molybdenum from the impurities. As seen in **Figure 8,** the Mo elutes significantly later than the impurities, allowing for production of pure Mo stream.

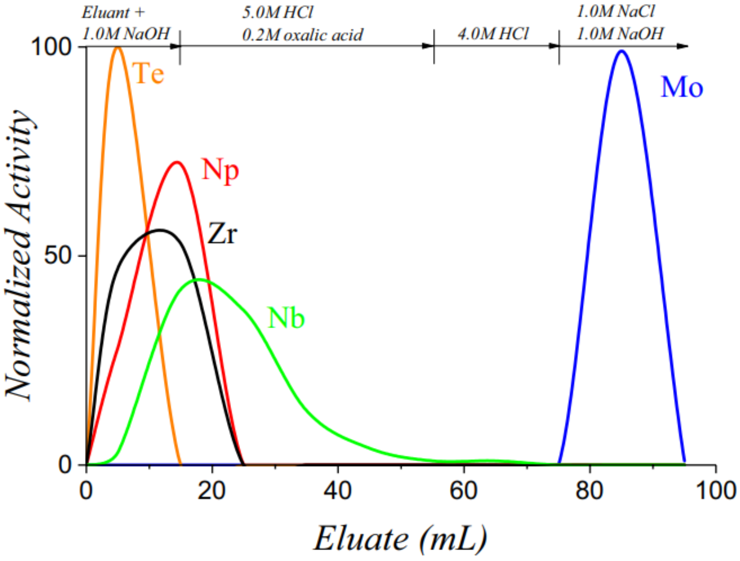

Figure 8: An elution profile for the final anionic exchange chromatography step in the UREX+MoLLE process. The feed solution was derived from irradiated uranyl sulfate that has gone through the previous UREX+MoLLE steps. Flow Rate: ≈ 2 mL/min. Adapted from Ref. 19.

Several washes are implemented to achieve the desired purity of the Mo-99 product. After loading the column, NaOH is used to wash out impurities such as Te, Zr and Np. The next wash is a mixture of HCl and oxalic acid, which is specifically design to remove Nb. This is followed by an HCl wash to remove oxalic acid and the remaining iodine. Mo is then stripped from the column using NaOH/NaCl.

4. Conclusion

M3 funds U.S. national laboratories to provide non-proprietary technical support to U.S. companies working to produce the vital medical isotope Mo-99 without the use of proliferation-sensitive HEU. As part of this program, ANL has developed an important new chemical process that will allow commercial producers to produce pure Mo-99 product. This paper provided an overview of the new ANL process for non-scientific readers, starting with explanations of key underlying scientific concepts such as chromatography, adsorption, dissolution, precipitation, and liquid-liquid extraction.

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6. Acknowledgements

Editorial assistance was provided by Max Postman, Peter Tkac, and Alex Brown.